University of Alberta

Intramolecular conjugate displacement for making carbocycles and studies on the total synthesis of MPC1001

by

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A thesis submitted to the Faculty of Graduate Studies and Research
in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

Department of Chemistry

Fall 2011
Edmonton, Alberta

DEDICATED TO

MY PARENTS AND MY WIFE JIE RU

ABSTRACT

The first chapter of this thesis describes methodology on an all-carbon intramolecular conjugate displacement between a carbon nucleophile and a Morita-Baylis-Hillman adduct for making carbocyclic skeletons. The reaction scope was examined with different electron-withdrawing groups, types of carbon nucleophile and leaving groups. The study demonstrated that this transformation is a convenient and effective way of constructing carbocycles, including some synthetically challenging structures. The mechanism of this transformation was probed by experiments designed to trap a possible anionic species of a non-concerted pathway.

The second part of my thesis describes studies towards the total synthesis of the natural product MPC1001, which is a potential anti-tumor agent. Effort was focused on inventing a way of installing a disulfur bridge in a stereo-controlled manner. Difficulties were encountered for thiol deprotection, as attempted removal of many known thiol-protecting groups gave either no reaction or loss of the sulfur, possibly expelled by the nitrogen on the same carbon. Therefore, a new protecting group for thiols was designed, which could be deprotected under mild conditions. Although this protecting group allowed smooth deprotection with one specific reagent, additional problems prohibited carrying the research further using this group. A new route for installing the disulfide bridge was conceived and is still under examination.

ACKNOWLEDGEMENTS

I would like to thank my supervisor Dr. D. L. J. Clive for his guidance, encouragement and assistance during the course of my Ph.D. program. His teaching and discussion made it possible for me to learn organic synthesis quickly.

Many thanks to the current and past group members for their friendship and assistance over the years. I would specially thank Che-Chien Chang, Jianbiao Peng and Dazhan Liu for helping me in the laboratory at the beginning of my research.

My thanks are also extended to the support staff of the department (IR, MS, NMR, elemental analysis laboratories, glass blowing, electronic, machine and chemical shops), especially to Mark Miskolzie for his assistance with NMR problems and Dr. Angie Morales-Izquierdo for MS characterization.

I would like to thank the Alberta Heritage Foundation for Medical Research (now known as Alberta Innovates-Health Solutions), Boehringer Ingelheim (Canada) Ltd., Novartis Pharmaceuticals Canada Inc., and the University of Alberta for the scholarships, and the ACS Graduate Symposium organizers.

Finally, I would like to express my thanks to my parents, sisters and my wife Jie Ru for their support and encouragement.

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LIST OF ABBREVIATIONS

Ac	Acetyl
acac	Acetylacetonato
AIBN	2,2'-azobisisobutyronitrile
All	Allyl
APT	Attached proton test
Ar	Aromatic ring
BHT	2,6-Di-*tert*-butyl-4-methylphenol
Bn	Benzyl
Boc	*tert*-butoxycarbonyl
brsm	Based on recovered starting materials
Bu	*n*-Butyl
t-Bu (or Bu-*t*)	*tert*-Butyl
Bz	Benzoyl
CD	Circular Dichroism
Cinn	Cinnamoyl
Cp	Cyclopentadienyl
DABCO	1,4-Diazabicyclo[2.2.2]octane
dba	Dibenzylidene acetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
$(DHQD)_2PHAL$	Hydroquinidine 1,4-phthalazinediyl diether
DIBAL	Diisobutylaluminum hydride
DKP	Diketopiperazine
DMAP	4-Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
EDCI	*N*-Ethyl-*N*-(3-dimethylaminopropyl)carbodiimide
dr	Diastereomeric ratio
ee	Enantiomeric excess
Et	Ethyl

ETP	Epidithiodioxopiperazine
EWG	Electron-withdrawing group
Fmoc	9-fluorenylmethyloxycarbonyl
FTIR	Fourier transform infrared spectroscopy
HMPA	4-Hydroxymethyl-3-methoxyphenoxyacetic acid
HSQC	Heteronuclear Single Quantum Coherence
IBX	2-Iodoxybenzoic acid
ICD	Intramolecular conjugate displacement
Im	Imidazo
KHMDS	Potassium bis(trimethylsilyl)amide
LDA	Lithium diisopropylamide
LiHMDS	Lithium bis(trimethylsilyl)amide
LUMO	Lowest unoccupied molecular orbital
MBH	Morita-Baylis-Hillman
m-CPBA	3-Chloroperbenzoic acid
Me	Methyl
MEM	β-Methoxyethoxymethyl
MOM	Methoxymethyl
mp	Melting point
Ms	Methanesulfonyl
MS	Molecular sieves
NaHMDS	Sodium bis(trimethylsilyl)amide
NBS	*N*-bromosuccinimide
NMO	*N*-Methyl morpholine-*N*-oxide
NMR	Nuclear magnetic resonance
PCC	Pyridinium chlorochromate
Ph	Phenyl
PMB	*para*-Methoxybenzyl
PMP	*para*-Methoxyphenyl
PPTS	Pyridinium *p*-toluenesulfonate
i-Pr	Isopropyl

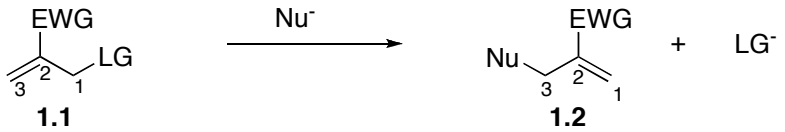
Pro	Proline
PTSA	*p*-Toluenesulfonic acid
pyr	Pyridine
quant.	Quantitative yield
rt	Room temperature
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
Tol	Tolyl
Tr	Trityl
Triton B	Benzyltrimethylammonium hydroxide
TROESY	Transverse rotating-frame Overhauser enhancement spectroscopy
Ts	Toluenesulfonyl

Chapter 1

Formation of carbocycles by intramolecular conjugate displacement: scope and mechanistic insights

1. Introduction

It has long been known[1] that the presence of an electron-withdrawing group (EWG) at the C2 position can greatly enhance the S_N2' displacement reactivity of an allylic system bearing a leaving group at its C1 position (Scheme 1). In contrast to palladium catalyzed nucleophilic substitution of allylic acetates, known as the Tsuji-Trost reaction, a variety of nucleophiles can directly displace the EWG-activated allylic acetate in an S_N2' fashion without the aid of a transition metal catalyst. Although much research has been conducted on S_N2' reactions using this EWG activated allylic theme,[2] either exploring new transformations[3] or applying it in total syntheses,[4] the intramolecular version (S_N' substitution) is far less explored and its synthetic possibilities were largely unrecognized. In the past few years, work in this laboratory has demonstrated the great usefulness of this intramolecular substitution by applying it in the construction of the core structures of several complex natural products.[5] Detailed methodology work in this group, using either a carbanion[‡] or a heteroatom as the nucleophile, was also published, and the reaction was termed "intramolecular conjugate displacement" (ICD).[5b,6] The corresponding *intermolecular* process is well-known.[2a,b]



1.1 **1.2**

EWG: electron-withdrawing group
LG: leaving group
Nu: nucleophile

Scheme 1

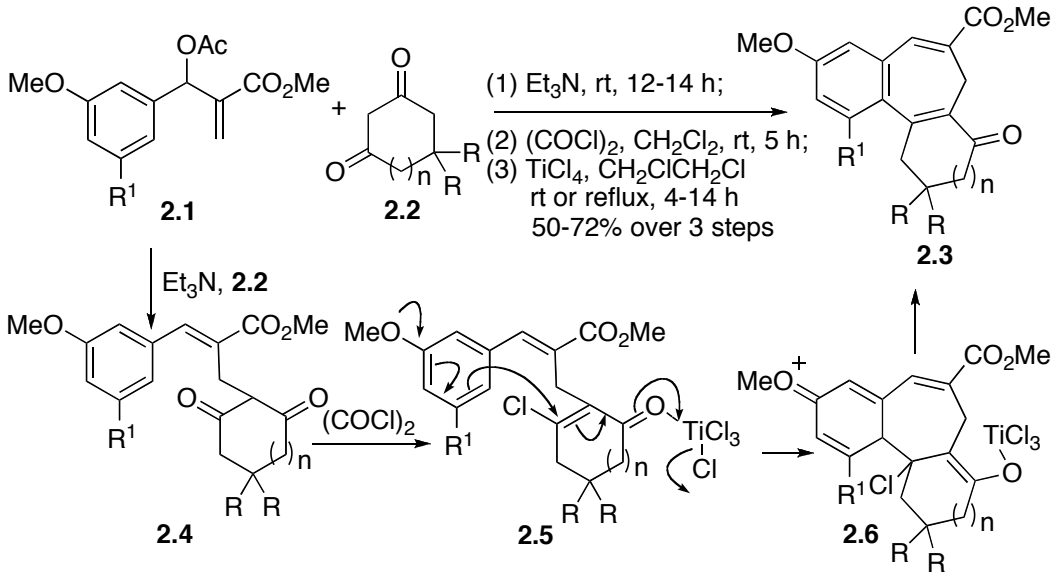
[‡]Some experiments done by a previous group member, Dr. B. Prabhudas, are included in this Thesis in order to present a complete study of ICD reactions for carbocycles; those experiments are clearly indicated in the experimental section and have already been published in our paper: Wang, L.; Prabhudas, B.; Clive, D. L. J. *J. Am. Chem. Soc.* **2009**, *131*, 6003-6012.

1.1. Intermolecular conjugate displacements of Morita-Baylis-Hillman adducts

Most of the reported reactions using compounds of type **1.1** involve intermolecular processes and have AcO^- as the leaving group; these starting materials can be simply made by acetylation of the Morita-Baylis-Hillman (MBH) alcohols.[2a,b,7] These compounds will be called MBH acetates in the following discussion and the corresponding halides will be called MBH halides. Reviews on the utility of MBH reactions in synthesis have been published; these reviews deal with many examples of *intermolecular* transformations.[2]

1.1.1. Intermolecular reactions between MBH acetates and carbon nucleophiles

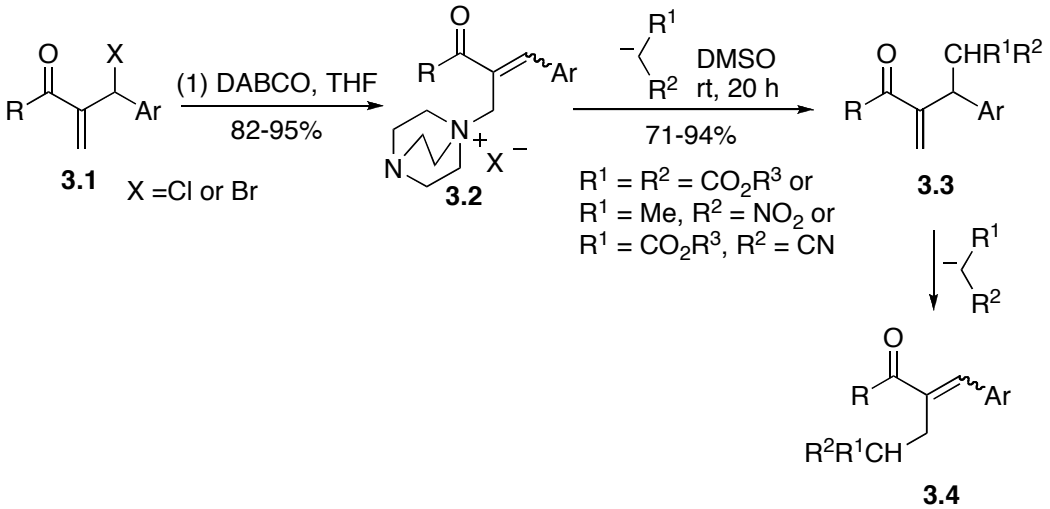
The most common nucleophilic carbanions used in this type of S_N2' reaction are those stabilized by two electron-withdrawing groups, of which 1,3-dicarbonyl compounds are the classic representatives.[8] For example, Basavaiah and coworkers applied this reaction as the key transformation in making fused [6-7-5], [6-7-6] and [6-7-7] tricyclic structures **2.3**.[8j] Under mild basic conditions (Et_3N), the cyclic diketone **2.2** displaced the acetate in an S_N2' fashion, and



Scheme 2

treatment of the resulting products with $(COCl)_2$ and $TiCl_4$ in sequence gave the tricyclic compounds **2.3** in 50-72% yield over 3 steps.

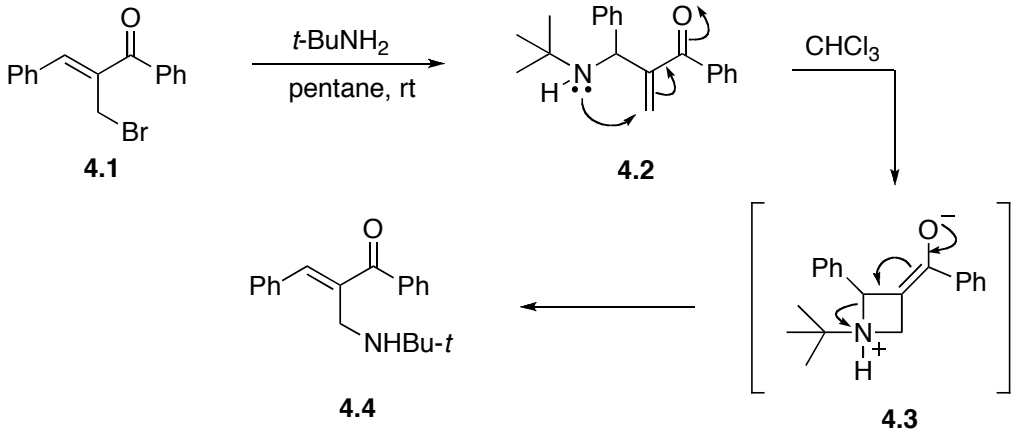
It is possible to retain the regiochemistry of the double bond by an S_N2'-S_N2' sequence if a promoter is used, commonly R_3P[3a,9] or a tertiary amine.[8i,10] Mayr and coworkers used DABCO as the promoter for the first S_N2' reaction so as to generate the ammonium salt **3.2**, and this intermediate was converted to **3.3** when treated with a carbanion.[8i] The overall transformation resembles an S_N2 substitution of the halogen by the carbanion. However, the amount of the carbanion has to be controlled (0.9 equiv of salt **3.2**) if double bond isomerization to a more stable product is possible. For example, with the same reaction time, the thermodynamically more stable alkene **3.4** was formed exclusively if 1.2 equivalents of carbanion were used, indicating that another *in situ* S_N2' displacement occurred (**3.3→3.4**). The choice of solvent for the reaction also has an influence on this isomerization. For example, use of THF-water (1:1) gave only the kinetic product, whereas DMSO, with other parameters unchanged, gave extensive isomerization to the thermodynamic product. In a kinetic study of the S_N2' reaction, using different isolated ammonium salts (from different amine promoters including DABCO, quinuclidine and pyridine derivatives), no difference in the reaction rates was observed. It was known from a previous study



Scheme 3

that DABCO is a better (10^6-fold) nucleofuge than DMAP.[11] Mayr and coworkers concluded that the independence of the reaction rates to differences in the nature of the ammonium salt indicates an addition-elimination mechanism for this S_N2' reaction; this conclusion is in line with Bordwell's skepticism of the validity of a bimolecular concerted mechanism involving four or more bonds.[12]

The above-mentioned isomerization phenomenon is common if the nucleophile itself can act as leaving group,[10a,13] and even intramolecular rearrangement to the more stable alkene product is possible when an amine is used as the nucleophile.[13-14] For example, reaction between *t*-butylamine and compound **4.1** in pentane gave the crystalline substance **4.2** exclusively (Scheme 4); when the latter was dissolved in $CHCl_3$, slow rearrangement to compound **4.4** occurred at room temperature.[13]

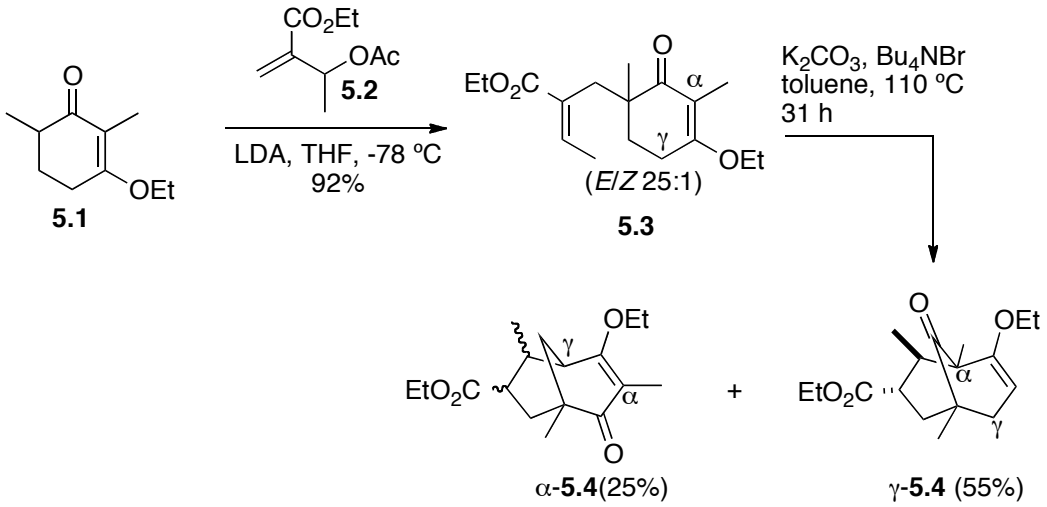


Scheme 4

In addition to stable carbanions as the nucleophile, other nucleophilic carbons can also be used for this S_N2' displacement with MBH acetates, including enolates,[15] enol ethers,[3a,9b] enamines,[16] aromatic compounds,[4e,17] organocuprates and organozinc compounds,[18] and even organolithium or Grignard reagents.[19]

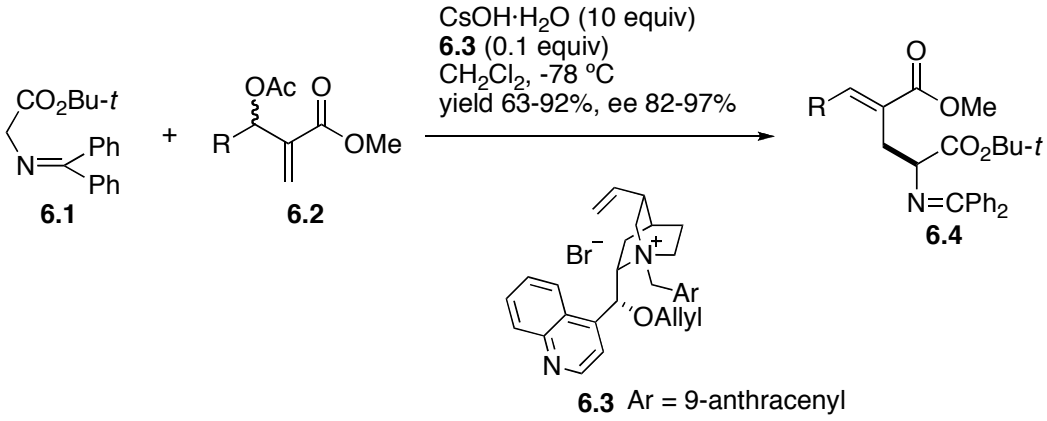
Takagi *et al*. used an S_N2' reaction between the enolate generated from enone **5.1** and MBH acetate **5.2** to gain access to the intermediate **5.3** (Scheme 5).[15c] Then, base-mediated intramolecular Michael addition afforded the bicyclic

compound α-**5.4**, plus γ-**5.4**. The former could be further transformed into a compound resembling the core structure of the natural product plukenetione A.

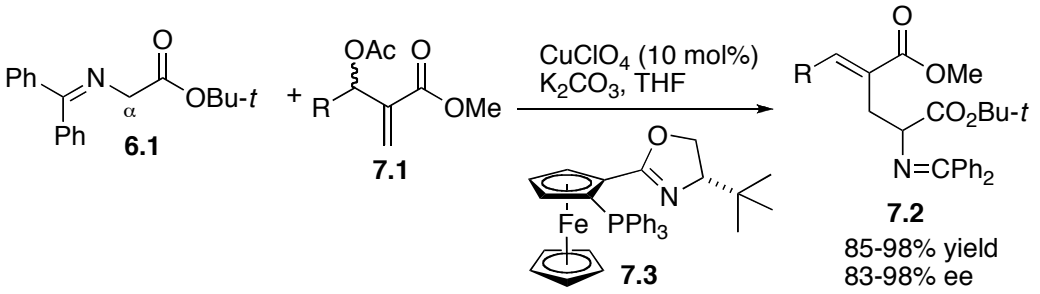


Scheme 5

By *in situ* exchange of the alkali counterion of the enolate with a chiral ammonium cation, Ramachandran and coworkers achieved asymmetric induction in an S_N2' reaction between MBH acetates **6.2** and the benzophenone imine of glycine *t*-butyl ester **6.1** (Scheme 6).[3b] CsOH was used as the base and ammonium salt **6.3** was used as a phase-transfer catalyst. The reaction afforded 4-substituted glutamic acid derivatives in 63-92% yield and 82-97% ee.



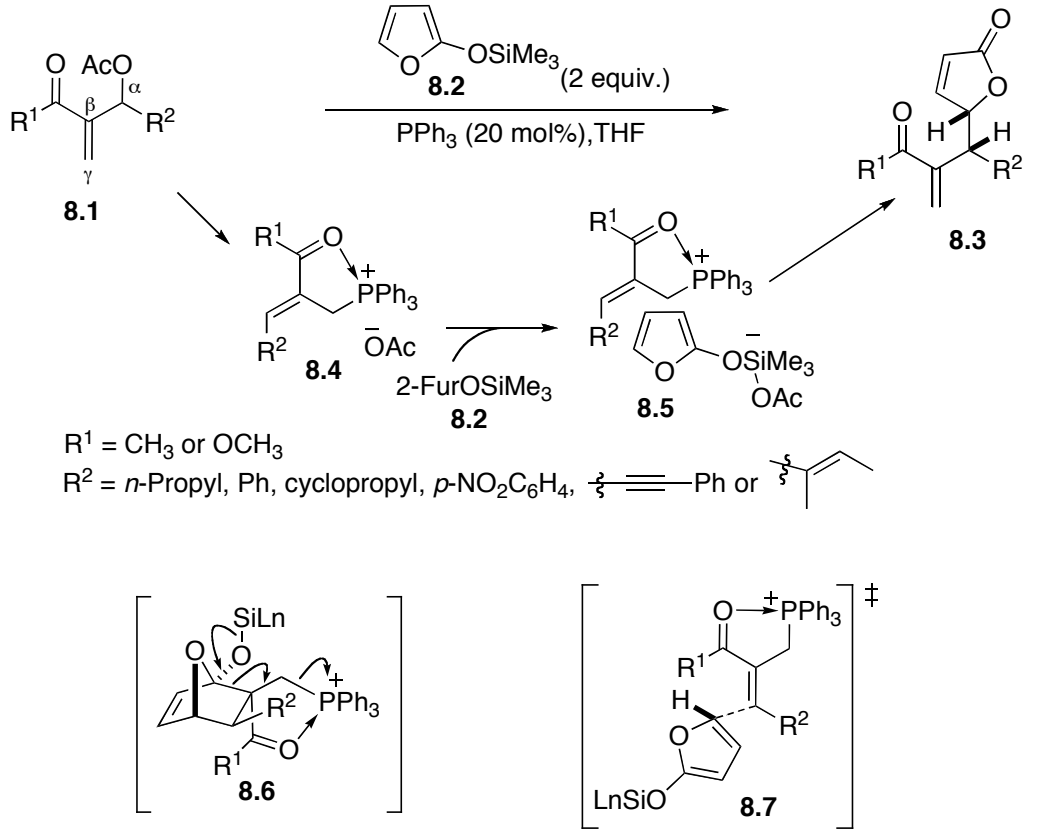
Scheme 6



Scheme 7

Using the same glycine ester **6.1** and similar MBH acetates, Hou *et al*. also asymmetrically synthesized glutamic acid derivatives using a copper salt combined with the chiral ferrocenyl ligand **7.3** (Scheme 7).[20] They also found that increasing the steric bulk at the α position of the glycine ester **6.1** by introducing a substituent lowered both the yield and ee.

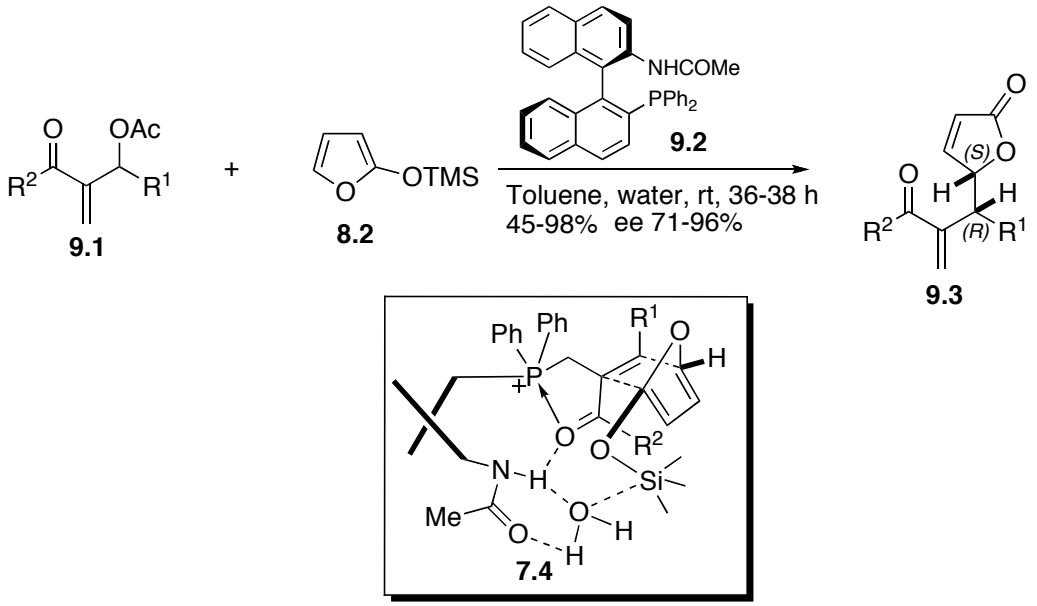
Krische's group used 2-(trimethylsiloxy)furan (**8.2**) as the nucleophile and



Scheme 8

examined the reaction with MBH acetates **8.1**, using Ph_3P as the promoter, to give the α substitution products **8.3**.[3a] It was proposed that electrophile-nucleophile ion pair **8.5** is formed after displacement of AcO^- by Ph_3P and attack on the silyl group of furan **8.2** by the released AcO^-. Both MBH acetates with a ketone (R^1 = Me) and a methyl ester (R^1 = OMe) as the electron-withdrawing group were tested; most of the reactions afforded high yields (>80%) and excellent regioselectivity (in favor of the α substituted product) and diastereoselectivity (*syn*/*anti* >20:1; *syn*/*anti* refer to the hydrogens indicated in **8.3**). Krische and coworkers invoked the Diels-Alder cycloadduct **8.6** to account for the high diastereoselectivity, although a pathway through an open transition state **8.7** is also possible. However, they emphasized that the enone geometry of the phosphonium salt **8.4**, involving internal chelation, is the key factor responsible for the high dr, regardless of the reaction pathway.

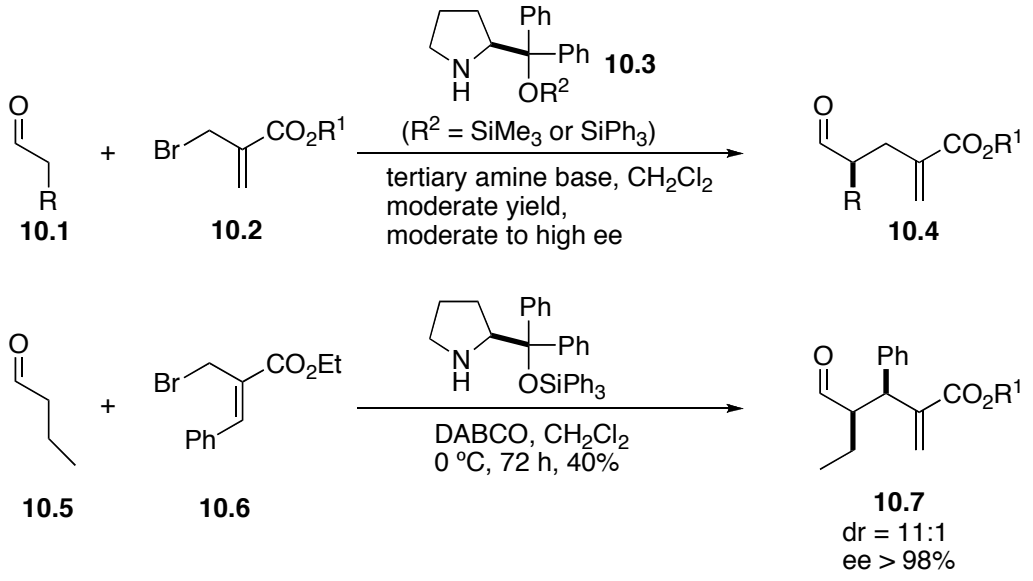
Shi's group investigated an asymmetric version of this organophosphine promoted S_N2'-S_N2' reaction, using chiral phosphines.[9b] After screening several bisnaphthalene type chiral phosphines, they found that phosphine **9.2** gave a satisfactory yield and ee as a starting point for further optimization, and, as expected from Krische's research (*vide supra*), the product with *syn* geometry



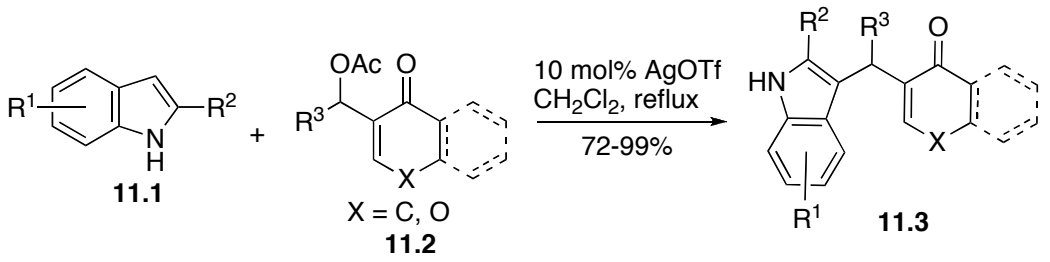
Scheme 9

predominated (Scheme 9). After realizing that the active proton on the amide of **9.2** is crucial for the asymmetric induction, Shi and coworkers deliberately introduced a controlled amount of water into the reaction mixture and were delighted to discover that this indeed boosted both the yield and the ee. A series of MBH acetates were tested, and in most cases both high yields (>85%) and high ee's (>90%) could be obtained. The stereochemistry of the product was rationalized using Krische's *endo* [4+2] cycloaddition mechanism (**9.4**) with the proposal that the amide proton and external water are involved in the transition state.

Examples of the use of enamines, indoles and phenols are illustrated in Schemes 10[16d], 11[17b] and 12,[4e] respectively. In Scheme 10, the S_N2' reaction pathway (instead of S_N2) to the products was established by the reaction between aldehyde **10.5** and MBH bromide **10.6**, which gave S_N2' product **10.7**. In the indole example (Scheme 11), it is interesting to note that AgOTf also promoted the apparent S_N2 reaction, similar to an S_N2'-S_N2' sequence catalyzed by tertiary amines and phosphines; a control experiment using DABCO, a typical promoter, gave back unchanged starting material. Porco and coworkers used the phenoxide

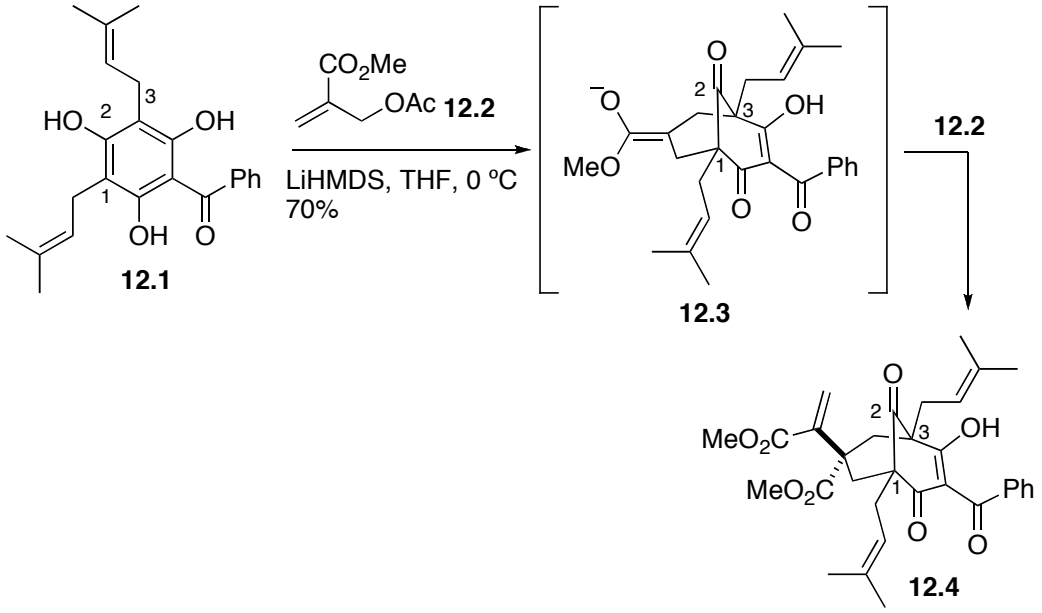


Scheme 10



Scheme 11

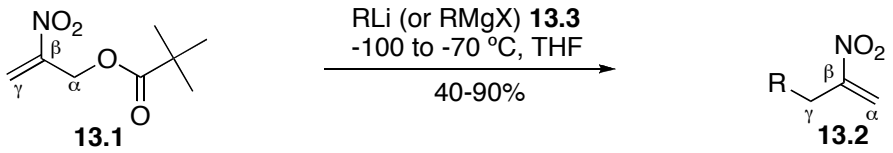
generated from phenol **12.1** (Scheme 12) as the nucleophile to construct a highly functionalized core structure for the total synthesis of the natural product (±)-clusianone.



Scheme 12

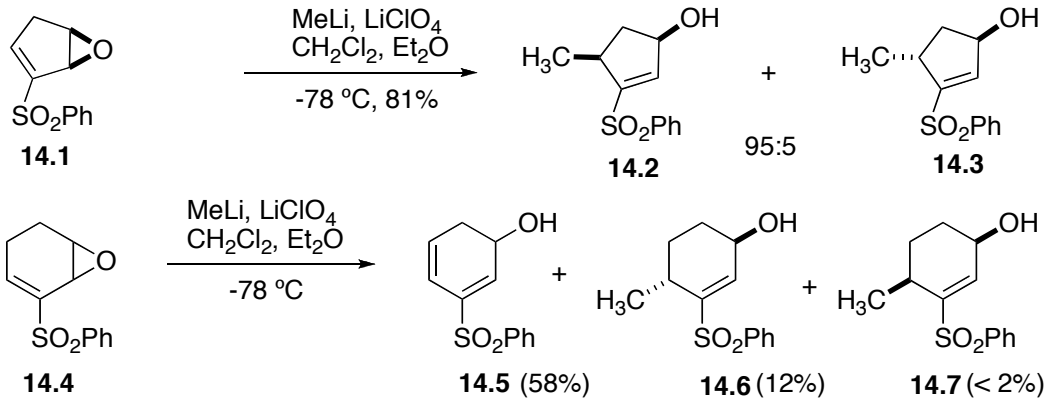
Reactive Grignard reagents and organolithium compounds can also be used to afford an S_N2' product by attacking an MBH-acetate. Seebach and co-workers[19a,19c,d] found that the pivaloate **13.1** reacts with organolithium or Grignard reagents to produce exclusively vinyl compounds **13.2**, with no detection of the possible side product arising from Michael addition between **13.2** and the reagents **13.3**. These authors reasoned that the presence of the pivaloate at the allylic

position enhanced the acceptor properties of the double bond, thus making the reaction very selective. Seebach *et al*. also briefly discussed the mechanism of this transformation and excluded the possibility of single electron transfer, as the *cis* geometry of the double bond is conserved when *cis*-1-hexenyllithium was used as the reagent. The S_N2 pathway was also excluded by other experiments using starting materials with substituents at the α or γ position. The stop-and-go mechanism did not match with what they observed, as quenching the mixture at low temperature after a short time gave only the final product **13.2** and starting material. The mechanism must be either a concerted or a fast elimination process after the initial addition.



Scheme 13

Fuchs and coworkers demonstrated that MeLi reacts to vinyl sulfonyl epoxide **14.1** in an S_N2' fashion to afford mainly the *syn* product **14.2**.[4a] However, when a six-membered ring (**14.4**) was used, the major product was the diene **14.5**.



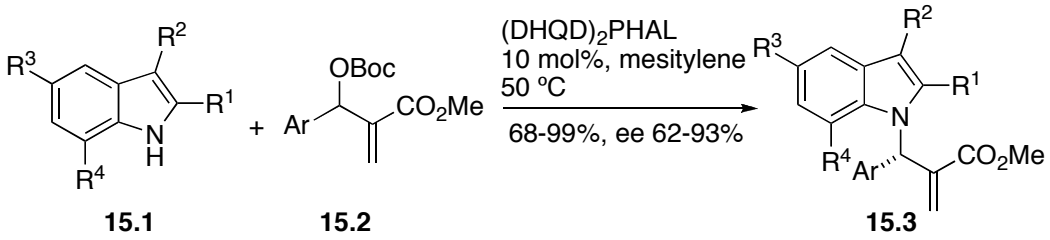
Scheme 14

1.1.2. Intermolecular reactions between MBH acetates and heteroatom nucleophiles

Besides carbon nucleophiles, heteroatoms have also been used in this type of reaction, and the good reactivity of MBH acetates and halides also allows weak nucleophiles such as alcohols to react.

Nitrogen nucleophiles such as amines,[13a,21] imidazoles,[14,22] pyrroles,[23] indoles,[24] azides,[25] sulfonamides[3c,10a,26] and phthalimide[9a,10a,27] have been used in either direct S_N2' or S_N2'-S_N2' reactions.

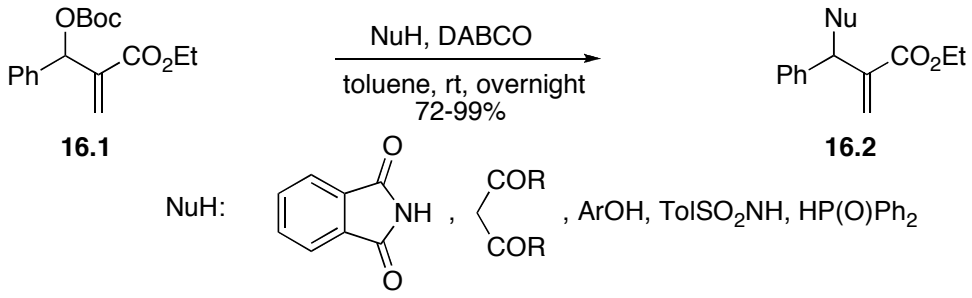
In contrast to the AgOTf-mediated coupling between the indole C3 position and MBH acetates (Scheme 11), Chen's group found that the tertiary amine catalyzed reaction between indoles and MBH acetates occurs via the nitrogen (Scheme 15).[24] Use of Boc^- as the leaving group instead of AcO^- is crucial in this experiment. As the indole nitrogen is not a good nucleophile, it is



15.1 **15.2** **15.3**

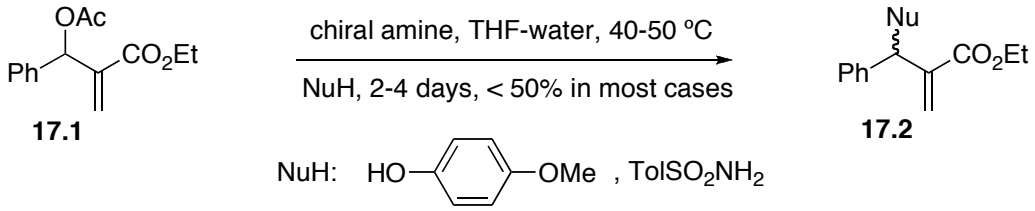
Scheme 15

essential to activate it (deprotonate) for the S_N2' displacement of the $(DHQD)_2PHAL$ promoted MBH substrate; however, using an external strong base to deprotonate the indole at the beginning of the reaction should be avoided as the nitrogen anion of indole will compete with $(DHQD)_2PHAL$ for the MBH acetate. Thus the BocO group was used to deal with this particular situation, as after its departure the $BocO^-$ will decompose *in situ* to provide the strongly basic *t*-butoxide anion which can deprotonate the indole. This strategy was earlier used in Lu's group[10a] and they demonstrated that pronucleophiles such as phthalimide, phenol, sulfonamide and diphenylphosphinous acid all react with MBH *t*-butyl carbonate to afford the products in satisfactory yields (Scheme 16).



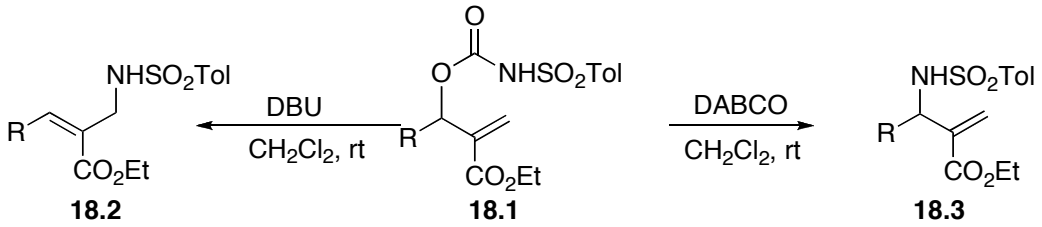
Scheme 16

However, Lu and coauthors did not mention if *t*-butyl carbonate as the leaving group was essential. Kim and coworkers showed that AcO^- as the leaving group also worked, albeit in lower yields and with a much slower reaction rate (Scheme 17).[26]



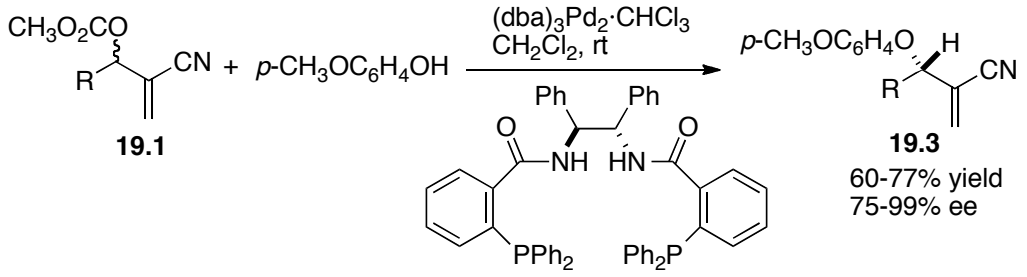
Scheme 17

The basicity of the reaction medium sometimes not only affects the reactivity of the nucleophile but also alters the pathway of the reaction. Orena's group observed that when MBH carbamate **18.1** was treated with DBU (a strong base) the 3,3-sigmatropic rearrangement pathway is followed, giving the primary sulfonamide **18.2**, while the less basic amine DABCO afforded the S_N2'-S_N2' product **18.3** (Scheme 18).[3c]



Scheme 18

During an effort towards making asymmetric MBH alcohols by means of deracemization of racemic MBH adducts, Trost's group demonstrated that Pd catalyzed asymmetric allylation, using ArOH as a nucleophile and **19.2** as the ligand, could deliver the desired product in 60-77% yield and 75-99% ee.[28] The ee values were higher when a nitrile group was used in the MBH carbonate starting materials compared to an ester group. Running the reaction at a lower concentration (0.05 M as opposed to 0.1 M) substantially increased the enantioselectivity. The target MBH alcohol could be obtained by removal of the *p*-methoxyphenyl group of **19.3** using DDQ. This deracemization method was successfully applied during the total synthesis of the natural products furaquinocin A, B, and E.[29]

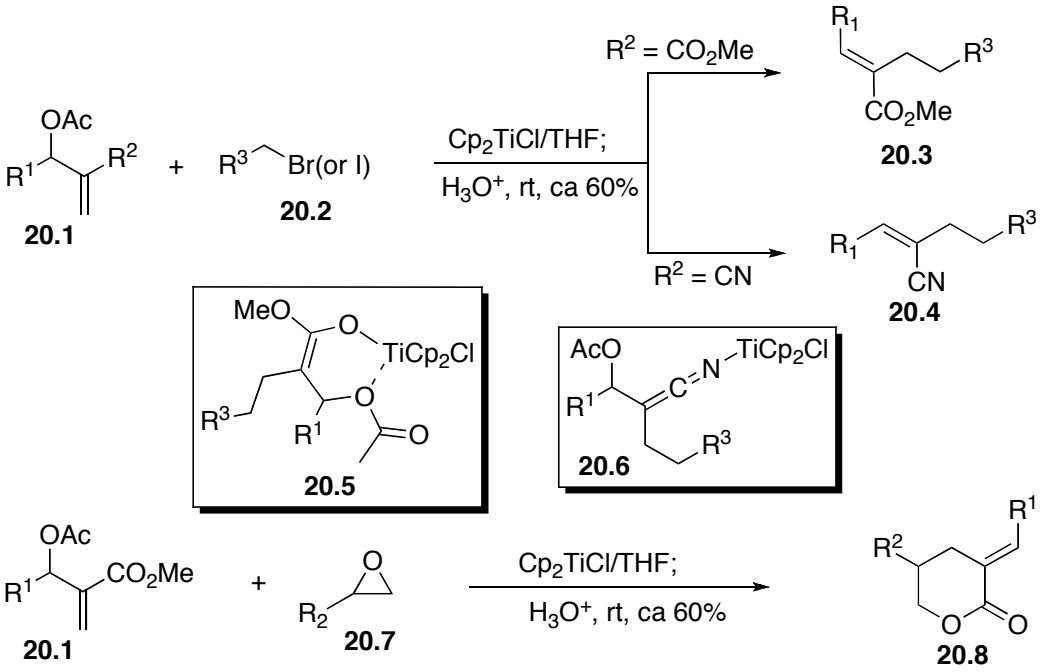


Scheme 19

1.1.3. Miscellaneous intermolecular reactions with MBH derivatives

Kim's group also demonstrated that sodium borohydride can be used in the S_N2'-S_N2' process to afford products of overall displacement of AcO^- by hydride.[30]

S_N2' reactions using a radical species generated from epoxides or activated halides by Cp_2TiCl were reported by Roy and coworkers (Scheme 20).[31] The initial radical generated from halide **20.2** and Cp_2TiCl attacks the MBH acetate **20.1** in a Michael addition fashion, and the resulting radical species is reduced by Cp_2TiCl to form a carbanion, which expels OAc^- and produces the final product **20.3**. When the epoxide **20.7** was used, after S_N2' displacement further lactonization occurred to give lactone **20.8**. For the reactions between **20.1** and **20.2**, nitrile and ester groups (R^2) showed dramatically different *E*/*Z* ratios of the



Scheme 20

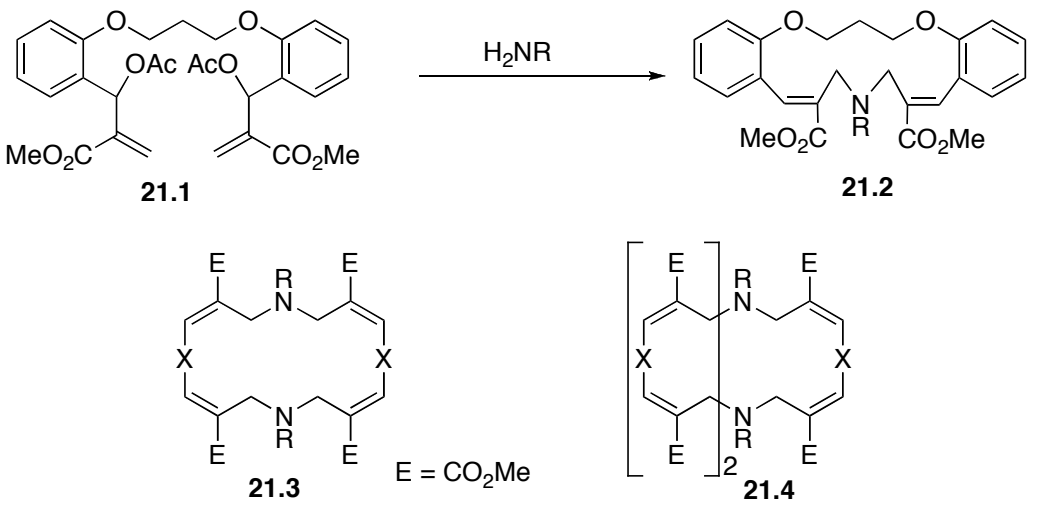
alkene product. The esters gave extensively the *E* isomer, whereas for the nitriles, an isomeric mixture in favor of the *Z* geometry was generally observed. This *E*/*Z* selectivity difference between nitrile and ester substrates appears to be general[32] and was rationalized by invoking the chelation and nonchelation models **20.5** and **20.6**, respectively.

1.2. Intramolecular conjugate displacement (ICD) of MBH adducts

1.2.1. ICD reaction between MBH acetates and nitrogen nucleophiles

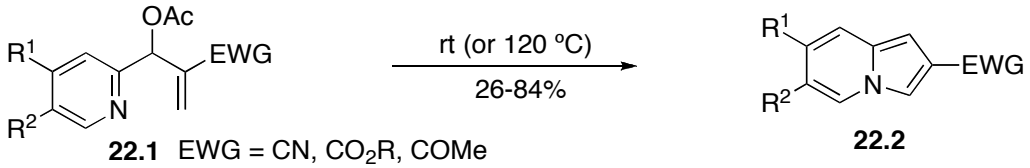
One early example of an ICD process was in the formation of macrocyclic compounds (cyclophanes and cryptophanes), using a molecule having two MBH acetate units. This was reacted with either a primary amine or ammonia. One particular example is shown on Scheme 21.[33]

In the early 1990s, Kaye's group used MBH acetates for making indolizines with pyridine nitrogen as the nucleophile (Scheme 22).[34] The precursor **22.1** was made by an MBH reaction between the corresponding



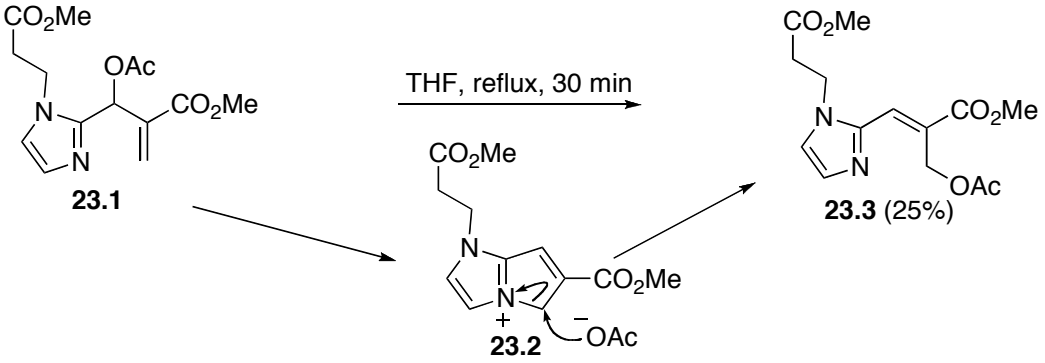
Scheme 21

aromatic aldehyde and a vinyl compound. Depending on the activation ability of the EWG, the thermal ring closure occurred as a neat mixture at room temperature (EWG = COMe) or at an elevated temperature (120 ºC, EWG = CN or CO_2R). When a methyl ketone was used as the electron-withdrawing group, the final product **22.2** was formed concomitantly during the esterification step, and a small amount was even formed during the MBH reaction. The authors proposed that the mechanism might be a Michael addition followed by elimination. While the mechanism is uncertain, the great facility of this ring closure, boosted by the electron-withdrawing group, is obvious, as an earlier experiment with a similar substrate without an EWG required a much higher temperature (450 ºC) for ring closure.[35]



Scheme 22

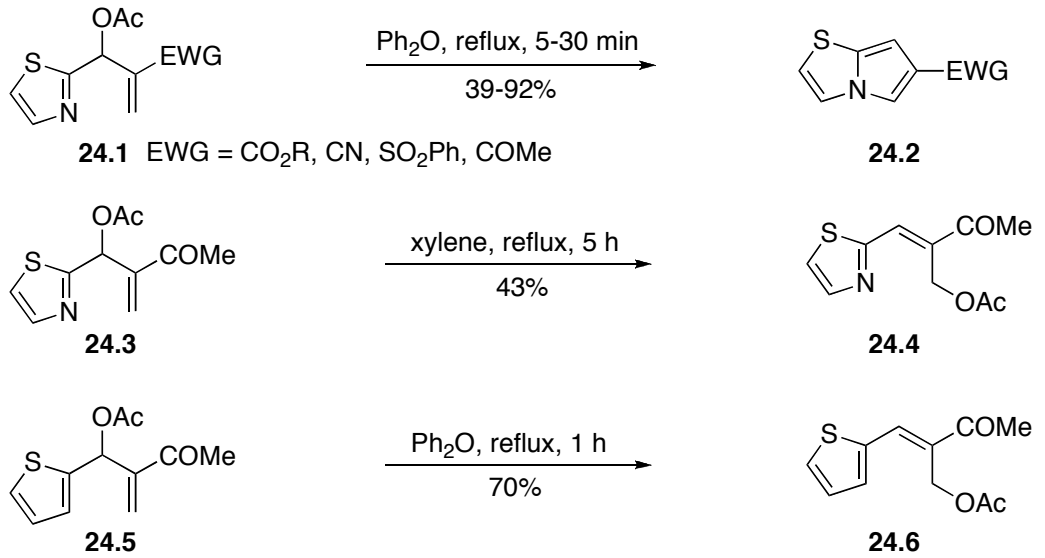
The mechanism of the above transformation, which seems to violate Baldwin's rules (5-*endo-trig*) is probably complicated and is likely to involve a



Scheme 23

preliminary migration of the leaving group. For example, when Drewes and Rohwer heated an imidazole-based substrate **23.1** in refluxing THF, only allylic rearrangement product **23.3** was obtained (Scheme 23).[36] These authors proposed that ring closure did occur but the resulting cationic intermediate was attacked by the fugitive acetate anion, giving the overall rearrangement product.

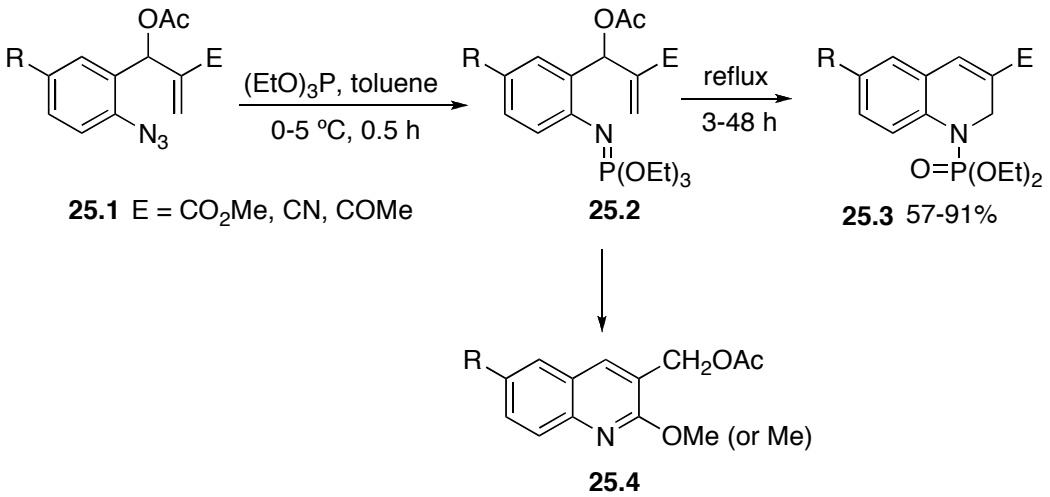
However, based on the examination of a thiazole-based counterpart, conducted by Lee's group, this is probably not the correct mechanism, because allylic rearrangement was found to occur at a lower temperature than ring closure.[37] When compound **24.1** was heated in refluxing Ph_2O (boiling point 259



Scheme 24

ºC) for a short time, the cyclized product **24.2** was formed (Scheme 24), while heating the methyl ketone **24.3** in refluxing xylene (boiling point 137-140 ºC) for 5 h afforded only the acetate migration product **24.4**. A substrate with a thiophene subunit (**24.5**), lacking the nitrogen nucleophilic site, yielded only the migration product **24.6** on heating in refluxing Ph_2O. Based on these observations it is very possible that the seemingly disfavored 5-*endo-trig* is in fact a combination of 1,3-acetate migration followed by displacement of the acetate by nitrogen, or via a cationic species formed at high temperature by departure of the allylic acetate, a process resembling the Nazarov reaction.

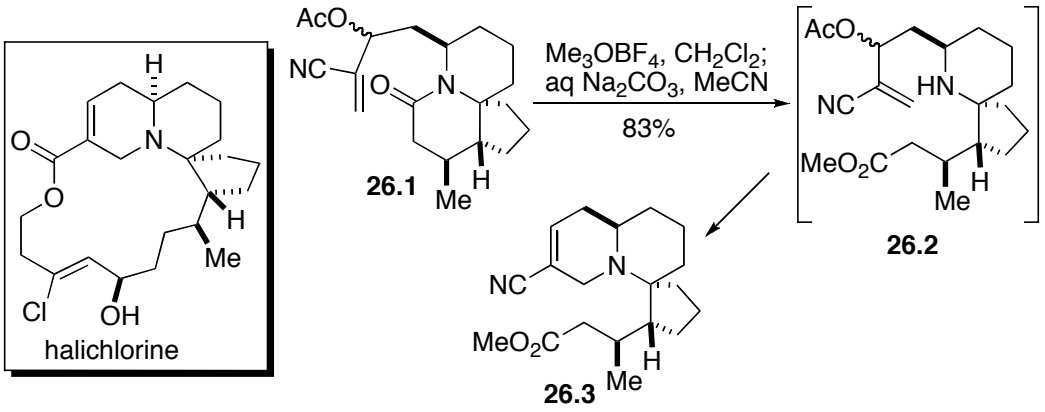
Lee's group also used the *in situ* generated iminophosphorane unit as the nucleophile for a 6-*endo-trig* ring closure (Scheme 25).[38] The starting materials **25.1** were prepared by MBH reaction followed by acetylation of the resulting alcohols. Treatment of azide **25.1** with $(EtO)_3P$ in PhMe generated iminophosphorane **25.2**, and further refluxing of the mixture afforded the desired dihydroquinoline derivatives **25.3** in moderate to high yields. However, when the electron-withdrawing group is a methyl ester, small amounts of quinoline derivatives **25.4** were also produced, via a combination of aza-Wittig reaction and allylic acetate shift; this process predominated when a methyl ketone was used as the electron-withdrawing group, and quinoline was then the only product, formed easily at room temperature. The ratio of **25.3** to **25.4** also depends on the nature



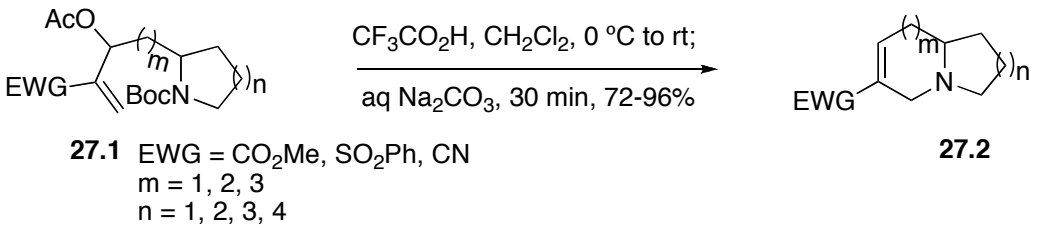
Scheme 25

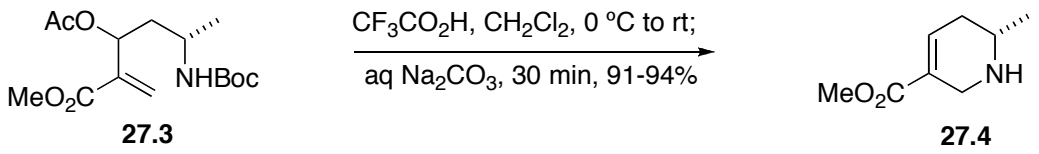
of the aromatic substituent R: a higher ratio is observed with a more electron-donating group.

Many examples of nitrogen-based ICD reactions were reported from this laboratory. The idea was developed during the total synthesis of the natural product halichlorine, a marine alkaloid (Scheme 26).[5a,6a] As depicted in Scheme 26, the amide bond of tricyclic compound **26.1** was cleaved by treatment with $Me_3O^+BF_4^-$, followed by aqueous Na_2CO_3. Then a nitrogen-based ICD reaction afforded the tricyclic core structure of the natural product in high yield (83%). Similar ICD approaches towards the total synthesis of halichlorine were adopted by both Heathcock's and Martin's groups.[39]



Scheme 26

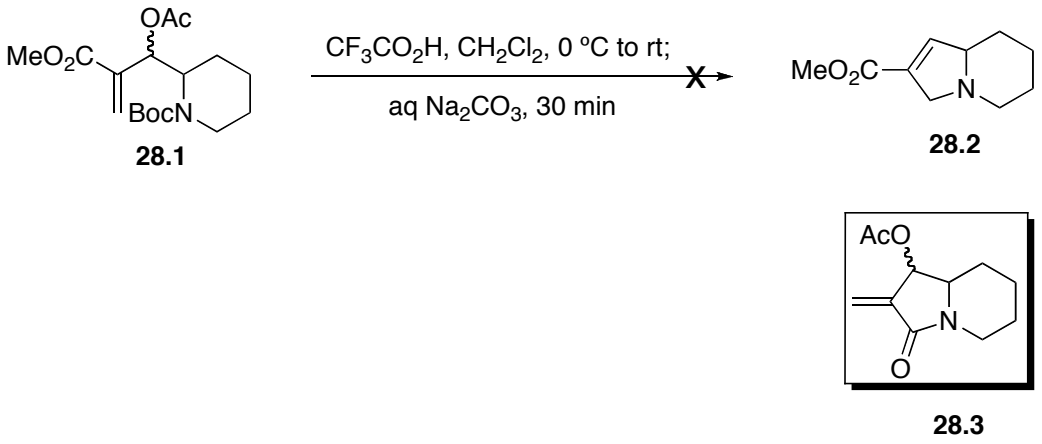




Scheme 27

This nitrogen-based ICD reaction proved to be a general method of making nitrogen-containing heterocycles and a range of monocyclic and bicyclic compounds was prepared in high yields (Scheme 27).[6a,b] It is worth mentioning that even 8-membered rings could be generated efficiently (92%, m = 3). However, ICD reactions with precursors having trisubstituted or tetrasubstituted double bonds in the Michael acceptor subunit tend to give lower yields.

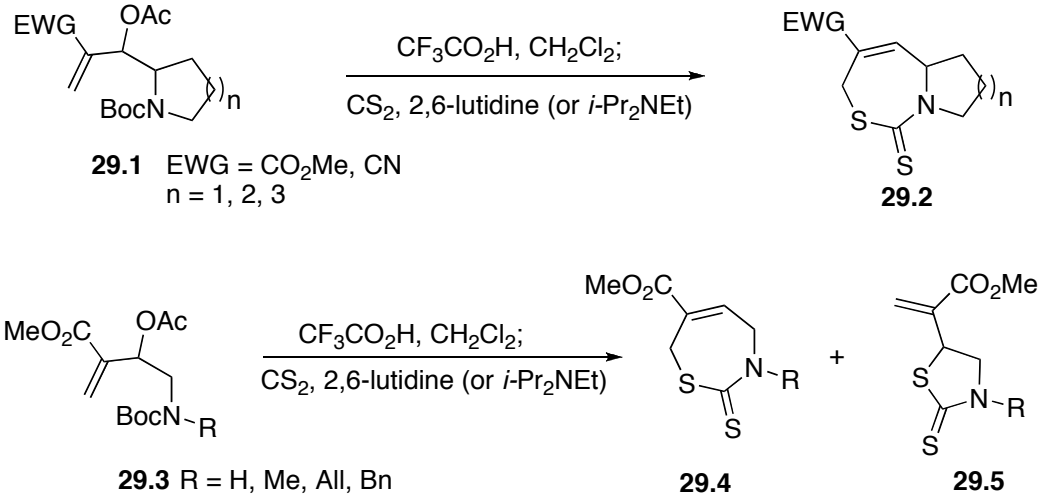
Encouraged by the apparent facility of this ring closure, a disfavored 5-*endo-trig* cyclization using substrate **28.1** was tried.[6b] The reaction did not afford the ICD product **28.2**; instead it produced lactam **28.3**, generated from attack of the deprotected nitrogen on the methyl ester.



Scheme 28

The inherent inactivity of type **28.1** towards the ICD pathway, however, provided an opportunity to introduce a new element to bridge the gap between the nitrogen and the MBH olefin: the nitrogen, after deprotection, could potentially attack an external neutral electrophile X=Y, which in turn would then generate an anionic site $^{-}$X-Y-N that could, in principle, attack the MBH olefin in an ICD fashion (7-*endo-trig*) without violating Baldwin's rules. After examination of several potential neutral electrophiles (PhNCO, PhNCS, SO_2, BnN=CH_2, $(Cl_3C)_2C$=NBn, CO_2, CS_2, and H_2NCN), CS_2 was found to satisfy the requirements and produce the desired products.[6d] A series of cyclic and acyclic substrates (**29.1** and **29.3**, Scheme 29) was tested, and the desired products were

generally formed in 60-70% yield. In some cases, a 5-membered side product **29.5** was also generated. Subjecting the 7-membered product to the reaction conditions showed no isomerization to the side product; neither did the 5-membered product isomerize. This indicates that both products were formed kinetically. The ratio of side product to the desired product was influenced by several factors: the base used, the nature of the electron-withdrawing group on the MBH moiety, the leaving group and the substituents on the nitrogen atom. Generally, 2,6-lutidine helps minimize formation of the side product compared to *i*-Pr_2NEt; a CN group as the EWG increases the ratio of the side product to the desired product; formation of the side product from acyclic precursors is more extensive than in the case of cyclic counterparts; replacement of the AcO group with a carbonate OCO_2Et can greatly suppress the generation of the side product.[6d]



29.1 EWG = CO_2Me, CN
n = 1, 2, 3

29.2

29.3 R = H, Me, All, Bn

29.4

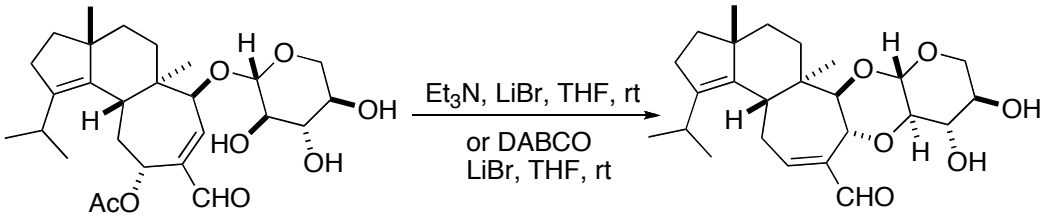
29.5

Scheme 29

1.2.2. ICD reaction between the MBH acetate and an oxygen nucleophile

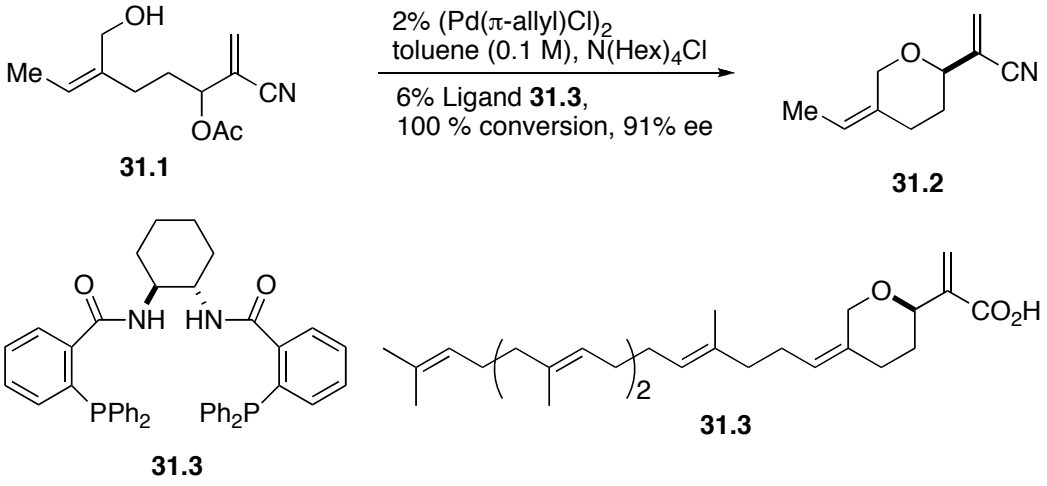
When Sassa and coworkers isolated and elucidated a new cyathane, erinacine P (Scheme 30), its close skeletal resemblance to the known erinacine B inspired them to propose a biogenesis of erinacine B from erinacine P via a sequence of 1,4-addition of a hydroxy group to the enal, followed by elimination

of the acetate group.[40] Indeed, exposure to Et_3N-LiBr in THF at room temperature smoothly converted erinacine P to erinacine B in 72% yield. DABCO-LiBr also caused this transformation, but prolonged treatment converted the erinacine B to other products. Nakada *et al*. further validated this proposal during their enantioselective total synthesis of (–)-erinacine B, using benzoate as a leaving group.[41]



Scheme 30

During research on achieving deracemization of racemic MBH adducts using asymmetric allylation (*vide supra*), the Trost group also made an effort to realize a process related to intramolecular conjugate displacement, but mediated by a palladium catalyst. After extensive screening of the reaction conditions it

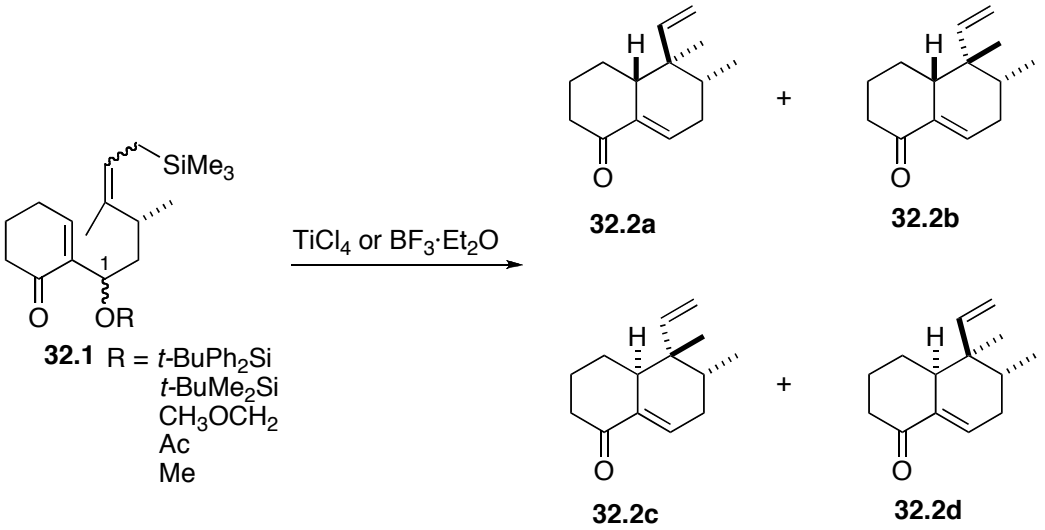


Scheme 31

was found possible to transform the racemic MBH acetate **31.1** to the desired product **31.2** in a high yield and high ee (Scheme 31).[42] This method was applied as a key step in the total synthesis of (+)-hippospongic acid A **31.3** and gave a 50% yield and a 91% ee.[42] It should be noted that this process is mediated by a transition metal, unlike the ICD process described in this Thesis.

1.2.3. ICD reaction between MBH acetates and carbon nucleophiles

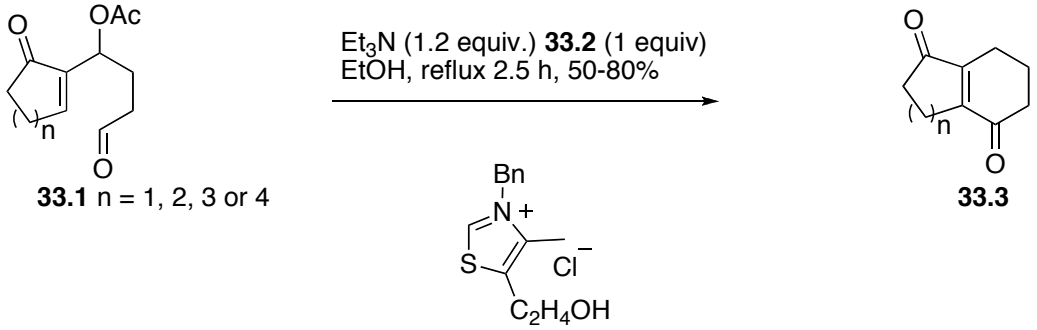
Tokoroyama and coworkers investigated the effects of a removable group OR at C1 of enone **32.1** during a cyclization reaction catalyzed by the Lewis acids $TiCl_4$ or $BF_3{\cdot}Et_2O$.[43] The reaction outcome was rather complicated, and no simple correlation with the substrate configuration (*syn* or *anti*), the oxy leaving group or the Lewis acid emerged. Although in many cases diastereomer **32.2a** is the major product, usually 3-4 diastereomers were isolated. A very similar study of this intramolecular Sakurai cyclization for making fused bicyclic skeletons was reported by Majetich *et al*.[44]



Scheme 32

The Markó group applied an intramolecular Stetter reaction for making bicycloenediones (Scheme 33).[45] Using stoichiometric amounts of thiazolium

catalyst **33.2** and Et_3N as the base, the desired bicyclic compounds **33.3** were obtained in 50-80% yield. Apparently, a based-mediated double bond shift occurred after cyclization. It was also noticed that increasing the ring size of the Michael acceptor tended to result in a higher yield.



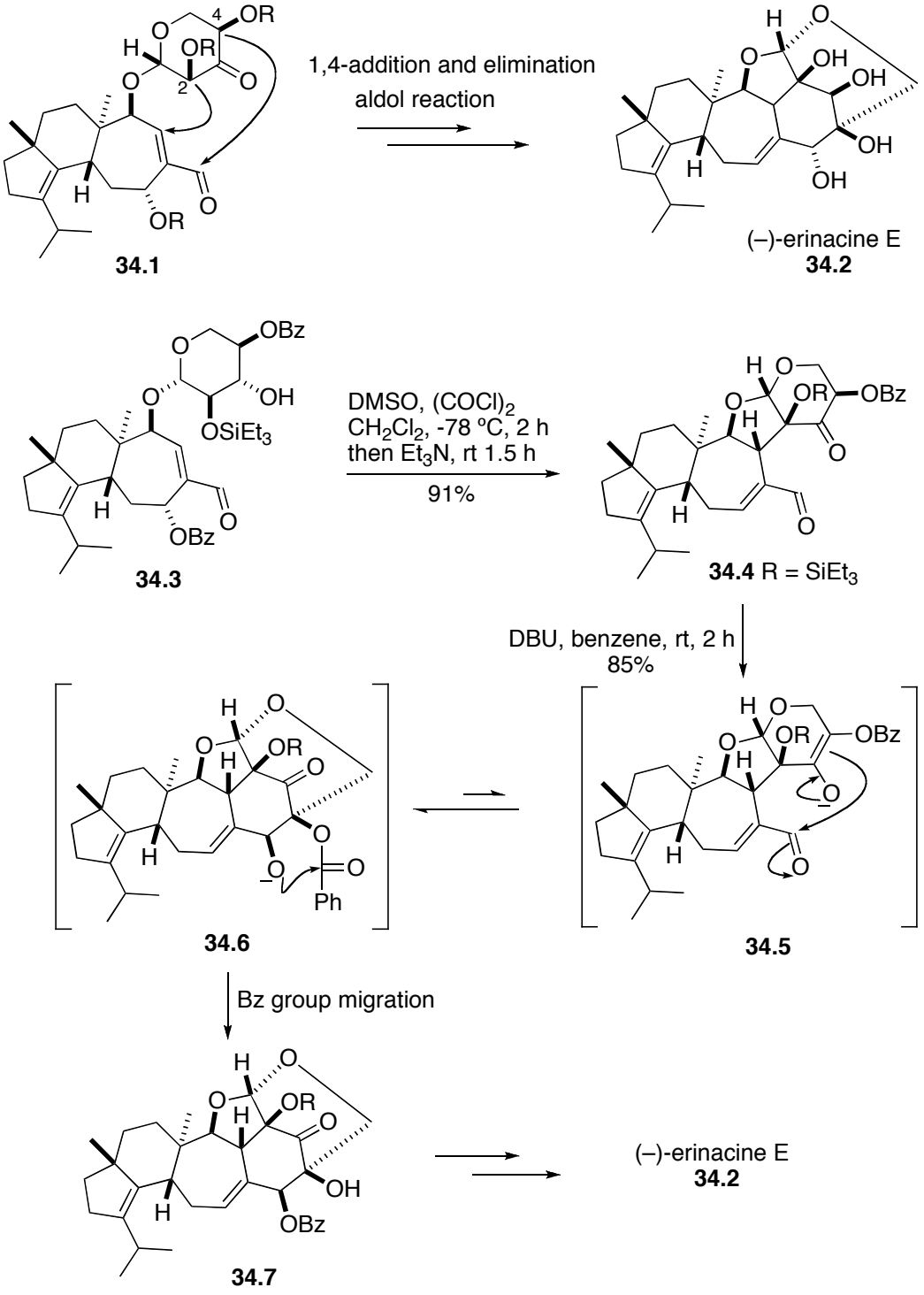
33.1 n = 1, 2, 3 or 4

33.3

33.2

Scheme 33

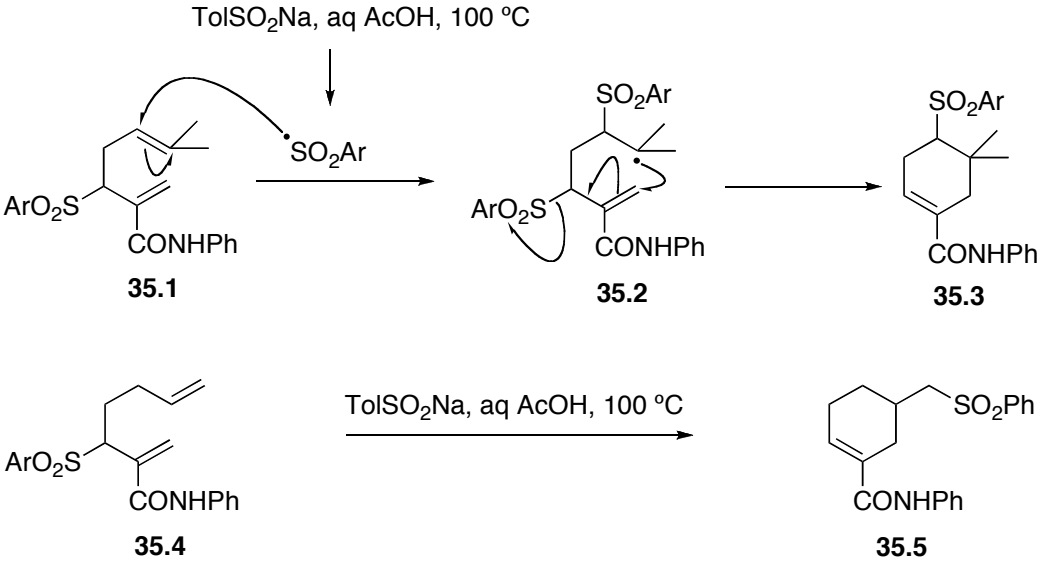
When Sassa *et al*. proposed the biogenesis of erinacine B (see Scheme 10), they also postulated a possible biogenetic pathway to erinacine E: a sequence of a Michael addition–elimination (i.e. an intramolecular conjugate displacement) and an aldol reaction as outlined in Scheme 34 (**34.1→34.2**). Other authors also proposed this idea.[46] It was again the Nakada group who validated this possibility by a biomimetic total synthesis of (–)-erinacine E using this hypothesis.[47] As shown in Scheme 34, Swern oxidation accomplished both oxidation of the secondary alcohol and a concomitant ICD reaction. A DBU-mediated aldol reaction generated the final 6-membered ring, accompanied by a benzoyl group migration, in 85% overall yield. This benzoyl group was used as a means of avoiding a retro-aldol reaction. Further functional group manipulations then delivered the final natural product.



Scheme 34

ICD reactions using radicals are rare. However, Whitham and Harvey did observe several cases of such a transformation during their study of radial induced

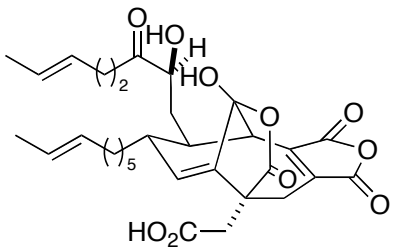
cyclization of double bonds onto certain sulfones.[48] As depicted in Scheme 35, heating $TolSO_2Na$ in aqueous acetic acid at 100 ºC generates a sulfone radical, and the resulting electrophilic sulfone radical attacks the electron-rich double bond of substrate **35.1** to give a nucleophilic radical species **35.2**, which then performs a radical type ICD reaction to form **35.3**. Similarly, **35.4** was converted into **35.5**.



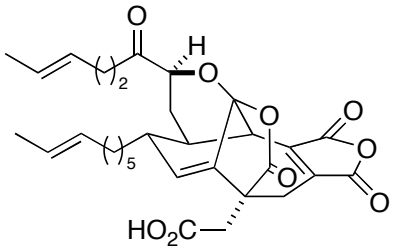
Scheme 35

2. Results and Discussion

After the successful application of the nitrogen-based ICD reaction and detailed methodology study on the scope of this transformation for making nitrogen-containing heterocycles, the idea of an all-carbon-based ICD reaction came to mind in the course of studies aimed at the synthesis of CP-225,917 (**36.1**) and CP-263,114 (**36.2**). When silyl ether **37.1** was treated with AcOH-buffered



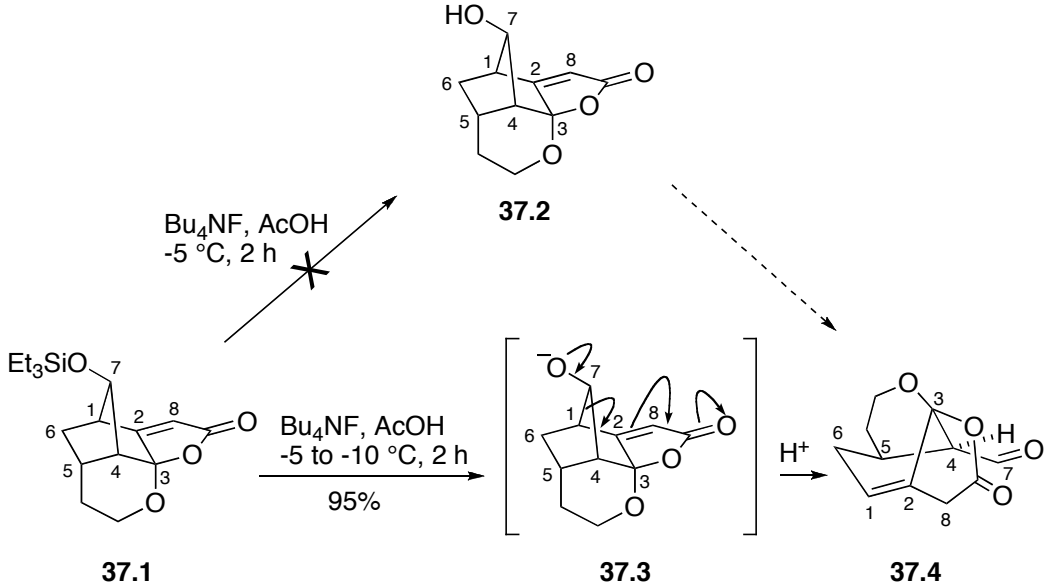
36.1 CP-225,917



36.2 CP-263,114

Scheme 36

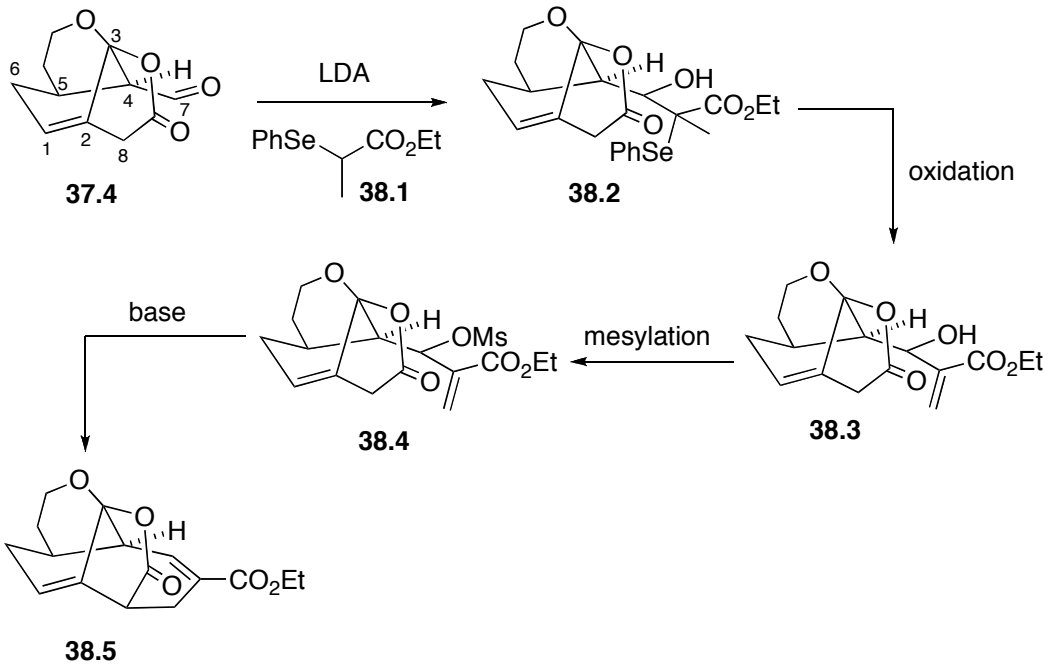
Bu_4NF, none of the expected deprotection product **37.2** was observed and only the fragmentation product **37.4** was isolated in a high yield (95%) (Scheme 37).[5b]



37.1 **37.2** **37.3** **37.4**

Scheme 37

Although not the desired product, it was soon realized that aldehyde **37.4** provided an opportunity for testing the ICD reaction in an all-carbon system. To validate this potential, the ICD precursor **38.4** was synthesized from **37.4** using the route depicted in Scheme 38. Treatment of **38.4** with base (DBU) at room



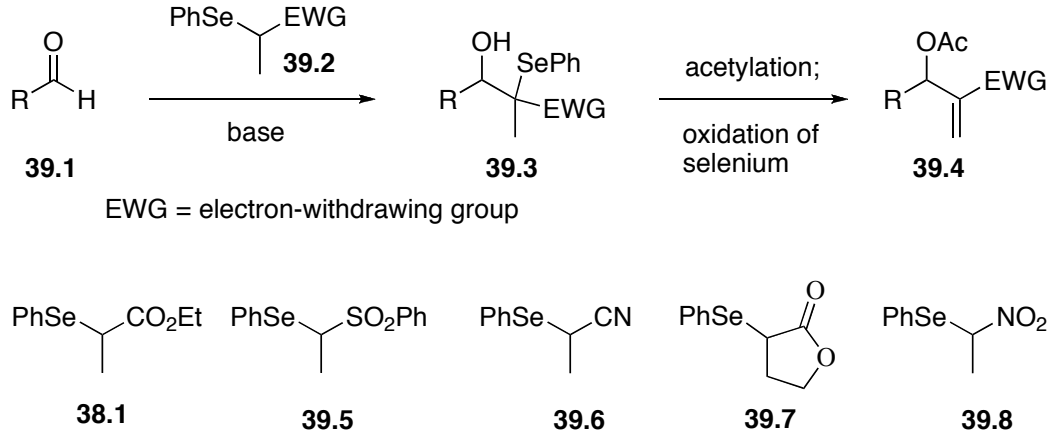
Scheme 38

temperature for 30 minutes delivered the desired ICD product **38.5** in high yield (96%). Other examples, bearing a substituent at C8 of **37.4** (as required for the natural products), showed that AcO as the leaving group was also suitable for this ring closure.[5b] These preliminary results done by a previous group member made it obvious that a comprehensive study of the scope of the ICD route to carbocycles was appropriate. This facile ring closure also required research on the underlying mechanism.

2.1. Preparation of the ICD Precursors

Most of the ICD precursors (MBH acetates) for my research were prepared using a selenium-based route, as outlined in Scheme 39. This method

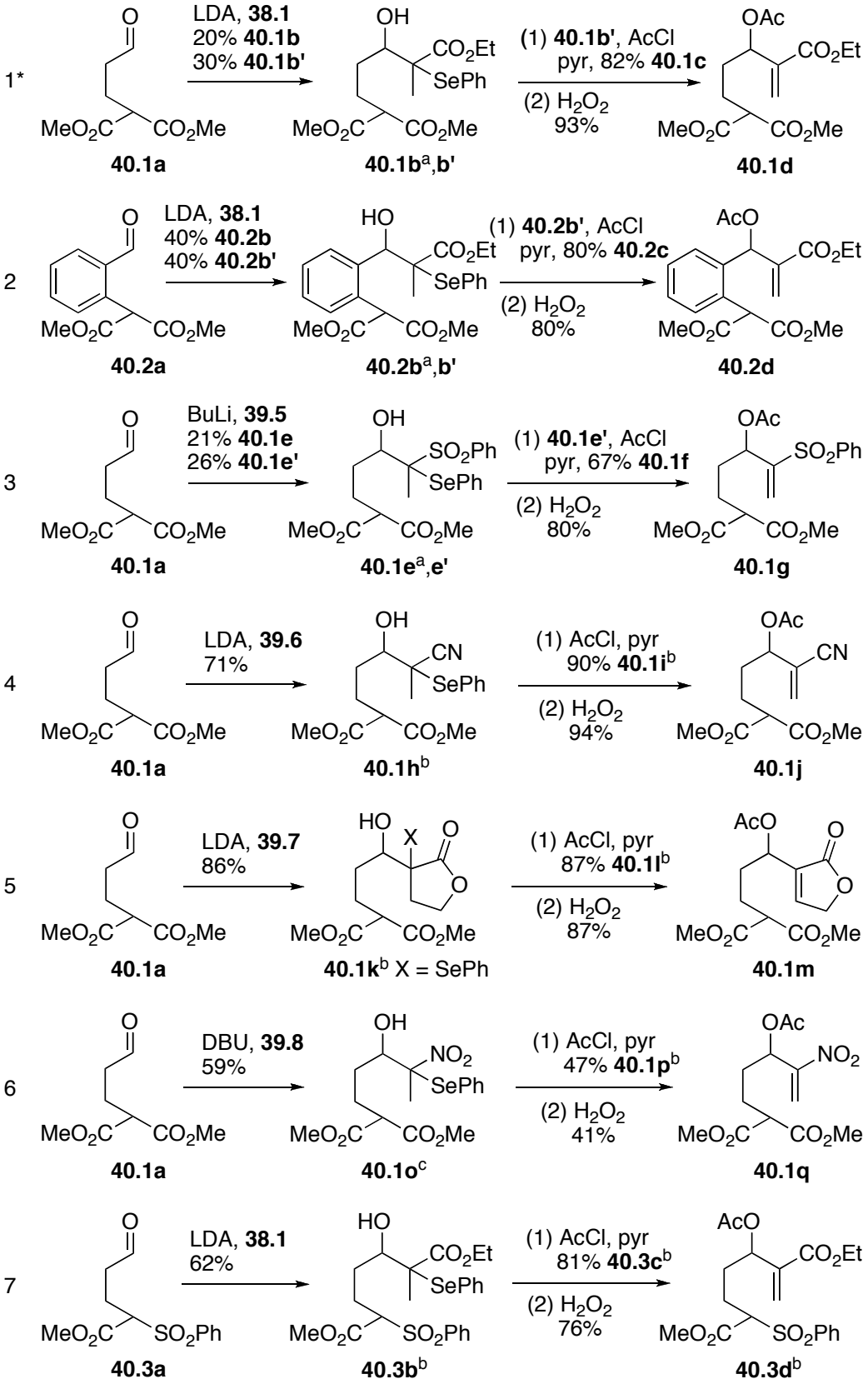
had been tested with many examples in the study of nitrogen-based ICD cyclizations and proved to be both efficient and general.[6b] In the single case where a comparison was made (preparation of **40.1d**), the standard Baylis-Hillman conditions (DABCO, room temperature, 2 days) produced a complex mixture.



Scheme 39

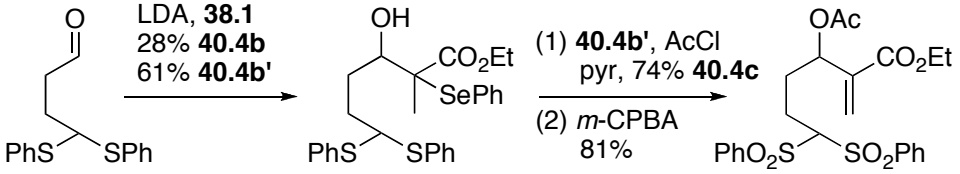
As illustrated in Scheme 39, aldehydes **39.1** were first condensed with the selenium compound **39.2** to form seleno alcohols **39.3**, and acetylation, followed by oxidation of the selenium afforded the desired Morita-Baylis-Hillman acetates **39.4**. Sometimes the acetylation was done after the selenide oxidation. Most of the aldehydes that we used in our study are listed in Scheme 40, along with the steps for converting them to the corresponding MBH acetates.

The selenium starting materials used in Scheme 40 are listed in Scheme 39 (**38.1**,[49] **39.5**,[50] **39.6**,[51] **39.7**,[52] **39.8**[53]). They are all known compounds. Compound **38.1** was prepared by nucleophilic displacement of the corresponding ethyl 2-bromopropanoate with PhSeNa (generated *in situ* by reduction of PhSeSePh with $NaBH_4$). The other four selenides were easily prepared by quenching the appropriate carbanion with PhSeCl.


1*
LDA, 38.1
20% 40.1b
30% 40.1b'
(1) 40.1b', AcCl
pyr, 82% 40.1c
(2) H2O2
93%
40.1a
40.1b[a],b'
40.1d
2
LDA, 38.1
40% 40.2b
40% 40.2b'
(1) 40.2b', AcCl
pyr, 80% 40.2c
(2) H2O2
80%
40.2a
40.2b[a],b'
40.2d
3
BuLi, 39.5
21% 40.1e
26% 40.1e'
(1) 40.1e', AcCl
pyr, 67% 40.1f
(2) H2O2
80%
40.1a
40.1e[a],e'
40.1g
4
LDA, 39.6
71%
(1) AcCl, pyr
90% 40.1i[b]
(2) H2O2
94%
40.1a
40.1h[b]
40.1j
5
LDA, 39.7
86%
(1) AcCl, pyr
87% 40.1l[b]
(2) H2O2
87%
40.1a
40.1k[b] X = SePh
40.1m
6
DBU, 39.8
59%
(1) AcCl, pyr
47% 40.1p[b]
(2) H2O2
41%
40.1a
40.1o[c]
40.1q
7
LDA, 38.1
62%
(1) AcCl, pyr
81% 40.3c[b]
(2) H2O2
76%
40.3a
40.3b[b]
40.3d[b]

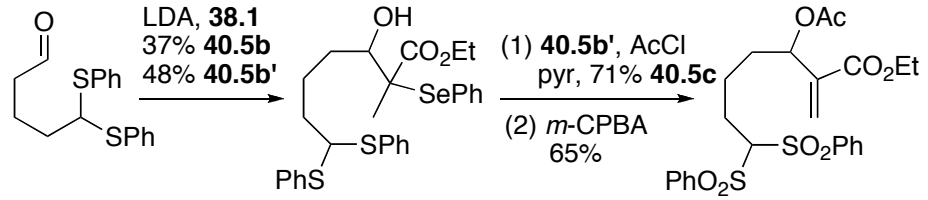
Scheme 40

8



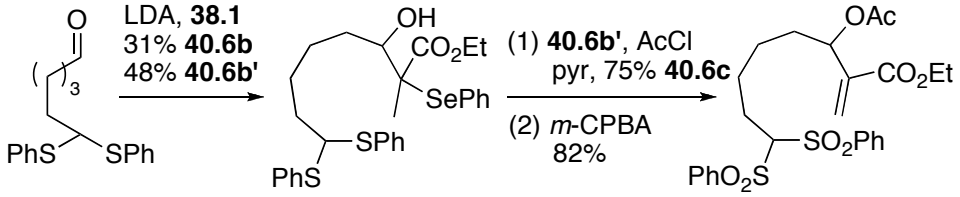
40.4a **40.4b[a],b'** **40.4d**

9



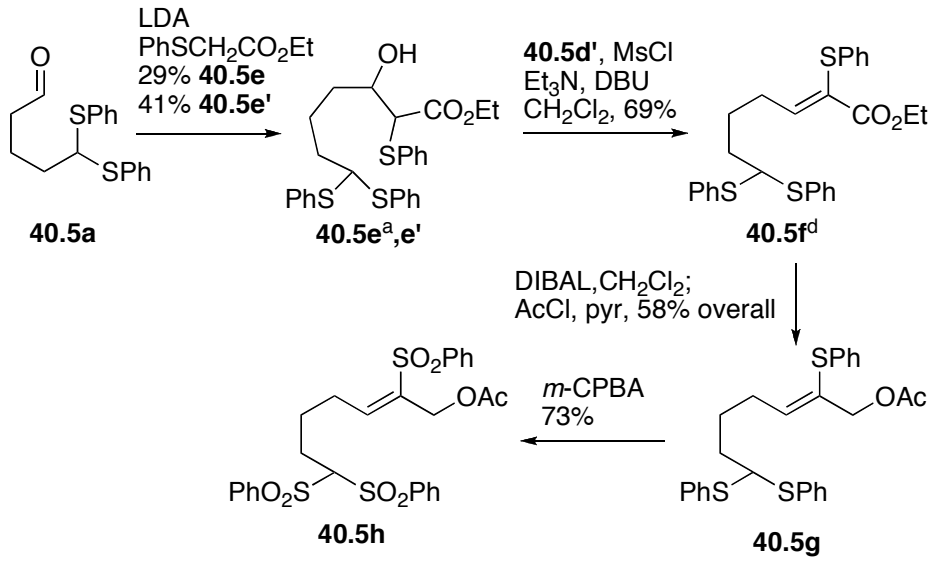
40.5a **40.5b[a],b'** **40.5d**

10



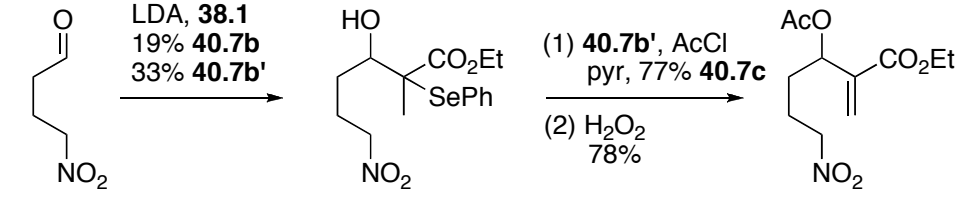
40.6a **40.6b[a],b'** **40.6d**

11



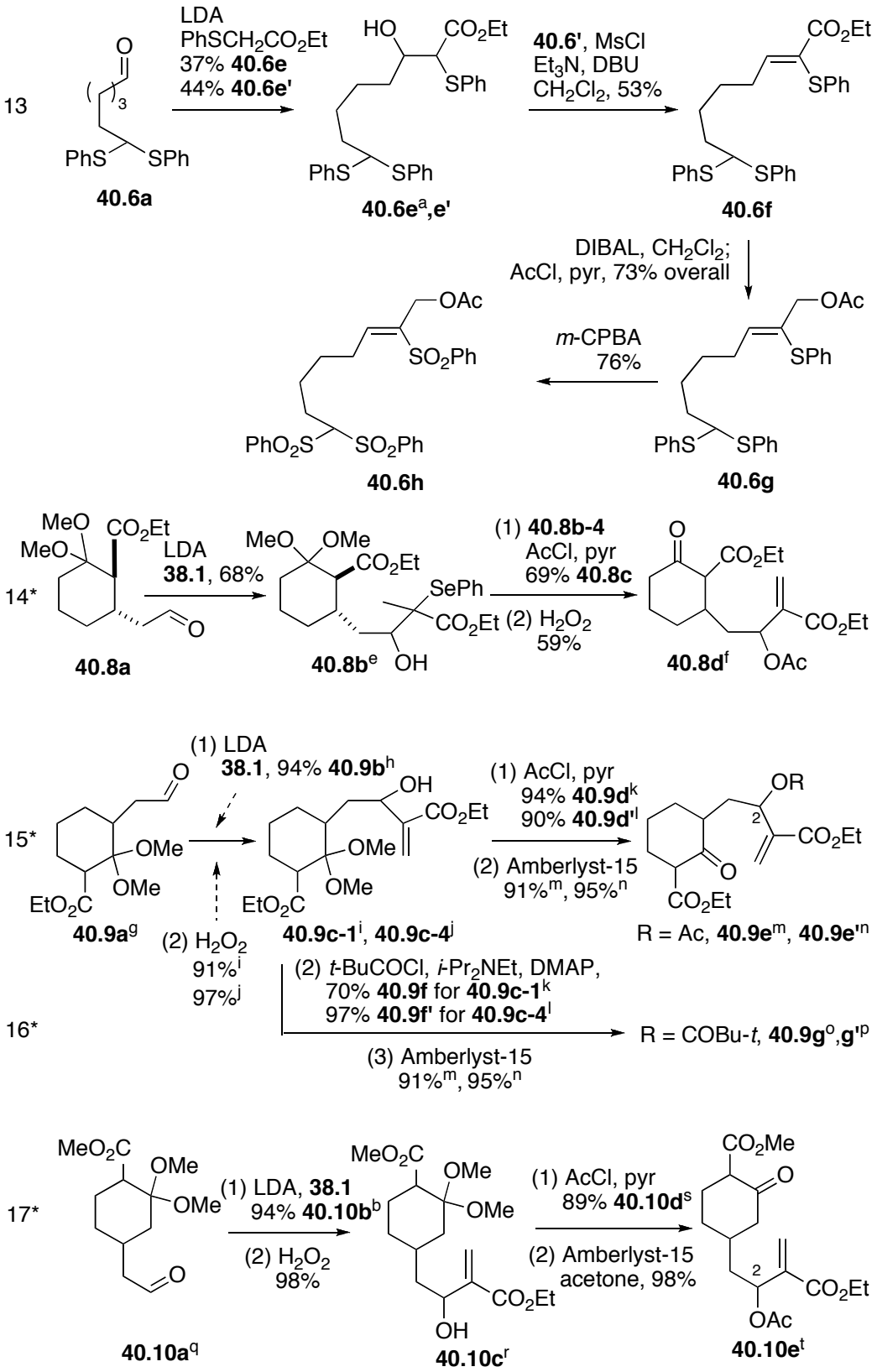
40.5a **40.5e[a],e'** **40.5f[d]** **40.5g** **40.5h**

12

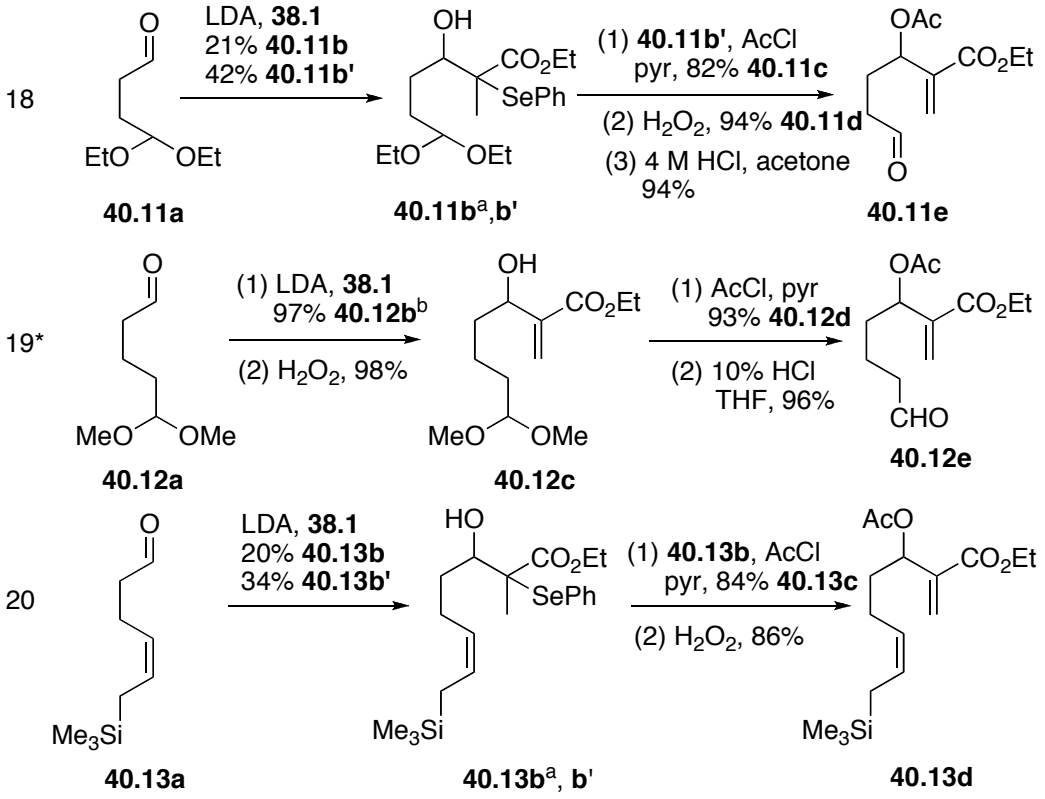


40.7a **40.7b[a],b'** **40.7d**

Scheme 40 (continued)



Scheme 40 (continued)



Scheme 40 (continued)

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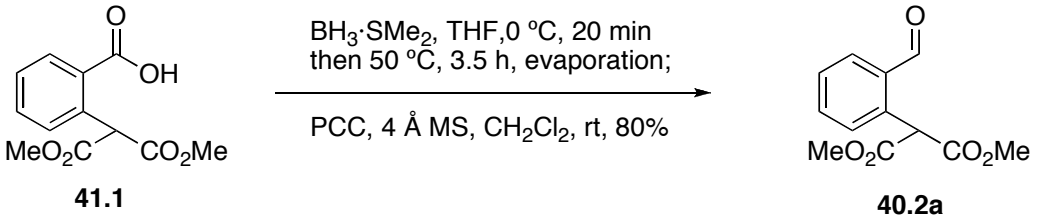
*Examples done by Dr. B. Prabhudas,[5b] a previous group member. [a]Less polar isomer. [b]Mixture of diastereoisomers. [c]Two inseparable isomers contaminated by starting aldehyde. [d]Assignment of double bond geometry was tentative. [e]This product was separated into three fractions: least polar, a single isomer, 15%; a mixture of two isomers, 35%; and most polar, a single isomer. Only the most polar one was taken forward. [f]An equilibrium mixture of keto-enol tautomers. [g]A single isomer of unestablished stereochemistry. [h]This product was separated into three fractions: the least polar one, a single isomer, 19%; a mixture of two isomers, 46%; and the most polar one, a single isomer, 29%. Only the least polar isomer **40.9b-1** and the most polar isomer **40.9b-4** were taken further. [i, k, m, o]The products were derived from **40.9c-1**. [j, l, n, p, o]The products were derived from **40.9c-4**. [q]Single isomer. [r]Inseparable mixture of two isomers that differ in stereochemistry at the hydroxyl-bearing carbon. [s]Inseparable mixture of two isomers that differ in stereochemistry at the acetoxy-bearing carbon. [t]Mixture of isomers including keto-enol tautomers.

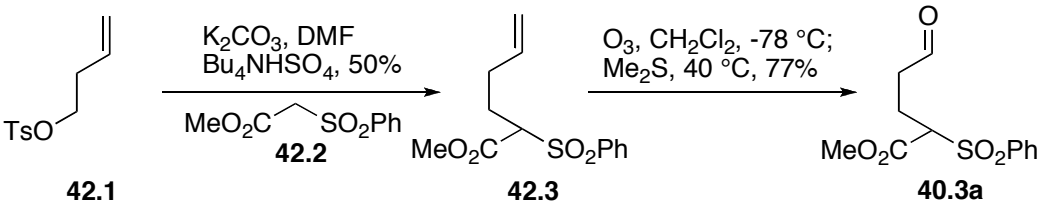
2.1.1. Preparation of the Aldehydes

Aldehyde **40.1a** was prepared using a literature procedure by Michael addition of dimethyl malonate to acrolein catalyzed by MeONa.[54] The aromatic aldehyde **40.2a** was prepared (Scheme 41) by diborane reduction of the known corresponding acid **41.1**[55] followed by immediate PCC oxidation of the crude product (80% overall). It is essential to avoid aqueous workup, as the released free alcohol from the boronate rapidly forms a lactone by attacking one ester group of the malonate subunit.

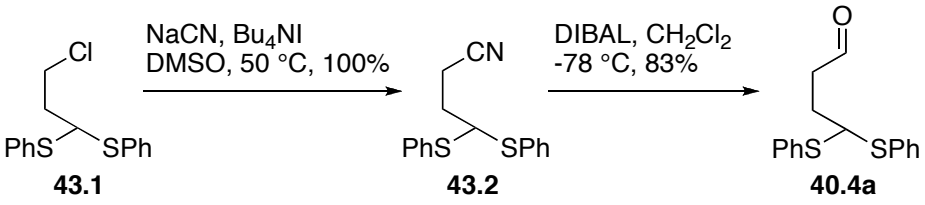


Scheme 41

Aldehyde **40.3a** was made in two steps from sulfonate **42.1**[56] and commercially available sulfone-ester **42.2** as shown in Scheme 42.



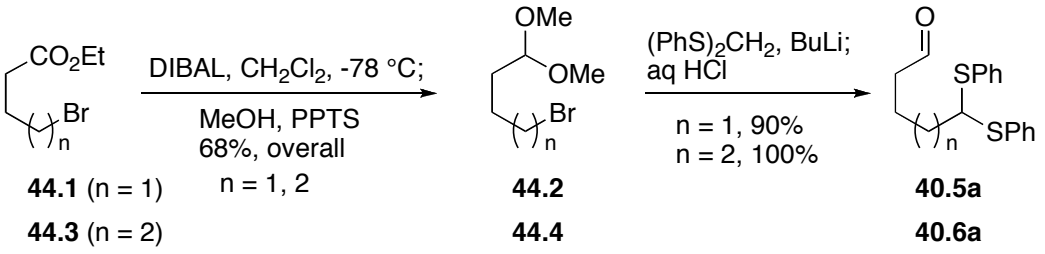
Scheme 42



Scheme 43

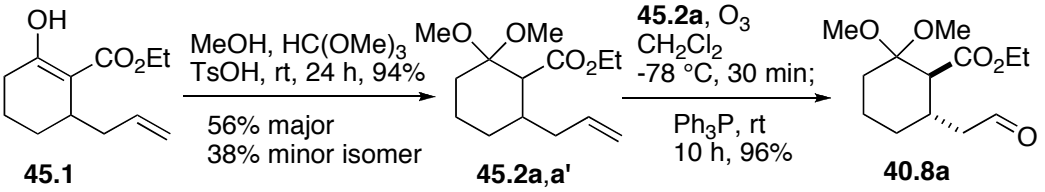
4-Bis(phenylthio)butyraldehyde **40.4a** was prepared in a straightforward way; the aldehyde group was generated from a nitrile group which, in turn, was incorporated by S_N2 displacement of chlorine in compound **43.1**[57] (Scheme 43).

The same sequence of reactions was applied for making both aldehydes **40.5a** and **40.6a**, as summarized in Scheme 44. The known acetals **44.2**[58] and **44.4**[59] were prepared from the corresponding commercially available bromo esters. Replacement of the bromine with the carbanion from bis(phenylthio)methane, followed by hydrolysis of the acetal group, delivered the desired products.



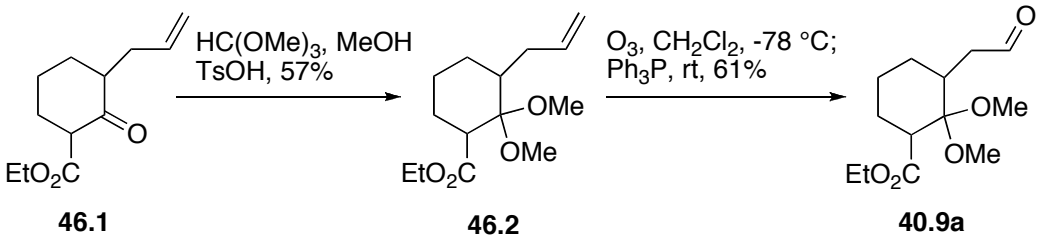
Scheme 44

Our route to aldehyde **40.8a** (Scheme 45) is the same as that reported[60] for the corresponding methyl esters. The intermediate **45.2a**,**a'** was a mixture of *cis* and *trans* isomers, but only the major (*trans*) component was ozonized; consequently, **40.8a** was a single isomer (Dr. Prabhudas's work).[5b]

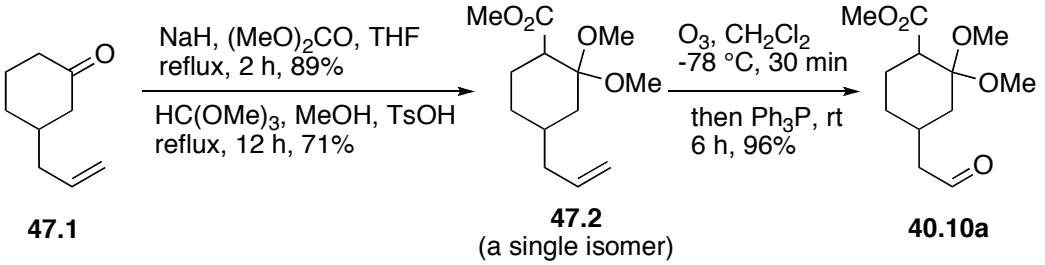


Scheme 45

Aldehyde **40.9a** was available as a single isomer in two steps from **46.1**[61] (Scheme 46) by ketalization and ozonolysis, and a similar approach (Scheme 47)



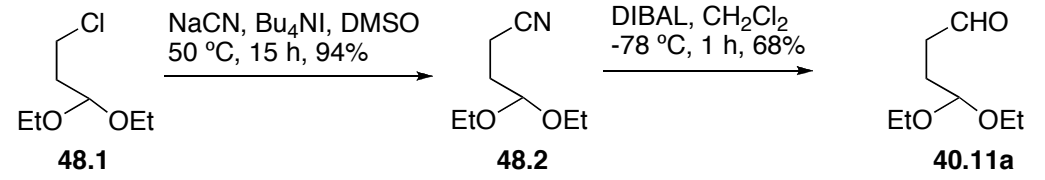
Scheme 46



Scheme 47

was used to make the isomeric aldehyde **40.10a** from ketone **47.1** (Dr. Prabhudas's work).[5b,62]

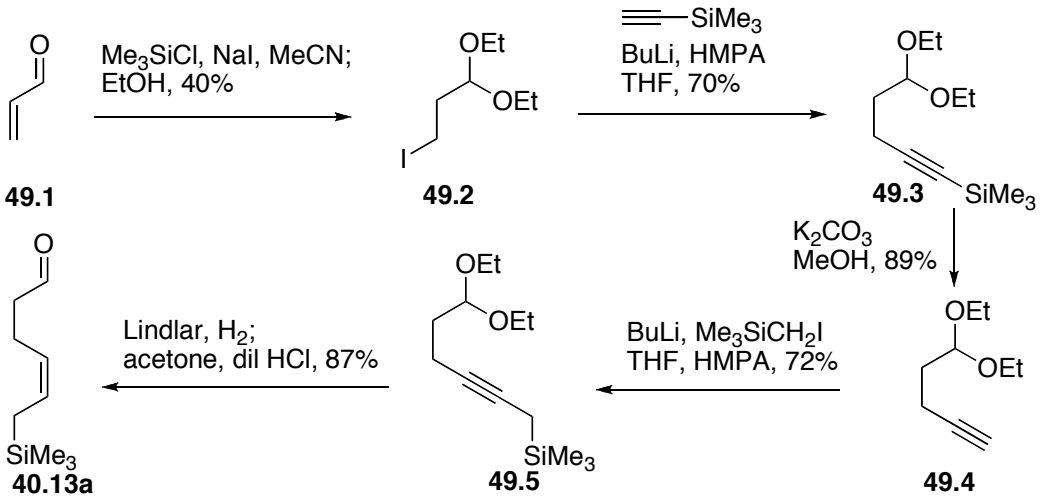
Both aldehydes **40.11a**[63] and **40.12a** are known substances reported in the literature. The former was made by DIBAL reduction of nitrile **48.2**;[64] itself prepared from commercially available chloride **48.1** by displacement with NaCN. The latter (**40.12a**) was obtained in one step by ozonolysis of the cyclopentene (Dr. Prabhudas's work).[5b,65]



Scheme 48

4-Nitrobutanal (**40.7a**) was available by Michael addition of $MeNO_2$ to acrolein, as described in the literature.[66] Acrolein also served as the starting point for making aldehyde **40.13a**. Treatment of acrolein with Me_3SiI (generated *in situ*) in MeCN, followed by addition of anhydrous EtOH yielded iodide **49.2**, as

reported in the literature.[67] Displacement of iodide with lithium trimethylsilyl acetylide and removal of the Me_3Si group in basic MeOH gave alkyne **49.4**. Elongation of **49.4** by deprotonation with BuLi and quenching the resulting carbanion with Me_3SiCH_2I, controlled reduction of the alkyne to a *cis* double bond, and deprotection of the acetal group in an acidic medium gave the desired aldehyde **40.13a**.



Scheme 49

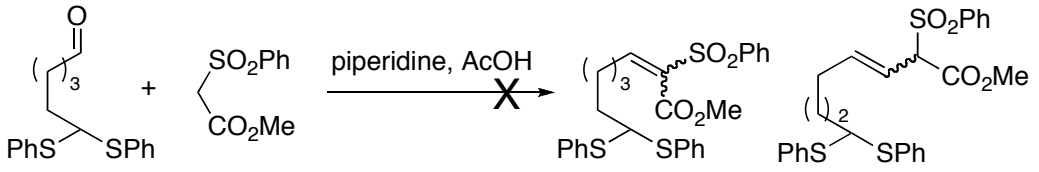
2.1.2. Preparation of the MBH Acetates from the Aldehydes

As mentioned earlier, most of the ICD precursors were prepared using the selenium method involving an aldol reaction between an aldehyde and a selenium-containing substrate (**38.1**, **39.5**-**39.8**), followed by oxidative elimination of the selenium to install the double bond. The *syn* elimination of the selenoxide occurs away from the hydroxyl, a fact that is well documented in the literature.[68] Usually, the aldol reaction was performed using LDA as the base (Scheme 40, entries 1, 2, 4, 5, and 7-20), and the products were obtained in yields ranging from 50% to 97%. In several cases, other bases were used: a strong base (BuLi) for entry 3, and DBU for entry 6 as in this case a stronger base such as LDA or BuLi caused loss of PhSe. In all the cases, diastereomeric mixtures were produced. Sometimes they could be separated and then only one pure

diastereomer was carried forward; however, using the mixture for further processing causes no problems, and in most examples, after elimination of the selenoxide, a single diastereomer could be obtained. Acetylation of the hydroxyl group with AcCl and pyridine in the presence of a catalytic amount of DMAP proceeded uneventfully. Oxidation of the selenium could be executed with 30% H_2O_2 or *m*-CPBA to give the double bond with the desired regiochemistry in satisfactory yield (71-94%). Alternatively, the sequence could be altered by first generating the allylic alcohol, followed by acetylation, as shown in entries 15-17 and 19.

After the sequence of aldol condensation, acetylation and elimination, an extra step was needed for entries 15-19, namely, unmasking an aldehyde group (or ketone) from the acetal (or ketal).

The preparation of the ICD precursors **40.5h** and **40.6h** (for the *exo*-ICD examples, *vide infra*) (entries 11 and 13) are different from the other routes. The aldehydes were first condensed with $PhSCH_2CO_2Et$,[69] and the double bond of the MBH acetate subunit was generated not by selenoxide elimination, but by dehydration via a mesylate. Reduction of the ethyl ester to the alcohol with DIBAL and subsequent acetylation of the OH group installed the AcO unit as the leaving group, and formation of the electron-withdrawing group of the MBH acetate unit via oxidation of the sulfide was delayed until the last step. It should be noted that a more direct way of preparing these two MBH acetates using a Knoevenagel reaction between the aldehyde and sulfone ester **42.2** failed to yield the desired product **50.1**, but gave a mixture containing predominantly the double bond migration product **50.2**, contaminated by an impurity. The propensity for vinyl sulfones to isomerize to the allylic sulfones has precedent.[70]



40.6a **42.2** **50.1** **50.2**

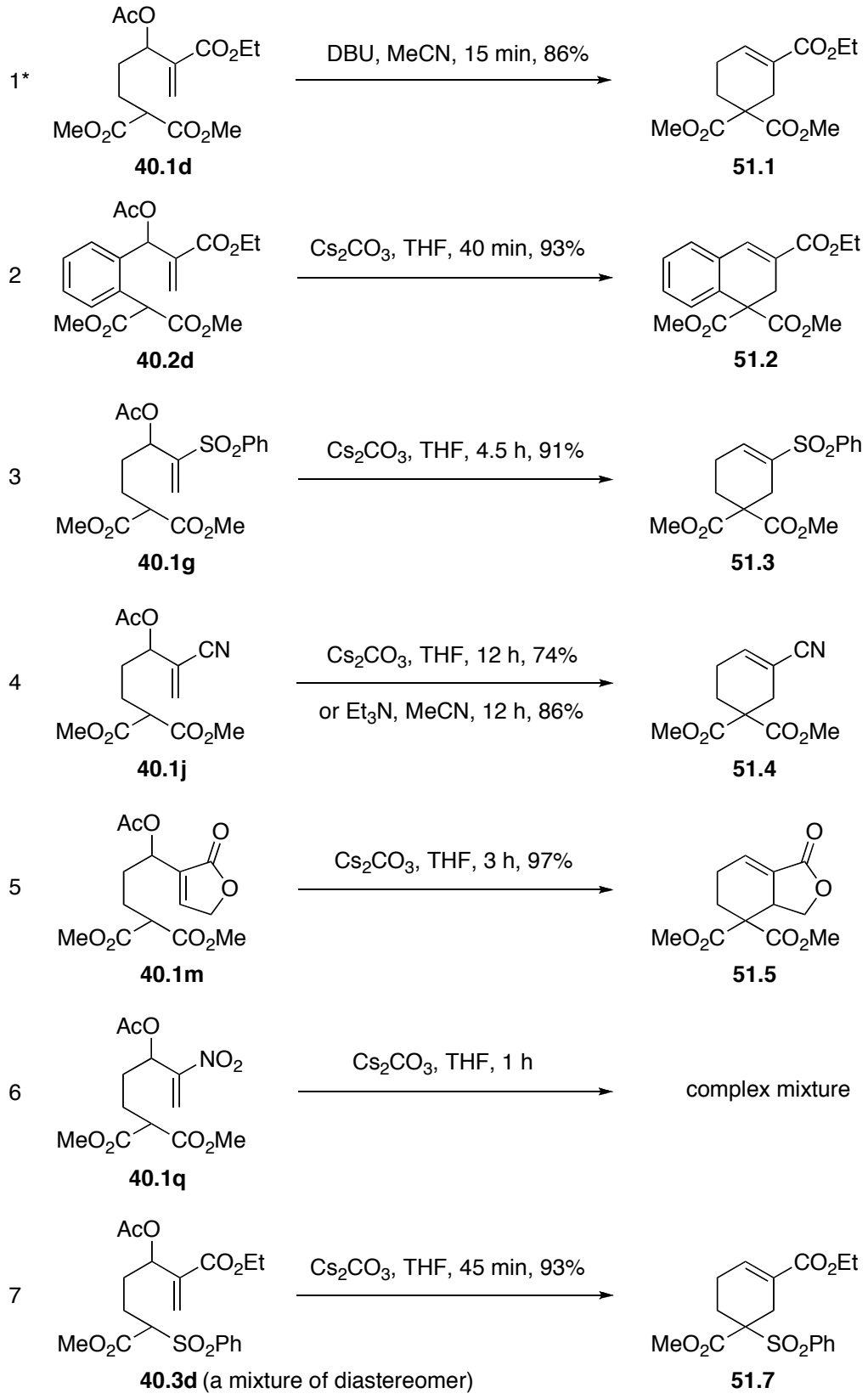
Scheme 50

For entries 8-11 and 13, using PhS as a precursor for $PhSO_2$ is convenient and also essential, as earlier introduction of two $PhSO_2$ groups on the same carbon would substantially increase the acidity of the adjacent proton to an extent that would likely interfere with subsequent transformations.

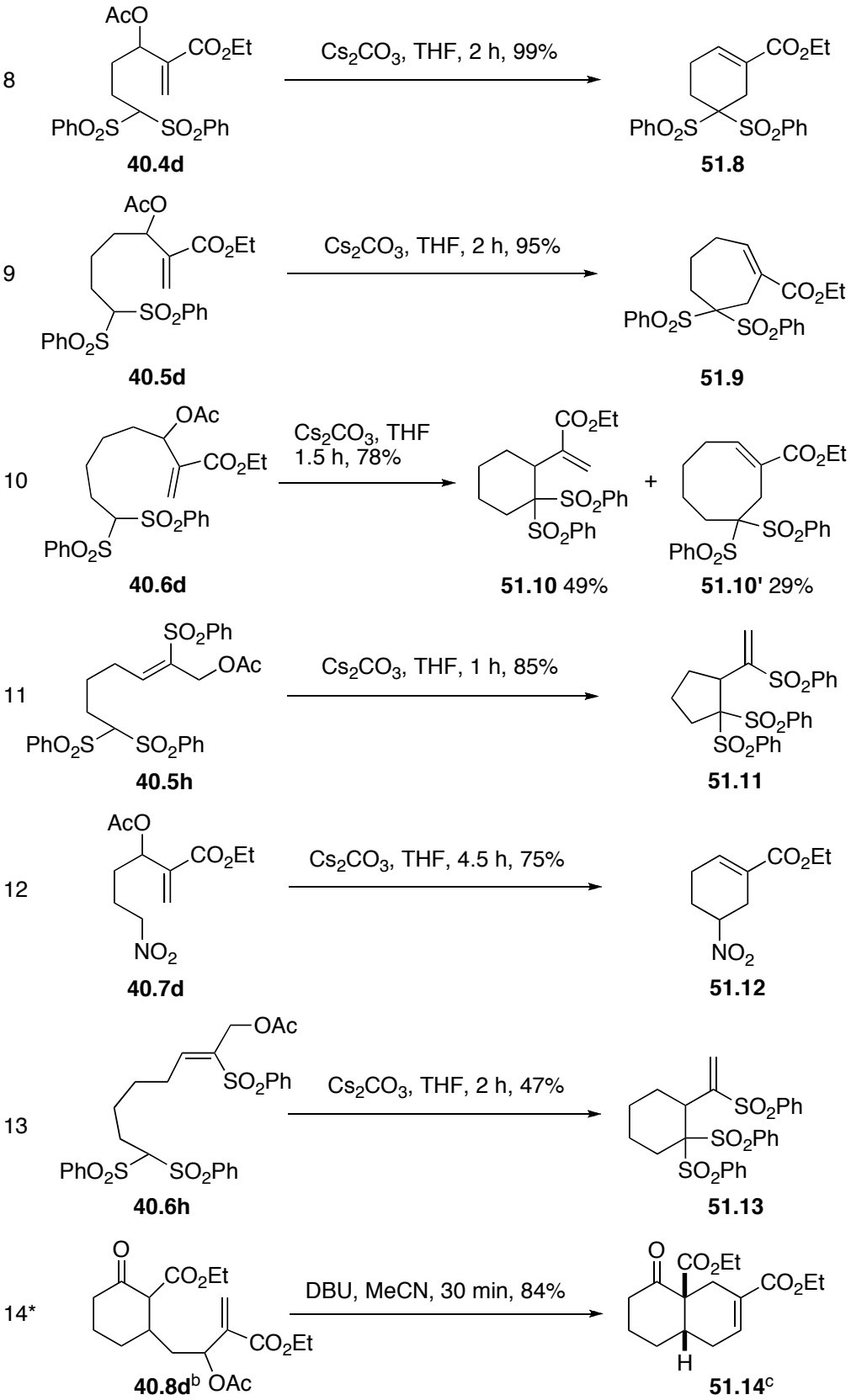
Most of the examples were designed to examine the *endo* cyclization mode of the ICD reactions: entries 1-8, 12, 14, and 18-20 for 6-*endo-trig*; entries 9, 15 and 16 for 7-*endo-trig*; and entries 10 and 17 for 8-*endo-trig*. Two examples were prepared to test the feasibility of *exo* ring closure: entry 11 for 5-*exo-trig* and entry 13 for 6-*exo-trig* modes.

2.2. Ring Closure Using ICD Reactions

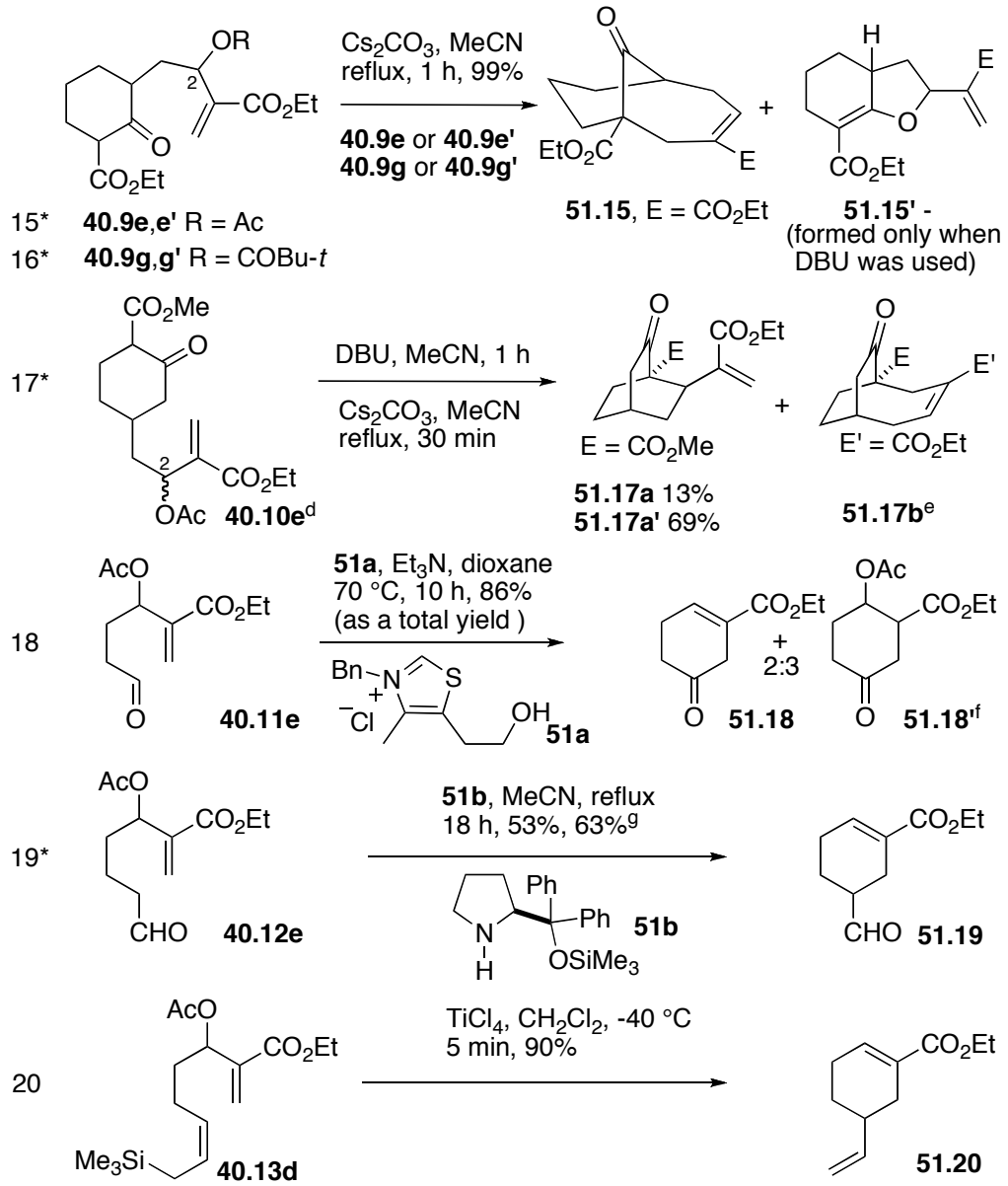
During the initial study by a previous group member to implement the carbon based ICD reaction on the CP-molecule **38.5**, the arbitrary combination of DBU in MeCN, was found to be very effective in terms of the reaction rate (30 min, at room temperature) and yield (96%).[5b] Although no screening of the reaction conditions was conducted, it was observed at that time that a strong base $(Me_3Si)_2NLi$ gave a complex mixture. The DBU-MeCN system also served well in the first few examples using OAc as the leaving group and an ethyl ester as the electron-withdrawing group on the MBH acetate subunit.[5b] Cs_2CO_3-MeCN was also demonstrated to be a good base-solvent combination when DBU-MeCN failed to perform well on compound **40.9e** (Scheme 51, entry 15).[5b] However, both base–solvent combinations gave very low yields with the nitrile substrate **40.1j**, and we were forced to conduct an extensive survey that is summarized in Scheme 52. No clear trend for the relationship between the yield and the base-solvent pair could be observed; Et_3N-MeCN gave a satisfactory yield (86%) and addition of Me_3SiCl or heating both shorten the reaction time but with no improvement in yield. However, Et_3N-MeCN did not perform well for cyclization of **40.1m**, and all efforts to effect the ring closure gave either complete decomposition or a yield less than 5%. In an attempt to run the reaction at -78 ºC using Cs_2CO_3 in THF no reaction was observed, however, when warming the


1*
AcO
CO2Et
MeO2C
CO2Me
40.1d
DBU, MeCN, 15 min, 86%
51.1
2
40.2d
Cs2CO3, THF, 40 min, 93%
51.2
3
SO2Ph
40.1g
Cs2CO3, THF, 4.5 h, 91%
51.3
4
CN
40.1j
Cs2CO3, THF, 12 h, 74%
or Et3N, MeCN, 12 h, 86%
51.4
5
O
40.1m
Cs2CO3, THF, 3 h, 97%
51.5
6
NO2
40.1q
Cs2CO3, THF, 1 h
complex mixture
7
40.3d (a mixture of diastereomer)
Cs2CO3, THF, 45 min, 93%
51.7

Scheme 51[a]

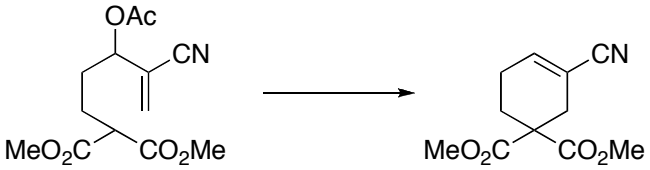


Scheme 51 (continued)



Scheme 51 (continued)

*Previous group member Dr. Prabhudas's work.[5b] [a]All reactions at room temperature, unless otherwise indicated. [b]A mixture of keto-enol tautomers. [c]The stereochemistry assignment of **51.14** is tentative. [d]A mixture of isomers including keto-enol tautomers. Both stereochemistries at acetoxy-bearing carbon. [e]Only a trace amount of **51.17b** was detected with DBU; with Cs_2CO_3 the yield of **51.17b** is 11%, but **51.17a**,**a'** was not formed. [f]Single isomer of unestablished stereochemistry. [g]Yield 69% after correction for recovered starting material.



40.1j **51.4**

1	DBU	MeCN	rt	10 min	47%
2	DBU	CH_2Cl_2	rt	25 min	52%
3	DBU	DMSO	rt	25 min	40%
4	DBU	PhMe	rt	15 min	16%
5	DBU	MeCN	-10 °C	6 min	33%
6	DBU	MeCN	reflux	5 min	38%
7	Cs_2CO_3	MeCN	reflux	50 min	55%
8	Cs_2CO_3	CH_2Cl_2	rt	several h	CM[b]
9	Cs_2CO_3	THF	rt	12 h[c]	74%
10	Et_3N	MeCN	rt	12 h	86%
11	Et_3N	MeCN	reflux	4.5 h	78%
12	Et_3N, Me_3SiCl	MeCN	rt	15 min	74%
13	*i*-Pr_2NEt	MeCN	reflux	24 h	40%
14	DABCO	MeCN	rt	15 min	-[d]
15	pyridine, Me_3SiCl	MeCN	reflux	12 h	CM

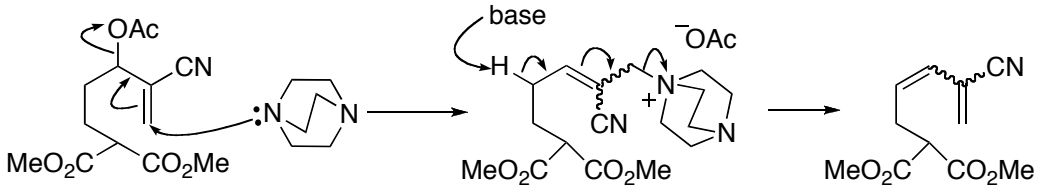
Scheme 52

[a]Reactions were monitored by TLC and, except for overnight runs, were stopped when all starting material had been consumed. [b]CM = complex mixture. [c]Reaction appeared to be half over after 80 min. [d]Elimination of acetate from **40.1j** occurred (^{1}H NMR).

reaction mixture in ca 10 ºC increments, clean formation of the desired product **51.5** occurred at room temperature in excellent yield (97%) (Scheme 51, entry 5). Therefore this combination was employed as our first choice and, since

satisfactory yields were obtained in most cases, comparison with other conditions was not made. Another merit of using Cs_2CO_3–THF is the convenience of the workup; usually, a simple filtration through a short pad of silica gel (or Celite) would suffice and no impurity was detectable by ^1H NMR measurement.

In a few of the examples, a diene species, formed via an apparent S_N2 elimination of the leaving group, was noticed (DABCO with **40.1j**, and Hünig's base with **40.1m**), but this was not observed when Cs_2CO_3 was used. A speculative mechanism involves S_N2' displacement of the AcO^- by the amine base, followed by elimination as depicted in Scheme 53. Intermediates **53.1** and **53.2** could lead to further reactions (such as Diels-Alder cycloaddition, intermolecular Michael addition, etc.), which might account for the low yields in some cases where an amine was used as the base.



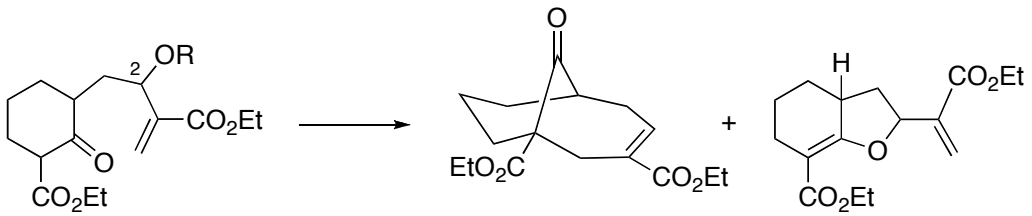
40.1j **53.1** **53.2**

Scheme 53

In addition to base-mediated ICD reactions with carbanions, entries 18-20 in Scheme 51 represent other ways of generating a nucleophilic carbon.

The formation of 6- and 7-membered rings via 6-*endo-trig* and 7-*endo-trig* cyclization, using either Cs_2CO_3 or DBU, proceeded smoothly and in high yield (75-99%), except for the nitro example **40.1q** (Scheme 51, entry 6) which gave a complicated mixture. The [6,6]-bicyclic compounds **51.14** could be constructed without incident (Dr. Prabhudas's work),[5b] and the *syn* geometry was assigned tentatively by analogy with similar *cis*-fused decalin systems in the literature.[71] Interesting observations were made in an attempt to implement the 7-*endo-trig* ring closure for making [6,7]-bicyclic structure **51.15** (Dr. Prabhudas's work).[5b] Brief exposure (30–50 min) of either **40.9e**,**e'** (acetate as the leaving group) or

40.9g,g' (pivaloate as the leaving group) to DBU in MeCN led to both **51.15** and **51.15'**. The side product **51.15'** was isolated as a pair of epimers in a 7:3 ratio, irrespective of the stereochemistry at C2 in the starting material. The formation of **51.15'** is reversible, as it could be converted to **51.15** either by using a longer reaction time *in situ* (150 min) or by the action of DBU–MeCN after isolation. In



40.9e,e' (R = Ac) or **40.9g,g'** (R = *t*-BuCO) | **51.15** | **51.15'**

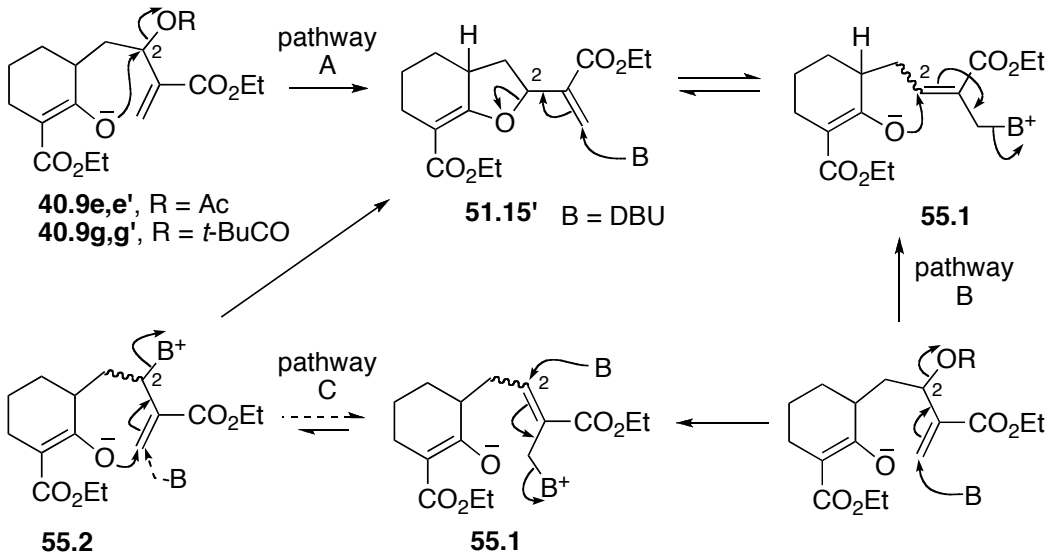
R = Ac, less polar		
DBU, MeCN, room temp, 30 min	5%	79%[a]
Cs_2CO_3, MeCN, reflux, 60 min	100%	-%[b]
R = Ac, more polar		
DBU, MeCN, room temp, 50 min	53%	38%[a]
Cs_2CO_3, MeCN, reflux, 45 min	99%	-%[b]
R = *t*-BuCO, less polar		
DBU, MeCN, room temp, 30 min	5%	80%[a]
Cs_2CO_3, MeCN, reflux, 60 min	100%	-%
R = *t*-BuCO, more polar		
DBU, MeCN, room temp, 20 min	23%	51%[a]
DBU, MeCN, room temp, 150 min	73%	-%
Cs_2CO_3, MeCN, reflux, 60 min	99%	-%

Scheme 54

[a]Diastereoisomeric mixture (7:3). [b]Compound **51.15'** not isolated.

contrast to this complicated behavior, **51.15** was formed as the sole product when **40.9e,e'** and **40.9g,g'** were treated with Cs_2CO_3 in refluxing MeCN; no **51.15'** was observed by TLC during the reaction. The above experiments are summarized in Scheme 54 (Dr. Prabhudas's work).[5b]

The constant ratio of the **51.15'** isomers (7:3) regardless of the C2 stereochemistry of the starting materials implicates possible mechanistic pathways leading to a thermodynamic ratio. Three potential mechanisms are outlined in Scheme 55. All three pathways involve elimination of the C2 stereochemistry by changing it from an sp^3 to an sp^2 hybridization via species **55.1**. This constant ratio could be explained by an equilibration between **51.15** and **55.1**, initiated by either an intramolecular displacement (5-*exo-tet*) of acetate (or pivaloate) by the enolate oxygen (pathway A), followed by an S_N2' displacement with DBU as the external nucleophile. Alternatively an S_N2' displacement of acetate (or pivaloate) by DBU could also initiate the equilibration (pathway B). Pathway C involves



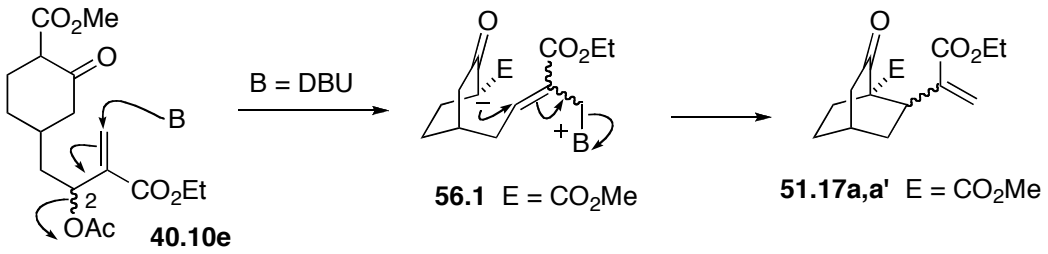
Scheme 55

equilibration between **55.1** and **55.2** and an oxy-ICD with DBU as the leaving group. It is possible that the desired product **51.15** itself arises from either intermediate **55.1** (by a 7-*exo-tet* cyclization of the *E*-isomer) or **55.2** (by 7-*endo-trig* ICD). When **51.15'** was treated with Cs_2CO_3 in MeCN at room temperature (12 h), no **51.15** was formed but slight decomposition occurred; at higher temperature (refluxing, 2 h) **51.15'** simply decomposed and again **51.15** was not detected.[5b] These observations are consistent with the suggested mechanism for

DBU-mediated reactions, as Cs_2CO_3 is apparently unable to participate in the reversible nucleophilic process proposed for DBU.

Formation of an 8-membered ring is more challenging because of additional strains for rings of medium size.[72] Cyclization of **40.6d** using Cs_2CO_3 in THF gave the desired product **51.10a'** in 29% yield, plus a 6-membered compound (**51.10a**) in 49% yield, presumably from direct displacement of the allylic acetate by the carbanion (Dr. Prabhudas's work).[5b] Treatment with DBU in MeCN (room temperature, 2.5 h) resulted in a complex mixture with a trace amount of the 6-membered product and no detectable amount of the 8-membered compound.

When **40.10e** was treated with DBU in MeCN, the 6-membered product predominated (82% yield), with little formation of the 8-membered product **51.17b**, which was isolated in a slightly impure form in ca 3% yield.[5b] Possibly, the formation of **51.17a**,**a'** with DBU is a result of an S_N2'-S_N' sequential process (Scheme 56), similar to the S_N2'-S_N2' mechanism mentioned in connection with intermolecular conjugate displacements in the introduction section. Such a pathway accounts for the fact that an epimeric 1:5 mixture was obtained for **51.17a**,**a'** from **40.10e** that itself was a 1:1 mixture of C2 epimers. Further observations consistent with the essential role of DBU in the formation of



Scheme 56

51.17a,**a'** came from the Cs_2CO_3-mediated reactions: in refluxing MeCN, 11% pure **51.17b** was isolated and only a trace amount (<1%) of **51.17a**,**a'** was formed;[5b] in THF at room temperature (12 h), a complex mixture resulted and the

presence of a trace amount of **51.17b** was suggested by the ^{1}H NMR spectrum of the crude material.

Exo cyclization modes (5-*exo-trig* and 6-*exo-trig*) were examined using substrates **40.5h** and **40.6h** (Scheme 51). The 5-*exo* ICD proceeded smoothly to give **51.11** in high yield (85%); formation of the 6-membered product **51.13** via a 6-*exo* ICD gave only a low yield (47%).

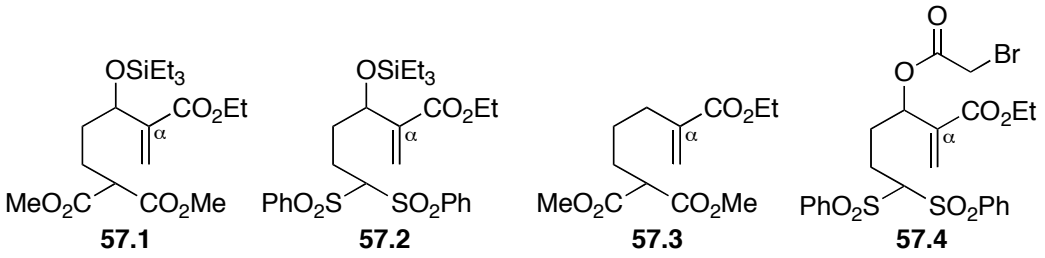
ICD cyclizations utilizing other nucleophilic carbons were explored briefly (Scheme 51, entries 18-20). Entry 18 represents an intramolecular Stetter reaction using thiazolium salt **51a** as the catalyst and Et_3N as the base; a similar reaction[45] was mentioned in the introduction section. The reaction generated two species, **51.18** and **51.18'** in a 2:3 ratio; the former is the expected ICD product and the latter arises from a simple Michael addition. This is the only example in which the leaving group acetate was retained after cyclization, and the mechanistic implications will be discussed in the following section. Treatment of aldehyde **40.12e** with DBU in MeCN did not deliver any ICD product, but caused elimination of AcOH from the substrate to give a diene that underwent further reaction(s).

Attempted ICD reaction via an *in situ* generated enamine using the organocatalyst proline and its derivative **51b**[73] gave only inferior yields: 29% with proline (53% after correlation for recovered starting material) and 53% with **51b** (69% after correlation for recovered starting material) (Dr. Prabhudas's work).[5b] The desired reaction pathway is probably diverted by direct nucleophilic attack of the proline (or **51b**) nitrogen onto the MBH acetate subunit, followed by other side reactions. As this *in situ* enamine-generation method did not seem to be a promising ICD reaction, further exploration was not attempted and the ee of the product **51.19** was not measured.

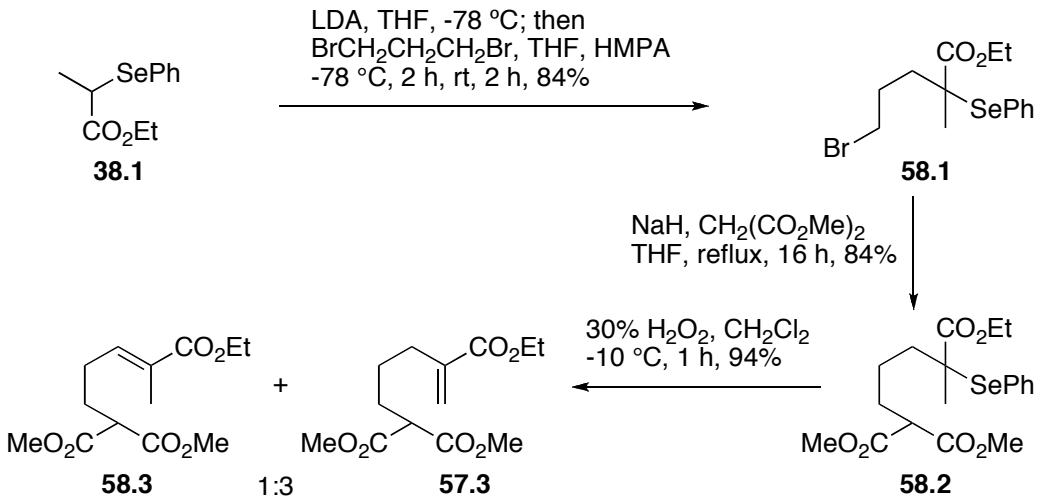
An allylic silane could be used as the nucleophile, and when substrate **40.13d** was treated with $TiCl_4$ in CH_2Cl_2 at a low temperature (-40 ºC), the desired product was obtained in 90% yield. Single experiments with $BF_3{\cdot}OEt_2$ or Bu_4NF were unsuccessful. Similar ring closures of allylic silanes[43-44] are mentioned in the introduction section.

2.3. Mechanistic studies

Some substrates and reactions used in the study of the reaction scope are relevant to the exploration of the mechanisms, but more precursors for probing the mechanism were specially prepared and additional experiments were performed to address the mechanistic questions. These new compounds are listed in Scheme 57. Among them, compounds **57.1**, **57.2** and **57.4** were made using the same route as for the ICD precursors, viz. silylation or acetylation of alcohols **40.1b** and **40.4b**, followed by elimination via selenoxides; compound **57.3** was



Scheme 57



Scheme 58

prepared by a slightly different route as indicated in Scheme 58, but selenoxide elimination proceeded with poor regioselectivity and generated a mixture of the

desired compound **57.3** and its regioisomer **58.3** in a ratio of 3:1. As they were inseparable, we used the material as a mixture.

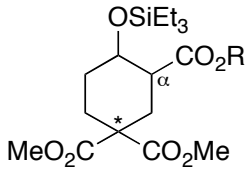
Reexamination of the enhanced reactivity of the MBH adducts due to the presence of a leaving group, as indicated in the literature (see the introduction section), revealed a clear trend in reactivity: the better the nucleofuge, the faster the reaction. With DBU in MeCN at room temperature, **40.1d** cyclized in 15 min in a yield of 86%; **57.1** cyclized at a much slower reaction rate and required 90 min to give the same product in a yield of 96%, while **57.3** (together with **58.3**) did not undergo any cyclization after a prolonged reaction time (32 h) as indicated by the ^{1}H NMR spectrum of the crude reaction mixture. When treated with DBU in MeOH at room temperature for 41 h, compound **57.3** underwent an intermolecular Michael addition with MeOH, accompanied by ester exchange (CO_2Et to CO_2Me), but again no cyclization was detected.

The enhanced reactivity of the MBH adduct towards a nucleophile conferred by the presence of a leaving group is in line with many S_N2' examples, as discussed in the introduction. It is possible that the departure of the leaving group acts as an irreversible sink, thus trapping the initial anionic Michael addition intermediate. More likely, orbital interactions between the electronegative leaving group and the Michael acceptor lower the LUMO of the terminal double bond and increase its susceptibility towards nucleophiles: for example, in contrast to the persistent resistance of **57.3** to undergo intramolecular Michael addition, the same reaction did occur for substrate **40.11e** after umpolung of the aldehyde group, although the reaction conditions are not exactly the same.

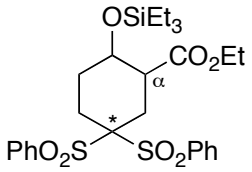
It is not clear if the ICD reactions occur via a concerted or stepwise mechanism; nor is this point clear for the inter- and intramolecular cases with MBH adducts reported in the literature — although researchers commonly refer to the reactions as "addition and elimination" sequences and some authors are biased towards the stepwise mechanism, as preliminary kinetic studies showed no relationship between the nature of the leaving group and the rate of the reaction.[8i,13a]

We probed the mechanism of the reaction by experiments designed to trap any Michael addition species with significant carbanionic character at Cβ (see Scheme 57) of the MBH adduct subunit. To this end, sulfone ester **40.4d** was treated with Cs_2CO_3 in THF-*t*-BuOH, *t*-BuOH, or MeOH at room temperature and the reactions were quenched before complete consumption of the starting material; in each case, the reaction produced only the ICD product, plus remaining starting material, as indicated by ^{1}H NMR examination of the crude material. It is possible that protonation of the carbanion, being a bimolecular process, is not competitive with expulsion of the leaving group; thus we designed substrate **57.4**, with the appended bromo acetate serving as an intramolecular carbanion trap. Subjecting compound **57.4** to the standard ICD conditions (Cs_2CO_3 in THF at room temperature) and quenching the mixture before disappearance of the starting materials gave only the ICD product **51.8** and starting material (based on the ^{1}H NMR spectrum of the crude material).

As described earlier, the use of $OSiEt_3$ as the leaving group will retard the ICD reaction, and so we next examined the behavior of these compounds in trapping experiments. When **57.1**, carrying the malonate moiety was treated with DBU in MeOH (room temperature, 34 h), in addition to the normal ICD product, in which some ester exchange occurred, we also isolated the Michael addition product **59.1** in 28% yield as a mixture in which some ester exchange had occurred. The stereochemistry of **59.1** was not established. In contrast to **57.1**, which requires an excess of a proton source in order to intercept the putative



59.1 R = Me, Et



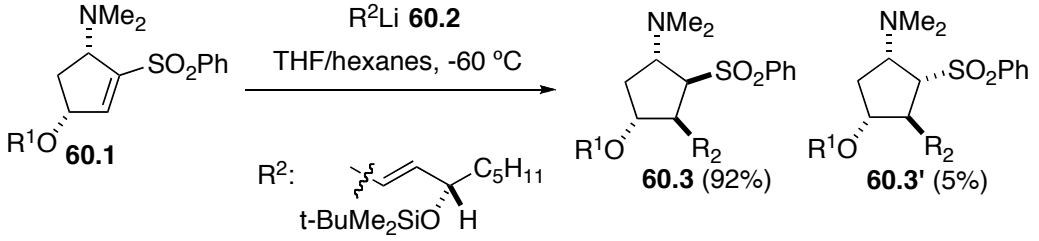
59.2 and **59.2'**

Scheme 59

carbanion, treatment of **57.2** with DBU in MeCN (room temperature, 40 min) afforded the two diastereomeric Michael adducts **59.2** (44%, *trans*) and **59.2'**

(4%, *cis*), plus the normal ICD product (27%). Subjecting either **59.2** or **59.2'** to the reaction conditions (DBU in CD_3CN) showed no change after 45 min, the reaction being periodically monitored by ^1H NMR measurements.

Similar observations have been reported in the literature for MBH adduct-based *intermolecular* reactions: switching to a poor leaving group leads to partial or total formation of the Michael addition product.[4a,74] Fuchs *et al*. speculated that elimination of the leaving group could be completely suppressed if the p*K*a of such a leaving group is much greater than that of the C-H α to the electron-withdrawing group in the MBH adduct subunit.[4a] This speculation was supported by the reaction depicted in Scheme 60. Using Me_2N (p*K*a Me_2NH = ca 35) on the allylic position of sulfone **60.1** (p*K*a of the α position of sulfone = ca 25), treatment with the vinyllithium reagent **60.2** gave only the Michael addition product in an almost quantitative yield; while replacement of the NMe_2 group by OH (p*K*a ROH = ca 16) and using the corresponding cuprate of **60.2** resulted in an S_N2' reaction. In other words, the larger the value for Δp*K*a [Δp*K*a = p*K*a(Cα-H of sulfone)-p*K*a(leaving group)], the easier the formation of the ICD product. However, it should be noted that the two experiments are not strictly comparable because an organolithium and a cuprate are being compared.



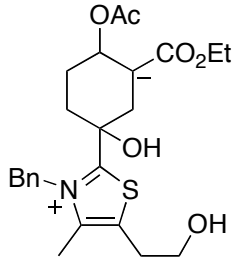
Scheme 60

This hypothesis may help explain the different behavior of substrates **57.1** and **57.2** under the same reaction conditions: as mentioned earlier, with DBU in MeCN, **57.1** gave only the ICD product, while **57.2** produced mainly the Michael adduct. This discrimination is probably caused by different p*K*a values of the α position to the ester group (see Scheme 59); as the geminal diesters groups at C*

on **59.1** are less electronegative than the disulfone on **59.2** (or **59.2'**) and have a less strong inductive effect on the α position, the α position of **59.1** accordingly has a higher p*K*a value, meaning that with the same leaving group ($OSiEt_3$) Δp*K*a of **59.1** is larger than that of **59.2** and thus the carbanion at the α position of **59.1** (generated after Michael addition in the stepwise pathway) would be more likely to expel the $OSiEt_3$.

To summarize the above discussions, the overall conclusion based on our examination is that the transformations based on MBH acetates could be either concerted — in which the extent of bond formation and the extent of bond breakage may be synchronous or asynchronous — or may occur in a stepwise manner but with the negative charge on the MBH acetate part (after initial ring closure) of sufficiently small magnitude and/or short lifetime that it evades capture by an external or internal electrophile. However, a range of mechanisms may apply, depending on the structure and conformation of the substrates, as well as the reaction conditions.

As stated earlier, when aldehyde **40.11e** was subjected to standard Stetter conditions (Scheme 51, entry 18), both ICD product **51.18** and Michael adduct **51.18'** were obtained. In this case it is likely that after initial ring closure the carbanion on intermediate **61.1** (Scheme 61) is stabilized by Coulombic attraction with the cation on the thiazolium unit; this attraction could also prolong the



61.1

Scheme 61

lifetime of the carbanion and increase the chance of its being trapped by an external or internal proton source. The ICD product **51.18** could be formed either

by a concerted pathway or stepwise via the same intermediate **61.1**. The normal ICD cyclizations are over within a few hours when DBU is used in MeCN at room temperature, but some **51.18'** remained in a complex mixture after treatment with DBU in MeCN at an elevated temperature (50 ºC) for 12 h. Clearly, none of the ICD products in Scheme 51 is formed via a simple protonated Michael addition species followed by base mediated elimination of AcOH, in line with the expectation based on the p*K*a values.

3. Conclusions

The carbon nucleophile-based ICD reaction is a general method of making 5-, 6-, and 7-membered carbocycles in high yields under very mild conditions. The scope study showed that a variety of functional groups (electron-withdrawing groups) could be incorporated, which provide handles for further functionalization; the product itself is a Michael acceptor, a useful theme in synthesis. Unlike palladium-mediated S_N' reactions involving allylic acetates and a carbanion, the current method requires no transition metal and therefore can tolerate groups that might be affected by palladium.

The precursors are easily accessible using a sequential aldol condensation, elimination of selenoxide and acetylation.

The utility of the all-carbon ICD has been demonstrated in constructions of several complex models related to CP-225,917 and CP-263,114. Its potential for making carbocycles in an asymmetric manner using a chiral auxiliary is now under study in this group.

The mechanism can be stepwise, at least in the cases when a poor leaving group is used; while for examples with AcO^- as a leaving group, the pathway could be concerted, although a stepwise pathway involving a very fast elimination can not be excluded.

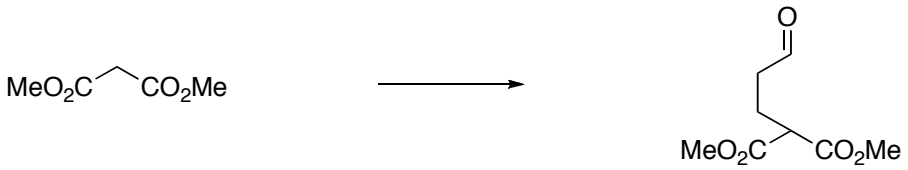
4. Experimental Section

Unless specified, reactions were carried out under a slight static pressure of Ar or N_2 that had been purified by passage through a column (3.5 × 42 cm) of R-311 catalyst and then through a similar column of Drierite. Solvents for reactions were dried as described below. Glassware was dried in an oven (140 °C) overnight before use and either cooled in a desiccator over Drierite, or assembled quickly, sealed with rubber septa, and allowed to cool under a light static pressure of Ar or N_2.

Solvents used for chromatography were distilled before use. Commercial thin layer chromatography plates (silica gel, Merck 60F-254 was used. Silica gel for flash chromatography was Merck type 60 (230-400 mesh). Dry solvents were prepared under an inert atmosphere and transferred by syringe or cannula. Dry THF and Et_2O were distilled from sodium and benzophenone ketyl. Dry MeCN, Et_3N and pyridine were distilled from CaH_2.

The symbols s, d, t and q used for ^{13}C NMR spectra indicate zero, one, two, or three attached hydrogens, respectively, the assignments being made by from APT and HSQC spectra.

2-(3-Oxopropyl)malonic Acid Dimethyl Ester (40.1a).[†54]

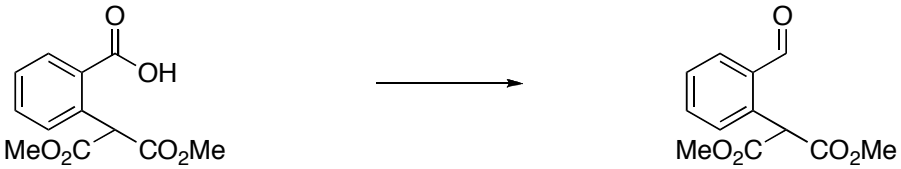


- **40.1a**

Acrolein (3.9 mL, 59 mmol) was added dropwise over 30 min to a stirred and cooled (0 °C) solution of dimethyl malonate (6.0 g, 45 mmol) and sodium (10 mg, 0.45 mmol) in anhydrous MeOH (60 mL). The ice bath was left in place but not recharged and stirring was continued for 16 h. The solvent was evaporated and the residue was dissolved in Et_2O (150 mL). The solution was washed with

water (25 mL) and brine (25 mL), dried (Na_2SO_4) and evaporated. Distillation of the residue under reduced pressure (100 °C, 0.5 mm Hg) gave **40.1a** as a colorless viscous liquid (4.6 g, 54%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.22 (q, *J* = 7.5 Hz, 2 H), 2.57 (td, *J* = 7.5, 1.0 Hz, 2 H), 3.45 (t, *J* = 7.5 Hz, 1 H), 3.74 (s, 6 H), 9.75 (t, *J* = 1.0 Hz, 1 H).

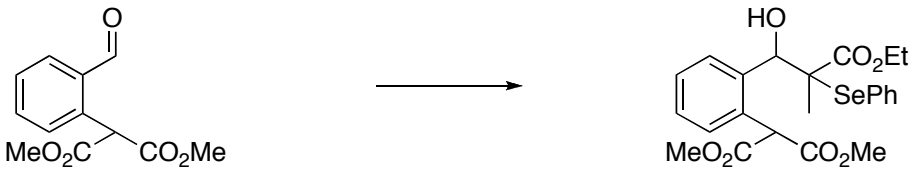
2-(2-Formylphenyl)malonic Acid Dimethyl Ester (40.2a).



41.1 **40.2a**

$BH_3{\cdot}SMe_2$ (10.1 M, 0.22 mL, 2.2 mmol) was added dropwise to a stirred and cooled (0 °C) solution of 2-(2-carboxyphenyl)malonic acid dimethyl ester[55] (500 mg, 1.98 mmol) in THF (10 mL). Stirring was continued at 0 °C for 20 min and then at 50 °C for 3.5 h. The solvent was evaporated and the residue was dissolved in CH_2Cl_2 (5.0 mL). The resulting solution was added to a stirred mixture of PCC (855 mg, 3.97 mmol) and 4 Å molecular sieves (855 mg) in CH_2Cl_2 (30 mL), and stirring was continued for 40 min. The solvent was evaporated, and the residue was filtered through a pad of Celite, using Et_2O as a rinse. Evaporation of the solvent and flash chromatography of the residue over silica gel (2.5 x 15 cm), using 1:2 EtOAc-hexane, gave **40.2a** (374 mg, 80%) as an oil: FTIR ($CDCl_3$, cast) 3003, 2955, 2924, 2851, 2753, 1734, 1695, 1600, 1578, 1491, 1451, 1435 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.77 (s, 6 H), 5.90 (s, 1 H), 7.47 (dd, *J* = 7.7, 0.4 Hz, 1 H), 7.56 (td, *J* = 7.5, 1.3 Hz, 1 H), 7.61 (td, *J* = 7.6, 1.6 Hz, 1 H), 7.82 (dd, *J* = 7.5, 1.6 Hz, 1 H), 10.05 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 52.8 (q), 53. 4 (d), 128.7 (d), 130.4 (d), 133.5 (s), 133.7 (s), 133.9 (d), 135.3 (d), 168.5 (s), 193.2 (d); exact mass (electrospray) *m*/*z* calcd for $C_{12}H_{12}NaO_5$ 259.0577, found 259.0575.

2-[2-[2-Ethoxycarbonyl-1-hydroxy-2-(phenylseleno)propyl]phenyl]-malonic Acid Dimethyl Ester (40.2b,b').



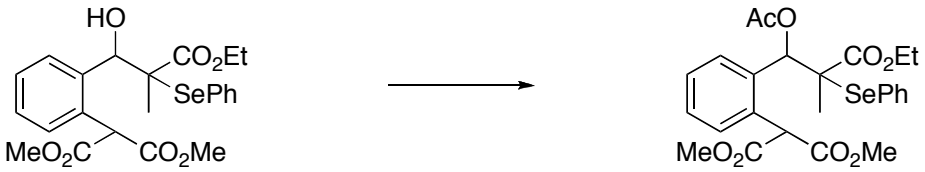
40.2a **40.2b,b'**

n-BuLi (1.60 M in hexane, 1.47 mL, 2.34 mmol) was added dropwise to a stirred and cooled (0 °C) solution of *i*-Pr_2NH (237 mg, 2.34 mmol) in THF (25.0 mL). Stirring at 0 °C was continued for 25 min. The mixture was then cooled to -78 °C and a solution of **38.1** (599.0 mg, 2.34 mmol) in THF (5 mL) was added dropwise. Stirring at -78 °C was continued for 70 min, and a solution of **40.2a** (220.0 mg, 0.94 mmol) in THF (6 mL) was added dropwise. Stirring at -78 °C was continued for 40 min, and the mixture was quenched with saturated aqueous NH_4Cl (10 mL). The cold bath was removed, stirring was continued for 15 min and the mixture was diluted with water (80 mL. The aqueous phase was extracted with EtOAc (3 x 40 mL) and the combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2.5 x 15 cm), using 9:20 EtOAc-hexane, gave **40.2b** (less polar isomer, 135 mg, 40%) as a viscous oil containing an impurity which could not be removed, and pure **40.2b'** (more polar isomer, 135 mg, 40%) as a viscous oil.

Compound **40.2b'** had: FTIR ($CDCl_3$ cast) 3486, 2985, 2954, 1735, 1579, 1476, 1437 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.20 (dd, *J* = 7.2, 7.1, 3 H), 1.37 (s, 3 H), 3.73 (s, 3 H), 3.75 (s, 3 H), 3.84 (d, *J* = 7.0 Hz, 1 H), 4.09 (dq, *J* = 10.8, 7.2 Hz, 1 H), 4.17 (dq, *J* = 10.8, 7.1 Hz, 1 H), 5.39 (s, 1 H), 5.45 (d, *J* = 6.9 Hz, 1 H), 7.26-7.32 (m, 3 H), 7.34-7.40 (m, 3 H), 7.48-7.50 (m, 2 H), 7.53-7.55 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.8 (q), 19.9 (q), 52.8 (q), 52.9 (q), 53.4 (d), 54.8 (s), 61.7 (t), 74.9 (d), 126.5 (s), 127.8 (d), 127.9 (d), 128.3 (d), 128.8 (d), 129.5 (d), 130.1 (d), 132.0 (s), 137.6 (s), 138.2 (d), 168.88 (s), 168.91 (s), 173.9

(s); exact mass (electrospray) *m/z* calcd for $C_{23}H_{26}NaO_7{}^{80}Se$ 517.0736, found 517.0740.

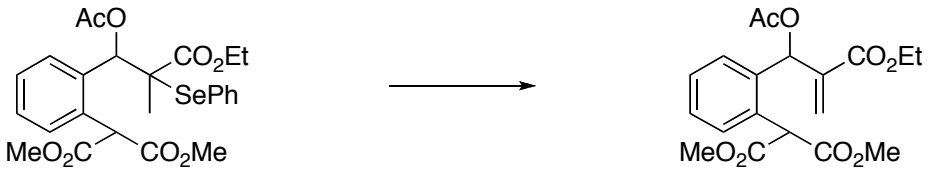
2-[2-[1-Acetoxy-2-ethoxycarbonyl-2-(phenylseleno)propyl)]phenyl]-malonic Acid Dimethyl Ester (40.2c).



40.2b' **40.2c**

Pyridine (99.2 mg, 1.25 mmol) and AcCl (49.2 mg, 0.63 mmol) were added sequentially to a stirred and cooled (-10 °C, ice-acetone bath) solution of **40.2b'** (103 mg, 0.21 mmol) and DMAP (2.6 mg, 0.021 mmol) in CH_2Cl_2 (1 mL). The cold bath was left in place but not recharged and stirring was continued for 16 h, by which time the temperature had risen to room temperature. The mixture was diluted with water (5 mL), acidified with hydrochloric acid (1 M, 2 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 15 cm), using 1:2 EtOAc-hexane, gave the product (89.4 mg, 80%) as an oil: FTIR ($CDCl_3$ cast) 2985, 2954, 1738, 1477, 1437 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.23 (dd, *J* = 7.1, 7.1 Hz, 3 H), 1.46 (s, 3 H), 1.96 (s, 3 H), 3.74 (s, 3 H), 3.80 (s, 3 H), 4.04 (dq, *J* = 10.7, 7.1 Hz, 1 H), 4.14 (dq, *J* = 10.8, 7.1 Hz, 1 H), 5.74 (s, 1 H), 6.73 (s, 1 H), 7.14-7.19 (m, 4 H), 7.28-7.32 (m, 2 H), 7.37 (dd, *J* = 8.0, 1.2 Hz, 1 H), 7.40-7.43 (m, 1 H), 7.57 (dd, *J* = 7.9, 1.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.9 (q), 18.6 (q), 20.6 (q), 52.7 and 52.9 (these two signals incorporate two q and one d), 53.0 (s), 54.1 (d), 61.5 (t), 125.8 (s), 127.6 (d), 128.6 (d), 128.7 (d), 129.4 (d), 130.4 (d), 132.7 (s), 134.7 (s), 138.1 (d), 168.56 (s), 168.57 (s), 167.0 (s), 171.7 (s); exact mass (electrospray) *m/z* calcd for $C_{25}H_{28}NaO_8{}^{80}Se$ 559.0842, found 559.0845.

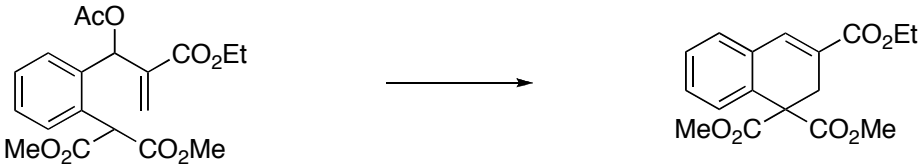
2-[2-(1-Acetoxy-2-ethoxycarbonylallyl)phenyl]malonic Acid Dimethyl Ester (40.2d).



40.2c **40.2d**

H_2O_2 (30%, 0.18 mL, 1.8 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **40.2c** (79 mg, 0.15 mmol) in CH_2Cl_2 (2 mL). Stirring was continued at 0 °C for 90 min and the mixture was quenched with saturated aqueous $Na_2S_2O_3$ (1.0 mL). The mixture was stirred at 0 °C for 5 min, the ice bath was removed, stirring was continued for 30 min and the mixture was diluted with water (5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (0.7 x 15 cm), using 1:2 EtOAc-hexane, gave **40.2d** (45 mg, 80%) as a viscous oil: FTIR ($CDCl_3$ cast) 2956, 1741, 1636, 1436 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.21 (t, *J* = 7.1 Hz, 3 H), 2.07 (s, 3 H), 3.73 (s, 3 H), 3.74 (s, 3 H), 4.16 (q, *J* = 7.1 Hz, 2 H), 5.24 (s, 1 H), 5.69 (d, *J* = 1.3 Hz, 1 H), 6.41 (s, 1 H), 6.86 (s, 1 H), 7.30-7.38 (m, 3 H), 7.47-7.49 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.0 (q), 20.8 (q), 52.7 (q), 52.9 (d), 53.0 (q), 61.0 (t), 70.6 (d), 126.8 (s), 128.3 (d), 128.8 (d), 128.9 (d), 130.0 (d), 131.6 (s), 135.8 (s), 139.2 (t), 164.8 (s), 168.60 (s), 168.63 (s), 169.1 (s); exact mass (electrospray) *m/z* calcd for $C_{19}H_{22}NaO_8$ 401.1207, found 401.1207.

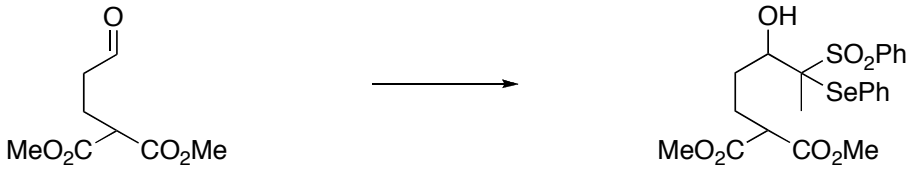
2*H*-Naphthalene-1,1,3-tricarboxylic Acid 3-Ethyl Ester 1,1-Dimethyl Ester (51.2).



40.2d **51.2**

Cs_2CO_3 (45.3 mg, 0.139 mmol) was added to a stirred solution of **40.2d** (26.3 mg, 0.0695 mmol) in THF (1.0 mL), and stirring at room temperature was continued for 40 min. Filtration of the mixture through a pad (ca 5 cm) of silica gel in a Pasteur pipette, using 1:1 EtOAc-hexane, gave **51.2** (20.5 mg, 92.8%) as a colorless, viscous oil: FTIR ($CDCl_3$ cast) 3000, 2955, 1735, 1707, 1636, 1570, 1435 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.35 (t, *J* = 7.1 Hz, 3 H), 3.35 (d, *J* = 1.5 Hz, 2 H), 3.77 (s, 6 H), 4.29 (q, *J* = 7.1 Hz, 2 H), 7.25-7.29 (m, 2 H), 7.33-7.38 (m, 2 H), 7.50 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.3 (q), 30.0 (t), 53.1 (q), 59.2 (s), 60.9 (t), 127.0 (s), 127.9 (d), 128.7 (d), 128.88 (d), 129.89 (d), 131.9 (s), 132.6 (s), 135.5 (d), 166.2 (s), 170.8 (s); exact mass *m/z* calcd for $C_{17}H_{18}O_6$ 318.1104, found 318.1104.

2-[4-Benzenesulfonyl-3-hydroxy-4-(phenylseleno)pentyl]malonic Acid Dimethyl Ester (40.1e,e').



40.1a **40.1e,e'**

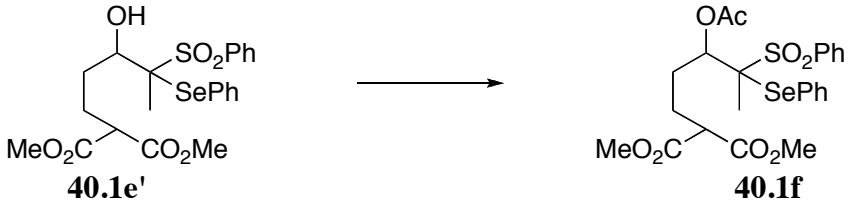
n-BuLi (1.6 M in hexane, 0.33 mL, 0.53 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of **39.5**[50] (182.0 mg, 0.53 mmol) in THF (2 mL). Stirring at -78 °C was continued for 50 min. A solution of **40.1a** (70 mg,

0.37 mmol) in THF (1 mL) was added dropwise, and stirring at -78 °C was continued for 1 h. The mixture was quenched with saturated aqueous NH_4Cl (3 mL), the cold bath was removed, stirring was continued for 15 min and water (5 mL) was added. The aqueous phase was extracted with EtOAc (3 x 10 mL) and the combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2.5 x 15 cm), using 2:5 EtOAc-hexane, gave **40.1e** (less polar isomer, 40 mg, 21%) as a viscous oil and **40.1e'** (more polar isomer, 50 mg, 26%) as a viscous oil.

Compound **40.1e** had: FTIR ($CDCl_3$ cast) 3498, 3061, 2953, 2866, 1750, 1734, 1583, 1477, 1438 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.08 (s, 3 H), 1.58 (ddd, *J* = 10.0, 10.0, 2.4 Hz, 1 H), 1.94-2.05 (m, 2 H), 2.22-2.31 (m, 1 H), 3.46 (dd, *J* = 7.2 Hz, 1 H), 3.72 (s, 3 H), 3.75 (s, 3 H), 4.04 (d, *J* = 7.2 Hz, 1 H), 4.20 (s, 1 H), 7.25 (t, *J* = 8.0 Hz, 2 H), 7.37 (td, *J* = 7.6, 0.8 Hz, 1 H), 7.53 (dd, *J* = 8.0, 1.2 Hz, 2 H), 7.59 (t, *J* = 7.6 Hz, 2 H), 7.72 (td, *J* = 7.6, 0.8 Hz, 1 H), 7.92 (dd, *J* = 8.0, 1.2 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.2, 25.0, 29.2, 51.1, 52.40, 52.42, 72.6, 77.5, 124.6, 128.64, 128.9, 129.5, 130.8, 134.1, 134.6, 138.9, 169.6, 169.7; exact mass (electrospray) *m/z* calcd for $C_{22}H_{26}NaO_7S^{80}Se$ 537.0457, found 537.0455.

Compound **40.1e'** had: FTIR ($CDCl_3$ cast) 3499, 3061, 2953, 1750, 1734, 1583, 1477, 1446, 1438 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.08 (s, 3 H), 1.61-1.72 (m, 1 H), 1.93-2.03 (m, 1 H), 2.19-2.28 (m, 1 H), 2.32-2.39 (m, 1 H), 3.47 (s, 1 H), 3.48 (dd, *J* = 7.2, 7.2 Hz, 1 H), 3.75 (s, 3 H), 3.77 (s, 3 H), 4.08 (ddd, *J* = 10.4, 5.6, 1.6 Hz, 1 H), 7.21 (tt, *J* = 7.6, 1.6 Hz, 2 H), 7.29 (dt, *J* = 6.8, 1.2 Hz, 2 H), 7.35 (tt, *J* = 7.2, 1.2 Hz, 1 H). 7.60 (tt, *J* = 7.6, 2.0 Hz, 2 H), 7.72 (tt, *J* = 7.6, 1.2 Hz, 1 H), 8.04 (dt, *J* = 7.2, 1.2 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.6, 26.2, 31.1, 51.1, 52.5, 74.6, 75.8, 125.1, 128.6, 128.9, 129.8, 131.5, 134.1, 136.0, 138.1, 169.7, 169.8; exact mass (electrospray) *m/z* calcd for $C_{22}H_{26}NaO_7S^{80}Se$ 537.0457, found 537.0452.

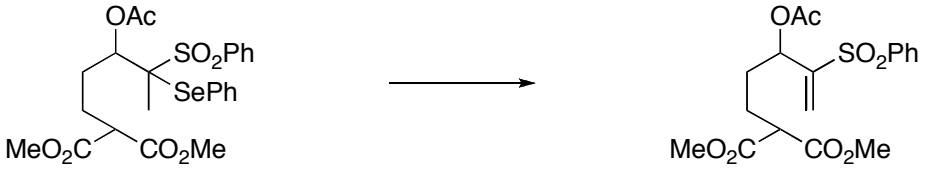
2-[3-Acetoxy-4-benzenesulfonyl-4-(phenylseleno)pentyl]malonic Acid Dimethyl Ester (40.1f).



40.1e' **40.1f**

Pyridine (166.3 mg, 2.12 mmol) and AcCl (110 mg, 1.41 mmol) were added sequentially to a stirred and cooled (-10 °C, ice-acetone bath) solution of **40.1e'** (181.2 mg, 0.353 mmol) and DMAP (6.1 mg, 0.05 mmol) in CH_2Cl_2 (2 mL). The cold bath was left in place but not recharged and stirring was continued for 12 h, by which time the temperature had risen to room temperature. The mixture was diluted with water (10 mL), acidified with hydrochloric acid (1 M, 5 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2.5 x 15 cm), using 2:5 EtOAc-hexane, gave **40.1f** (130 mg, 67%) as an oil: FTIR ($CDCl_3$ cast) 3062, 2954, 1738, 1583, 1477, 1446, 1438 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.14 (s, 3 H), 1.73-1.83 (m, 1 H), 1.84-1.97 (m, 2 H), 1.99 (s, 3 H), 2.01-2.11 (m, 1 H), 3.42 (dd, *J* = 7.2, 7.2 Hz, 1 H), 3.69 (s, 3 H), 3.72 (s, 3 H), 5.42 (dd, *J* = 10.0, 2.8 Hz, 1 H), 7.31 (tt, *J* = 7.6, 1.2 Hz, 2 H), 7.41 (tt, *J* = 7.6, 1.2 Hz, 1 H), 7.55 (tt, *J* = 8.0, 1.6 Hz, 2 H), 7.66 (tt, *J* = 7.2, 1.2 Hz, 1 H), 7.74 (dt, *J* = 8.0, 1.2 Hz, 2 H), 7.96 (dt, *J* = 8.0, 1.6 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.65, 20.67, 24.6, 29.2, 50.7, 52.4, 52.5, 73.2, 74.4, 124.9, 128.7, 128.8, 129.8, 131.1, 133.7, 135.8, 139.1, 169.2, 169.3, 170.2; exact mass (electrospray) *m/z* calcd for $C_{24}H_{28}NaO_8S^{80}Se$ 579.0562, found 579.0561.

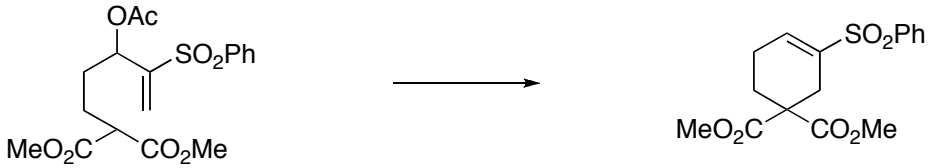
2-[3-Acetoxy-4-(benzenesulfonyl)pent-4-enyl]malonic Acid Dimethyl Ester (40.1g).



40.1f **40.1g**

H_2O_2 (30%, 0.24 mL, 2.4 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **40.1f** (110 mg, 0.20 mmol) in CH_2Cl_2 (2 mL). Stirring was continued at 0 °C for 1 h and the mixture was quenched with saturated aqueous $Na_2S_2O_3$ (0.5 mL). The mixture was stirred at 0 °C for 5 min, the ice bath was removed, stirring was continued for 35 min and the mixture was diluted with water (5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ (3 mL), dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 x 11 cm), using 1:3 EtOAc-hexane, gave **40.1g** (63 mg, 80%) as a viscous oil: FTIR ($CDCl_3$ cast) 2956, 1746, 1584, 1447, 1437 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.80 (s, 3 H), 1.79-1.97 (m, 4 H), 3.33 (dd, *J* = 7.2, 7.2 Hz, 1 H), 3.72 (s, 3 H), 3.73 (s, 3 H), 5.35-5.38 (m, 1 H), 6.07 (dd, *J* = 1.2, 0.8 Hz, 1 H), 6.54 (d, *J* = 0.8 Hz, 1 H), 7.54 (tt, *J* = 7.2, 1.2 Hz, 2 H), 7.64 (tt, *J* = 7.6, 1.2 Hz, 1 H), 7.87 (dt, *J* = 7.2, 1.2 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.5, 24.4, 31.7, 50.9, 52.6, 69.7, 126.5, 128.3, 129.2, 133.7, 139.1, 149.3, 169.2, 169.27, 169.30; exact mass (electrospray) *m/z* calcd for $C_{18}H_{22}NaO_8S$ 421.0928, found 421.0932.

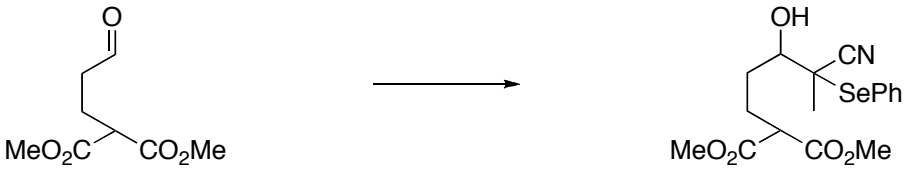
3-(Benzenesulfonyl)cyclohex-3-ene-1,1-dicarboxylic Acid Dimethyl Ester (51.3).



40.1g **51.3**

Cs_2CO_3 (13.4 mg, 0.041 mmol) was added to a stirred solution of **40.1g** (8.2 mg, 0.021 mmol) in THF (0.5 mL), and stirring at room temperature was continued for 4.5 h. Evaporation of the solvent and filtration of the residue through a pad (ca 5 cm) of silica gel in a Pasteur pipette, using 7:10 EtOAc-hexane, gave **51.3** (7.0 mg, 91%) as a colorless viscous oil: FTIR ($CDCl_3$ cast) 2955, 2924, 2852, 1735, 1651, 1447, 1435 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.11 (t, *J* = 6.4 Hz, 2 H), 2.39-2.44 (m, 2 H), 2.74 (d, *J* = 1.6 Hz, 2 H), 3.56 (s, 6 H), 7.05-7.06 (m, 1 H), 7.55 (t, *J* = 7.6 Hz, 2 H), 7.62-7.65 (m, 1 H), 7.87 (d, *J* = 7.6 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.2 (t), 26.3 (t), 28.3 (t), 52.71 (s), 52.72 (q), 152.7 (s), 128.1 (d), 129.0 (d), 133.2 (d), 137.2 (s), 137.3 (d), 138.7 (s), 170.3 (s); exact mass (electrospray) *m/z* calcd for $C_{16}H_{18}NaO_6S$ 361.0716, found 361.0713.

2-[4-Cyano-3-hydroxy-4-(phenylseleno)pentyl]malonic Acid Dimethyl Ester (40.1h).

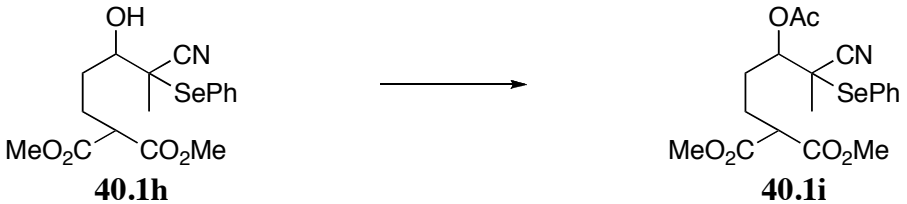


40.1a **40.1h**

n-BuLi (1.6 M in hexane, 2.8 mL, 4.5 mmol) was added dropwise to a stirred and cooled (0 °C) solution of *i*-Pr_2NH (484.7 mg, 4.8 mmol) in THF (10

mL). Stirring at 0 °C was continued for 20 min, the mixture was cooled to -78 °C and a solution of **39.6**[51] (1.0 g, 4.8 mmol) in THF (8 mL) was added dropwise. Stirring at -78 °C was continued for 40 min, and a solution of **40.1a** (600 mg, 3.2 mmol) in THF (8 mL) was added dropwise. Stirring at -78 °C was continued for 80 min, and the mixture was quenched with saturated aqueous NH_4Cl (10 mL). The cold bath was removed, stirring was continued for 15 min and the mixture was diluted with water (50 mL). The aqueous phase was extracted with Et_2O (3 x 30 mL) and the combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 15 cm), using 7:20 EtOAc-hexane, gave **40.1h** (0.9 g, 71%) as a 1:1 mixture of diastereomers: FTIR (CH_2Cl_2 cast) 3474, 3056, 2954, 2226, 1736, 1578, 1477, 1438 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.56 (s, 1.5 H), 1.59 (s, 1.5 H), 1.53-1.68 (m, 1 H), 1.74-1.83 (m, 0.5 H), 1.93-2.05 (m, 1.5 H), 2.15-2.25 (m, 1 H), 2.59 (d, *J* = 6.0 Hz, 0.5 H), 2.70 (dd, *J* = 4.0, 1.6 Hz, 0.5 H), 3.42 (dd, *J* = 7.6, 7.6 Hz, 0.5 H), 3.45 (dd, *J* = 7.6, 7.6 Hz, 0.5 H), 3.55 (ddd, *J* = 10.4, 4.0, 2.0 Hz, 0.5 H), 3.62 (ddd, *J* = 10.4, 6.0, 2.0 Hz, 0.5 H), 3.72 (s, 1.5 H), 3.73 (s, 1.5 H), 3.75 (s, 1.5 H), 3.76 (s, 1.5 H), 7.38-7.43 (m, 2 H), 7.45-7.51 (m, 1 H), 7.74-7.77 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.4 (q), 21.6 (q), 25.5 (q), 25.7 (t), 29.3 (t), 29.4 (t), 43.0 (s), 43.3 (s), 50.93 (d), 50.95 (d), 52.51 (q), 52.54 (q), 52.6 (q), 72.7 (d), 74.8 (d), 120.7 (s), 121.1 (s), 124.8 (s), 125.0 (s), 129.4 (d), 129.5 (d), 130.2 (d), 130.4 (d), 137.65 (d), 137.70 (d), 137.9 (d), 169.45 (s), 169.49 (s), 169.54 (s); exact mass (electrospray) *m/z* calcd for $C_{17}H_{21}NNaO_5{}^{80}Se$ 422.0477, found 422.0476.

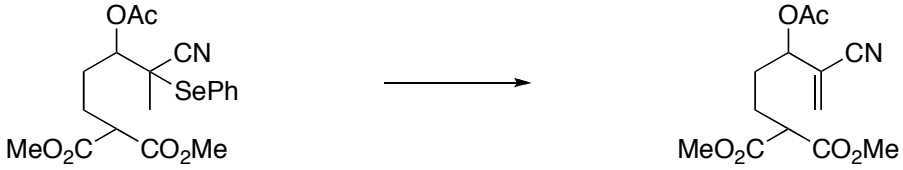
2-[3-Acetoxy-4-cyano-4-(phenylseleno)pentyl]malonic Acid Dimethyl Ester (40.1i).



40.1h **40.1i**

Pyridine (596.0 mg, 7.54 mmol) and AcCl (295.9 mg, 3.77 mmol) were added sequentially to a stirred and cooled (-10 °C, ice-acetone bath) solution of **40.1h** (500.0 mg, 1.26 mmol) and DMAP (17.0 mg, 0.14 mmol) in CH_2Cl_2 (12 mL). The cold bath was left in place but not recharged and stirring was continued for 9 h, by which time the temperature had risen to room temperature. The mixture was diluted with water (10 mL), acidified with hydrochloric acid (1 M, 8 mL) and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2.5 x 15 cm), using 2:5 EtOAc-hexane, gave **40.1i** (497 mg, 90%) as an oil which was a 1:1 mixture of diastereomers: FTIR (CH_2Cl_2 cast) 2955, 2228, 1750, 1438 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.56 (s, 1.5 H), 1.58 (s, 1.5 H), 1.73-2.08 (m, 4 H), 2.127 (s, 1.5 H), 2.131 (s, 1.5 H), 3.41 (dd, *J* = 7.2, 7.2 Hz, 1 H), 3.74 (s, 1.5 H), 3.75 (s, 1.5 H), 3.755 (s, 1.5 H), 3.756 (s, 1.5 H), 5.11 (dd, *J* = 10.0, 2.0 Hz, 0.5 H), 5.16 (dd, *J* = 10.0, 2.0 Hz, 0.5 H), 7.41 (td, *J* = 8.0, 1.6 Hz, 2 H), 7.46-7.50 (m, 1 H), 7.77 (*J* = 8.1, 1.2 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.55 (q), 20.57 (q), 22.2 (q), 22.3 (q), 24.88 (t), 24.92 (t), 28.0 (t), 29.2 (t), 39.6 (s), 50.65 (d), 50.71 (d), 52.5 (q), 52.56 (q), 52.57 (q), 74.1 (d), 74.3 (d), 120.0 (s), 120.3 (s), 124.9 (s), 125.1 (s), 129.37 (d), 129.44 (d), 130.3 (d), 130.4 (d), 137.8 (d), 138.1 (d), 169.1 (s), 169.16 (s), 169.17 (s), 169.9 (s), 170.0 (s); exact mass (electrospray) *m/z* calcd for $C_{19}H_{23}NNaO_6{}^{80}Se$ 464.0583, found 464.0583.

2-(3-Acetoxy-4-cyanopent-4-enyl)malonic Acid Dimethyl Ester (40.1j).

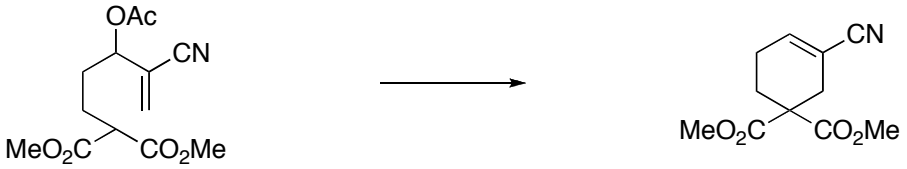


40.1i **40.1j**

H_2O_2 (30%, 0.83 mL, 8.2 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **40.1i** (300 mg, 0.68 mmol) in CH_2Cl_2 (4 mL). Stirring

was continued at 0 °C for 1 h and the mixture was quenched with saturated aqueous $Na_2S_2O_3$ (1.0 mL). The mixture was stirred at 0 °C for 5 min, the ice bath was removed, stirring was continued for 5 min and the mixture was diluted with water (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ (3 mL), dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 13 cm), using 1:2 EtOAc-hexane, gave **40.1j** (180 mg, 94%) as a viscous oil: FTIR (neat) 3117, 3004, 2957, 2849, 2228, 1744, 1626, 1437 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.74-2.01 (m, 4 H), 2.11 (s, 3 H), 3.39 (dd, *J* = 7.2,7.2 Hz, 1 H), 3.75 (s, 6 H), 5.28 (dd, *J* = 6.4, 6.4 Hz, 1 H), 6.01 (d, *J* = 0.8 Hz, 1 H), 6.06 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.8 (q), 24.1 (t), 30.4 (t), 50.9 (d), 52.7 (q), 72.4 (d), 115.9 (s), 122.2 (s), 133.1 (t), 169.1 (s), 169.12 (s), 169.7 (s); exact mass (electrospray) *m/z* calcd for $C_{13}H_{17}NNaO_6$ 306.0948, found 306.0946.

3-Cyanocyclohex-3-ene-1,1-dicarboxylic Acid Dimethyl Ester (51.4).

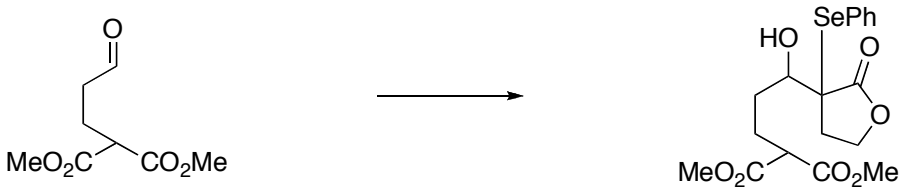


40.1j **51.4**

Cs_2CO_3 (43.3 mg, 0.13 mmol) was added to a stirred solution of **40.1j** (18.8 mg, 0.066 mmol) in THF (2.5 mL), and stirring at room temperature was continued for 12 h. Evaporation of the solvent and filtration of the residue through a pad (ca 5 cm) of silica gel in a Pasteur pipette, using 7:10 EtOAc-hexane, gave **51.4** (11.0 mg, 74%) as a colorless viscous oil: FTIR ($CDCl_3$ cast) 2957, 2845, 2219, 1737, 1642, 1452, 1435 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.15 (t, *J* = 6.4 Hz, 2 H), 2.31 (tdt, *J* = 6.4, 4.4, 2.4 Hz, 2 H), 2.78 (td, *J* = 2.4, 2.0 Hz, 2 H), 3.76 (s, 6 H), 6.59 (tt, *J* = 4.4, 2.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100

MHz) δ 23.3 (t), 26.0 (t), 31.2 (t), 52.1 (s), 53.0 (q), 109.9 (s), 118.4 (s), 143.6 (d), 170.3 (s); exact mass *m/z* calcd for $C_{11}H_{13}NO_4$ 223.0845, found 223.0846.

2-[3-Hydroxy-3-[2-oxo-3-(phenylseleno)tetrahydrofuran-3-yl]propyl]-malonic Acid Dimethyl Ester (40.1k).

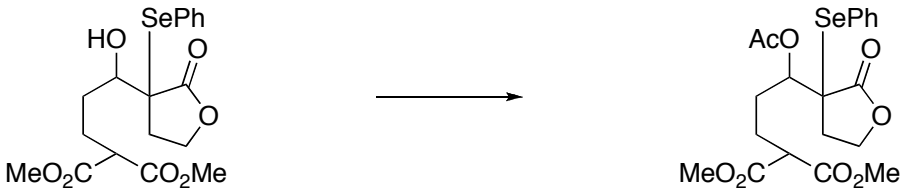


40.1a **40.1k**

n-BuLi (1.6 M in hexane, 1.5 mL, 2.37 mmol) was added dropwise to a stirred and cooled (-10 °C, ice-acetone bath) solution of *i*-Pr_2NH (240 mg, 2.37 mmol) in THF (10 mL). Stirring at -10 °C was continued for 30 min, the mixture was cooled to -78 °C and a solution of **39.7**[52] (572.0 mg, 2.37 mmol) in THF (10 mL) was then added dropwise. Stirring at -78 °C was continued for 1 h, and a solution of **40.1a** (297.0 mg, 1.58 mmol) in THF (4 mL) was added dropwise. Stirring at -78 °C was continued for 1 h, and the mixture was quenched with saturated aqueous NH_4Cl (3 mL). The cold bath was removed, stirring was continued for 15 min and the mixture was diluted with water (100 mL). The aqueous phase was extracted with EtOAc (3 x 30 mL) and the combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (3 x 15 cm), using 1:1 EtOAc-hexane, gave **40.1k** (601 mg, 86%) as an oil which was an inseparable 1:1 mixture of diastereomers: FTIR ($CHCl_3$ cast) 3502, 2954, 1750, 1576, 1477, 1438 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.32-1.40 (m, 0.5 H), 1.41-1.49 (m, 0.5 H), 1.82 (dddd, *J* = 13.6, 9.8, 9.8, 5.2 Hz, 0.5 H), 1.94-2.06 (m, 1.5 H), 2.11 (ddd, *J* = 14.3, 6.4, 0.8 Hz, 0.5 H), 2.16-2.32 (m, 2 H), 2.42 (ddd, *J* = 14.2, 10.5, 9.1 Hz, 0.5 H), 2.75 (ddd, *J* = 13.8, 10.8, 9.2 Hz, 0.5 H), 3.46 (dd, *J* = 7.5, 7.5 Hz, 0.5 H), 3.47 (dd, *J* = 7.2, 7.2 Hz, 0.5 H), 3.59 (dd, *J* = 1.9, 1.9 Hz, 0.5 H), 3.73 (s, 1.5 H),

3.74 (s, 1.5 H), 3.77 (s, 1.5 H), 3.78 (s, 1.5 H), 3.85 (ddd, *J* = 10.9, 4.6, 1.5 Hz, 0.5 H), 4.01 (ddd, *J* = 10.5, 9.0, 6.4 Hz, 0.5 H), 4.22 (ddd, *J* = 9.0, 9.0, 1.0 Hz, 0.5 H), 4.26-4.35 (m, 1 H), 7.31-7.38 (m, 2 H), 7.41-7.46 (m, 1 H), 7.62-7.65 (m, 1 H), 7.68-7.71 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.4 (t), 25.8 (t), 28.4 (t), 28.8 (t), 29.6 (t), 31.8 (t), 51.5 (d), 52.43 (q), 52.5 (s), 54.6 (s), 65.5 (t), 65.6 (t), 71.1 (d), 73.2 (d), 124.3 (s), 124.9 (s), 129.2 (d), 130.01 (d), 130.04 (d), 137.9 (d), 138.2 (d), 169.57 (s), 169.58 (s), 169.64 (s), 176.1 (s), 176.7 (s); exact mass (electrospray) *m/z* calcd for $C_{18}H_{22}NaO_7{}^{80}Se$ 453.0423, found 453.0422.

2-[3-Acetoxy-3-[2-oxo-3-(phenylseleno)tetrahydrofuran-3-yl]propyl]-malonic Acid Dimethyl Ester (40.1l).

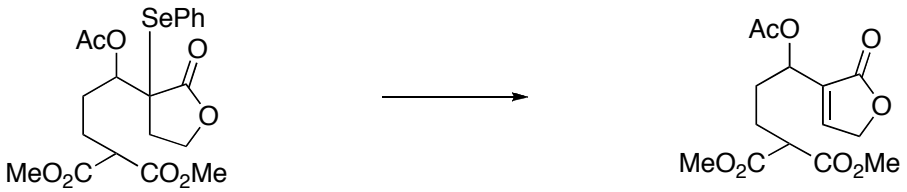


40.1k **40.1l**

Pyridine (221.0 mg, 2.80 mmol) and AcCl (109.8 mg, 1.40 mmol) were added sequentially to a stirred and cooled (-10 °C, ice-acetone bath) solution of **40.1k** (200.0 mg, 0.47 mmol) and DMAP (6.0 mg, 0.05 mmol) in CH_2Cl_2 (5 mL). The cold bath was left in place but not recharged and stirring was continued for 5 h, by which time the temperature had risen to room temperature. The mixture was diluted with water (5 mL), acidified with hydrochloric acid (1 M, 1 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 19:20 EtOAc-hexane, gave **40.1l** (190 mg, 87%) as an oil which was a 1.4:1.6 inseparable mixture of diastereomers: FTIR ($CDCl_3$ cast) 2955, 1752, 1478,1438 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.59-1.70 (m, 1.0 H), 1.79-1.98 (m, 3.5 H), 2.04-2.14 (m, 2.5 H), 2.34-2.42 (m, 0.5 H), 2.53 (ddd, *J* = 14.3, 10.2, 9.0 Hz, 0.6 H), 2.68 (ddd, *J* = 13.8, 10.7, 9.0 Hz, 0.6 H), 3.38

(dd, *J* = 8.5, 6.0, 0.6 H), 3.47 (dd, *J* = 7.4, 7.3 Hz, 0.5 H), 3.69 (s, 1.6 H), 3.71 (s, 1.6 H), 3.76 (s, 1.4 H), 3.77 (s, 1.4 H), 4.23-4.34 (m, 2.2 H), 5.23 (dd, *J* = 10.1, 2.2, 0.5 H), 5.35 (dd, *J* = 9.9, 2.5 Hz, 0.6 H), 7.32- 7.38 (m, 2 H), 7.41-7.46 (m, 1 H), 7.64-7.68 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.7 (q), 20.9 (q), 25.1 (t), 25.2 (t), 28.2 (t), 28.5 (t), 30.8 (t), 31.5 (t), 50.8 (d), 51.0 (d), 51.6 (s), 52.5 (q), 52.6 (q), 65.0 (t), 65.2 (t), 72.3 (d), 72.4 (d), 124.4 (s), 125.4 (s), 129.2 (d), 129.4 (d), 130.1 (d), 130.3 (d), 137.8 (d), 138.1 (d), 169.3 (s), 169.4 (s), 169.5 (s), 170.4 (s), 173.3 (s), 173.9 (s); exact mass *m/z* calcd for $C_{20}H_{24}O_8{}^{80}Se$ 472.0636, found 472.0636.

2-[3-Acetoxy-3-(2-oxo-2,5-dihydrofuran-3-yl)propyl]malonic Acid Dimethyl Ester (40.1m).

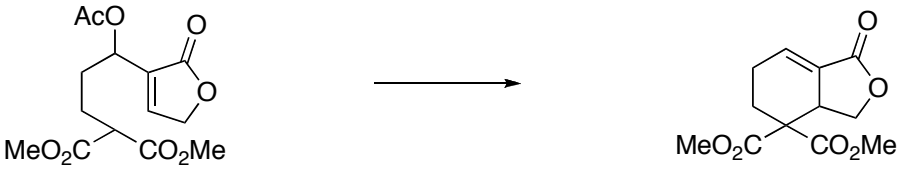


40.1l **40.1m**

H_2O_2 (30%, 0.41 mL, 4.0 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **40.1l** (157 mg, 0.33 mmol) in CH_2Cl_2 (2 mL). Stirring was continued at 0 °C for 1 h and the mixture was quenched with saturated aqueous $Na_2S_2O_3$ (1.0 mL). The mixture was stirred at 0 °C for 5 min, the ice bath was removed, stirring was continued for 10 min and the mixture was diluted with water (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ (3 mL), dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 17:10 EtOAc-hexane, gave **40.1m** (90 mg, 87%) as a viscous oil: FTIR ($CDCl_3$ cast) 2956, 1753, 1438 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.81-1.92 (m, 4 H), 2.08 (s, 3 H), 3.34-3.38 (m, 1 H), 3.70 (s, 6 H), 4.79-4.80 (m, 2 H), 5.56-5.58 (m, 1 H), 7.33 (dd, *J* = 3.1, 1.6 Hz, 1 H); ^{13}C NMR

($CDCl_3$, 100 MHz) δ 20.7 (q), 24.0 (t), 29.7 (t), 50.8 (d), 52.5 (q), 68.1 (d), 70.2 (t), 132.5 (s), 146.9 (d), 169.2 (s), 169.3 (s), 169.7 (s), 171.3 (s); exact mass (electrospray) *m*/*z* calcd for $C_{14}H_{18}NaO_8$ 337.0894, found 337.0895.

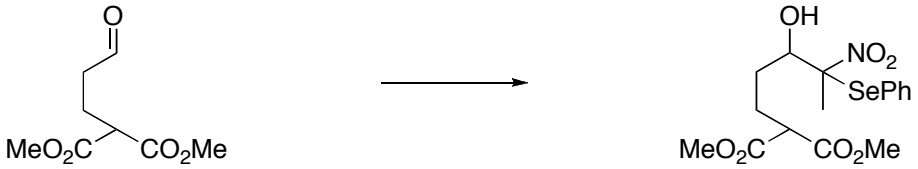
1-Oxo-3,3a,5,6-tetrahydro-1*H*-isobenzofuran-4,4-dicarboxylic Acid Dimethyl Ester (51.5).



40.1m **51.5**

Cs_2CO_3 (29.1 mg, 0.089 mmol) was added to a stirred solution of **40.1m** (14.0 mg, 0.045 mmol) in THF (1 mL), and stirring at room temperature was continued for 3 h. Evaporation of the solvent and filtration of the residue through a pad (ca 5 cm) of silica gel in a Pasteur pipette, using 3:2 EtOAc-hexane, gave **51.5** (11.0 mg, 97%) as a colorless viscous oil: FTIR ($CDCl_3$ cast) 2957, 2923, 1760, 1736, 1687 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.94 (ddd, *J* = 13.9, 10.3, 7.4 Hz, 1 H), 2.41-2.57 (m, 3 H), 3.35-3.41 (m, 1 H), 3.71 (s, 3 H), 3.79 (s, 3 H), 4.59-4.61 (m, 2 H), 6.84 (dd, *J* = 7.0, 3.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 24.1 (t), 28.8 (t), 40.9 (d), 52.7 (q), 53.1 (q), 54.1 (s), 68.9 (t), 126.4 (s), 135.1 (d), 168.4 (s), 169.0 (s), 170.7 (s); exact mass *m*/*z* calcd for $C_{12}H_{14}O_6$ 254.0790, found 254.0784.

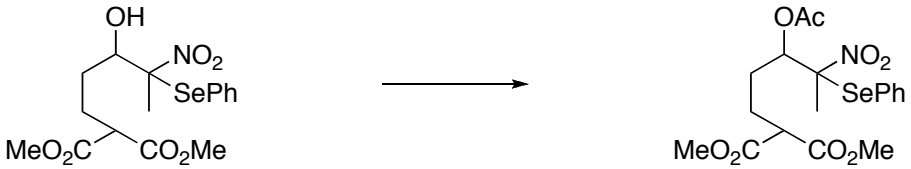
2-[3-Hydroxy-4-nitro-4-(phenylseleno)pentyl]malonic Acid Dimethyl Ester (40.1o).



40.1a **40.1o**

DBU (23 mg, 0.15 mmol) was added to a stirred solution of **39.8**[53] (345 mg, 1.5 mmol) and aldehyde **40.1a** (94 mg, 0.5 mmol) in THF (3 mL). Stirring at room temperature was continued for 110 min. The reaction was quenched with hydrochloric acid (1 M, 3 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 x 1 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 15 cm), using 1:2 EtOAc, gave **40.1o** (124 mg, 59%) as an oil which consisted of two inseparable diastereoisomers contaminated by the starting aldehyde **40.1a**.

2-[3-Acetoxy-4-nitro-4-(phenylseleno)pentyl]malonic Acid Dimethyl Ester (40.1p).

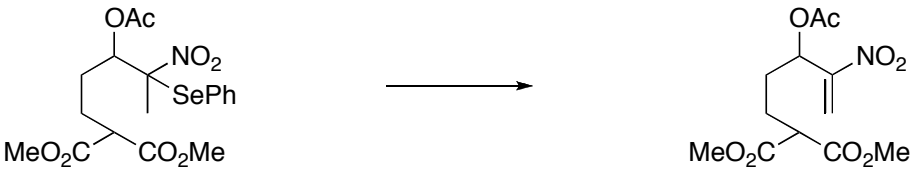


40.1o **40.1p**

Pyridine (147.6 mg, 1.87 mmol) and AcCl (73 mg, 0.93 mmol) were added sequentially to a stirred and cooled (-10 °C, ice-acetone bath) solution of **40.1o** (130 mg, 0.31 mmol) and DMAP (3.7 mg, 0.03 mmol) in CH_2Cl_2 (1 mL). The cold bath was left in place but not recharged and stirring was continued for 6 h, by which time the temperature had risen to room temperature. The mixture was diluted with water (10 mL), acidified with hydrochloric acid (1 M, 3 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 9:20 EtOAc-hexane, gave **40.1p** (67 mg, 47%) as an oil which was an 8:5 mixture of diastereoisomers: FTIR ($CHCl_3$ cast) 2954, 1752, 1545, 1439 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.58-1.69 (m, 1.8 H), 1.77 (s, 2.5 H), 1.78-1.97 (m, 4.6 H), 2.15-2.25 (m, 1 H), 3.39 (dd, *J* = 8.2, 6.5 Hz, 0.23 H), 3.45 (dd, *J* = 7.2, 7.2 Hz, 0.74 H), 3.72 (s, 1.3 H), 3.76 (s, 4.6 H), 5.59

(dd, *J* = 10.2, 1.7 Hz, 0.74 H), 5.64 (dd, *J* = 9.9, 2.2 Hz, 0.23 H), 7.34-7.41 (m, 2 H), 7.44-7.50 (m, 1 H), 7.55-7.58 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.0 (q), 20.5 (q), 20.7 (q), 20.8 (q), 25.1 (t), 25.3 (t), 28.2 (t), 28.9 (t), 50.6 (d), 50.8 (d), 52.55 (q), 52.59 (q), 73.6 (d), 74.0 (d), 92.0 (s), 92.9 (s), 124.8 (s), 125.4 (s), 129.4 (d), 129.6 (d), 130.5 (d), 137.6 (d), 137.7 (d), 169.1 (s), 169.2 (s), 169.3 (s), 169.9 (s); exact mass *m*/*z* calcd for $C_{18}H_{23}NO_8{}^{80}Se$ 461.0589, found 461.0590.

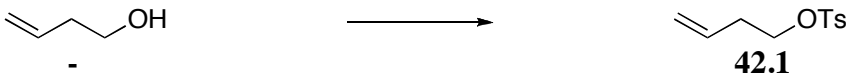
2-(3-Acetoxy-4-nitropent-4-enyl)malonic Acid Dimethyl Ester (20t).



40.1p **40.1q**

H_2O_2 (30%, 0.14 mL, 1.37 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **40.1p** (51 mg, 0.11 mmol) in CH_2Cl_2 (1 mL). Stirring was continued at 0 °C for 1.5 h and the mixture was quenched with saturated aqueous $Na_2S_2O_3$ (1.0 mL). The mixture was stirred at 0 °C for 5 min, the ice bath was removed, stirring was continued for 1 h and the mixture was diluted with water (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (0.7 x 15 cm), using 7:20 EtOAc-hexane, gave **40.1q** (13.7 mg, 41%) as a viscous oil. The material contained minor impurities (^{1}H NMR); the compound is unstable and partial decomposition occurred on chromatography: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.78-2.03 (m, 4 H), 2.11 (s, 3 H), 3.40 (dd, *J* = 7.0, 7.0 Hz, 1 H), 3.74 (s, 6 H), 5.85-5.89 (m, 2 H), 6.62 (d, *J* = 2.4 Hz, 1 H).

Toluene-4-sulfonic Acid But-3-enyl Ester (42.1).[56]



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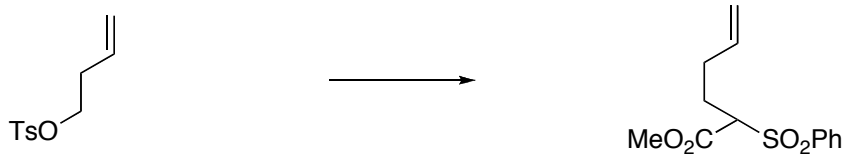
42.1

$TolSO_2Cl$ (2.91 g, 15.3 mmol) and Et_3N (1.54 g, 15.3 mmol) were added sequentially to a stirred solution of 3-buten-1-ol (1.0 g, 14.0 mmol) and DMAP (17.0 mg, 0.14 mmol) in CH_2Cl_2 (50 mL), and the mixture was stirred at room temperature for 24 h and then poured into water (40 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 50 ml) and the combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (4 x 15 cm), using 3:25 EtOAc-hexane, gave **42.1** (2.25 g, 100%) as an oil.

2-(Phenylsulfonyl)hex-5-enoic Acid Methyl Ester (42.3).

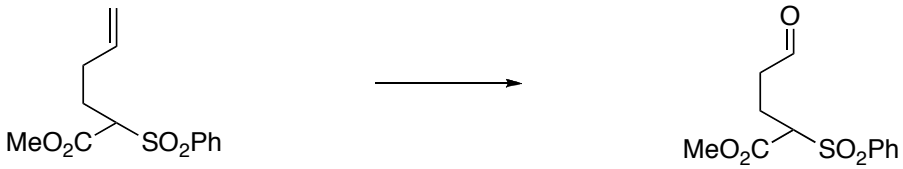


42.1 **42.3**

K_2CO_3 (1.29 g, 9.35 mmol) and Bu_4NHSO_4 (158 mg, 0.47 mmol) were added to a solution of **42.2** (1.0 g, 4.67 mmol) and **42.1** (0.757 g, 4.67 mmol) in DMF (24 mL). The mixture was stirred at 80 °C for 24 h, cooled to room temperature and diluted with water (250 mL). The aqueous phase was extracted with EtOAc (3 x 40 mL) and the combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (3.5 x 15 cm), using 1:2 EtOAc-hexane, gave **42.3** (626 mg, 50%) as an oil: FTIR ($CHCl_3$ cast) 3070, 2954, 1742, 1641, 1448 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.99-2.20 (m, 4 H), 3.66 (s, 3 H), 3.97 (dd, *J* = 10.2, 3.7 Hz, 1 H), 4.98-5.01 (m, 1 H), 5.02-5.03 (m, 1 H), 5.63-5.73 (m, 1 H), 7.55-7.59 (m, 2 H), 7.66-

7.71 (m, 1 H), 7.85-7.88 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.9 (t), 30.8 (t), 52.9 (q), 70.0 (d), 116.8 (t), 129.0 (d), 129.3 (d), 134.3 (d), 135.6 (d), 137.1 (s), 116.3 (s); exact mass *m/z* calcd for $C_9H_{10}O_4S$ (M-C_4H_6) 214.0300, found 214.0305.

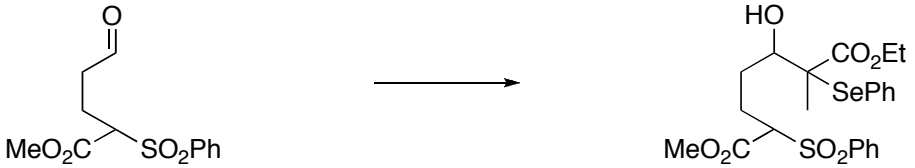
2-(Benzenesulfonyl)-5-oxopentanoic Acid Methyl Ester (40.3a).



42.3 **40.3a**

O_3 was bubbled into a stirred and cooled (-78 °C) solution **42.3** (577.0 mg, 2.15 mmol) in CH_2Cl_2 (50 mL) until the solution became blue and then the excess of O_3 was removed by bubbling oxygen through the mixture. Me_2S (400 mg, 6.26 mmol) was added to the mixture, the cold bath was removed and replaced by a prewarmed water bath at 40 °C. Stirring at 40 °C was continued for 2 h, and then the solvent was evaporated. Flash chromatography of the residue over silica gel (2.5 x 15 cm), using 7:10 EtOAc-hexane, gave **40.3a** (400 mg, 77%) as an colorless oil: FTIR ($CHCl_3$ cast) 3067, 3008, 2955, 1741, 1585, 1479, 1448 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.18-2.31 (m, 1 H), 2.39 (dddd, *J* = 14.3, 7.7, 6.7, 5.0 Hz, 1 H), 2.54-2.74 (m, 2 H), 3.65 (s, 3 H), 4.07 (dd, *J* = 9.7, 5.0 Hz, 1 H), 7.55-7.61 (m, 2 H), 7.67-7.73 (m, 1 H), 7.85-7.91 (m, 2 H), 9.71 (t, *J* = 1.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.5 (t), 40.3 (t), 53.1 (q), 69.2 (d), 129.1 (d), 129.2 (d), 134.4 (d), 137.0 (s), 165.9 (s), 199.5 (d); exact mass (electrospray) *m/z* calcd for $C_{12}H_{14}NaO_5S$ 293.0454, found 293.0455.

6-Benzenesulfonyl-3-hydroxy-2-methyl-2-(phenylseleno)heptanedioic Acid 1-Ethyl Ester 7-Methyl Ester (40.3b).

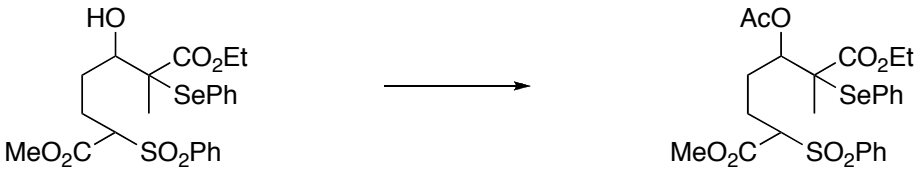


40.3a **40.3b**

n-BuLi (1.6 M in hexane, 0.83 mL, 1.33 mmol) was added dropwise to a stirred and cooled (-10 °C, ice-acetone bath) solution of *i*-Pr_2NH (134.0 mg, 1.33 mmol) in THF (4 mL). Stirring at -10 °C was continued for 25 min, the mixture was cooled to -78 °C and a solution of **38.1** (342.0 mg, 1.33 mmol) in THF (1 mL) was then added dropwise. Stirring at -78 °C was continued for 50 min, and a solution of **40.3a** (240.0 mg, 0.89 mmol) in THF (3 mL) was added dropwise. Stirring at -78 °C was continued for 40 min, and the mixture was quenched with saturated aqueous NH_4Cl (3 mL). The cold bath was removed, stirring was continued for 15 min and the mixture was diluted with water (50 mL). The aqueous phase was extracted with EtOAc (3 x 20 mL) and the combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2.5 x 15 cm), using 4:5 EtOAc-hexane, gave **40.3b** (290 mg, 62%) as an inseparable 10:8:6:5 mixture of four diastereoisomers: FTIR ($CDCl_3$ cast) 3515, 3060, 2954, 2927, 2854, 1740, 1584, 1448 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.11-1.22 (m, 3 H), 1.32-1.58 (m, 4 H), 1.96-2.01 (m, 1.5 H), 2.13-2.37 (m, 1.5 H), 2.82 (t, *J* = 6.8 Hz, 0.6 H), 3.06 (s, 0.2 H), 3.12 (s, 0.2 H), 3.63 (s, 0.6 H), 3.64 (s, 0.6 H), 3.67 (s, 0.8 H), 3.70 (s, 1 H), 3.75-3.86 (m, 1 H), 3.91-4.15 (m, 3 H), 7.27-7.34 (m, 2 H), 7.37-7.44 (m, 1 H), 7.50-7.60 (m, 4 H), 7.66-7.72 (m, 1 H), 7.85-7.90 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.70 (q), 13.72 (q), 13.82 (q), 13.84 (q), 16.99 (q), 17.02 (q), 17.5 (q), 17.8 (q), 24.1 (t), 24.3 (t), 24.5 (t), 24.7 (t), 28.1 (t), 28.56 (t), 28.62 (t), 52.8 (q), 52.85 (q), 52.88 (q), 53.9 (s), 54.1 (s), 56.8 (s), 61.1 (t), 61.2 (t), 61.4 (t), 70.3 (d), 70.38 (d), 70.42 (d), 71.8 (d), 72.8 (d), 74.2 (d), 74.8 (d), 126.00 (s), 126.03

(s), 126.2 (s), 128.80 (d), 128.84 (d), 128.9 (d), 128.95 (d), 128.96 (d), 129.1 (d), 129.2 (d), 129.3 (d), 129.48 (d), 129.53 (d), 134.11 (s), 134.13 (s), 134.14 (s), 134.2 (s), 137.0 (d), 137.1 (d), 137.9 (d), 138.0 (d), 166.17 (s), 166.22 (s), 166.26 (s), 166.34 (s), 172.9 (s), 173.6 (s), 173.8 (s); exact mass (electrospray) *m*/*z* calcd for $C_{23}H_{28}NaO_7S^{80}Se$ 551.0613, found 551.0614.

3-Acetoxy-6-benzenesulfonyl-2-methyl-2-(phenylseleno)heptanedioic Acid 1-Ethyl Ester 7-Methyl Ester (40.3c).

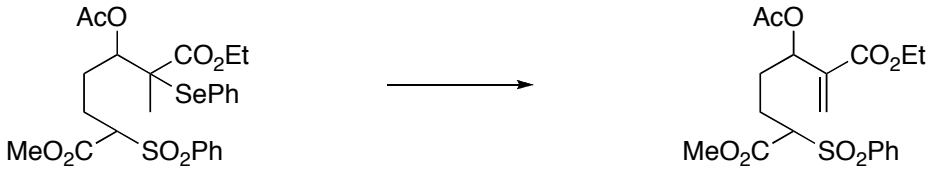


40.3b **40.3c**

Pyridine (86.9 mg, 1.10 mmol) and AcCl (43.1 mg, 0.55 mmol) were added sequentially to a stirred and cooled (-10 °C, ice-acetone bath) solution of **40.3b** (mixture of four diastereoisomers) (96.5 mg, 0.18 mmol) and DMAP (2.2 mg, 0.018 mmol) in CH_2Cl_2 (1 mL). The cold bath was left in place but not recharged and stirring was continued for 5 h, by which time the temperature had risen to room temperature. The mixture was diluted with water (5 mL), acidified with hydrochloric acid (1 M, 1 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 15 cm), using 13:20 EtOAc-hexane, gave **40.3c** (84 mg, 81%) as an oil which was a 29:29:21:21 mixture of diastereomers (^{1}H NMR): FTIR ($CHCl_3$ cast) 3062, 2982, 2954, 1743, 1584, 1477, 1448, 1439 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.98-1.18 (m, 3 H), 1.42-1.79 (m, 4 H), 1.86 (s, 1 H), 1.92 (s, 1 H), 1.95-2.28 (m, 4 H), 3.61 (s, 0.6 H), 3.63 (s, 0.5 H), 3.72 (s, 1.6 H), 3.74-4.05 (m, 2.5 H), 4.11 (dd, *J* = 10.8, 4.4 Hz, 0.3 H), 4.26 (dd, *J* = 10.9, 4.3 Hz, 0.3 H), 5.28-5.45 (m, 1 H), 7.25-7.31 (m, 2 H), 7.36-7.41 (m, 1 H), 7.52-7.60 (m, 4 H), 7.66-7.72 (m, 1 H), 7.82-7.91 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.66 (q), 13.70 (q), 13.8 (q), 17.6

(q), 17.8 (q), 17.86 (q), 17.90 (q), 20.6 (q), 20.8 (q), 20.9 (q), 21.1 (q), 23.1 (t), 23.3 (t), 24.1 (t), 24.5 (t), 27.3 (t), 28.0 (t), 28.1 (t), 29.2 (t), 52.5 (s), 52.6 (s), 52.92 (q), 52.93 (q), 53.0 (q), 53.1 (q), 54.1 (s), 54.3 (s), 61.2 (t), 61.3 (t), 61.4 (t), 69.2 (d), 69.4 (d), 70.2 (d), 70.4 (d), 73.0 (d), 73.9 (d), 74.1 (d), 75.0 (d), 125.9 (s), 126.1 (s), 126.57 (s), 126.59 (s), 128.8 (d), 128.95 (d), 128.98 (d), 129.02 (d), 129.1 (d), 129.21 (d), 129.24 (d), 129.28 (d), 129.33 (d), 129.4 (d), 129.6 (d), 129.7 (d), 134.2 (d), 134.3 (d), 136.85 (s), 136.93 (s), 137.25 (s), 137.30 (s), 137.96 (d), 138.01 (d), 165.8 (s), 166.0 (s), 166.05 (s), 166.14 (s), 169.6 (s), 170.46 (s), 170.49 (s), 170.98 (s), 171.01 (s), 171.6 (s), 171.8 (s); exact mass (electrospray) *m/z* calcd for $C_{25}H_{30}NaO_8S^{80}Se$ 593.0719, found 593.0717.

3-Acetoxy-6-benzenesulfonyl-2-methyleneheptanedioic Acid 1-Ethyl Ester 7-Methyl Ester (40.3d).

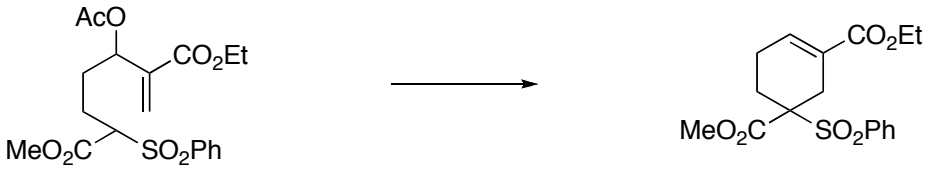


40.3c **40.3d**

H_2O_2 (30%, 0.17 mL, 1.7 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **40.3c** (four diastereoisomers) (81 mg, 0.14 mmol) in CH_2Cl_2 (2 mL). Stirring was continued at 0 °C for 90 min and the mixture was quenched with saturated aqueous $Na_2S_2O_3$ (1.0 mL). The mixture was stirred at 0 °C for 5 min, the ice bath was removed, stirring was continued for 10 min and the mixture was diluted with water (5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ (5 mL), dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (0.7 x 15 cm), using 1:1 EtOAc-hexane, gave **40.3d** (44 mg, 76%) as a viscous oil which was a 1:1 mixture of diastereomers: FTIR ($CDCl_3$ cast) 2955, 2971, 2854, 1743, 1634, 1585, 1448 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.28 (t, *J* = 7.1 Hz, 1.5 H), 1.29 (t, *J* = 7.1 Hz, 1.5 H), 1.69-1.87 (m,

2 H), 1.98- 2.15 (m, 5 H), 3.63 (s, 1.5 H), 3.65 (s, 1.5 H), 3.94 (dd, *J* = 10.5, 3.9 Hz, 0.5 H), 4.00-4.03 (m, 0.5 H), 4.16-4.25 (m, 2 H), 5.54 (dd, *J* = 7.2, 4.7 Hz, 0.5 H), 5.59 (dd, *J* = 7.8, 3.8 Hz, 0.5 H), 5.72 (t, *J* = 1.0 Hz, 0.5 H), 5.74 (t, *J* = 0.9 Hz, 0.5 H), 6.27 (s, 0.5 H), 6.29 (s, 0.5 H), 7.56-7.59 (m, 2 H), 7.67-7.71 (m, 1 H), 7.84-7.87 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.0 (q), 20.88 (q), 20.93 (q), 22.3 (t), 22.5 (t), 30.8 (t), 31.1 (t), 52.90 (q), 52.94 (q), 60.98 (t), 61.01 (t), 69.8 (d), 70.27 (d), 70.28 (d), 70.7 (d), 125.3 (s), 125.6 (s), 129.055 (d), 129.063 (d), 129.15 (d), 129.17 (d), 134.28 (d), 134.32 (d), 137.0 (s), 137.1 (s), 139.06 (t), 139.13 (t), 164.78 (s), 164.83 (s), 165.9 (s), 166.1 (s), 169.61 (s), 169.64 (s); exact mass (electrospray) *m*/*z* calcd for $C_{19}H_{24}NaO_8S$ 435.1084, found 435.1081.

1-(Benzenesulfonyl)cyclohex-3-ene-1,3-dicarboxylic Acid 3-Ethyl Ester 1-Methyl Ester (51.7).

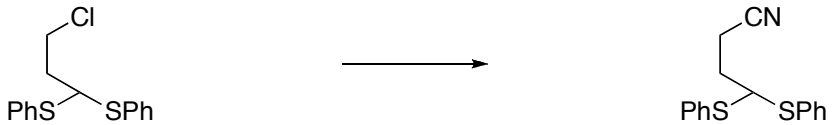


40.3d **51.7**

Cs_2CO_3 (40.0 mg, 0.123 mmol) was added to a stirred solution of **40.3d** (25.3 mg, 0.061 mmol) in THF (2.4 mL), and stirring at room temperature was continued for 45 min. Filtration of the mixture through a pad (ca 5 cm) of silica gel in a Pasteur pipette, using 2:1 EtOAc-hexane, gave **51.7** (20.0 mg, 93%) as a colorless viscous oil: FTIR ($CDCl_3$ cast) 3066, 2981, 2953, 1736, 1709, 1655, 1584, 1448, 1435 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.28 (t, *J* = 7.1 Hz, 3 H), 2.03 (ddd, *J* = 12.9, 11.3, 6.4 Hz, 1 H), 2.22-2.31 (m, 1 H), 2.41-2.48 (m, 1 H), 2.53 (dddd, *J* = 12.9, 6.3, 2.5, 2.5 Hz, 1 H), 2.80 (dddd, *J* = 17.2, 4.3, 2.6, 2.6 Hz, 1 H), 3.21 (dddd, *J* = 17.2, 2.4, 1.4, 1.4 Hz, 1 H), 3.62 (s, 3 H), 4.18 (q, *J* = 7.2 Hz, 2 H), 6.91 (ddd, *J* = 5.0, 2.5, 2.5 Hz, 1 H), 7.56-7.59 (m, 2 H), 7.68-7.71 (m, 1 H), 7.82-7.85 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.2 (q), 23.5 (t), 23.8 (t), 26.9 (t), 53.2 (q), 60.8 (t), 72.0 (s), 127.3 (s), 128.9 (d), 130.2 (d), 134.4 (d), 135.4

(s), 137.6 (d), 165.9 (s), 167.4 (s); exact mass *m/z* calcd for $C_{17}H_{20}O_6S$ 352.0981, found 352.0981.

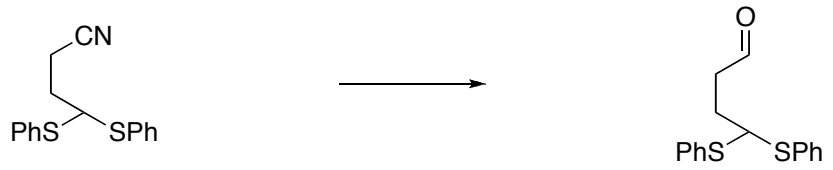
4,4-Bis(phenylthio)butyronitrile (43.2).



43.1 **43.2**

A solution of **43.1**[57] (200 mg, 0.68 mmol) in DMSO (2.5 mL) was added to a stirred mixture of NaCN (166.6 mg, 3.4 mmol) and Bu_4NI (26 mg, 0.07 mmol) in DMSO (2.5 mL), and the resulting mixture was stirred at 50 °C for 15 h, cooled to room temperature and diluted with water (20 mL). The aqueous phase was extracted with EtOAc (3 x 15) and the combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 15 cm), using 7:20 EtOAc-hexane, gave **43.2** (193 mg, 100%) as a liquid: FTIR ($CDCl_3$ cast) 3058, 2929, 2248, 1582, 1479, 1439, 1419 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.15 (tq, *J* = 7.2, 6.9 Hz, 2 H), 2.68 (t, *J* = 7.2 Hz, 2 H), 4.45 (t, *J* = 6.9 Hz, 1 H), 7.33-7.37 (m, 6 H), 7.48-7.51 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.1 (t), 31.2 (t), 56.9 (d), 118.7 (s), 128.5 (d), 129.2 (d), 132.7 (s), 133.3 (d); exact mass *m/z* calcd for $C_{16}H_{15}NS_2$ 285.0646, found 285.0647.

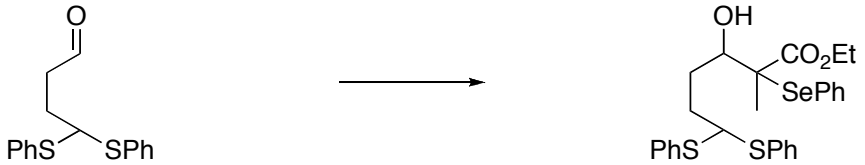
4,4-Bis(phenylthio)butyraldehyde (40.4a).[75]



43.2 **40.4a**

DIBAL (1.0 M in PhMe, 2.63 mL, 2.63 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of **43.2** (500 mg, 1.75 mmol) in CH_2Cl_2 (10 mL). Stirring at -78 °C was continued for 2 h, and the mixture was quenched with hydrochloric acid (1 M, 10 mL). The cold bath was removed, stirring was continued for 30 min and the mixture was diluted with water (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 1:5 EtOAc-hexane, gave **40.4a** (419 mg, 83%) as a liquid: FTIR (CH_2Cl_2 cast) 3057, 2926, 2827, 2724, 1723, 1479, 1438 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.19 (td, *J* = 7.2, 6.7 Hz, 2 H), 2.81 (td, *J* = 7.2, 1.0 Hz, 2 H), 4.49 (t, *J* = 6.7 Hz, 1 H), 7.28-7.35 (m, 6 H), 7.46-7.49 (m, 4 H), 9.77 (t, *J* = 1.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.2 (t), 41.1 (t), 57.4 (d), 127.9 (d), 129.0 (d), 132.8 (d), 133.6 (s), 200.8 (d); exact mass *m/z* calcd for $C_{16}H_{16}OS_2$ 288.0643, found 288.0640.

3-Hydroxy-2-methyl-2-(phenylseleno)-6,6-bis(phenylthio)hexanoic Acid Ethyl Ester (40.4b,b').



40.4a **40.4b,b'**

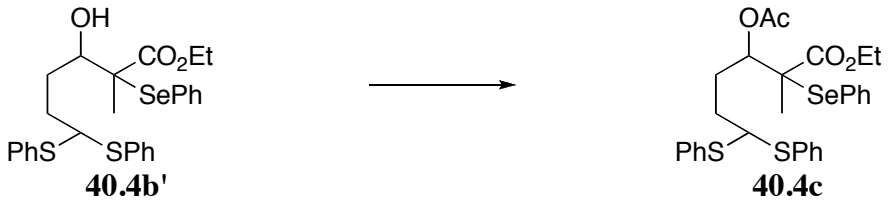
n-BuLi (1.5 M in hexane, 0.34 mL, 0.51 mmol) was added dropwise to a stirred and cooled (0 °C) solution of *i*-Pr_2NH (51.6 mg, 0.51 mmol) in THF (2 mL). Stirring at 0 °C was continued for 15 min, the mixture was cooled to -78 °C, and a solution of **38.1** (131 mg, 0.51 mmol) in THF (1 mL) was added dropwise. Stirring at -78 °C was continued for 50 min, and a solution of **40.4a** (105 mg, 0.36 mmol) in THF (1 mL) was added dropwise. Stirring at -78 °C was continued for 90 min, and the mixture was quenched with saturated aqueous NH_4Cl (10 mL). The cold bath was removed, stirring was continued for 15 min

and the mixture was diluted with water (10 mL). The aqueous phase was extracted with EtOAc (3 x 5 mL) and the combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 9:50 EtOAc-hexane and then 13:50 EtOAc-hexane, gave **40.4b** (less polar isomer) (55 mg, 28%) as a viscous oil and **40.4b'** (more polar isomer) (120 mg, 61%) as a viscous oil.

Compound **40.4b** had: FTIR ($CDCl_3$ cast) 3504, 3072, 3057, 2980, 2933, 2868, 1718, 1582, 1475, 1438 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.14 (t, *J* = 7.1 Hz, 3 H), 1.42 (s, 3 H), 1.73-1.79 (m, 1 H), 1.80-1.87 (m, 1 H), 1.94 (dddd, *J* = 14.3, 9.2, 6.3, 6.2 Hz, 1 H), 2.17-2.25 (m, 1 H), 3.00 (s, 1 H), 3.87 (dd, *J* = 9.7, 2.0 Hz, 1 H), 4.02 (dq, *J* = 10.8, 7.1 Hz, 1 H), 4.09 (dq, *J* = 10.8, 7.1 Hz, 1 H), 4.47 (dd, *J* = 6.7, 6.7 Hz, 1 H), 7.27-7.34 (m, 8 H), 7.41-7.48 (m, 5 H), 7.59-7.61 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.9 (q), 17.2 (q), 29.1 (t), 33.2 (t), 57.3 (s), 58.0 (d), 61.2 (t), 72.6 (d), 126.3 (s), 127.6 (d), 128.8 (d), 129.5 (d), 132.6 (d), 132.7 (d), 134.05 (s), 134.12 (s), 138.1 (d), 173.1 (s); exact mass *m/z* calcd for $C_{27}H_{30}O_3S_2{}^{80}Se$ 546.0801, found 546.0813.

Compound **40.4b'** had: FTIR (CH_2Cl_2 cast) 3498, 3072, 3057, 2980, 2957, 2933, 1721, 1706, 1582, 1476, 1438 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.21 (t, *J* = 7.1 Hz, 3 H), 1.42 (s, 3 H), 1.63-1.71 (m, 1 H), 1.87-1.94 (m, 1 H), 2.17-2.30 (m, 2 H), 2.76 (d, *J* = 6.9 Hz, 1 H), 3.79 (ddd, *J* = 10.7, 6.9, 1.4 Hz, 1 H), 4.11 (q, *J* = 7.1 Hz, 2 H), 4.51 (dd, *J* = 6.4, 6.4 Hz, 1 H), 7.25-7.34 (m, 8 H), 7.36-7.40 (m, 1 H), 7.48-7.51 (m, 4 H), 7.53-7.55 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.0 (q), 18.1 (q), 28.8 (t), 33.2 (t), 54.4 (s), 58.1 (d), 61.4 (t), 75.0 (d), 126.5 (s), 127.70 (d), 127.72 (d), 128.8 (d), 128.9 (d), 129.4 (d), 132.7 (d), 132.8 (d), 134.09 (s), 134.14 (s), 138.1 (d), 174.0 (s); exact mass *m/z* calcd for $C_{27}H_{30}O_3S_2{}^{80}Se$ 546.0801, found 546.0793.

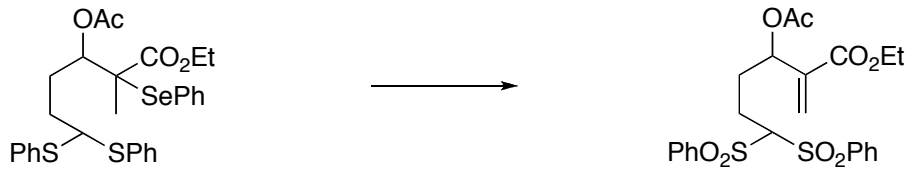
3-Acetoxy-2-methyl-2-(phenylseleno)-6,6-bis(phenylthio)hexanoic Acid Ethyl Ester (40.4c).



40.4b' **40.4c**

Pyridine (98.0 mg, 1.23 mmol) and AcCl (48.4 mg, 0.62 mmol) were added sequentially to a stirred and cooled (-10 °C, ice-acetone bath) solution of **40.4b'** (112 mg, 0.21 mmol) and DMAP (2 mg, 0.02 mmol) in CH_2Cl_2 (2 mL). The cold bath was left in place but not recharged and stirring was continued for 13 h, by which time the temperature had risen to room temperature. The mixture was diluted with water (10 mL), acidified with hydrochloric acid (1 M, 2 mL) and extracted with CH_2Cl_2 (3 x 8 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 1:4 EtOAc-hexane, gave **40.4c** (90 mg, 74%) as an oil: FTIR ($CDCl_3$ cast) 3057, 2981, 2932, 1745, 1725, 1582, 1476, 1439 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.06 (t, *J* = 7.1 Hz, 3 H), 1.51 (s, 3 H), 1.82 (s, 3 H), 1.85-1.99 (m, 3 H), 2.51-2.60 (m, 1 H), 3.86 (dq, *J* = 10.8, 7.1 Hz, 1 H), 4.00 (dq, *J* = 10.8, 7.1 Hz, 1 H), 4.50 (dd, *J* = 6.2, 6.2 Hz, 1 H), 5.36 (dd, *J* = 10.1, 1.7 Hz, 1 H), 7.24-7.40 (m, 9 H), 7.49-7.52 (m, 4 H), 7.56-7.58 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.8 (q), 17.7 (q), 20.7 (q), 27.8 (t), 32.2 (t), 52.8 (s), 57.9 (d), 61.1 (t), 75.0 (d), 126.2 (s), 127.8 (d), 127.9 (d), 128.91 (d), 128.94 (d), 129.6 (d), 132.9 (d), 133.1 (d), 133.87 (s), 133.90 (s), 138.1 (d), 169.5 (s), 171.9 (s); exact mass *m/z* calcd for $C_{29}H_{32}O_4S_2{}^{80}Se$ 588.0907, found 588.0916.

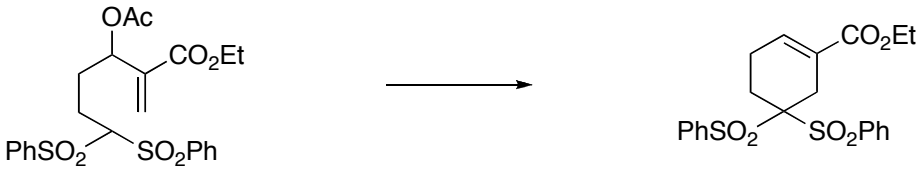
2-[1-Acetoxy-4,4-bis(benzenesulfonyl)butyl]acrylic Acid Ethyl Ester (40.4d).



40.4c **40.4d**

m-CPBA (70-75%, 164 mg, 0.66 mmol) was added to a solution of **40.4c** (39 mg, 0.066 mmol) in CH_2Cl_2 (2 mL), and the mixture was stirred at 40 °C for 23 h, cooled to room temperature and evaporated. Flash chromatography of the residue over silica gel (0.7 x 15 cm), using 15:20 EtOAc-hexane, gave **40.4d** (23 mg, 81%) as a viscous oil: FTIR (CH_2Cl_2 cast) 3066, 2983, 2933, 1743, 1635, 1584, 1448 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.31 (t, *J* = 7.1 Hz, 3 H), 1.99-2.05 (m, 1 H), 2.06 (s, 3 H), 2.16-2.30 (m, 3 H), 4.19-4.28 (m, 2 H), 4.51-4.53 (m, 1 H), 5.57 (dd, *J* = 8.0, 2.9 Hz, 1 H), 5.73 (dd, *J* = 1.1, 1.1 Hz, 1 H), 6.29 (dd, *J* = 0.7, 0.7 Hz, 1 H), 7.55-7.59 (m, 4 H), 7.67-7.71 (m, 2 H), 7.93-7.95 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.1 (q), 21.0 (q), 21.4 (t), 31.8 (t), 61.1 (t), 70.4 (d), 82.6 (d), 125.4 (t), 129.08 (d), 129.11 (d), 129.57 (d), 129.61 (d), 134.56 (d), 134.57 (d), 137.7 (s), 137.8 (s), 139.1 (s), 164.9 (s), 169.7 (s); exact mass (electrospray) *m/z* calcd for $C_{23}H_{26}NaO_8S_2$ 517.0961, found 517.0961.

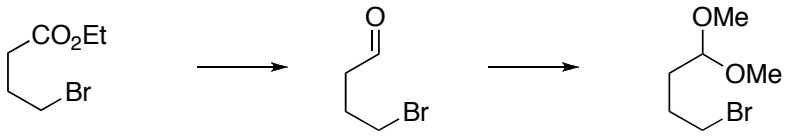
5,5-Bis(benzenesulfonyl)cyclohex-1-enecarboxylic Acid Ethyl Ester (51.8).



40.4d **51.8**

Cs_2CO_3 (20.0 mg, 0.062 mmol) was added to a stirred solution of **40.4d** (15.2 mg, 0.031 mmol) in THF (1 mL), and stirring at room temperature was continued for 2 h. Evaporation of the solvent and filtration of the residue through a pad (ca 5 cm) of silica gel in a Pasteur pipette, using 1:1 EtOAc-hexane, gave **51.8** (13.2 mg, 99%) as a colorless viscous oil: FTIR (CH_2Cl_2 cast) 3066, 2982, 1707, 1663, 1583, 1448 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.27 (t, *J* = 7.1 Hz, 3 H), 2.42 (t, *J* = 6.5 Hz, 2 H), 2.56-2.62 (m, 2 H), 3.12 (ddd, *J* = 2.1, 2.1, 2.1 Hz, 2 H), 4.18 (q, *J* = 7.2 Hz, 2 H), 7.01 (dddd, *J* = 4.0, 4.0, 2.0, 2.0 Hz, 1 H), 7.56-7.60 (m, 4 H), 7.69-7.73 (m, 2 H), 8.01-8.03 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2 (q), 23.0 (t), 23.3 (t), 25.4 (t), 60.8 (t), 86.7 (s), 125.5 (s), 128.8 (d), 131.2 (d), 134.7 (d), 136.3 (s), 138.0 (d), 165.5 (s); exact mass *m/z* calcd for $C_{21}H_{22}O_6S_2$ 434.0858, found 434.0859.

4-Bromo-1,1-dimethoxybutane (44.2).[58]

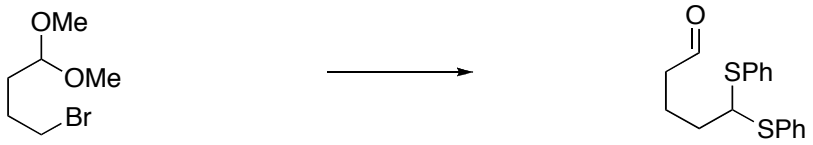


44.1 - **44.2**

DIBAL (1.0 M in PhMe, 6.2 mL) was added slowly to a stirred and cooled (-78 °C) solution of **44.1** (1.0 g, 5.1 mmol) in CH_2Cl_2 (50 mL), the internal temperature being kept below -75 °C. Stirring at -78 °C was continued for 40 min, and MeOH (2.2 mL) and saturated aqueous Rochelle salt (97 mL) were added. The cold bath was removed and vigorous stirring was continued for 2 h. The aqueous phase was extracted with CH_2Cl_2 (2 x 50 mL) and the combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. The residue was dissolved in MeOH (20 mL), pyridinium *p*-toluene sulfonate (64 mg, 0.26 mmol) was added, and stirring at room temperature was continued for 7 h. The mixture was diluted with water (100 mL) and the aqueous phase was extracted with EtOAc (3 x 80 mL). The combined organic extracts were washed

with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2.5 x 15 cm), using 17:25 EtOAc-hexane, gave **44.2** (691 mg, 68%) as an oil.

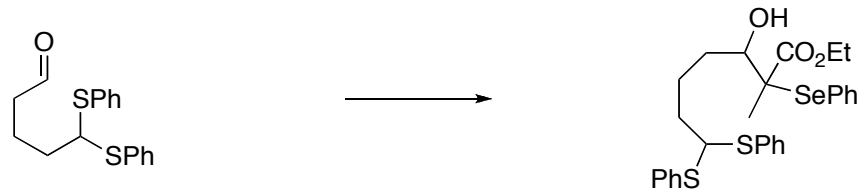
5,5-Bis(phenylthio)pentanal (40.5a).



44.2 **40.5a**

n-BuLi (1.5 M in hexane, 2.8 mL, 4.19 mmol) was added dropwise to a stirred and cooled (0 °C) solution of $(PhS)_2CH_2$ (885.3 mg, 3.81 mmol) in THF (20 mL).[57] Stirring at 0 °C was continued for 15 min, and a solution of **44.2** (250 mg, 1.27 mmol) in THF (2 mL) was added rapidly in one portion. Stirring at 0 °C was continued for 1.5 h, and hydrochloric acid (4 M, 2.5 mL) was added. The cold bath was removed, stirring was continued for 1 h and the mixture was diluted with water (100 mL). The aqueous phase was extracted with EtOAc (3 x 50 mL) and the combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 15 cm), using 1:3 EtOAc-hexane, gave **40.5a** (345 mg, 90%) as a liquid: FTIR ($CDCl_3$ cast) 3057, 2934, 2826, 2723, 1722, 1582, 1480, 1439 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.85-2.00 (m, 4 H), 2.42 (td, *J* = 7.2, 1.5 Hz, 2 H), 4.40 (t, *J* = 6.4 Hz, 1 H), 7.26-7.35 (m, 6 H), 7.46-7.49 (m, 4 H), 9.72 (t, *J* = 1.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.7 (t), 35.16 (t), 43.2 (t), 58.2 (d), 127.9 (d), 129.0 (d), 132.8 (d), 134.0 (s), 201.6 (d); exact mass *m/z* calcd for $C_{17}H_{18}OS_2$ 302.0799, found 302.0801.

3-Hydroxy-2-methyl-2-(phenylseleno)-7,7-bis(phenylthio)heptanoic Acid Ethyl Ester (40.5b,b').



40.5a **40.5b,b'**

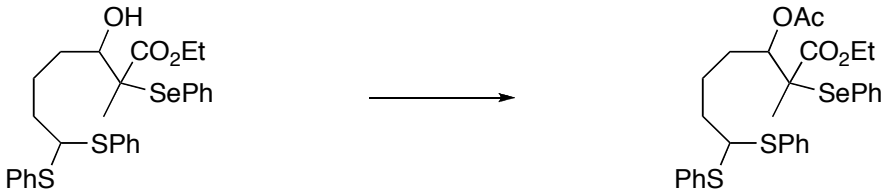
n-BuLi (1.5 M in hexane, 0.41 mL, 0.62 mmol) was added dropwise to a stirred and cooled (0 °C) solution of *i*-Pr_2NH (62.7 mg, 0.62 mmol) in THF (3 mL). Stirring at 0 °C was continued for 15 min, the mixture was cooled to -78 °C, and a solution of **38.1** (159.3 mg, 0.62 mmol) in THF (2 mL) was then added dropwise. Stirring at -78 °C was continued for 1 h, and a solution of **40.5a** (124 mg, 0.41 mmol) in THF (1 mL) was added dropwise. Stirring at -78 °C was continued for 40 min, and the mixture was quenched with saturated aqueous NH_4Cl (5 mL). The cold bath was removed, stirring was continued for 15 min and the mixture was diluted with water (40 mL). The aqueous phase was extracted with EtOAc (3 x 20 mL) and the combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 3:20 EtOAc-hexane and then 1:5 EtOAc-hexane, gave **40.5b** (less polar isomer) (84 mg, 37%) as a viscous oil and **40.5b'** (more polar) (110 mg, 48%) as a viscous oil.

Compound **40.5b** had: FTIR (CH_2Cl_2 cast) 3498, 3057, 2979, 2937, 2867, 1720, 1582, 1476, 1438 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.12 (t, *J* = 7.1 Hz, 3 H), 1.28-1.37 (m, 1 H), 1.38 (s, 3 H), 1.49-1.57 (m, 1 H), 1.66-1.74 (m, 1 H), 1.83-1.99 (m, 3 H), 2.95 (dd, *J* = 2.9, 1.7 Hz, 1 H), 3.86 (ddd, *J* = 9.8, 2.3, 2.3 Hz, 1 H), 3.98 (dq, *J* = 10.8, 7.1 Hz, 1 H), 4.06 (dq, *J* = 10.8, 7.1 Hz, 1 H), 4.39 (dd, *J* = 6.5, 6.5 Hz, 1 H), 7.25-7.33 (m, 8 H), 7.39-7.50 (m, 5 H), 7.58-7.60 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.8 (q), 17.0 (q), 24.5 (t), 31.3 (t), 35.6 (t), 57.4 (s), 58.4 (d), 61.1 (t), 72.6 (d), 126.4 (s), 127.6 (d), 128.82 (d), 128.84 (d), 128.86

(d), 128.93 (d), 129.5 (d), 132.7 (d), 132.8 (d), 134.2 (s), 134.3 (s), 138.0 (d), 173.1 (s); exact mass (electrospray) *m/z* calcd for $C_{28}H_{32}NaO_3S_2{}^{80}Se$ 583.0850, found 583.0842.

Compound **40.5b'** had: FTIR (CH_2Cl_2 cast) 3502, 3072, 3057, 2979, 2937, 2866, 1722, 1582, 1476, 1438 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.20 (t, *J* = 7.1 Hz, 3 H), 1.31-1.37 (m, 1 H), 1.39 (s, 3 H), 1.64-1.75 (m, 1 H), 1.83-1.95 (m, 4 H), 2.77 (s, 1 H), 3.84 (d, *J* = 10.3 Hz, 1 H), 4.10 (q, *J* = 7.1 Hz, 2 H), 4.42 (t, *J* = 6.4 Hz, 1 H), 7.27-7.34 (m, 8 H), 7.38-7.42 (m, 1 H), 7.46-7.50 (m, 4 H), 7.55-7.57 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.9 (q), 18.0 (q), 24.5 (t), 30.8 (t), 35.7 (t), 54.6 (s), 58.5 (d), 61.3 (t), 75.0 (d), 126.5 (s), 127.7 (d), 128.8 (d), 128.85 (d), 128.86 (d), 129.4 (d), 132.78 (d), 132.80 (d), 134.18 (s), 134.19 (s), 138.0 (d), 173.9 (s); exact mass (electrospray) *m/z* calcd for $C_{28}H_{32}NaO_3S_2{}^{80}Se$ 583.0850, found 583.0849.

3-Acetoxy-2-methyl-2-(phenylseleno)-7,7-bis(phenylthio)heptanoic Acid Ethyl Ester (40.5c).

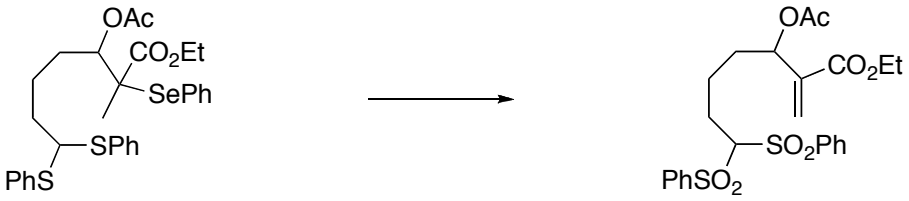


40.5b' **40.5c**

Pyridine (93.4 mg, 1.18 mmol) and AcCl (46.3 mg, 0.59 mmol) were added sequentially to a stirred and cooled (-10 °C, ice-acetone bath) solution of **40.5b'** (110 mg, 0.197 mmol) and DMAP (2.5 mg, 0.02 mmol) in CH_2Cl_2 (2 mL). The cold bath was left in place but not recharged and stirring was continued for 16 h, by which time the temperature had risen to room temperature. The mixture was diluted with water (10 mL), acidified with hydrochloric acid (1 M, 2 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue

over silica gel (1 x 15 cm), using 17:100 EtOAc-hexane, gave **40.5c** (84 mg, 71%) as an oil: FTIR ($CHCl_3$ cast) 3057, 2981, 2936, 1745, 1725, 1582, 1476, 1438 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.09 (t, *J* = 7.1 Hz, 3 H), 1.48 (s, 3 H), 1.51-1.60 (m, 1 H), 1.62-1.72 (m, 2 H), 1.86 (dddd, *J* = 14.3,14.3, 6.8, 6.8 Hz, 1 H), 1.91-2.00 (m, 1 H), 1.94 (s, 3 H), 2.03-2.12 (m, 1 H), 3.89 (dq, *J* = 10.7, 7.1 Hz, 1 H), 4.02 (dq, *J* = 10.7, 7.1 Hz, 1 H), 4.40 (dd, *J* = 6.8, 6.8 Hz, 1 H), 5.44 (dd, *J* = 10.1, 1.8 Hz, 1 H), 7.28-7.35 (m, 8 H), 7.37-7.42 (m, 1 H), 7.46-7.49 (m, 4 H), 7.56-7.59 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.8 (q), 17.9 (q), 20.9 (q), 24.02 (t), 30.0 (t), 35.7 (t), 53.0 (s), 58.2 (d), 61.1 (t), 75.4 (d), 126.3 (s), 127.6 (d), 127.7 (d), 128.87 (d), 128.90 (d), 129.6 (d), 132.7 (d), 132.9 (d), 134.16 (s), 134.22 (s), 138.0 (d), 169.5 (s), 172.0 (s); exact mass (electrospray) *m/z* calcd for $C_{30}H_{34}NaO_4S_2{}^{80}Se$ 625.0956, found 625.09501.

2-[1-Acetoxy-5,5-bis(benzenesulfonyl)pentyl]acrylic Acid Ethyl Ester (40.5d).

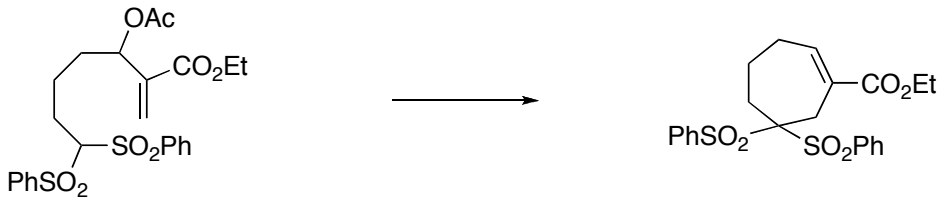


40.5c **40.5d**

m-CPBA (70-75%, 151.8 mg, ca 0.62 mmol) was added to a solution of **40.5c** (37 mg, 0.062 mmol) in CH_2Cl_2 (2 mL), and the mixture was stirred at 40 °C for 23 h, cooled to room temperature and evaporated. Flash chromatography of the residue over silica gel (0.7 x 15 cm), using 3:5 EtOAc-hexane, gave **40.5d** (19.8 mg, 65%) as a viscous oil: FTIR ($CDCl_3$ cast) 3064, 2981, 2928, 1739, 1584, 1478, 1448 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.31 (t, *J* = 7.1 Hz, 3 H), 1.59-1.79 (m, 4 H), 2.08 (s, 3 H), 2.18 (dd, *J* = 13.4, 7.0 Hz, 2 H), 4.18-4.29 (m, 2 H), 4.41 (dd, *J* = 5.7, 5.7 Hz, 1 H), 5.55 (dd, *J* = 6.3, 4.0 Hz, 1 H), 5.73 (s, 1 H), 6.28 (s, 1 H), 7.56-7.60 (m, 4 H), 7.69-7.72 (m, 2 H), 7.94-7.96 (m, 4 H); ^{13}C

NMR ($CDCl_3$, 100 MHz) δ 14.1 (q), 21.0 (q), 23.8 (t), 25.2 (t), 33.3 (t), 61.0 (t), 71.0 (d), 83.3 (d), 125.2 (t), 129.1 (d), 129.55 (d), 129.58 (d), 134.6 (d), 137.7 (s), 137.8 (s), 139.6 (s), 165.0 (s), 169.8 (s); exact mass (electrospray) *m/z* calcd for $C_{24}H_{28}NaO_8S_2$ 531.1118, found 531.1112.

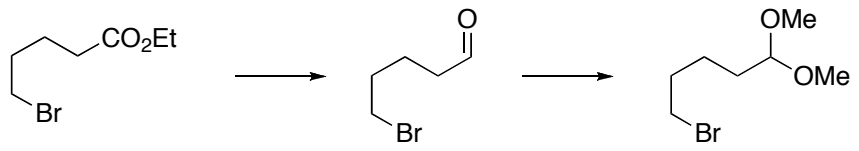
6,6-Bis(benzenesulfonyl)cyclohept-1-enecarboxylic Acid Ethyl Ester (51.9).



40.5d **51.9**

Cs_2CO_3 (25.7 mg, 0.079 mmol) was added to a stirred solution of **40.5d** (20.0 mg, 0.039 mmol) in THF (1 mL), and stirring at room temperature was continued for 2 h. Evaporation of the solvent and filtration of the residue through a pad (ca 5 cm) of silica gel in a Pasteur pipette, using 2:5 EtOAc-hexane, gave **51.9** (16.6 mg, 95%) as a colorless viscous oil: FTIR ($CDCl_3$ cast) 3067, 2927, 1704, 1650, 1583, 1466, 1448 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.28 (t, *J* = 7.1 Hz, 3 H), 1.68-1.74 (m, 2 H), 2.43 (dd, *J* = 11.7, 6.5 Hz, 2 H), 2.52-2.54 (m, 2 H), 3.51 (s, 2 H), 4.21 (q, *J* = 7.1 Hz, 2 H), 6.95 (dd, *J* = 5.0, 5.0 Hz, 1 H), 7.56-7.60 (m, 4 H), 7.68-7.72 (m, 2 H), 8.05-8.08 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2 (q), 19.1 (t), 25.7 (t), 28.3 (t), 30.3 (t), 61.2 (t), 91.0 (s), 127.0 (s), 128.7 (s), 131.4 (d), 134.5 (d), 136.7 (s), 140.4 (d), 166.9 (s); exact mass (electrospray) *m/z* calcd for $C_{22}H_{24}NaO_6S_2$ 471.0907, found 471.0906.

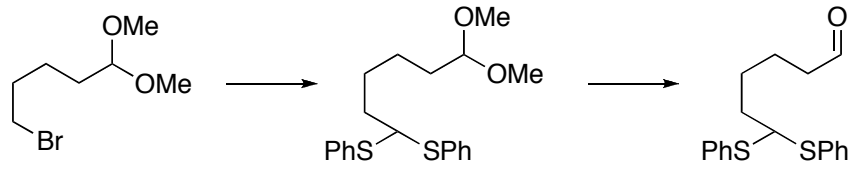
5-Bromo-1,1-dimethoxypentane (44.4).[59]



44.3 **-** **44.4**

DIBAL (1.0 M in PhMe, 5.7 mL) was added slowly to a stirred and cooled (-78 °C) solution of **44.3** (1.0 g, 4.8 mmol) in CH_2Cl_2 (50 mL), the internal temperature being kept below -75 °C. Stirring at -78 °C was continued for 40 min, and MeOH (2.5 mL) and saturated aqueous Rochelle salt (100 mL) were added. The cold bath was removed, and vigorous stirring was continued for 2 h. The aqueous phase was extracted with CH_2Cl_2 (2 x 50 mL) and the combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. The residue was dissolved in MeOH (20 mL), pyridinium *p*-toluenesulfonate (60 mg, 0.24 mmol) was added, and stirring at room temperature was continued for 7 h. The mixture was diluted with water (150 mL) and the aqueous phase was extracted with EtOAc (3 x 80 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2.5 x 15 cm), using 17:25 EtOAc-hexane, gave **44.4** (681 mg, 68%) as an oil.

6,6-Bis(phenylthio)hexanal (40.6a).

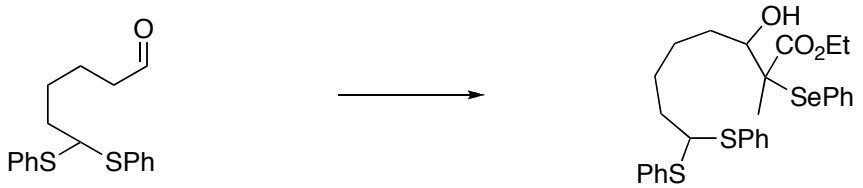


44.4 **-** **40.6a**

n-BuLi (1.5 M in hexane, 2.1 mL, 3.13 mmol) was added dropwise to a stirred and cooled (0 °C) solution of $(PhS)_2CH_2$ (660 mg, 2.84 mmol) in THF (14

mL).[57] Stirring at 0 °C was continued for 15 min, and a solution of **44.4** (200 mg, 0.95 mmol) in THF (2 mL) was added rapidly in one portion. Stirring at 0 °C was continued for 3.5 h, and hydrochloric acid (4 M, 2.2 mL) was added. The cold bath was removed, stirring was continued for 1 h and the mixture was diluted with water (100 mL). The aqueous phase was extracted with EtOAc (3 x 50 mL) and the combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 1:5 EtOAc-hexane, gave **40.6a** (300 mg, 100%) as a liquid: FTIR (CH_2Cl_2 cast) 3057, 2938, 2860, 2722, 1723, 1582, 1480, 1439, 1408 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.54-1.71 (m, 4 H), 1.86 (dd, *J* = 14.8, 6.6 Hz, 2 H), 2.41 (td, *J* = 7.0, 1.5 Hz, 2 H), 4.39 (t, *J* = 6.6 Hz, 1 H), 7.27-7.37 (m, 6 H), 7.45-7.49 (m, 4 H), 9.74 (t, *J* = 1.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.4 (t), 26.5 (t), 35.5 (t), 43.6 (t), 58.2 (d), 127.8 (d), 128.9 (d), 132.8 (d), 134.1 (s), 202.2 (d); exact mass *m/z* calcd for $C_{18}H_{20}OS_2$ 316.0956, found 316.0954.

3-Hydroxy-2-methyl-2-(phenylseleno)-8,8-bis(phenylthio)octanoic Acid Ethyl Ester (40.6b,b').



40.6a **40.6b,b'**

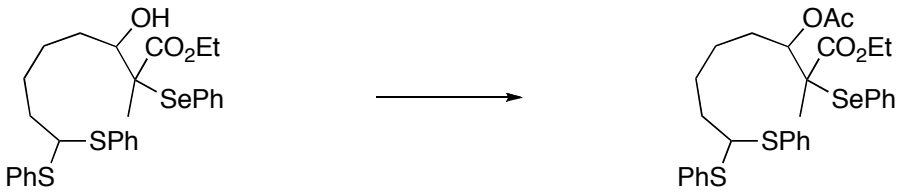
n-BuLi (1.5 M in hexane, 0.51 mL, 0.76 mmol) was added dropwise to a stirred and cooled (0 °C) solution of *i*-Pr_2NH (76.9 mg, 0.76 mmol) in THF (3 mL). Stirring at 0 °C was continued for 15 min, the mixture was cooled to -78 °C, and a solution of **38.1** (195.3 mg, 0.76 mmol) in THF (2 mL) was then added dropwise. Stirring at -78 °C was continued for 1 h, and a solution of **40.6a** (150 mg, 0.48 mmol) in THF (1 mL) was added dropwise. Stirring at -78 °C was continued for 40 min, and the mixture was quenched with saturated aqueous NH_4Cl (5 mL). The cold bath was removed, stirring was continued for 15 min

and the mixture was diluted with water (40 mL). The aqueous phase was extracted with EtOAc (3 x 20 mL) and the combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 4:25 EtOAc-hexane and then 1:5 EtOAc-hexane, gave **40.6b** (less polar isomer) (85 mg, 31%) as a viscous oil and **40.6b'** (more polar isomer) (130 mg, 48%) as a viscous oil.

Compound **40.6b** had: FTIR (CH_2Cl_2 cast) 3498, 3057, 2979, 2937, 2858, 1720, 1582, 1476, 1438 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.14 (t, *J* = 7.1 Hz, 3 H), 1.27-1.36 (m, 2 H), 1.39 (s, 3 H), 1.47-1.68 (m, 4 H), 1.80-1.89 (m, 2 H), 2.97 (s, 1 H), 3.86 (dd, *J* = 9.8, 1.6 Hz, 1 H), 4.00 (dq, *J* = 10.8, 7.1 Hz, 1 H), 4.08 (dq, *J* = 10.8, 7.2 Hz, 1 H), 4.39 (t, *J* = 4.4 Hz, 1 H), 7.25-7.33 (m, 8 H), 7.39-7.49 (m, 5 H), 7.59-7.61 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.9 (q), 17.0 (q), 26.3 (t), 26.9 (t), 31.6 (t), 35.6 (t), 57.5 (s), 58.3 (d), 61.1 (t), 72.7 (d), 126.4 (s), 127.6 (d), 128.8 (d), 129.5 (d), 132.7 (d), 134.3 (s), 138.0 (d), 173.1 (s); exact mass (electrospray) *m/z* calcd for $C_{29}H_{34}NaO_3S_2{}^{80}Se$ 597.1007, found 597.1011.

Compound **40.6b'** had: FTIR (CH_2Cl_2 cast) 3504, 3057, 2979, 2939, 2858, 1721, 1582, 1476, 1457, 1438 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.21 (t, *J* = 7.1 Hz, 3 H), 1.27-1.38 (m, 2 H), 1.40 (s, 3 H), 1.57-1.76 (m, 3 H), 1.82-1.91 (m, 3 H), 2.80 (s, 1 H), 3.84 (d, *J* = 9.0 Hz, 1 H), 4.11 (qd, *J* = 7.1, 1.6 Hz, 2 H), 4.43 (t, *J* = 6.7 Hz, 1 H), 7.28-7.34 (m, 8 H), 7.37-7.42 (m, 1 H), 7.45-7.49 (m, 4 H), 7.56-7.58 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.9 (q), 18.3 (q), 26.2 (t), 26.9 (t), 31.3 (t), 35.7 (t), 54.7 (s), 58.3 (d), 61.3 (t), 75.2 (d), 126.6 (s), 127.6 (d), 128.8 (d), 128.9 (d), 129.37 (d), 132.65 (d), 132.68 (d), 134.3 (s), 138.1 (d), 174.0 (s); exact mass (electrospray) *m/z* calcd for $C_{29}H_{34}NaO_3S_2{}^{80}Se$ 597.1007, found 597.1012.

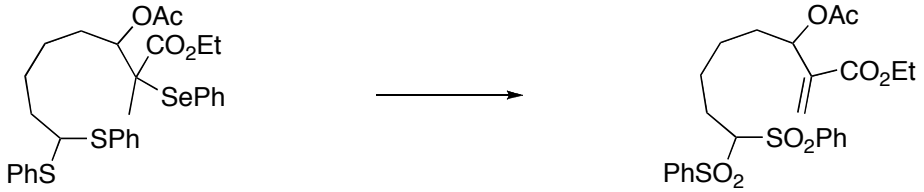
3-Acetoxy-2-methyl-2-(phenylseleno)-8,8-bis(phenylthio)octanoic Acid Ethyl Ester (40.6c).



40.6b' **40.6c**

Pyridine (107.6 mg, 1.36 mmol) and AcCl (53.4 mg, 0.68 mmol) were added sequentially to a stirred and cooled (-10 °C, ice-acetone bath) solution of **40.6b'** (130 mg, 0.227 mmol) and DMAP (2.8 mg, 0.02 mmol) in CH_2Cl_2 (2 mL). The cold bath was left in place but not recharged and stirring was continued for 16 h, by which time the temperature had risen to room temperature. The mixture was diluted with water (10 mL), acidified with hydrochloric acid (1 M, 2 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 15 cm), using 9:50 EtOAc-hexane, gave **40.6c** (104 mg, 75%) as an oil: FTIR ($CDCl_3$ cast) 3057, 2981, 2937, 2859, 1744, 1725, 1582, 1477, 1438 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.09 (t, *J* = 7.1 Hz, 3 H), 1.29-1.36 (m, 2 H), 1.49 (s, 3 H), 1.52-1.77 (m, 3 H), 1.87 (dd, *J* = 14.8, 7.4 Hz, 2 H), 1.94 (s, 3 H), 2.03-2.12 (m, 1 H), 3.88 (dq, *J* = 10.8, 7.1 Hz, 1 H), 4.02 (dq, *J* = 10.8, 7.1 Hz, 1 H), 4.42 (dd, *J* = 6.6, 6.6 Hz, 1 H), 5.43 (dd, *J* = 10.5, 1.7 Hz, 1 H), 7.27-7.34 (m, 8 H), 7.37-7.42 (m, 1 H), 7.46-7.49 (m, 4 H), 7.57-7.60 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.8 (q), 17.9 (q), 20.9 (q), 25.9 (t), 27.0 (t), 30.3 (t), 35.6 (t), 53.0 (s), 58.3 (d), 61.1 (t), 75.6 (d), 126.3 (s), 127.6 (d), 127.7 (d), 28.9 (d), 129.6 (d), 132.70 (d), 132.73 (d), 134.2 (s), 138.0 (d), 169.6 (s), 172.1 (s); exact mass (electrospray) *m/z* calcd for $C_{31}H_{36}NaO_4S_2{}^{80}Se$ 639.1113, found 639.1108.

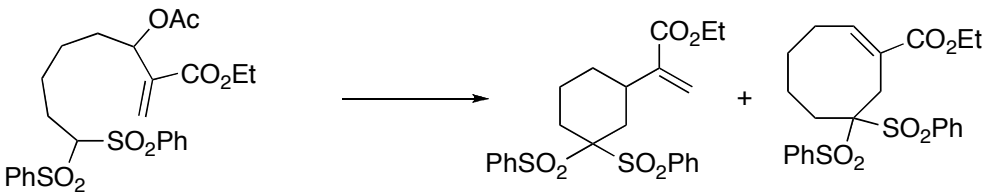
2-[1-Acetoxy-6,6-bis(benzenesulfonyl)hexyl]acrylic Acid Ethyl Ester (40.6d).



40.6c **40.6d**

m-CPBA(70-75%, 204 mg, 0.83 mmol) was added to a stirred solution of **40.6c** (51 mg, 0.083 mmol) in CH_2Cl_2 (2 mL), and the mixture was stirred at 40 °C for 23 h, cooled to room temperature and evaporated. Flash chromatography of the residue over silica gel (0.7 x 15 cm), using 3:5 EtOAc-hexane, gave **40.6d** (35.4 mg, 82%) as a viscous oil: FTIR ($CDCl_3$ cast) 3067, 2933, 2869, 1738, 1632, 1584, 1478, 1448 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.31 (t, *J* = 7.1 Hz, 3 H), 1.24-1.33 (m, 2 H), 1.56-1.65 (m, 3 H), 1.66-1.76 (m, 1 H), 2.08 (s, 3 H), 2.13-2.18 (m, 2 H), 4.23 (qd), *J* = 7.1, 1.8 Hz, 2 H), 4.37 (t, *J* = 5.6 Hz, 1 H), 5.57 (dd, *J* = 7.7, 4.4 Hz, 1 H), 5.73 (s, 1 H), 6.28 (s, 1 H), 7.56-7.60 (m, 4 H), 7.68-7.72 (m, 2 H), 7.94-7.96 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1 (q), 21.1 (q), 24.8 (t), 25.4 (t), 27.8 (t), 33.6 (t), 60.9 (t), 71.4 (d), 83.6 (d), 124.9 (t), 129.1 (d), 129.6 (d), 134.5 (d), 137.82 (d), 137.85 (s), 140.1 (s), 165.2 (s), 169.9 (s); exact mass (electrospray) *m/z* calcd for $C_{25}H_{30}NaO_8S_2$ 545.1274, found 545.1277.

7,7-Bis(benzenesulfonyl)cyclooct-1-enecarboxylic Acid Ethyl Ester (51.10') and 2-[3,3-Bis(benzenesulfonyl)cyclohexyl]acrylic Acid Ethyl Ester (51.10).



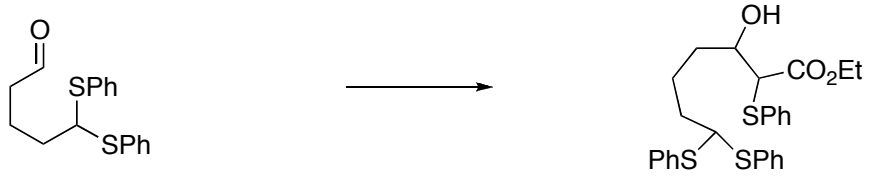
40.6d **51.10** **51.10'**

Cs_2CO_3 (43.7 mg, 0.134 mmol) was added to a stirred solution of **25d** (35.0 mg, 0.067 mmol) in THF (2 mL). Stirring at room temperature was continued for 1.5 h, and the solvent was evaporated. Flash chromatography of the residue over silica gel (0.7 x 15 cm), using 60:1 CH_2Cl_2-EtOAc, gave **51.10** (10.9 mg, 49%) as a white solid and **51.10'** (6.5 mg, 29.4%) as a viscous oil.

Compound **51.10'** had: FTIR ($CDCl_3$ cast) 3067, 2925, 2854, 1711, 1648, 1583, 1467, 1447 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.23 (t, *J* = 7.1 Hz, 3 H), 1.71-1.76 (m, 2 H), 2.01-2.05 (m, 2 H), 2.22-2.26 (m, 2 H), 2.37-2.39 (m, 2 H), 3.56 (s, 2 H), 4.19 (q, *J* = 7.1 Hz, 2 H), 7.05 (t, *J* = 8.3 Hz, 1 H), 7.57-7.60 (m, 4 H), 7.68-7.72 (m, 2 H), 8.05-8.07 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.1 (q), 26.7 (t), 27.0 (t), 27.7 (t), 27.9 (t), 29.7 (t), 61.0 (t), 92.3 (s), 128.5 (s), 129.4 (d), 131.4 (d), 134.4 (d), 137.1 (s), 142.0 (d), 167.1 (s); exact mass (electrospray) *m/z* calcd for $C_{23}H_{26}NaO_6S_2$ 485.1063, found 485.1062.

Compound **51.10** had: mp 213-215 °C; FTIR ($CDCl_3$ cast) 3094, 3056, 2966, 2930, 2871, 2856, 1710, 1620, 1581, 1479, 1449, 1419 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.10 (dddd, *J* = 13.3, 13.0, 3.8, 3.6 Hz, 1 H), 1.39 (t, *J* = 7.1 Hz, 3 H), 1.52-1.60 (m, 2 H), 1.74-1.84 (m, 2 H), 2.05-2.19 (m, 2 H), 2.57 (dddd, *J* = 13.4, 13.4, 13.1, 3.8 Hz, 1 H), 3.71 (dd, *J* = 12.6, 4.4 Hz, 1 H), 4.29-4.40 (m, 2 H), 6.61 (s, 1 H), 6.64 (s, 1 H), 7.51-7.57 (m, 4 H), 7.63-7.69 (m, 2 H), 8.03-8.06 (m, 2 H), 8.16-8.19 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.3 (q), 21.0 (t), 25.2 (t), 32.0 (t), 32.1 (t), 40.2 (d), 61.3 (t), 91.6 (s), 128.2 (d), 128.9 (d), 129.9 (t), 131.41 (d), 131.44 (d), 134.0 (d), 134.3 (d), 137.0 (s), 139.8 (s), 140.1 (s), 168.7 (s); exact mass (electrospray) *m/z* calcd for $C_{23}H_{26}NaO_6S_2$ 485.1063, found 485.1066.

3-Hydroxy-2,7,7-tris(phenylthio)heptanoic Acid Ethyl Ester (40.5e,e').



40.5a **40.5e,e'**

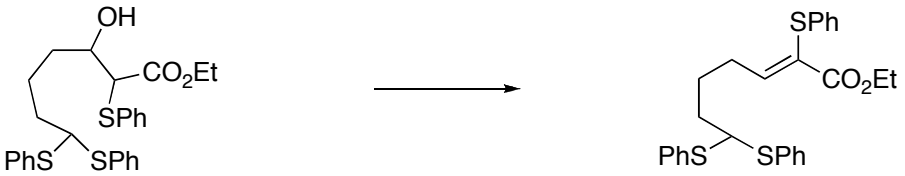
n-BuLi (1.3 M in hexane, 0.68 mL, 0.88 mmol) was added dropwise to a stirred and cooled (0 °C) solution of *i*-Pr_2NH (89.0 mg, 0.88 mmol) in THF (4 mL). Stirring at 0 °C was continued for 15 min, the mixture was cooled to -78 °C, and a solution of (phenylthio)acetic acid ethyl ester[69] (172.5 mg, 0.88 mmol) in THF (2.5 mL) was then added dropwise. Stirring at -78 °C was continued for 40 min, and a solution of **40.5a** (190 mg, 0.63 mmol) in THF (2 mL) was added dropwise. Stirring at -78 °C was continued for 70 min and the mixture was quenched with saturated aqueous NH_4Cl (5 mL). The cold bath was removed, stirring was continued for 15 min and the mixture was diluted with water (50 mL). The aqueous phase was extracted with EtOAc (3 x 20 mL) and the combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2.5 x 15 cm), using 1:3 Et_2O-hexane, 9:20 Et_2O-hexane and then 7:10 Et_2O-hexane, gave **40.5e** (less polar isomer) (91 mg, 29%) as a viscous oil, which appeared to contain an impurity (NMR), and **40.5e'** (more polar isomer) (130 mg, 41%) as a viscous oil.

Compound **40.5e** had: FTIR ($CDCl_3$ cast) 3514, 3058, 2933, 1727, 1583, 1480, 1439 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.90 (t, *J* = 7.4 Hz, 0.7 H), 1.20 (t, *J* = 7.1 Hz, 2.3 H), 1.27-1.38 (m, 0.5 H), 1.51-1.77 (m, 2.5 H), 1.81-1.91 (m, 3 H), 2.71 (d, *J* = 6.6 Hz, 0.2 H), 3.12 (dd, *J* = 2.9, 0.8 Hz, 0.8 H), 3.59 (d, *J* = 5.7 Hz, 0.8 H), 3.63 (d, *J* = 7.1 Hz, 0.2 H), 3.86-3.91 (m, 0.2 H), 3.91-3.98 (m, 0.8 H), 4.09-4.22 (m, 2 H), 4.40 (dd, *J* = 6.5, 6.5 Hz, 1 H), 7.25-7.34 (m, 9 H), 7.44-7.52 (m, 6 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.6 (q), 134.0 (q), 19.0 (t), 23.19 (t), 23.23 (t), 30.4 (t), 33.2 (t), 33.6 (t), 35.50 (t), 35.53 (t), 59.0 (d), 57.7 (d), 58.2 (d), 58.3 (d), 61.4 (t), 65.3 (t), 70.2 (t), 71.4 (t), 127.66 (d), 127.68 (d), 128.1 (d), 128.2 (d), 128.8 (d), 128.85 (d), 128.86 (d), 129.06 (d), 129.07 (d), 132.72 (d), 132.74 (d), 132.76 (d), 132.9 (d), 133.0 (d), 133.3 (s), 134.11 (s), 134.14 (s), 171.66 (s), 171.72 (s); exact mass (electrospray) *m/z* calcd for $C_{27}H_{30}NaO_3S_3$ 521.1249, found 521.1252.

Compound **40.5e'** had: FTIR ($CDCl_3$ cast) 3497, 3058, 2980, 2917, 2849, 1729, 1583, 1480, 1474, 1439 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.21 (t, *J* = 7.1 Hz, 3 H), 1.44-1.59 (m, 1 H), 1.66-1.75 (m, 1 H), 1.78-1.89 (m, 4 H), 2.70 (d, *J* =

6.6 Hz, 1 H), 3.61 (d, *J* = 7.1 Hz, 1 H), 3.89 (dddd, *J* = 8.5, 6.8, 6.8, 2.6 Hz, 1 H), 4.10-4.21 (m, 2 H), 4.39 (dd, *J* = 6.4, 6.4 Hz, 1 H), 7.27-7.33 (m, 9 H), 7.45-7.48 (m, 6 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.0 (q), 23.2 (t), 33.6 (t), 35.5 (t), 56.0 (d), 58.3 (d), 61.4 (t), 71.4 (d), 127.7 (d), 128.2 (d), 128.9 (d), 129.1 (d), 132.8 (d), 133.1 (d), 134.1 (d), 171.6 (s); exact mass (electrospray) *m*/*z* calcd for $C_{27}H_{30}NaO_3S_3$ 521.1249, found 521.1248.

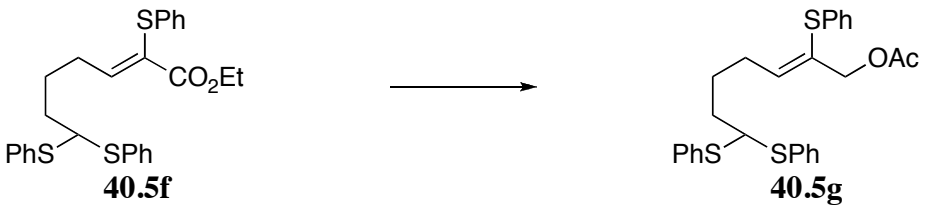
(*Z*)-2,7,7-Tris(phenylthio)hept-2-enoic Acid Ethyl Ester (40.5f).



40.5e' **40.5f**

MsCl (24.8 mg, 0.216 mmol) and Et_3N (43.7 mg, 0.432 mmol) were added sequentially to a stirred and cooled (0 °C) solution of **40.5e'** (36 mg, 0.072 mmol) in CH_2Cl_2 (1 mL). Stirring at 0 °C was continued for 3 h and DBU (65.8 mg, 0.432 mmol) was added. The cold bath was removed, stirring was continued for 3 h and the mixture was diluted with water (3 mL) and acidified with hydrochloric acid (1 M, 3 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 2:25 EtOAc-hexane, gave **40.5f** (24 mg, 69%) as an oil: FTIR ($CDCl_3$ cast) 3073, 3058, 2980, 2935, 2859, 1712, 1608, 1583, 1479, 1439 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.09 (t, *J* = 7.1 Hz, 3 H), 1.79-1.92 (m, 4 H), 2.51 (t, *J* = 7.1 Hz, 2 H), 4.11 (q, 7.1 Hz, 2 H), 4.39 (t, *J* = 1.0 Hz, 1 H), 7.13-7.35 (m, 12 H), 7.44-7.47 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.9 (q), 25.8 (t), 30.1 (t), 35.3 (t), 58.2 (d), 61.5 (t), 126.1 (d), 127.5 (s), 127.8 (d), 128.2 (d), 128.9 (d), 132.9 (d), 133.9 (s), 135.8 (s), 151.7 (d), 165.2 (s); exact mass (electrospray) *m*/*z* calcd for $C_{27}H_{28}NaO_2S_3$ 503.1144, found 503.1143. We assign the *Z* geometry by analogy with the assignment to **40.6g**.

Acetic Acid (*Z*)-2,7,7-tris(phenylthio)hept-2-enyl Ester (40.5g).



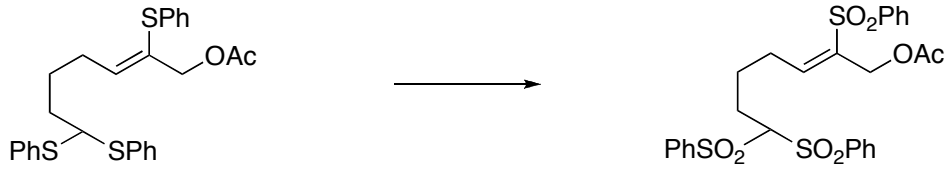
40.5f **40.5g**

DIBAL (1.0 M in PhMe, 0.1 mL, 0.1 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of **40.5f** (14.1 mg, 0.029 mmol) in CH_2Cl_2 (1 mL), and stirring at -78 °C was continued for 15 min. The cold bath was removed and stirring was continued for 15 min. MeOH (0.4 mL) and saturated aqueous Rochelle salt (1 mL) were added sequentially, and stirring was continued for 30 min. The aqueous phase was extracted with CH_2Cl_2 (2 x 1 mL) and the combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. The residual crude alcohol (9.4 mg, 86%) was used directly for the next step.

Pyridine (12 mg, 0.15 mmol) and AcCl (5.9 mg, 0.075 mmol) were added sequentially to a stirred and cooled (-10 °C, ice-acetone bath) solution of the above crude alcohol (9.4 mg, 0.025 mmol) and DMAP (0.4 mg, 0.003 mmol) in CH_2Cl_2 (0.5 mL). The cold bath was left in place but not recharged and stirring was continued for 16 h, by which time the temperature had risen to room temperature. The mixture was diluted with water (2 mL), acidified with hydrochloric acid (1 M, 0.1 mL) and extracted with CH_2Cl_2 (3 x 2 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (0.7 x 7.5 cm), using 1:10 EtOAc-hexane, gave **40.5g** (7 mg, 58% from **40.5f**) as an oil: FTIR ($CDCl_3$ cast) 3058, 3019, 2934, 2856, 1741, 1583, 1478, 1438 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.74-1.80 (m, 2 H), 1.85-1.90 (m, 2 H), 2.00 (s, 3 H), 2.39 (q, J = 7.3 Hz, 2 H), 4.41 (t, J = 6.6 Hz, 1 H), 4.54 (d, J = 0.6 Hz, 2 H), 6.17 (t, J = 7.2 Hz, 1 H), 7.18-7.22 (m, 1 H), 7.27-7.32 (m, 10 H), 7.45-7.47 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.8 (q), 26.3 (t), 29.0 (t), 35.2 (t), 58.3 (d), 66.9 (t), 126.5 (d), 127.8 (d), 128.6 (s), 128.9 (d), 129.0 (d), 129.5 (d), 132.9 (d), 134.1 (s),

134.2 (s), 139.6 (d), 170.4 (s); exact mass (electrospray) *m*/*z* calcd for $C_{27}H_{28}NaO_2S_3$ 503.1144, found 503.1145. We assign the *Z* geometry by analogy with the assignment to **25h**.

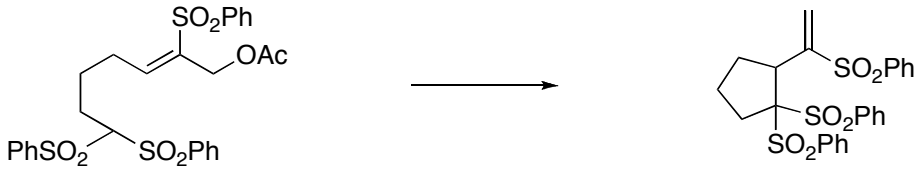
Acetic Acid (*Z*)-2,7,7-Tris(benzenesulfonyl)hept-2-enyl Ester (40.5h).



40.5g **40.5h**

m-CPBA (70-75%, 39 mg, 0.16 mmol) was added to a solution of **40.5g** (6.3 mg, 0.013 mmol) in CH_2Cl_2 (1 mL), and the mixture was stirred at 40 °C for 24 h, cooled to room temperature and evaporated. Flash chromatography of the residue over silica gel (0.7 x 7 cm), using 4:5 EtOAc-hexane, gave **40.5h** (5.5 mg, 73%) as a viscous oil: FTIR ($CDCl_3$ cast) 3060, 2934, 1742, 1640, 1580, 1447 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.83-1.89 (tt, *J* = 15.0, 15.0 Hz, 2 H), 1.92 (s, 3 H), 2.21-2.25 (m, 2 H), 2.70 (q, *J* = 7.7 Hz, 2 H), 4.59 (t, *J* = 5.7 Hz, 1 H), 4.79 (s, 2 H), 6.39 (t, *J* = 8.0 Hz, 1 H), 7.55-7.59 (m, 6 H), 7.63-7.66 (m, 1 H), 7.69-7.72 (m, 2 H), 7.92-7.96 (m, 6 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.7 (q), 24.9 (t), 26.8 (t), 27.6 (t), 63.8 (t), 82.5 (d), 127.6 (d), 129.1 (d), 129.3 (d), 129.6 (d), 133.7 (d), 134.6 (d), 137.6 (s), 137.8 (s), 141.1 (s), 147.4 (d), 170.0 (s); exact mass (electrospray) *m*/*z* calcd for $C_{27}H_{28}NaO_8S_3$ 599.0839, found 599.0842.

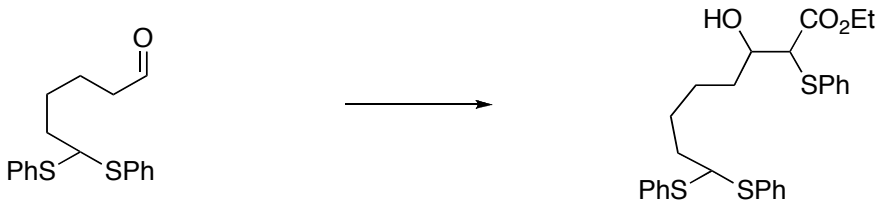
[[1-[2,2-Bis(phenylsulfonyl)cyclopent-1-yl]ethenyl]sulfonyl]benzene (51.11).



40.5h **51.11**

Cs_2CO_3 (6.0 mg, 0.018 mmol) was added to a stirred solution of **40.5h** (5.10 mg, 0.0089 mmol) in THF (0.5 mL). Stirring at room temperature was continued for 1 h, and the solvent was evaporated. Flash chromatography of the residue over silica gel (0.7 x 7 cm), using 3:5 EtOAc-hexane, gave **51.11** (3.9 mg, 85%) as a viscous oil: FTIR ($CDCl_3$ cast) 3066, 2962, 2925, 1583, 1478, 1447 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.44-1.52 (m, 1 H), 1.83-1.92 (m, 2 H), 2.20-2.08 (m, 1 H), 2.19-2.25 (m, 1 H), 2.60 (ddd, *J* = 15.2, 9.5, 6.9 Hz, 1 H), 4.13 (ddd, *J* = 10.5, 1.2 Hz, 1 H), 6.38 (d, *J* = 2.5 Hz, 1 H), 6.77 (dd, *J* = 2.5, 1.2 Hz, 1 H), 7.53-7.59 (m, 6 H), 7.61-7.64 (m, 1 H), 7.68-7.71 (m, 2 H), 7.91-7.93 (m, 2 H), 8.09-8.11 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.1 (t), 33.8 (t), 34.5 (t), 47.5 (d), 96.0 (s), 128.1 (d), 128.6 (d), 128.9 (d), 129.1 (d), 130.8 (t), 131.0 (d), 131.9 (d), 133.4 (d), 134.6 (d), 134.8 (d), 136.5 (s), 138.4 (s), 140.1 (s), 147.0 (s); exact mass (electrospray) *m/z* calcd for $C_{25}H_{24}NaO_6S_3$ 539.0627, found 539.0622.

3-Hydroxy-2,8,8-tris(phenylthio)octanoic Acid Ethyl Ester (40.6e,e').



40.6a **40.6e,e'**

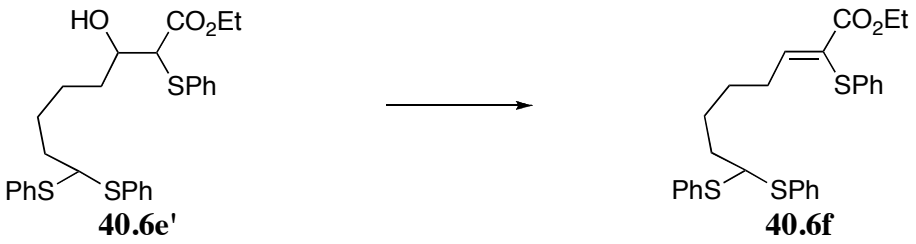
n-BuLi (1.3 M in hexane, 0.95 mL, 1.23 mmol) was added dropwise to a stirred and cooled (0 °C) solution of *i*-Pr_2NH (124.4 mg, 1.23 mmol) in THF (6 mL). Stirring at 0 °C was continued for 15 min, the mixture was cooled to -78 °C, and a solution of (phenylthio)acetic acid ethyl ester[69] (241.1 mg, 1.23 mmol) in THF (1 mL) was then added dropwise. Stirring at -78 °C was continued for 40 min, and a solution of **40.6a** (277.5 mg, 0.88 mmol) in THF (1.5 mL) was added dropwise. Stirring at -78 °C was continued for 1 h, and the mixture was quenched with saturated aqueous NH_4Cl (5 mL). The cold bath was removed, stirring was continued for 15 min and the mixture was diluted with water (50 mL). The

aqueous phase was extracted with EtOAc (3 x 20 mL) and the combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2.5 x 15 cm), using 1:3 Et_2O-hexane and then 2:5 Et_2O-hexane, gave **40.6e** (less polar isomer) (166 mg, 37%) as a viscous oil and **40.6e'** (more polar isomer) (200 mg, 44%) as a viscous oil.

Compound **40.6e** had: FTIR ($CDCl_3$ cast) 3512, 3073, 3058, 3018, 2979, 2938, 2859, 1728, 1583, 1480, 1439 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.22 (t, *J* = 7.1 Hz, 3 H), 1.32-1.39 (m, 1 H), 1.48-1.71 (m, 5 H), 1.86 (dd, *J* = 14.9, 7.3 Hz, 2 H), 3.11 (dd, *J* = 2.9, 0.7 Hz, 1 H), 3.59 (d, *J* = 5.8 Hz, 1 H), 3.96 (ddd, *J* = 8.8, 6.4, 3.4 Hz, 1 H), 4.11-4.22 (m, 2 H), 4.41 (dd, *J* = 6.7, 6.7 Hz, 1 H), 7.26-7.34 (m, 9 H), 7.45-7.48 (m, 4 H), 7.50-7.52 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.0 (q), 25.1 (t), 26.8 (t), 33.7 (t), 35.6 (t), 57.8 (d), 58.3 (d), 61.4 (t), 70.3 (d), 127.6 (d), 128.0 (d), 128.8 (d), 129.0 (d), 132.7 (d), 132.9 (d), 133.4 (s), 134.2 (s), 171.7 (s); exact mass (electrospray) *m/z* calcd for $C_{28}H_{32}NaO_3S_3$ 535.1406, found 535.1403.

Compound **40.6e'** had: FTIR ($CDCl_3$ cast) 3497, 3058, 2981, 2938, 2859, 1729, 1583, 1480, 1439 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.15 (t, *J* = 7.1 Hz, 3 H), 1.27-1.36 (m, 1 H), 1.41-1.50 (m, 2 H), 1.54-1.66 (m, 2 H), 1.72-1.77 (m, 1 H), 1.82 (dd, *J* = 14.8, 7.3 Hz, 2 H), 2.71 (d, *J* = 6.7 Hz, 1 H), 3.56 (d, *J* = 7.0 Hz, 1 H), 3.85 (dddd, *J* = 8.7, 6.9, 6.9, 3.4 Hz, 1 H), 4.06-4.15 (m, 2 H), 4.36 (dd, *J* = 6.7, 6.7 Hz, 1 H), 7.21-7.28 (m, 9 H), 7.40-7.44 (m, 6 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.0 (q), 25.9 (t), 26.7 (t), 34.0 (t), 35.6 (t), 56.1 (d), 58.3 (d), 61.4 (t), 71.4 (d), 127.6 (d), 128.1 (d), 128.8 (d), 129.0 (d), 132.6 (d), 132.7 (d), 132.9 (s), 133.0 (d), 134.2 (s), 171.6 (s); exact mass (electrospray) *m/z* calcd for $C_{28}H_{32}NaO_3S_3$ 535.1406, found 535.1407.

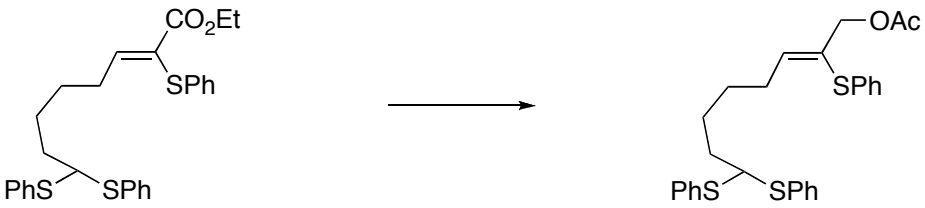
(*Z*)-2,8,8-Tris(phenylthio)octanoic Acid Ethyl Ester (40.6f).



40.6e' **40.6f**

MsCl (143.3 mg, 1.25 mmol) and Et_3N (254 mg, 2.51 mmol) were added sequentially to a stirred and cooled (0 °C) solution of **40.6e'** (214 mg, 0.42 mmol) in CH_2Cl_2 (3 mL). Stirring at 0 °C was continued for 2.5 h, DBU (382 mg, 2.51 mmol) was added and stirring at 0 °C was continued for 3 h. The mixture was diluted with water (5 mL) and acidified with hydrochloric acid (1 M, 3 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 15 cm), using 1:10 EtOAc-hexane, gave **40.6f** (110 mg, 53%) as an oil: FTIR ($CHCl_3$ cast) 3057, 2980, 2935, 2857, 1710, 1608, 1583, 1478, 1438 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.09 (t, *J* = 7.1 Hz, 3 H), 1.48 (dddd, *J* = 7.7 Hz, 2 H), 1.65-1.71 (m, 2 H), 1.85-1.90 (m, 2 H), 2.51 (dd, *J* = 15.0, 7.5 Hz, 2 H), 4.12 (q, *J* = 7.1 Hz, 2 H), 4.39 (t, *J* = 13.4 Hz, 1 H), 7.14-7.18 (m, 1 H), 7.22-7.33 (m, 10 H), 7.34-7.37 (t, *J* = 7.5 Hz, 1 H), 7.45-7.47 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.9 (q), 26.7 (t), 27.8 (t), 30.5 (t), 35.5 (t), 58.3 (d), 61.5 (t), 126.0 (d), 127.1 (s), 127.7 (d), 128.2 (d), 128.9 (d), 132.8 (d), 134.2 (s), 135.9 (s), 152.3 (d), 165.3 (s); exact mass (electrospray) *m*/*z* calcd for $C_{28}H_{30}NaO_2S_3$ 517.1300, found 517.1301. We assign a *Z* geometry based on the assignment made to the derived acetate **25h**.

Acetic Acid (*Z*)-2,8,8-Tris(phenylthio)oct-2-enyl Ester (40.6g).



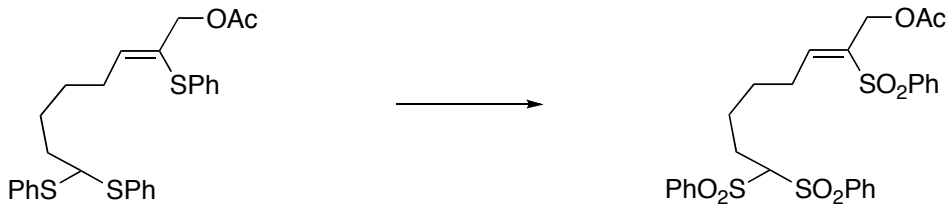
40.6f **40.6g**

DIBAL (1.0 M in PhMe, 0.44 mL, 0.44 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of **40.6f** (73.0 mg, 0.148 mmol) in CH_2Cl_2 (5 mL), and stirring at -78 °C was continued for 15 min. The cold bath was removed and stirring was continued for 15 min. MeOH (2 mL) and saturated aqueous Rochelle salt (4 mL) were added sequentially, and stirring was continued for 30 min. The aqueous phase was extracted with CH_2Cl_2 (2 x 1 mL) and the combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. The residual crude alcohol was used directly for the next step.

Pyridine (70.4 mg, 0.89 mmol) and AcCl (34.5 mg, 0.44 mmol) were added sequentially to a stirred and cooled (-10 °C, ice-acetone bath) solution of the above crude alcohol and DMAP (1.8 mg, 0.015 mmol) in CH_2Cl_2 (2 mL). The cold bath was left in place but not recharged and stirring was continued for 16 h, by which time the temperature had risen to room temperature. The mixture was diluted with water (10 mL), acidified with hydrochloric acid (1 M, 5 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.0 x 7.5 cm), using 3:25 EtOAc-hexane, gave **40.6g** (53.4 mg, 73% from **40.6f**) as an oil: FTIR ($CDCl_3$ cast) 3057, 2932, 2855, 1740, 1582, 1478, 1438 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.42 (tt, *J* = 15.2, 15.2 Hz, 2 H), 1.63-1.69 (m, 2 H), 1.85-1.89 (m, 2 H), 2.00 (s, 3 H), 2.38 (dd, *J* = 14.9, 7.4 Hz, 2 H), 4.40 (t, *J* = 6.7 Hz, 1 H), 4.57 (d, *J* = 0.9 Hz, 2 H), 6.21 (tt, *J* = 7.2, 1.2 Hz, 1 H), 7.18-7.21 (m, 1 H), 7.26-7.33 (m, 10 H), 7.45-7.47 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.8 (q), 26.7 (t), 28.3 (t), 29.4 (t), 35.6 (t), 58.4 (d), 67.0 (t),

126.4 (d), 127.7 (d), 128.2 (s), 128.9 (d), 129.0 (d), 129.5 (d), 132.7 (d), 134.2 (s), 134.3 (s), 140.3 (d), 170.4 (s); exact mass (electrospray) *m*/*z* calcd for $C_{28}H_{30}NaO_2S_3$ 517.1300, found 517.1305. TROESY measurements [nOe between vinyl hydrogen and C**H**$_2$O] suggested that the double bond has *Z* geometry.

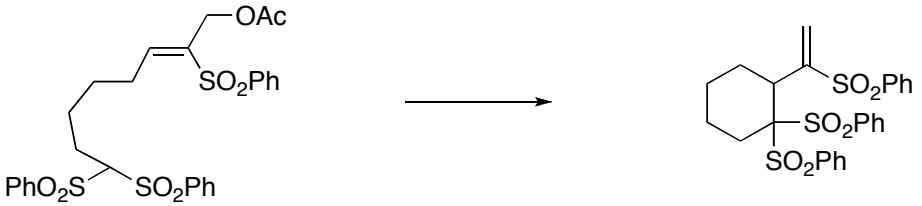
Acetic Acid (*Z*)-2,8,8-Tris(benzenesulfonyl)oct-2-enyl Ester (40.6h).



40.6g **40.6h**

m-CPBA (70-75%, 146 mg, 0.59 mmol) was added to a solution of **40.6g** (24.4 mg, 0.049 mmol) in CH_2Cl_2 (1 mL), and the mixture was stirred at 40 °C for 24 h, cooled to room temperature and evaporated. Flash chromatography of the residue over silica gel (0.7 x 15 cm), using 9:10 EtOAc-hexane, gave **40.6h** (22 mg, 76%) as a viscous oil: FTIR ($CDCl_3$ cast) 3066, 2928, 1743, 1639, 1584, 1448 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.39 (quintet, *J* = 15.3 Hz, 2 H), 1.60-1.67 (m, 2 H), 1.92 (s, 3 H), 2.15-2.19 (m, 2 H), 2.62 (dd, *J* = 15.3, 7.7 Hz, 2 H), 4.41 (t, *J* = 5.7 Hz, 1 H), 4.82 (s, 2 H), 6.40 (t, *J* = 7.9 Hz, 1 H), 7.54-7.64 (m, 7 H), 7.68-7.71 (m, 2 H), 7.91-7.96 (m, 6 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.7 (q), 25.2 (t), 27.5 (t), 28.0 (t), 28.1 (t), 64.0 (t), 83.3 (d), 127.5 (d), 129.1 (d), 129.3 (d), 133.5 (d), 134.6 (d), 136.9 (s), 137.8 (s), 141.4 (s), 148.7 (d), 170.1 (s); exact mass (electrospray) *m*/*z* calcd for $C_{28}H_{30}NaO_8S_3$ 613.0995, found 613.0996.

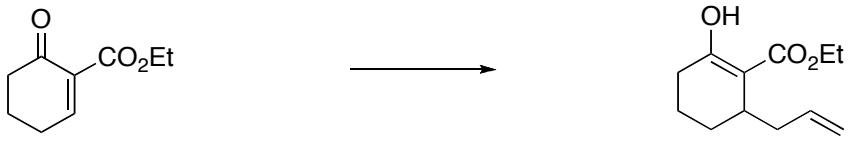
[[1-[2,2-Bis(phenylsulfonyl)cyclohex-1-yl]ethenyl]sulfonyl]benzene (51.13).



40.6h **51.13**

Cs_2CO_3 (13.9 mg, 0.043 mmol) was added to a stirred solution of **40.6h** (12.6 mg, 0.021 mmol) in THF (0.5 mL). Stirring at room temperature was continued for 2 h and the solvent was evaporated. Flash chromatography of the residue over silica gel (0.7 x 7 cm), using 3:2 Et_2O-hexane, gave **51.13** (5.3 mg, 47%) as a viscous oil: FTIR (CH_2Cl_2 cast) 3066, 2932, 2858, 1583, 1478, 1447 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.22-1.26 (m, 1 H), 1.54-1.60 (m, 1 H), 1.72-1.76 (m, 1 H), 1.86-1.98 (m, 3 H), 2.03-2.06 (m, 1 H), 2.40 (ddd, *J* = 15.7, 12.8, 3.9 Hz, 1 H), 3.87 (dd, *J* = 11.6, 4.1 Hz, 1 H), 6.28 (d, *J* = 3.0 Hz, 1 H), 7.01 (d, *J* = 3.0 Hz, 1 H), 7.52-7.59 (m, 6 H), 7.61-7.64 (m, 1 H), 7.66-7.71 (m, 2 H), 8.02 (dd, *J* = 8.4, 1.3 Hz, 2 H), 8.09 (dd, *J* = 8.5, 1.1 Hz, 2 H), 8.21 (dd, *J* = 8.4, 1.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.8 (t), 24.6 (t), 32.0 (t), 32.4 (t), 41.5 (d), 92.0 (s), 128.5 (d), 128.6 (d), 128.9 (d), 129.1 (d), 129.8 (t), 131.0 (d), 132.0 (d), 133.4 (d), 134.3 (d), 134.5 (d), 137.2 (s), 139.5 (s), 140.3 (s), 150.4 (s); exact mass (electrospray) *m*/*z* calcd for $C_{26}H_{26}NaO_6S_3$ 553.0784, found 553.0782.

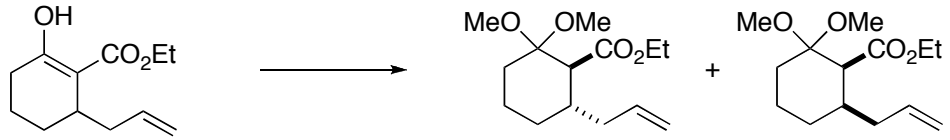
2-Allyl-6-oxocyclohexanecarboxylic Acid Ethyl Ester (45.1).[†]



- **45.1**

$TiCl_4$ (21 mL, 20.62 mmol) and allyltrimethylsilane (4.4 mL, 27.5 mmol) were added dropwise (over ca 10 min) to a stirred and cooled (-78 °C) solution of ethyl 6-oxocyclohex-1-enecarboxylate[76] (2.6 g, 19.6 mmol) in CH_2Cl_2 (50 mL). Stirring was continued for 20 min and aqueous Na_2CO_3 (20%, 50 mL) was added. The cold bath was removed and the aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (3 x 16 cm), using 20% EtOAc-hexane, gave **45.1** (3.81 g, 92%) as a colorless oil which was an inseparable equilibrium mixture of keto-enol tautomers (^{13}C NMR): FTIR (CH_2Cl_2 cast) 3076, 2979, 2940, 2870, 1743, 1714, 1642, 1614, 1216, 915 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.31-1.39 (m, 3 H), 1.42-1.83 (m, 3 H), 1.96-2.45 (5 H), 2.50-2.57 (m, 0.7 H), 2.63-2.68 (m, 0.4 H), 3.20 (dd, *J* = 11.1, 1.2 Hz, 0.5 H), 4.19-4.37 (m, 2 H), 5.02-5.15 (m, 2 H), 5.74-5.91 (m, 1 H), 12.47 (s, 0.4 H); exact mass (electrospray) *m/z* calcd for $C_{12}H_{18}NaO_3$ 233.1148, found 233.1147.

***Trans*-6-Allyl-2,2-dimethoxycyclohexanecarboxylic Acid Ethyl Ester (45.2a) and *Cis*-6-Allyl-2,2-dimethoxycyclohexanecarboxylic Acid Ethyl Ester (45.2a').**[†]



45.1 **45.2a** **45.2a'**

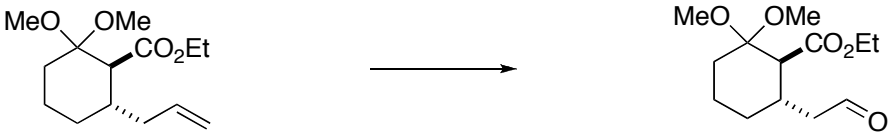
p-TsOH·H_2O (171 mg, 0.9 mmol) was added to a stirred solution of **45.1** (3.75 g, 17.83 mmol) and $HC(OMe)_3$ (2.54 mL, 23.18 mmol) in dry MeOH (35 mL). Stirring was continued for 24 h and the mixture was quenched with saturated aqueous $NaHCO_3$ (20 mL), diluted with water (30 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (4 x 20 cm), using 15% EtOAc-hexanes gave **45.2a'** (less polar isomer) (1.75 g, 38%, *cis*-

isomer) as a viscous oil and **45.2a** (more polar isomer) (2.55g, 56%, major, *trans*-isomer) as a viscous oil.

Compound **45.2a** had: FTIR (CH_2Cl_2 cast) 2942, 2832, 1734, 1641, 1447, 1182, 916 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.26 (t, *J* = 7.2 Hz, 3 H), 1.29-1.48 (m, 2 H), 1.56-1.70 (m, 2 H), 1.74-1.83 (m, 2 H), 1.87-2.03 (m, 3 H), 3.01 (dd, *J* = 4.4, 1.6 Hz, 1 H), 3.14 (s, 3 H), 3.2 (s, 3 H), 4.14 (q, *J* = 7.2 Hz, 2 H), 4.98-5.02 (m, 2 H), 5.73-5.83 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2 (q), 21.6 (t), 26.0 (t), 27.6 (t), 37.1 (d), 38.5 (t), 47.3 (q), 47.8 (q), 50.3 (d), 59.9 (t), 100.8 (s), 116.3 (t), 136.6 (d), 171.4 (s); exact mass (electrospray) *m/z* calcd for $C_{14}H_{24}NaO_4$ 279.1567, found 179.1565.

Compound **45.2a'** had: FTIR (CH_2Cl_2 cast) 2943, 2833, 1736, 1640, 1448, 1177, 1050, 913 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.10-1.18 (m, 1 H), 1.26 (t, *J* = 7.2 Hz, 3 H), 1.38-1.60 (m, 3 H), 1.80-1.88 (m, 1 H), 1.95-2.06 (m, 3 H), 2.14-2.20 (m, 1 H), 2.59 (d, *J* = 6.4 Hz, 1 H), 3.20 (s, 3 H), 3.21 (s, 3 H), 4.14 (q, *J* = 7.2 Hz, 2 H), 4.98-5.02 (m, 2 H), 5.67-5.78 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.1 (q), 19.7 (t), 27.5 (t), 30.2 (t), 36.7 (d), 38.0 (t), 48.2 (q), 48.6 (q), 53.2 (d), 60.1 (t), 100.8 (s), 116.4 (t), 136.9 (d), 172.4 (s); exact mass (electrospray) calcd for $C_{14}H_{24}NaO_4$ 279.15668, found 279.15672.

***Trans*-2,2-Dimethoxy-6-(2-oxoethyl)cyclohexanecarboxylic Acid Ethyl Ester (40.8a).**[†]

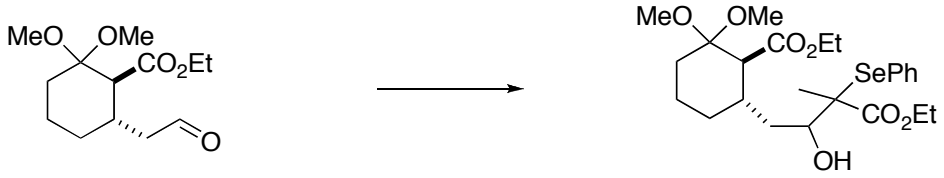


45.2a **40.8a**

O_3 was bubbled into a stirred and cooled (-78 °C) solution of **45.2a** (2.1 g, 8.2 mmol) in CH_2Cl_2 (100 mL) for 30 min, by which time a blue color persisted. O_2 was passed through the solution for 30 min and Ph_3P (3 g, 11.4 mmol) was then added. The cold bath was removed after 30 min and stirring was continued

for 10 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (4 x 18 cm), using 20% EtOAc-hexane, gave **40.8a** (2.02 g, 96%) as a colorless viscous oil: FTIR (CH_2Cl_2 cast) 2946, 1734, 1181, 1049 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.16-1.22 (m, 1 H), 1.25 (t, *J* = 7.0 Hz, 3 H), 1.49-1.54 (m, 2 H), 1.62-1.67 (m, 1 H), 1.92-2.02 (m, 2 H), 2.45 (ddd, *J* = 18.0, 9.5, 2.0 Hz, 1 H), 2.54-2.60 (m, 2 H), 2.65-2.66 (m, 1 H), 3.18 (s, 3 H), 3.19 (s, 3 H), 4.10-4.17 (m, 2 H), 9.69-9.70 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.1 (q), 19.1 (t), 27.6 (t), 29.3 (t), 31.1 (d), 48.0 (t), 48.2 (q), 48.3 (q), 52.1 (d), 60.4 (t), 100.5 (s), 171.9 (s), 201.9 (d). The aldehyde is sensitive and attempts to obtain its mass spectrum invariably led to the mass spectrum of the derived carboxylic acid.

6-[3-Ethoxycarbonyl-2-hydroxy-3-(phenylseleno)butyl]-2,2-dimethoxycyclohexanecarboxylic Acid Ethyl Ester (40.8b-1, 40.8b-2, 40.8b-3, 40.8b-4).[†]



40.8a **40.8b**

n-BuLi (2.5 M in hexane, 3.29 mL, 8.23 mmol) was added over ca 5 min to a stirred and cooled (-78 °C) solution of *i*-Pr_2NH (1.25 mL, 8.88 mmol) in THF (15 mL). Stirring was continued for 40 min and a solution of **38.1** (2.368 g, 9.21 mmol) in THF (10 mL plus 2 mL as a rinse) was added over ca 5 min. Stirring was continued for 1 h and a solution of **40.8a** (1.7 g, 6.58 mmol) in THF (10 mL plus 2 mL as a rinse) was added over ca 5 min. Stirring at -78 °C was continued for 3 h and the mixture was quenched with saturated aqueous NH_4Cl (10 mL). The cold bath was removed, stirring was continued for 10 min and the mixture was diluted with water (50 mL) and extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. ^1H NMR analysis of the crude residue indicated a 30:25:24:21 mixture of 4 diastereomers.

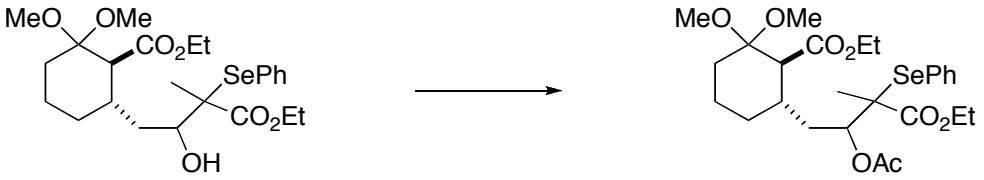
Flash chromatography of the residue over silica gel (4 x 22 cm), using 15% EtOAc-hexane, gave **40.8b** as four fractions: **40.8b-1** (least polar) (520 mg, 15%, single isomer) as a viscous oil, **40.8b-2** and **40.8b-3** (1.2 g, 35%, mixture of two diastereoisomers) as a viscous oil and **40.8b-4** (most polar) (610 mg, 18%, single isomer) as a viscous oil.

Compound **40.8b-1** had: FTIR (CH_2Cl_2 cast) 3507, 2938, 1722, 1246, 1050, 744 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.16 (t, *J* = 7.2 Hz, 3 H), 1.26 (t, *J* = 7.2 Hz, 3 H), 1.37 (s, 3 H), 1.50-1.55 (m, 4 H), 1.64-1.72 (m, 2 H), 1.96-2.05 (m, 2 H), 2.15-2.20 (m, 1 H), 2.71 (d, *J* = 5.2 Hz, 1 H), 3.15 (s, 3 H), 3.20 (s, 3 H), 3.99-4.20 (m, 5 H), 7.29-7.34 (m, 2 H), 7.38-7.42 (m, 1 H), 7.58-7.63 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.8 (q), 14.1 (q), 17.5 (q), 19.2 (t), 28.5 (t), 29.3 (t), 34.6 (d), 36.0 (t), 48.07 (q), 48.12 (q), 51.5 (d), 57.6 (s), 60.1 (t), 61.1 (t), 72.3 (d), 100.7 (s), 126.6 (s), 128.8 (d), 129.3 (d), 138.0 (d), 172.4 (s), 173.4 (s); exact mass (electrospray) *m/z* calcd for $C_{24}H_{36}NaO_7{}^{80}Se$ 539.1519, found 539.1512.

The middle fraction containing compounds **40.8b-2** and **40.8b-3** had: (data on a fraction containing a 76:24 mixture of diastereomers) FTIR (CH_2Cl_2 cast) 3507, 2939, 1727, 1439, 1247, 1051, 744 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.09 (t, *J* = 7.2 Hz, 0.7 H), 1.18 (t, *J* = 7.2 Hz, 2.3 H), 1.24-1.29 (m, 4 H), 1.39 (s, 2.3 H), 1.42 (s, 0.7 H), 1.44-1.57 (m, 2 H), 1.62-1.72 (m, 1 H), 1.89-2.26 (m, 4 H), 2.77 (br d, *J* = 4.8 Hz, 0.3 H), 2.83 (br d, *J* = 3.6 Hz, 0.7 H), 2.92 (br d, *J* = 7.6 Hz, 0.7 H), 3.08 (br d, *J* = 2.8 Hz, 0.3 H), 3.16 (s, 0.7 H), 3.18 (s, 2.3 H), 3.20 (s, 0.7 H), 3.24 (s, 2.3 H), 3.94-4.22 (m, 5 H), 7.28-7.32 (m, 2 H), 7.36-7.41 (m, 1 H), 7.58-7.63 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.8 (q), 13.9 (q), 14.2 (q), 16.9 (q), 18.7 (t), 18.8 (q), 19.2 (t), 25.7 (t), 28.7 (t), 29.2 (t), 29.3 (t), 34.0 (d), 34.3 (d), 35.5 (t), 35.9 (t), 48.0 (q), 48.05 (q), 48.1 (q), 50.8 (d), 52.3 (d), 55.2 (s), 57.4 (s), 60.3 (t), 61.0 (t), 61.2 (t), 70.9 (d), 74.5 (d), 100.7 (s), 100.8 (s), 126.6 (s), 126.9 (s), 128.7 (d), 128.8 (d), 129.3 (d), 129.4 (d), 138.0 (d), 138.2 (d), 172.4 (s), 172.5 (s), 172.8 (s), 174.0 (s); exact mass (electrospray) *m/z* calcd for $C_{24}H_{36}NaO_7{}^{80}Se$ 539.1519, found 539.1520.

Compound **40.8b-4** had: FTIR (CH_2Cl_2 cast) 3502, 2941, 2833, 1728, 1439, 1246, 1051, 744 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.19 (t, *J* = 7.2 Hz, 3 H), 1.24-1.30 (m, 1 H), 1.25 (t, *J* = 7.2 Hz, 3 H), 1.37-1.46 (m, 1 H), 1.38 (s, 3 H), 1.50-1.58 (m, 2 H), 1.65-1.71 (m, 1 H), 1.94-2.07 (m, 3 H), 2.24 (dddd, *J* = 9.6, 9.6, 5.2, 5.2 Hz, 1 H), 2.77 (dd, *J* = 5.2, 0.8 Hz, 1 H), 3.01-3.02 (m, 1 H), 3.201 (s, 3 H), 3.204 (s, 3 H), 3.99-4.03 (m, 1 H), 4.04-4.20 (m, 4 H), 7.27-7.31 (m, 2 H), 7.35-7.40 (m, 1 H), 7.55-7.58 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.9 (q), 14.1 (q), 18.3 (q), 19.0 (t), 26.1 (t), 29.5 (t), 33.8 (d), 35.4 (t), 48.13 (q), 48.20 (q), 52.8 (d), 54.9 (s), 60.3 (t), 61.2 (t), 73.4 (d), 100.8 (s), 126.7 (s), 128.7 (d), 129.3 (d), 138.0 (d), 172.4 (s), 173.8 (s); exact mass (electrospray) *m/z* calcd for $C_{24}H_{36}NaO_7{}^{80}Se$ 539.1519, found 539.1513.

***Trans*-6-[2-Acetoxy-3-ethoxycarbonyl-3-(phenylseleno)butyl]-2,2-dimethoxycyclohexanecarboxylic Acid Ethyl Ester (40.8c).**[†]

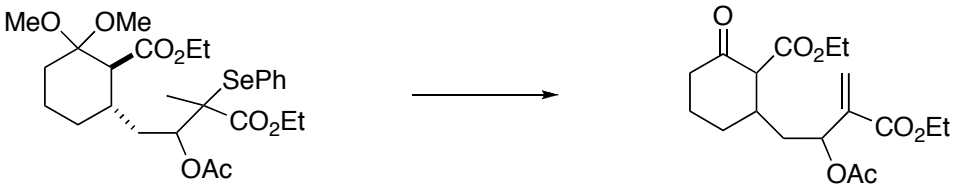


40.8b-4 **40.8c**

Pyridine (0.55 mL, 6.75 mmol) and AcCl (0.25 mL, 3.38 mmol) were added dropwise to a stirred and cooled (0 °C) solution of **26b-4** (580 mg, 1.125 mmol) and DMAP (15 mg, 0.12 mmol) in CH_2Cl_2 (8 mL). The ice bath was left in place but not recharged and stirring was continued for 12 h. The mixture was quenched with water (15 mL), acidified with hydrochloric acid (10%, 1 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 15% EtOAc-hexane, gave **40.8c** (435 mg, 69%) as a viscous oil: FTIR (CH_2Cl_2 cast) 2942, 2833, 1744, 1723, 1370, 1237, 744 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.07 (t, *J* = 7.2 Hz, 3 H), 1.25 (t, *J* = 7.2 Hz, 3 H), 1.29-1.38 (m, 1 H), 1.45 (s, 3 H), 1.46-1.69 (m, 4 H), 1.78-1.91 (m, 1 H), 1.94 (s, 3 H),

1.95-2.13 (m, 2 H), 2.18-2.28 (m, 1 H), 2.58 (d, J = 5.6 Hz, 1 H), 3.19 (s, 3 H), 3.22 (s, 3 H), 3.82-3.90 (m, 1 H), 3.94-4.02 (m, 1 H), 4.08-4.16 (m, 2 H), 5.65 (d, J = 10.4 Hz, 1 H), 7.26-7.32 (m, 2 H), 7.36-7.40 (m, 1 H), 7.57-7.60 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.8 (q), 14.2 (q), 18.0 (q), 19.2 (t), 20.9 (q), 26.2 (t), 29.9 (t), 33.2 (d), 34.6 (t), 48.1 (q), 48.4 (q), 53.3 (s), 54.1 (d), 60.2 (t), 61.2 (t), 73.6 (d), 100.6 (s), 126.4 (s), 128.9 (d), 129.5 (d), 137.9 (d), 169.7 (s), 172.0 (s), 172.11 (s); exact mass (electrospray) m/z calcd for $C_{26}H_{38}NaO_8{}^{80}Se$ 581.1624, found 581.1625.

2-(2-Acetoxy-3-ethoxycarbonylbut-3-enyl)-6-oxocyclohexanecarboxylic Acid Ethyl Ester (40.8d).[†]



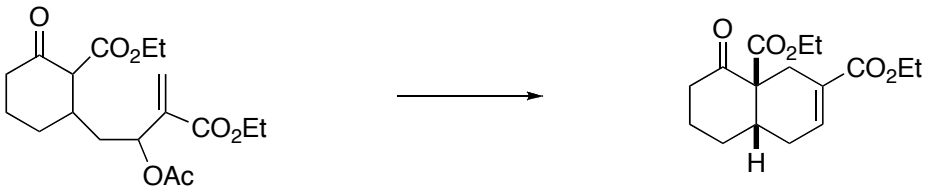
40.8c **40.8d**

H_2O_2 (30%, 1.0 mL, 9.8 mmol) was added dropwise to a stirred and cooled (-5 °C, ice-acetone bath) solution of **40.8c** (400 mg, 0.72 mmol) in THF (10 mL) and water (1 mL). The cold bath was left in place but not recharged and stirring was continued for 3 h, by which time the temperature had risen to 0 °C. The mixture was quenched with saturated aqueous $Na_2S_2O_3$ (3 mL) and stirred at 0 °C for 5 min. The cold bath was removed, stirring was continued for 5 min, and the mixture was diluted with water (15 mL) and extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 18 cm), using 25% EtOAc-hexane, gave **40.8d** (150 mg, 59%) as a viscous oil which was an equilibrium mixture of tautomers (^{13}C NMR): FTIR (CH_2Cl_2 cast) 2982, 2941, 1744, 1715, 1644, 1369, 1233, cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.26-1.38 (m, 6 H), 1.42-1.53 (m, 1 H), 1.60-1.81 (m, 4 H), 1.86-1.92 (m, 1 H), 2.10-2.11 (two s, 3 H), 2.19-2.36 (m, 2 H), 2.46-2.51 (m, 0.2 H), 2.64-2.69 (m, 0.7 H), 3.07 (dd, J = 10.8,

0.8 Hz, 0.2 H), 4.14-4.29 (m, 4 H), 5.69-5.77 (m, 2 H), 6.24-6.27 (m, 1 H), 12.40 (s, 0.7 H); ^{13}C NMR ($CDCl_3$, 100 MHz) (enol form) δ 14.1 (q), 14.2 (q), 16.9 (t), 21.0 (q), 24.7 (t), 28.3 (d), 29.0 (t), 38.9 (t), 60.2 (t), 60.9 (t), 69.9 (d), 101.6 (s), 123.9 (s), 140.2 (t), 165.1 (s), 170.0 (s), 172.3 (s), 173.1 (s); (keto form) δ 24.5 (t), 28.4 (t), 37.8 (d), 40.0 (t), 41.1 (t), 61.0 (t), 63.4 (d), 68.7 (d), 124.5 (s), 140.2 (t), 205.7 (s); exact mass (electrospray) *m*/*z* calcd for $C_{18}H_{26}NaO_7$ 377.1571, found 377.1573.

In this oxidation the acetal was hydrolyzed, presumably by PhSe(O)OH.

***Cis*-8-Oxo-4,4a,5,6,7,8-hexahydro-1*H*-naphthalene-2,8a-dicarboxylic Acid Diethyl Ester (51.14).**[†]

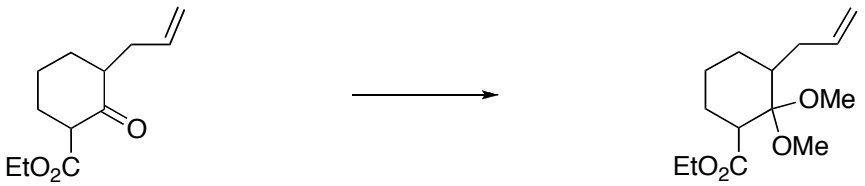


40.8d **51.14**

DBU (0.04 mL, 0.3 mmol) was added dropwise to a stirred solution of **40.8d** (52 mg, 0.146 mmol) in MeCN (1.5 mL). Stirring was continued for 30 min and the mixture was filtered through a pad of silica gel (2 x 2 cm), using 50% EtOAc-hexane (60 mL). Evaporation of the filtrate and flash chromatography of the residue over silica gel (0.5 x 8 cm), using 10% EtOAc-hexane, gave **51.14** (36 mg, 84%) as a colorless oil. The stereochemical assignment is tentative and is based on analogy:[71] FTIR (CH_2Cl_2 cast) 2939, 1713, 1660, 1427, 1245, 1096, 723, cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.25 (t, *J* = 7.2 Hz, 3 H), 1.29 (t, *J* = 7.2 Hz, 3 H), 1.60-1.70 (m, 1 H), 1.80-1.91 (m, 2 H), 1.99-2.15 (m, 2 H), 2.27-2.36 (m, 1 H), 2.40-2.47 (m, 1 H), 2.51-2.58 (m, 1 H), 2.70-2.76 (m, 3 H), 4.15-4.27 (m, 4 H), 6.90 (dddd, *J* = 4.0, 4.0, 2.0, 2.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1 (q), 14.2 (q), 23.9 (t), 26.5 (t), 26.6 (t), 28.2 (t), 36.2 (d), 38.0 (t), 6.56 (t),

60.61 (s), 61.4 (t), 126.8 (s), 136.4 (d), 166.2 (s), 171.6 (s), 207.3 (s); exact mass (electrospray) *m*/*z* calcd for $C_{16}H_{22}NaO_5$ 317.1359, found 317.1357.

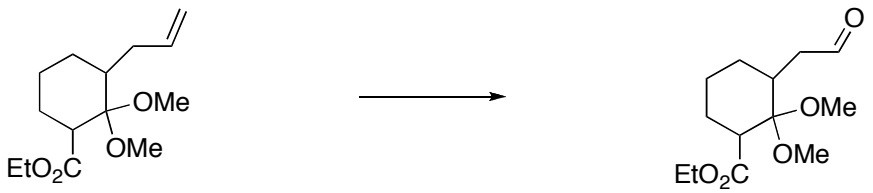
3-Allyl-2,2-dimethoxycyclohexanecarboxylic Acid Ethyl Ester (46.2).[†]



46.1 **46.2**

p-TsOH·H_2O (285 mg, 1.49 mmol) was added to a stirred solution of **46.1**[61] (6.0 g, 28.53 mmol) and $HC(OMe)_3$ (4.4 mL, 40.5 mmol) in MeOH (80 mL). Stirring was continued for 24 h and the mixture was quenched with saturated aqueous $NaHCO_3$ (15 mL), diluted with water (100 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (4 x 20 cm), using 10% EtOAc-hexane, gave **46.1** (4.13 g, 57%) as a colorless liquid which was very largely a single isomer, but contained impurities (^{13}C NMR): FTIR (CH_2Cl_2 cast) 2941, 2866, 1734, 1640, 1445, 1201, 1053, 910 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.26 (t, *J* = 7.2 Hz, 3 H), 1.39-1.96 (m, 7 H), 2.09-2.15 (m, 1 H), 2.49-2.54 (m, 1 H), 2.73 (dd, *J* = 8.4, 4.4 Hz, 1 H), 3.23 (s, 3 H), 3.25 (s, 3 H), 4.09-4.21 (m, 2 H), 4.95-5.07 (m, 2 H), 5.66-5.80 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1 (q), 20.0 (t), 25.3 (t), 26.7 (t), 32.5 (t), 40.7 (d), 46.9 (d), 49.0 (q), 49.1 (q), 60.3 (t), 101.8 (s), 115.6 (t), 137.9 (d), 173.4 (s); exact mass (electrospray) *m*/*z* calcd for $C_{14}H_{24}NaO_4$ 279.1567, found 279.1565.

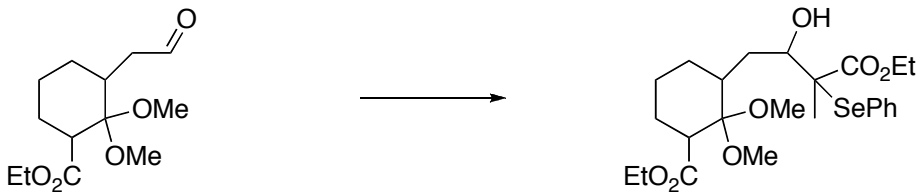
2,2-Dimethoxy-3-(2-oxoethyl)cyclohexanecarboxylic Acid Ethyl Ester (40.9a).[†]



46.2 **40.9a**

O_3 was bubbled into a stirred and cooled (-78 °C) solution of **46.2** (2.45 g, 9.55 mmol) in CH_2Cl_2 (120 mL) for 30 min, by which time a blue color persisted. O_2 was passed through the solution for 30 min and Ph_3P (3.26 g, 12.42 mmol) was then added. The cold bath was removed and stirring was continued for 8 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (4 x 20 cm), using 15% EtOAc-hexane, gave **40.9a** (1.51 g, 61%) as colorless oil which was a single isomer: FTIR (CH_2Cl_2 cast) 2945, 2868, 1735, 1132, 901 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.23 (t, J = 7.2 Hz, 3 H), 1.33-1.48 (m, 2 H), 1.58-1.86 (m, 4 H), 2.23 (ddd, J = 16.5, 8.7, 2.4 Hz, 1 H), 2.74-2.82 (m, 2 H), 2.86-2.98 (m, 1 H), 3.20 (s, 3 H), 3.22 (s, 3 H), 4.06-4.16 (m, 2 H), 9.64 (t, J = 2.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 14.1 (q), 20.4 (t), 26.6 (t), 28.1 (t), 35.9 (d), 44.4 (t), 46.8 (d), 48.9 (q), 49.7 (q), 60.3 (t), 100.8 (s), 172.7 (s), 201.9 (d); exact mass (electrospray) m/z calcd for $C_{13}H_{22}NaO_6$ 297.1309, found 297.1308 (the aldehyde is sensitive, and attempts to obtain its mass spectrum invariably led to the mass spectrum of the derived carboxylic acid).

3-[3-Ethoxycarbonyl-2-hydroxy-3-(phenylseleno)butyl]-2,2-dimethoxycyclohexanecarboxylic Acid Ethyl Ester (40.9b-1, 40.9b-2, 40.9b-3, 40.9b-4).[†]



40.9a **40.9b-1,b-2,b-3,b-4**

n-BuLi (2.5 M in hexane, 3.4 mL, 8.43 mmol) was added dropwise over ca 5 min to a stirred and cooled (-78 °C) solution of *i*-Pr_2NH (1.26 mL, 8.95 mmol) in THF (10 mL). Stirring was continued for 40 min and a solution of **38.1** (2.3 g, 8.95 mmol) in THF (10 mL plus 1 mL as a rinse) was added over 5 min. Stirring was continued for 1 h and a solution of **40.9a** (1.36 g, 5.26 mmol) in THF (10 mL plus 1 mL as a rinse) was added over 5 min. Stirring at -78 °C was continued for 4 h and the mixture was quenched with saturated aqueous NH_4Cl (10 mL). The cold bath was removed, stirring was continued for 10 min and the mixture was diluted with water (50 mL) and extracted with EtOAc (3 x 15 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (4 x 28 cm), using 15% EtOAc-hexane, gave a less polar isomer **40.9b-1** (510 mg, 19%), a 72:28 mixture of diastereoisomers **40.9b-2** and **40.9b-3** (1.25 g, 46%) and a more polar isomer **40.9b-4** (780 mg, 29%) as viscous oils. The stereochemical configuration at the carbinol carbon is the same in **40.9b-1** and **40.9b-2**, while the opposite configuration applies to **40.9b-3** and **40.9b-4** at the carbinol center.

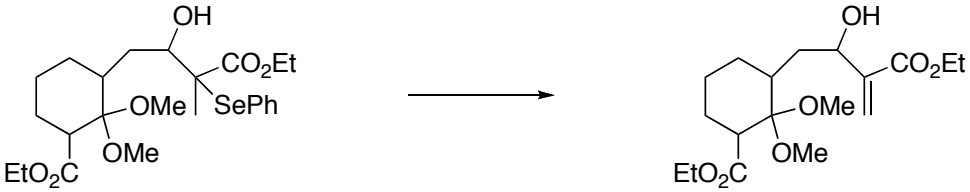
Compound **40.9b-1** had: FTIR (CH_2Cl_2 cast) 3510, 2940, 2867, 1723, 1247, 744 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.13 (t, *J* = 7.2 Hz, 3 H), 1.24 (t, *J* = 7.2 Hz, 3 H), 1.36-1.51 (m, 2 H), 1.44 (s, 3 H), 1.57-1.87 (m, 6 H), 2.26-2.32 (m, 1 H), 2.70 (dd, *J* = 8.4 4.4 Hz, 1 H), 3.16 (s, 3 H), 3.22 (s, 3 H), 3.95-4.15 (m, 5 H), 7.29-7.33 (m, 2 H), 7.37-7.42 (m, 1 H), 7.59-7.63 (m, 2 H); ^{13}C NMR

($CDCl_3$, 100 MHz) δ 13.7 (q), 14.1 (q), 16.9 (q), 20.3 (t), 26.8 (t), 27.8 (t), 31.4 (t), 39.9 (d), 46.9 (q), 48.7 (q), 49.2 (d), 57.9 (s), 60.2 (t), 61.0 (t), 73.6 (d), 102.1 (s), 126.7 (s), 128.7 (d), 129.3 (d), 138.0 (d), 173.1 (s), 173.2 (s); exact mass (electrospray) *m*/*z* calcd for $C_{24}H_{36}NaO_7{}^{80}Se$ 539.1519, found 539.1519.

The mixture of compounds **40.9b-2** and **40.9b-3** had: FTIR (CH_2Cl_2 cast) 3514, 2939, 2866, 1724, 1247, 1053 744 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.10 (t, *J* = 7.2 Hz, 1 H), 1.19 (t, *J* = 7.2 Hz, 2 H), 1.24-1.34 (m, 4 H), 1.38-1.48 (m, 1 H), 1.43 (s, 2 H), 1.46 (s, 1 H), 1.51-1.88 (m, 5 H), 2.29-2.40 (m, 2 H), 2.60 (dd, *J* = 10.0, 4.0 Hz, 0.28 H), 2.75 (dd, *J* = 8.4, 4.4 Hz, 0.72 H), 2.80-2.98 (br s, 1 H), 3.24 (s, 1 H), 3.25-3.26 (two s, 3 H), 3.28 (s, 3 H), 3.94-4.18 (m, 5 H), 7.27-7.33 (m, 2 H), 7.36-7.42 (m, 1 H), 7.59-7.63 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7 (q), 13.9 (q), 14.0 (q), 16.7 (q), 18.2 (q), 19.7 (t), 20.2 (t), 25.8 (t), 26.6 (t), 67.9 (t), 28.1 (t), 30.4 (t), 30.8 (t), 38.1 (d), 40.1 (d), 46.90 (q), 46.96 (q), 48.6 (q), 48.86 (d), 48.89 (q), 49.3 (d), 55.1 (s), 57.5 (s), 60.2 (t), 60.3 (t), 60.9 (t), 61.1 (t), 71.1 (d), 76.9 (d), 101.9 (s), 102.1 (s), 126.6 (s), 126.7 (s), 128.6 (d), 128.7 (d), 129.2 (d), 129.3 (d), 137.9 (d), 138.1 (d), 172.6 (s), 173.2 (s), 173.2 (s), 173.9 (s); exact mass (electrospray) *m*/*z* calcd for $C_{24}H_{36}NaO_7{}^{80}Se$ 539.1519, found 539.1518.

Compound **40.9b-4** had: FTIR (CH_2Cl_2 cast) 3507, 2941, 2866, 1725, 1439, 1246, 1158, 743 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.19 (t, *J* = 7.2 Hz, 3 H), 1.27 (t, *J* = 7.2 Hz, 3 H), 1.44-1.52 (m, 2 H), 1.45 (s, 3 H), 1.60-1.89 (m, 6 H), 2.39-2.42 (m, 1 H), 2.68 (dd, *J* = 10.0, 4.0 Hz, 1 H), 3.06 (br s, 1 H), 3.24 (s, 3 H), 3.26 (s, 3 H), 3.99 (dd, *J* = 9.6, 2.4 Hz, 1 H), 4.08 (q, *J* = 7.2 Hz, 2 H), 4.16 (q, *J* = 7.2 Hz, 2 H), 7.26-7.32 (m, 2 H), 7.36-7.41 (m, 1 H), 7.56-7.58 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.8 (q), 14.0 (q), 17.9 (q), 19.9 (t), 25.7 (t), 26.6 (t), 29.6 (t), 37.6 (d), 47.0 (d), 48.8 (q), 48.9 (q), 54.8 (s), 60.3 (t), 61.1 (t), 73.4 (d), 102.0 (s), 126.6 (s), 128.7 (d), 129.2 (d), 137.8 (d), 173.3 (s), 173.7 (s); exact mass (electrospray) *m*/*z* calcd for $C_{24}H_{36}NaO_7{}^{80}Se$ 539.1519, found 539.1518.

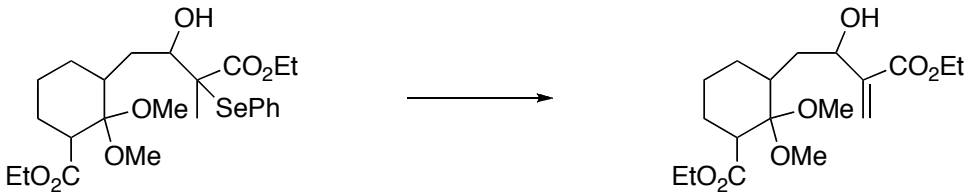
3-(3-Ethoxycarbonyl-2-hydroxybut-3-enyl)-2,2-dimethoxycyclohexanecarboxylic Acid Ethyl Ester (40.9c-1).[†]



40.9b-1 **40.9c-1**

H_2O_2 (30%, 0.2 mL, 1.96 mmol) was added dropwise to a stirred and cooled (-10 °C, ice-acetone bath) solution of **40.9b-1** (100 mg, 0.193 mmol) in CH_2Cl_2 (4 mL). The mixture was stirred vigorously for 1 h and quenched with saturated aqueous $NaHCO_3$ (1 mL) and saturated aqueous $Na_2S_2O_3$ (1 mL). The cold bath was removed after 5 min, stirring was continued for 10 min and the mixture was diluted with water (10 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (0.5 x 8 cm), using 20% EtOAc-hexane, gave **40.9c-1** (63 mg, 91%) as a colorless liquid: FTIR (CH_2Cl_2 cast) 3510, 2942, 2868, 2837, 1718, 1628, 1177, 1051 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.25 (t, *J* = 7.0 Hz, 3 H), 1.31 (t, *J* = 7.0 Hz, 3 H), 1.38-1.48 (m, 2 H), 1.55-1.63 (m, 3 H), 1.70-1.76 (m, 1 H), 1.79-1.86 (m, 1 H), 2.19-2.25 (m, 2 H), 2.78 (dd, *J* = 7.5, 4.5 Hz, 1 H), 3.251 (s, 3 H), 3.252 (s, 3 H), 3.38 (br s, 1 H), 4.13 (q, *J* = 7.0 Hz, 2 H), 4.18-4.26 (m, 2 H), 4.56 (m, 1 H), 5.91 (t, *J* = 1.5 Hz, 1 H), 6.28 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.1 (q), 14.2 (q), 20.5 (t), 26.9 (t), 28.8 (t), 35.1 (t), 36.9 (d), 47.1 (q), 48.6 (q), 49.7 (d), 60.3 (t), 60.6 (t), 70.6 (d), 101.8 (s), 125.3 (s), 142.2 (t), 166.5 (s), 173.0 (s); exact mass (electrospray) *m/z* calcd for $C_{18}H_{30}NaO_7$ 381.1884, found 381.1893.

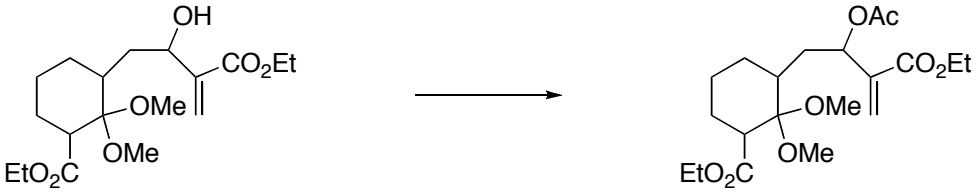
3-(3-Ethoxycarbonyl-2-hydroxybut-3-enyl)-2,2-dimethoxycyclohexanecarboxylic Acid Ethyl Ester (40.9c-4).[†]



40.9b-4 **40.9c-1**

H_2O_2 (30%, 1.5 mL, 14.7 mmol) was added dropwise to a stirred and cooled (-10 °C, ice-acetone bath) solution of **40.9b-4** (730 mg, 1.42 mmol) in CH_2Cl_2 (15 mL). Stirring was continued for 1 h and the mixture was quenched with saturated aqueous $NaHCO_3$ (5 mL) and saturated aqueous in $Na_2S_2O_3$ (5 mL). The cold bath was removed after 10 min, stirring was continued for 10 min and the mixture was diluted with water (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 25% EtOAc-hexane, gave **40.9c-4** (494 mg, 97%) as a viscous oil: FTIR (CH_2Cl_2 cast) 3501, 2941, 2867, 1714, 1629, 1374, 1061 cm^{-1}; ^1H NMR ($CDCl_3$, 400 mg) δ 1.24 (t, *J* = 7.2 Hz, 3 H), 1.30 (t, *J* = 7.2 Hz, 3 H), 1.36-1.65 (m, 4 H), 1.66-1.76 (m, 2 H), 1.79-1.89 (m, 2 H), 2.41-2.47 (m, 1 H), 2.69 (dd, *J* = 8.8, 4.4 Hz, 1 H), 3.03 (br d, *J* = 4.4 Hz, 1 H), 3.23 (s, 3 H), 3.26 (s, 3 H), 4.13 (q, *J* = 7.2 Hz, 2 H), 4.17-4.25 (m, 2 H), 4.42 (br d, *J* = 10.0 Hz, 1 H), 5.90 (t, *J* = 1.6 Hz, 1 H), 6.23 (dd, *J* = 1.6, 0.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.08 (q), 14.14 (q), 20.1 (t), 26.86 (t), 26.9 (t), 36.1 (t), 38.0 (d), 47.1 (q), 48.8 (q), 49.3 (d), 60.4 (t), 60.6 (t), 69.8 (d), 101.9 (s), 124.2 (s), 143.6 (t), 166.4 (s), 173.2 (s); exact mass (electrospray) *m/z* calcd for $C_{18}H_{30}NaO_7$ 381.1884, found 381.1882.

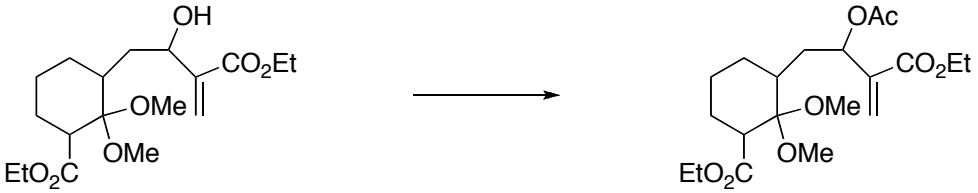
3-(2-Acetoxy-3-ethoxycarbonylbut-3-enyl)-2,2-dimethoxycyclohexane-carboxylic Acid Ethyl Ester (40.9d).[†]



40.9c-1 **40.9d**

Pyridine (0.05 mL, 0.56 mmol) and AcCl (0.02 mL, 0.28 mmol) were added dropwise to a stirred and cooled (0 °C) solution of **40.9c-1** (50 mg, 0.139 mmol) and DMAP (3 mg, 0.02 mmol) in CH_2Cl_2 (2 mL). Stirring was continued for 2 h and the mixture was quenched with water (5 mL), acidified with hydrochloric acid (10%, 0.5 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (0.5 x 8 cm), using 20% EtOAc-hexane, gave **40.9d** (52 mg, 94%) as a viscous oil: FTIR (CH_2Cl_2 cast) 2944, 2868, 1739, 1635, 1371, 1236, 1049 cm^{-1}; ^1H NMR ($CDCl_3$, 400 mg) δ 1.22 (t, *J* = 7.2 Hz, 3 H), 1.29 (t, *J* = 7.2 Hz, 3 H), 1.41-1.51 (m, 2 H), 1.55-1.86 (m, 5 H), 2.03 (s, 3 H), 2.11-2.24 (m, 2 H), 2.67 (dd, *J* = 8.4, 4.4 Hz, 1 H), 3.20 (s, 3 H) 3.21 (s, 3 H), 4.04-4.16 (m, 2 H), 4.18-4.27 (m, 2 H), 5.65 (t, *J* = 6.4 Hz, 1 H), 5.82 (m, 1 H), 6.29 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.0 (q), 20.1 (t), 21.0 (q), 26.4 (t), 27.1 (t), 32.7 (t), 38.0 (d), 46.9 (q), 48.7 (q), 49.1 (d), 60.1 (t), 60.7 (t), 71.8 (d), 101.6 (s), 125.6 (s), 140.2 (t), 165.2 (s), 169.7 (s), 173.0 (s); exact mass (electrospray) *m*/*z* calcd for $C_{20}H_{32}NaO_8$ 423.1989, found 423.1986.

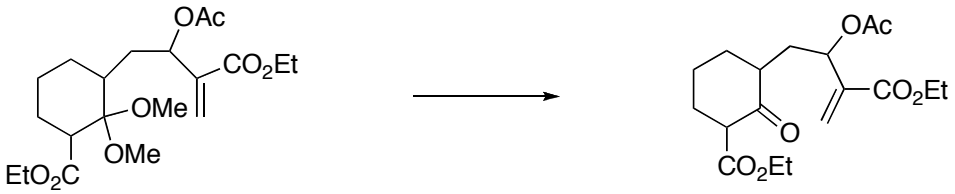
3-(2-Acetoxy-3-ethoxycarbonylbut-3-enyl)-2,2-dimethoxycyclohexane-carboxylic Acid Ethyl Ester (40.9d').[†]



40.9c-4 **40.9d'**

Pyridine (0.090 mL, 1.2 mmol) and AcCl (0.04 mL, 0.59 mmol) were added dropwise to a stirred and cooled (0 °C) solution of **40.9c-4** (105 mg, 0.293 mmol) and DMAP (6.0 mg, 0.045 mmol) in CH_2Cl_2 (3 mL). Stirring was continued for 2 h and the mixture was quenched with water (5 mL), acidified with hydrochloric acid (10%, 0.5 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 10 cm), using 20% EtOAc-hexane, gave **40.9d'** (105 mg, 90%) as a viscous oil which was used without full characterization: FTIR (CH_2Cl_2 cast) 2981, 2942, 2869, 1745, 1634, 1371, 1232 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.24 (t, J = 7.2 Hz, 3 H), 1.29 (t, J = 7.2 Hz, 3 H), 1.42-1.87 (m, 9 H), 2.08 (s, 3 H), 2.62 (dd, J = 9.6, 4.0 Hz, 1 H), 3.21 (s, 3 H), 3.24 (s, 3 H), 4.06-4.28 (m, 4 H), 5.61-5.64 (m, 1 H), 5.74 (t, J = 1.2 Hz, 1 H), 6.25 (br s, 1 H); exact mass (electrospray) m/z calcd for $C_{20}H_{32}NaO_8$ 423.1989, found 423.1991.

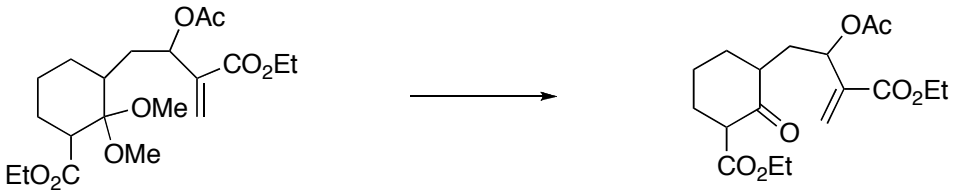
3-(2-Acetoxy-3-ethoxycarbonylbut-3-enyl)-2-oxocyclohexanecarbox-ylic Acid Ethyl Ester (40.9e).[†]



40.9d **40.9e**

A mixture of **40.9d** (84 mg, 0.21 mmol) and Amberlyst-15 (150 mg) in acetone (4 mL) was stirred for 1 h and filtered through a pad of silica gel (2 x 2 cm), using 70% EtOAc-hexane (50 mL). The filtrate was evaporated to give **40.9e** (67 mg, 91% as a viscous oil which was an inseparable mixture of keto-enol tautomers: FTIR (CH_2Cl_2 cast) 2982, 2938, 2865, 1744, 1716, 1648, 1371, 1235, 1026, 818 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.28-1.38 (m, 6 H), 1.45-2.07 (m, 5 H), 2.09 (s, 3 H), 2.11-2.34 (m, 1.7 H), 2.41-2.49 (m, 1.8 H), 2.69-2.75 (m, 0.3 H), 3.39-3.53 (m, 0.8 H), 4.20-4.32 (m, 4 H), 5.67-5.72 (m, 0.8 H), 5.82-5.88 (m, 1.2 H), 6.33-6.36 (m, 1 H), 12.42 (s, 0.2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.06 (q), 14.10 (q), 14.13 (q), 14.24 (q), 20.0 (t), 20.98 (q), 21.02 (q), 21.1 (q), 21.7 (t), 22.6 (t), 24.2 (t), 27.9 (t), 30.4 (t), 30.8 (t), 33.5 (t), 33.9 (t), 34.4 (t), 35.0 (t), 35.7 (d), 37.0 (t), 45.8 (d), 47.6 (d), 56.0 (d), 57.7 (d), 60.2 (t), 60.81 (t), 60.86 (t), 60.90 (t), 60.92 (t), 60.96 (t), 61.2 (t), 70.5 (d), 70.6 (d), 70.8 (d), 97.9 (s), 125.6 (s), 125.7 (s), 140.0 (t), 140.27 (t), 140.29 (t), 165.1 (s), 165.3 (s), 169.65 (s), 169.77 (s), 169.79 (s), 169.87 (s), 172.8 (s), 173.5 (s), 205.9 (s), 206.8 (s); exact mass (electrospray) *m/z* calcd for $C_{18}H_{26}NaO_7$ 377.1571, found 377.1571.

3-(2-Acetoxy-3-ethoxycarbonylbut-3-enyl)-2-oxocyclohexanecarboxylic Acid Ethyl Ester (40.9e').[†]

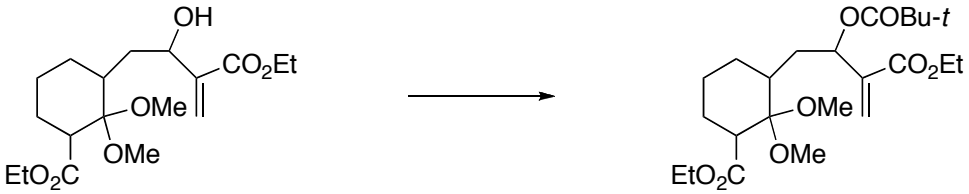


40.9d' **40.9e'**

A mixture of **40.9d'** (95 mg, 0.24 mmol) and Amberlyst-15 (200 mg) in acetone (4 mL) was stirred for 1 h and filtered through a pad of silica gel (2 x 2 cm), using 70% EtOAc-hexane (50 mL). The filtrate was evaporated to give **40.9e'** (80 mg, 95%) as a viscous oil which was an inseparable mixture of keto-enol tautomers: FTIR (CH_2Cl_2 cast) 2982, 2939, 2864, 1744, 1715, 1649, 1371,

1230, 1025 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.29-1.36 (m, 6 H), 1.41-2.09 (m, 5 H), 2.11-2.15 (three s, 3 H), 2.21-2.48 (m, 3.7 H), 2.67-2.73 (m, 0.3 H), 3.4-3.52 (m, 0.7 H), 4.19-4.31 (m, 4 H), 5.70 (br d, *J* = 10.0 Hz, 0.65 H), 5.77-5.83 (m, 1.35 H), 6.30-6.32 (m, 1 H), 12.43 (s, 0.3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.0 (q), 14.1 (q), 14.2 (q), 19.5 (t), 20.8 (q), 20.9 (q), 21.0 (q), 21.3 (t), 22.6 (t), 23.9 (t), 26.4 (t), 30.3 (t), 30.6 (t), 33.0 (t), 33.8 (t), 34.2 (t), 35.1 (d), 36.9 (t), 46.1 (d), 47.4 (d), 55.8 (d), 57.7 (d), 60.2 (t), 60.82 (t), 60.86 (t), 61.1 (t), 69.1 (d), 69.2 (d), 69.5 (d), 98.1 (s), 124.5 (s), 124.66 (s), 124.69 (s), 140.1 (t), 140.3 (t), 140.4 (t), 164.9 (s), 165.0 (s), 169.67 (s), 169.74 (s), 169.81 (s), 169.86 (s), 169.92 (s), 172.8 (s), 173.2 (s), 206.4 (s), 207.1 (s); exact mass (electrospray) *m/z* calcd for $C_{18}H_{26}NaO_7$ 377.1571, found 377.1572.

3-[2-(2,2-Dimethylpropionyloxy)-3-ethoxycarbonylbut-3-enyl]-2,2-dimethoxycyclohexanecarboxylic Acid Ethyl Ester (40.9f).[†]

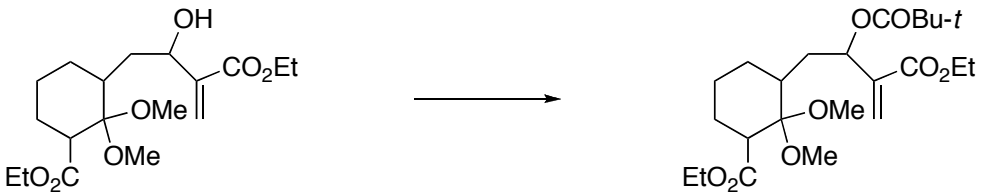


40.9c-1 **40.9f**

i-Pr_2NEt (0.20 mL, 1.0 mmol) and *t*-BuCOCl (0.060 mL, 0.51 mmol) were added dropwise to a stirred and cooled (0 °C) solution of **40.9c-1** (92 mg, 0.26 mmol) and DMAP (5 mg, 0.04 mmol) in CH_2Cl_2 (3 mL). The cold bath was removed after 15 min and stirring was continued for 16 h. The mixture was quenched with water (5 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 16 cm), using 20% EtOAc-hexane, gave **40.9f** (79 mg, 70%) and unreacted **40.9c-1** (5 mg, 5%) as viscous oils. Compound **40.9f** had: FTIR (CH_2Cl_2 cast); ^1H NMR ($CDCl_3$, 500 mg) δ 1.2 (s, 9 H), 1.25 (t, *J* = 7.0 Hz, 3 H), 1.31 (t, *J* = 7.0 Hz, 3 H), 1.39-1.55

(m, 2 H), 1.58-1.84 (m, 5 H), 2.14-2.24 (m, 2 H), 2.70 (dd, *J* = 9.0, 4.0 Hz, 1 H), 3.21 (s, 3 H), 3.23 (s, 3 H), 4.08-4.17 (m, 2 H), 4.18-4.28 (m, 2 H), 5.63 (ddd, *J* = 7.0, 6.0, 1.0 Hz, 1 H), 5.80 (t, *J* = 1.0 Hz, 1 H), 6.28 (d, *J* = 1.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.10 (q), 14.13 (q), 20.2 (t), 26.6 (t), 27.1 (q), 27.3 (t), 32.9 (t), 38.1 (d), 38.7 (s), 47.0 (d), 48.8 (q), 49.2 (q), 60.3 (t), 60.9 (t), 71.8 (d), 101.7 (s), 125.1 (s), 140.9 (t), 165.4 (s), 173.2 (s), 177.2 (s); exact mass (electrospray) *m*/*z* calcd for $C_{23}H_{38}NaO_8$ 465.2459, found 465.2455.

3-[2-(2,2-Dimethylpropionyloxy)-3-ethoxycarbonylbut-3-enyl]-2,2-dimethoxycyclohexanecarboxylic Acid Ethyl Ester (40.9f').[†]

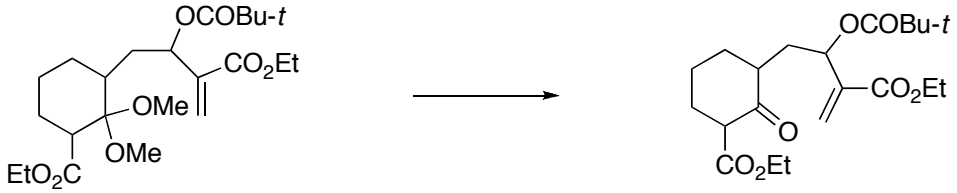


40.9c-4 **40.9f'**

i-Pr_2NEt (0.38 mL, 2.2 mmol) and *t*-BuCOCl (0.14 mL, 1.1 mmol) were added dropwise to a stirred and cooled (0 °C) solution of **40.9c-4** (198 mg, 0.55 mmol) and DMAP (7 mg, 0.06 mmol) in CH_2Cl_2 (8 mL). The ice bath was removed after 1 h, stirring was continued for 24 h and the mixture was diluted with water (8 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 18 cm), using 15% EtOAc-hexane, gave **40.9f'** (236 mg, 97%) as a viscous oil: FTIR (CH_2Cl_2 cast) 2958, 2871, 1733, 1632, 1148, 946 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.21 (s, 9 H), 1.23 (t, *J* = 7.0 Hz, 3 H), 1.29 (t, *J* = 7.0 Hz, 3 H), 1.41-1.64 (m, 3 H), 1.67-1.74 (m, 3 H), 1.78-1.85 (m, 1 H), 1.91-1.98 (m, 1 H), 2.14-2.17 (m, 1 H), 2.62 (dd, *J* = 10.0, 4.0 Hz, 1 H), 3.21 (s, 3 H), 3.22 (s, 3 H), 4.06-4.26 (m, 4 H), 5.58 (br d, *J* = 9.5 Hz, 1 H), 5.70 (t, *J* = 1.0 Hz, 1 H), 6.22 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.1 (q), 19.8 (t), 25.0 (t), 26.6 (t), 27.1 (q), 32.9 (t), 37.2 (d), 38.8 (s), 46.9 (q), 48.7 (d), 49.0 (q), 60.3

(t), 60.9 (t), 69.5 (d), 101.8 (s), 123.7 (s), 141.3 (t), 165.1 (s), 173.3 (s), 177.3 (s); exact mass (electrospray) *m/z* calcd for $C_{23}H_{38}NaO_8$ 465.2459, found 465.2457.

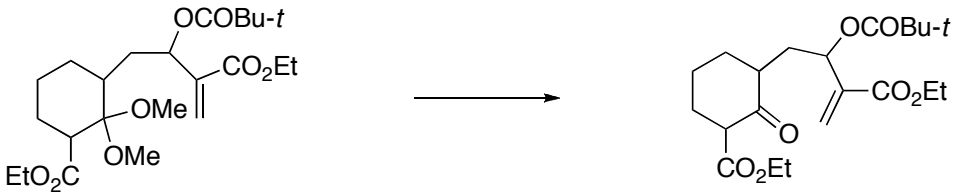
3-[2-(2,2-Dimethylpropionyloxy)-3-ethoxycarbonylbut-3-enyl]-2-oxo-cyclohexanecarboxylic Acid Ethyl Ester (40.9g).[†]



40.9f **40.9g**

A mixture of **40.9f** (35 mg, 0.08 mmol) and Amberlyst-15 (70 mg) in acetone (3 mL, reagent grade) was stirred for 1 h and filtered through a pad of silica gel (2 x 2 cm), using 70% EtOAc-hexane (30 mL). The filtrate was evaporated and the residual viscous oil [30 mg, 95%, a keto-enol mixture of tautomers (^{1}H NMR)], was used without further purification in the next step. The material (**40.9g**) had: FTIR (CH_2Cl_2 cast) 2979, 2872, 1732, 1650, 1283, 1148, 1029 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.246-1.252 (m, 9 H), 1.28-1.40 (m, 6 H), 1.44-1.92 (m, 5 H), 1.94-2.51 (m, 3.7 H), 2.66-2.76 (m, 0.5 H), 3.38-3.50 (m, 0.7 H), 4.16-4.35 (m, 4 H), 5.62-5.66 (m, 0.7 H), 5.79-5.85 (m, 1.2 H), 6.32-6.35 (m, 1 H), 12.42 (s, 0.26 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.10 (q), 14.12 (q), 14.15 (q), 14.3 (q), 19.9 (t), 21.7 (t), 22.7 (t), 24.2 (t), 27.0 (q), 27.1 (q), 28.0 (t), 30.3 (t), 30.8 (t), 33.7 (t), 34.0 (t), 34.3 (t), 35.0 (t), 35.7 (d), 37.1 (t), 38.7 (s), 46.0 (d), 47.9 (d), 56.1 (d), 57.7 (d), 60.2 (t), 60.9 (t), 60.95 (t), 60.99 (t), 61.3 (t), 70.3 (d), 70.4 (d), 70.7 (d), 97.8 (s), 125.1 (s), 125.3 (s), 140.6 (t), 140.8 (t), 165.27 (s), 165.31 (s), 169.8 (s), 172.9 (s), 173.5 (s), 177.0 (s), 177.1 (s), 205.8 (s), 206.6 (s); exact mass (electrospray) *m/z* calcd for $C_{21}H_{32}NaO_7$ 419.2040, found 419.2043.

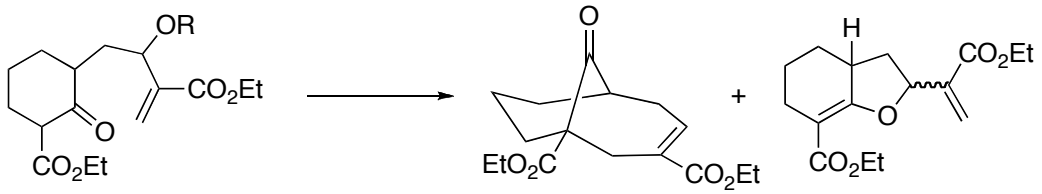
3-[2-(2,2-Dimethylpropionyloxy)-3-ethoxycarbonylbut-3-enyl]-2-oxo-cyclohexanecarboxylic Acid Ethyl Ester (40.9g').[†]



40.9f' **40.9g'**

A mixture of **40.9f'** (235 mg, 0.53 mmol) and Amberlyst-15 (500 mg) in acetone (6 mL) was stirred for 1 h and filtered through a pad of silica gel (2 x 2 cm), using 70% EtOAc-hexane (50 mL). The filtrate was evaporated and the residual viscous oil [208 mg, 99%, a keto-enol mixture of tautomers (^{1}H NMR)], was used without further purification in the next step. The material (**40.9g'**) had: FTIR (CH_2Cl_2 cast) 2978, 2873, 1733, 1716, 1652, 1293, 1147 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.19-1.22 (m, 9 H), 1.23-1.30 (m, 6 H), 1.32-1.86 (m, 5 H), 1.92-2.05 (m, 0.6 H), 2.15-2.43 (m, 4 H), 2.61-2.69 (m, 0.4 H), 3.32-3.40 (m, 0.6 H), 4.08-4.26 (m, 4 H), 5.59-5.65 (m, 0.6 H), 5.68-5.75 (m, 1.4 H), 6.23-6.24 (m, 1 H), 12.34 (s, 0.4 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1 (q), 14.13 (q), 14.2 (q), 19.6 (t), 21.6 (t), 22.7 (t), 24.1 (t), 26.4 (t), 27.0 (q), 27.1 (q), 29.2 (q), 30.3 (t), 30.7 (t), 32.7 (t), 33.7 (t), 33.8 (t), 34.0 (t), 35.3 (d), 37.1 (t), 38.76 (s), 38.82 (s), 45.6 (d), 47.5 (d), 56.1 (d), 57.8 (d), 60.2 (t), 60.86 (t), 60.91 (t), 61.2 (t), 68.7 (d), 68.84 (d), 68.88 (d), 98.1 (s), 124.2 (s), 124.34 (s), 124.37 (s), 140.5 (t), 140.8 (t), 164.98 (s), 165.04 (s), 169.7 (s), 169.8 (s), 172.9 (s), 173.4 (s), 177.1 (s), 177.2 (s), 177.3 (s), 206.3 (s), 207.0 (s); exact mass (electrospray) *m/z* calcd for $C_{21}H_{32}NaO_7$ 419.2040, found 419.2044.

10-Oxobicyclo[4.3.1]dec-3-ene-1,3-dicarboxylic Acid Diethyl Ester (51.15) and 2-(1-Ethoxycarbonylvinyl)-2,3,3a,4,5,6-hexahydrobenzofuran-7-carboxylic Acid Ethyl Ester (51.15').[†]



40.9e **51.15** **51.15'**

(a)

DBU (0.02 mL, 0.14 mmol) was added dropwise to a stirred solution of **40.9e** (R = Ac, less polar isomer) (26 mg, 0.073 mmol) in MeCN (2 mL). Stirring was continued for 30 min and the mixture was filtered through a pad of silica gel (2 x 2 cm), using 60% EtOAc-hexane (30 mL). Evaporation of the filtrate and flash chromatography of the residue over silica gel (0.5 x 8 cm), using 10% EtOAc-hexane, gave **51.15'** (17 mg, 79%) and **51.15** (1 mg, ca 5%) as viscous oils. Compound **51.15'** is a mixture of diastereoisomers (ca 7:3) with the ethoxycarbonylvinyl substituent *cis* and *trans* to the ring fusion hydrogen.

Compound **51.15'** had: FTIR (CH_2Cl_2 cast) 2982, 2938, 1714, 1660, 1448, 1269, 1146, 1036 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) (inseparable 72:28 mixture of diastereoisomers) δ 1.17-1.36 (m, 8 H), 1.43-1.53 (m, 1 H), 1.90-1.96 (m, 1.35 H), 2.0-2.1 (m, 1 H), 2.15 (dd, *J* = 12.5, 7.5 Hz, 0.3 H), 2.22-2.32 (m, 1 H), 2.38-2.44 (m, 1 H), 2.54-2.57 (m, 0.3 H), 2.69-2.81 (m, 1.4 H), 4.12-4.31 (m, 4 H), 5.14-5.18 (m, 0.7 H), 5.41 (br d, *J* = 8.5 Hz, 0.3 H), 5.80-5.81 (m, 0.28 H), 6.16-6.17 (m, 0.72 H), 6.30-6.31 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.06 (q), 14.38 (q), 22.1 (t), 22.2 (t), 23.9 (t), 27.1 (t), 27.4 (t), 34.8 (t), 37.4 (d), 38.2 (t), 41.7 (d), 59.41 (t), 59.47 (t), 60.72 (t), 60.76 (t), 79.6 (d), 80.5 (d), 97.5 (s), 97.6 (s), 124.3 (s), 124.5 (s), 139.1 (t), 139.5 (t), 165.12 (s), 165.14 (s), 166.6 (s), 166.7 (s), 167.0 (s), 167.4 (s); exact mass (electrospray) *m/z* calcd for $C_{16}H_{22}NaO_5$ 317.1359, found 317.1357.

Compound **51.15** had: FTIR (CH_2Cl_2 cast) 2981, 2934, 1737, 1710, 1633, 1447, 1281, 1072, 1037 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.24 (t, *J* = 7.0 Hz, 3 H), 1.29 (t, *J* = 7.0 Hz, 3 H), 1.59-1.65 (m, 1 H), 1.91-2.10 (m, 3 H), 2.18 (dtt, *J* = 14.5, 12.5, 4.5 Hz, 1 H), 2.41-2.51 (m, 2 H), 2.64 (dt, *J* = 15.5, 6.5 Hz, 1 H), 2.82-2.87 (m, 1 H), 2.94 (dd, *J* = 15.5, 2.0 Hz, 1 H), 3.07 (dd, *J* = 15.5, 0.5 Hz, 1 H), 4.14-4.24 (m, 4 H), 7.13 (t, *J* = 6.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.9 (q), 14.2 (q), 17.7 (t), 29.9 (t), 30.7 (t), 32.6 (t), 35.1 (t), 47.3 (d), 60.5 (s), 60.9 (t), 61.2 (t), 134.3 (s), 140.2 (t), 166.7 (s), 172.6 (s), 211.1 (s); exact mass (electrospray) *m/z* calcd for $C_{16}H_{22}NaO_5$ 317.1359, found 317.1354.

(**b**)

DBU (0.027 mL, 0.18 mmol) was added dropwise to a stirred solution of **40.9e'** (R = Ac, more polar isomer) (32 mg, 0.09 mmol) in MeCN (2 mL). Stirring was continued for 50 min and the mixture was filtered through a pad of silica gel (2 x 2 cm), using 60% EtOAc-hexane (30 mL). Evaporation of the filtrate and flash chromatography of the residue over silica gel (0.5 x 8 cm), using 10% EtOAc-hexane, gave **51.15'** (10 mg, 38%) and **51.15** (14 mg, 53%) as viscous oils. Compound **51.15'** is a mixture of diastereoisomers (ca 7:3) with the ethoxycarbonylvinyl substituent *cis* and *trans* to the ring fusion hydrogen.

(**c**) **40.9g**

DBU (0.027 mL, 0.18 mmol) was added dropwise to a stirred solution of **40.9g** (R = Piv, less polar isomer) (25 mg, 0.06 mmol) in MeCN (2 mL). Stirring was continued for 30 min and the mixture was filtered through a pad of silica gel (2 x 2 cm), using 60% EtOAc-hexane (30 mL). Evaporation of the filtrate and flash chromatography of the residue over silica gel (0.5 x 8 cm), using 10% EtOAc-hexane, gave **51.15'** (14 mg, 80%) and **51.15** (1 mg, 5%) as viscous oils. Compound **51.15'** is a mixture of diastereoisomers (ca 7:3) with the ethoxycarbonylvinyl substituent *cis* and *trans* to the ring fusion hydrogen.

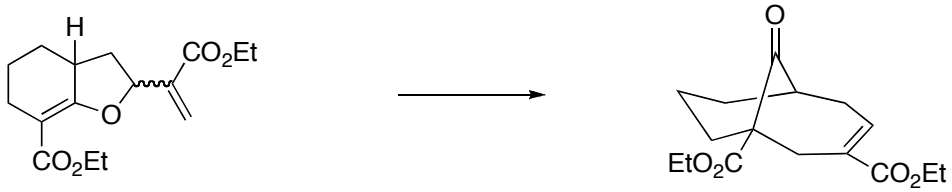
(**d**)

DBU (18 mg, 0.12 mmol) was added dropwise to a stirred solution of **40.9g'** (R = Piv, more polar isomer) (25 mg, 0.06 mmol) in MeCN (1.5 mL). Stirring was continued for 20 min and the mixture was filtered through a pad of silica gel (2 x 2 cm), using 60% EtOAc-hexane (30 mL). Evaporation of the filtrate and flash chromatography of the residue over silica gel (0.5 x 8 cm), using 10% EtOAc-hexane, gave **51.15'** (9 mg, 51%) and **51.15** (4 mg, 23%) as viscous oils. Compound **51.15'** is a mixture of diastereoisomers (ca 7:3) with the ethoxycarbonylvinyl substituent *cis* and *trans* to the ring fusion hydrogen.

(**e**)

DBU (0.024 mL, 0.16 mmol) was added dropwise to a stirred solution of **40.9g'** (R = Piv, more polar isomer) (30 mg, 0.075 mmol) in MeCN (2 mL). Stirring was continued for 2.5 h and the mixture was filtered through a pad of silica gel (2 x 2 cm), using 60% EtOAc-hexane (30 mL). Evaporation of the filtrate and flash chromatography of the residue over silica gel (0.5 x 8 cm), using 10% EtOAc-hexane, gave **51.15** (16 mg, 73%) (and no **51.15'**) as a viscous oil.

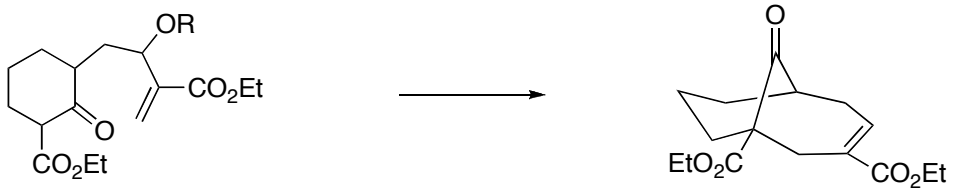
Conversion of 51.15' into 51.15.[†]



51.15' **51.15**

DBU (0.02 mL, 0.14 mmol) was added dropwise to a stirred solution of **51.15'** (20 mg, 0.068 mmol) in MeCN (2 mL). Stirring was continued for 12 h and the mixture was filtered through a pad of silica gel (2 x 2 cm), using 60% EtOAc-hexane (30 mL). Evaporation of the filtrate and flash chromatography of the residue over silica gel (0.5 x 8 cm), using 10% EtOAc-hexane, gave **51.15** (15 mg, 75%) as a viscous oil.

10-Oxobicyclo[4.3.1]dec-3-ene-1,3-dicarboxylic Acid Diethyl Ester (51.15).



40.9c,c'g,g' **51.15**

Specific examples of the Cs_2CO_3 reactions

(**a**)

A mixture of **40.9c** (R = OAc, less polar isomer) (31 mg, 0.087 mmol) and Cs_2CO_3 (57 mg, 0.174 mmol) in MeCN (1.5 mL) was refluxed for 1 h, cooled to room temperature and filtered through a pad of silica gel (2 x 2 cm), using EtOAc (20 mL). Evaporation of the filtrate gave **51.15** (26 mg, 100%) as a colorless liquid, which was pure by ^{1}H NMR.

(**b**)

A mixture of **40.9c'** (R = OAc, more polar isomer) (61 mg, 0.172 mmol) and Cs_2CO_3 (112 mg, 0.344 mmol) in MeCN (2 mL) was refluxed for 45 min, cooled to room temperature and filtered through a pad of silica gel (2 x 2 cm), using EtOAc (20 mL). Evaporation of the filtrate gave **51.15** (50 mg, 99%) as a colorless liquid, which was pure by ^{1}H NMR.

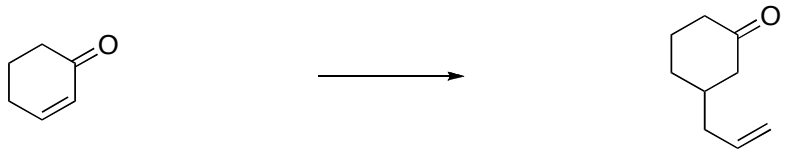
(**c**)

A mixture of **40.9g** (R = OPiv, less polar isomer) (6 mg, 0.015 mmol) and Cs_2CO_3 (10 mg, 0.03 mmol) in MeCN (1 mL) was refluxed for 1 h, cooled to room temperature and filtered through a pad of silica gel (2 x 2 cm), using EtOAc (20 mL). Evaporation of the filtrate and flash chromatography of the residue over silica gel (0.5 x 8 cm), using 20% EtOAc-hexane, gave **51.15** (5 mg, 100%) as a colorless liquid.

(**d**)

A mixture of **40.9g'** (130 mg, 0.327 mmol) and Cs_2CO_3 (214 mg, 0.656 mmol) in MeCN (5 mL) was refluxed for 1 h, cooled to room temperature and filtered through a pad of silica gel (2 x 2 cm), using EtOAc (20 mL). Evaporation of the filtrate and flash chromatography of the residue over silica gel (0.5 x 8 cm), using 20% EtOAc-hexane, gave **51.15** (95 mg, 99%) as a colorless liquid.

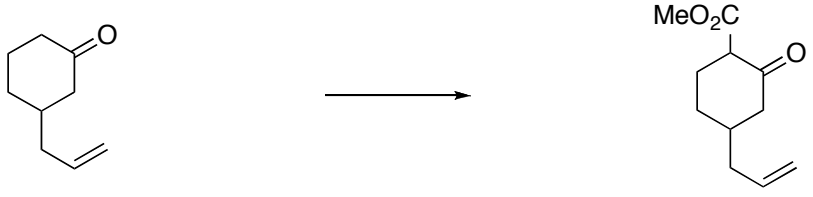
3-Allylcyclohexanone (47.1).[†62]



- **47.1**

$TiCl_4$ (7.9 mL, 72 mmol) was added dropwise over ca 20 min by syringe pump to a stirred and cooled (-78 °C) solution of 2-cyclohexenone (6.0 g, 62.415 mmol) in CH_2Cl_2 (100 mL). After 5 min, a solution of allyltrimethylsilane (11.0 mL, 68.7 mmol) in CH_2Cl_2 (50 mL) was added dropwise over ca 15 min (syringe pump). Stirring was continued at -78 °C for 1.5 h and then the cold bath was replaced by one at -30 °C, and stirring was continued for 15 min. Water (100 mL) was added and the cold bath was removed. The mixture was extracted with Et_2O (3 x 25 mL) and the combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (4 x 18 cm), using 10% EtOAc-hexane, gave **47.1** (6.82 g, 79%) as a viscous oil.

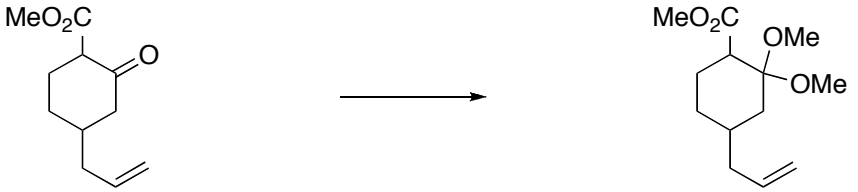
4-Allyl-2-oxocyclohexanecarboxylic Acid Ethyl Ester.[†]



47.1 **-**

A solution of **47.1** (1.0 g, 7.2 mmol) in THF (20 mL) was added dropwise over 1 h by syringe pump to a refluxing suspension of NaH (732 mg, 28.9 mmol) and $(MeO)_2CO$ (1.83 mL, 21.7 mmol) in THF (30 mL). The mixture was refluxed for 2 h, cooled to room temperature and then to 0 °C (ice bath), and quenched by slow addition of water (5 mL) and saturated aqueous NH_4Cl (20 mL). The cold bath was removed, stirring was continued for 10 min and the mixture was diluted with water (50 mL) and extracted with Et_2O (3 x 25 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (3 x 18 cm), using 15% EtOAc-hexane, gave 4-Allyl-2-oxocyclohexanecarboxylic Acid Ethyl Ester (1.26 g, 89%) as a viscous oil which was an inseparable mixture of keto-enol tautomers: FTIR (CH_2Cl_2 cast) 3358, 2923, 2852, 1734, 1463, 1031 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.25 (dtd, *J* = 13.0, 10.5, 5.5 Hz, 0.8 H, enol form), 1.61-1.86 (m, 2 H), 1.99-2.05 (m, 1.2 H), 2.10-2.22 (m, 3.2 H), 2.36-2.42 (m, 2 H), 3.79 (s, 3 H), 5.06-5.11 (m, 2 H), 5.78-5.86 (m, 1 H), 12.14 (s, 0.8 H, enol form); ^{13}C NMR ($CDCl_3$, 125 MHz) (enolic form) δ 21.9 (t), 28.1 (t), 33.1 (d), 35.0 (t), 40.1 (t), 51.3 (q), 97.3 (s), 116.4 (t), 136.2 (d), 171.5 (s), 172.9 (s); exact mass (electrospray) *m/z* calcd for $C_{11}H_{16}NaO_3$ 219.0992, found 219.0992.

4-Allyl-2,2-dimethoxycyclohexanecarboxylic Acid Ethyl Ester (47.2).[†]



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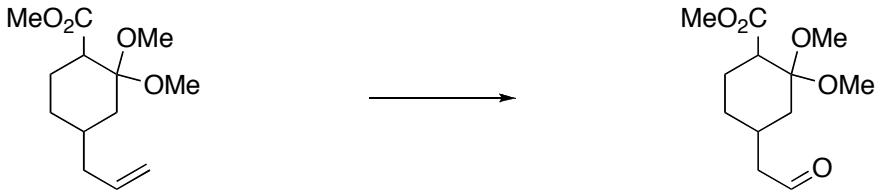
47.2

$HC(OMe)_3$ (1.38 mL, 12.6 mmol) and *p*-TsOH·H_2O (61 mg, 0.32 mmol) were added to a stirred solution of 4-Allyl-2-oxocyclohexanecarboxylic Acid Ethyl Ester (1.24 g, 6.32 mmol) in dry MeOH (25 mL). The mixture was stirred for 4 days and then refluxed for 12 h. The solvent was evaporated and the residue

was diluted with CH_2Cl_2 (50 mL). The mixture was quenched with saturated aqueous $NaHCO_3$ (5 mL), diluted with water (50 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 25 cm), using 15% EtOAc-hexane, gave **47.2** (1.08 g, 71%) as a viscous oil which was a single isomer: FTIR (CH_2Cl_2 cast) 2950, 2832, 1741, 1641, 1436, 1171, 1051 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.34-1.43 (m, 1 H), 1.47-1.55 (m, 2 H), 1.66-1.80 (m, 3 H), 1.85-1.89 (m, 1 H), 1.96-2.05 (m, 2 H), 2.96-2.98 (m, 1 H), 3.12 (s, 3 H), 3.18 (s, 3 H), 3.65 (s, 3 H), 4.96-5.01 (m, 2 H), 5.76 (ddt, *J* = 17.5, 10.0, 7.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 25.6 (t), 26.9 (t), 33.6 (d), 34.3 (t), 41.0 (t), 44.8 (d), 47.2 (q), 47.8 (q), 51.4 (q), 100.6 (s), 115.9 (t), 136.8 (d), 172.9 (s); exact mass (electrospray) *m/z* calcd for $C_{13}H_{22}NaO_4$ 265.1410, found 265.1411.

2,2-Dimethoxy-4-(2-oxoethyl)cyclohexanecarboxylic Acid Ethyl Ester (40.10a).[†]

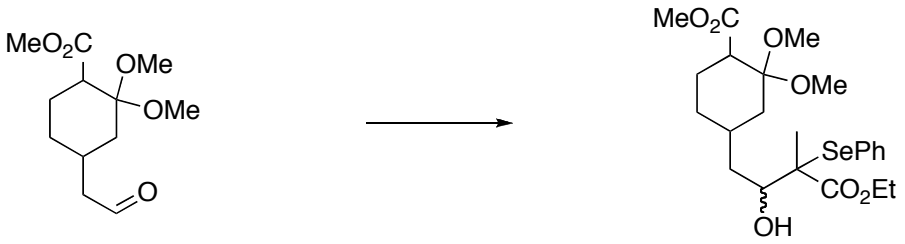


47.3 **40.10a**

O_3 was bubbled into a stirred and cooled (-78 °C) solution of **47.3** (1.4 g, 5.8 mmol) in CH_2Cl_2 (100 mL) until a blue color persisted (ca 30 min). O_2 was passed through the solution for 30 min and Ph_3P (1.97 g, 7.51 mmol) was then added. The cold bath was removed and stirring was continued for 6 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (3 x 25 cm), using 15% EtOAc-hexane, gave **40.10a** (1.36 g, 96%) as a viscous oil which was a single isomer: FTIR (CH_2Cl_2 cast) 2952, 2834, 1737, 1436, 1196, 1049 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.46-1.55 (m, 2 H), 1.74-1.82 (m, 3 H), 1.88-1.92 (m, 1 H), 2.07-2.16 (m, 1 H), 2.39 (dd, *J* = 7.0, 1.5 Hz, 2 H), 3.0-3.02

(m, 1 H), 3.188 (s, 3 H), 3.194 (s, 3 H), 3.67 (s, 3 H), 9.78 (t, J = 2.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 25.4 (t), 26.9 (t), 28.5 (d), 34.4 (t), 44.5 (d), 47.3 (q), 47.8 (q), 50.5 (t), 51.5 (q), 100.0 (s), 172.8 (s), 201.8 (d); exact mass (electrospray) m/z calcd for $C_{12}H_{20}NaO_5$ 267.1203, found 267.1207.

4-[3-Ethoxycarbonyl-2-hydroxy-3-(phenylseleno)butyl]-2,2-dimethoxycyclohexanecarboxylic Acid Ethyl Ester (40.10b).[†]

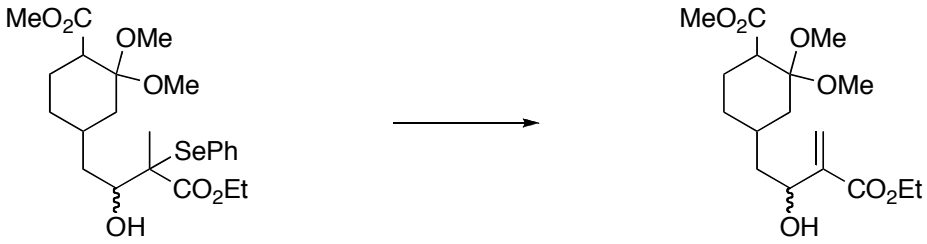


40.10a **40.10b**

n-BuLi (2.5 M in hexane, 3.3 mL, 8.2 mmol) was added dropwise over 3 min to a stirred and cooled (-78 °C) solution of *i*-Pr_2NH (1.27 mL, 8.98 mmol) in THF (20 mL). Stirring at -78 °C was continued for 40 min and a solution of **38.1** (2.38 g, 9.26 mmol) in THF (8 mL plus 2 mL as a rinse) was added dropwise over 5 min. Stirring was continued for 1.5 h at -78 °C and a solution of **40.10a** (1.33 g, 5.44 mmol) in THF (8 mL plus 2 mL as a rinse) was added over 5 min. Stirring was continued for 2 h and the mixture was quenched with saturated aqueous NH_4Cl (10 mL). The cold bath was removed, stirring was continued for 15 min and the mixture was diluted with water (25 mL) and extracted with EtOAc (3 x 15 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 22 cm), using 20% EtOAc-hexane, gave **40.10b** (2.57 g, 94%) as a viscous oil which was an inseparable mixture of diastereoisomers: FTIR (CH_2Cl_2 cast) 3508, 2945, 2831, 1725, 1438, 1051, 744 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.11-1.22 (m, 3 H), 1.37-1.38 (m, 3 H), 1.42-2.03 (m, 8 H), 2.89-3.08 (m, 2 H), 3.15-3.21 (m, 6 H), 3.65-3.68 (m, 3 H), 3.96-4.15 (m, 3 H), 7.28-7.33 (m, 2 H), 7.37-7.42 (m, 1 H), 7.56-7.61 (m, 2

H); exact mass (electrospray) *m/z* calcd for $C_{23}H_{34}NaO_7{}^{80}Se$ 525.1362, found 525.1363.

4-(3-Ethoxycarbonyl-2-hydroxy-but-3-enyl)-2,2-dimethoxycyclohexanecarboxylic Acid Ethyl Ester (40.10c).[†]

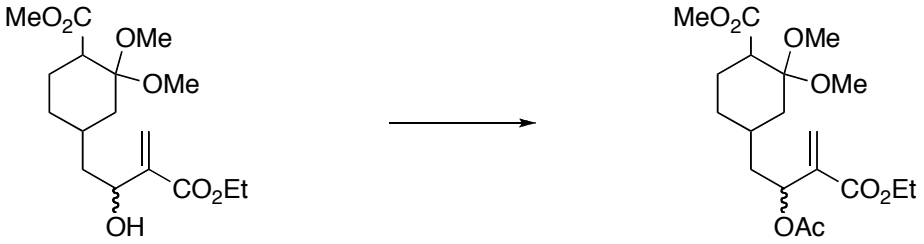


40.10b **40.10c**

H_2O_2 (30%, 0.55 mL, 5.38 mmol) was added dropwise over 2 min to a stirred and cooled (-10 °C) solution of **40.10b** (250 mg, 0.498 mmol) in CH_2Cl_2 (5 mL). Stirring was continued at -10 °C for 1 h and the mixture was quenched with saturated aqueous $NaHCO_3$ (1 mL) followed by saturated $Na_2S_2O_3$ (3 mL). The cold bath was removed after 10 min, stirring was continued for 5 min and the mixture was diluted with water (10 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 16 cm), using 15% EtOAc-hexane, gave **40.10c** (168 mg, 98%) as a viscous oil which was a 1:1 inseparable mixture of diastereoisomers which must differ in stereochemistry only at the hydroxyl-bearing carbon: FTIR (CH_2Cl_2 cast) 3476, 2949, 2833, 1738, 1715, 1628, 1436, 1171, 1053 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.32 (t, *J* = 7.2 Hz, 3 H), 1.34-2.04 (m, 9 H), 2.59 (dd, *J* = 18.4, 7.2 Hz, 1 H), 2.99-3.01 (m, 1 H), 3.15 (s, 1.4 H), 3.17 (s, 1.6 H), 3.20 (s, 1.4 H), 3.21 (s, 1.6 H), 3.67 (s, 3 H), 4.21-4.27 (m, 2 H), 4.48-4.55 (m, 1 H), 5.77-5.78 (m, 1 H), 6.207-6.21 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.1 (q), 25.6 (t), 25.7 (t), 26.4 (t), 27.9 (t), 30.3 (d), 30.4 (d), 33.9 (t), 35.4 (t), 43.0 (t), 43.4 (t), 44.85 (d), 44.94 (d), 47.27 (q), 47.29 (q), 47.8 (q), 47.82 (q), 51.4 (q), 60.8 (t), 69.2 (d), 69.5 (d), 100.365 (s), 100.373 (s),

124.4 (s), 124.5 (s), 143.1 (t), 143.2 (t), 166.55 (s), 166.58 (s), 172.9 (s); exact mass (electrospray) *m/z* calcd for $C_{17}H_{28}NaO_7$ 367.1727, found 367.1730.

4-(2-Acetoxy-3-ethoxycarbonylbut-3-enyl)-2,2-dimethoxycyclohexane-carboxylic Acid Ethyl Ester (40.10d).[†]

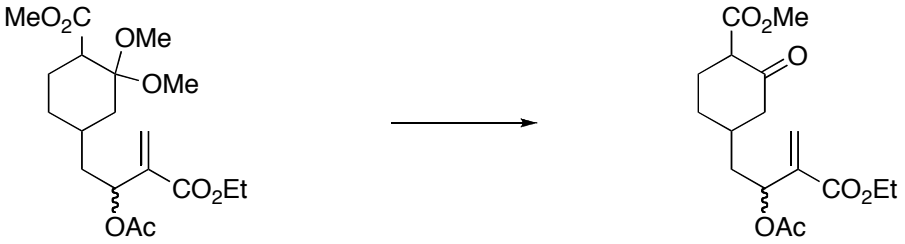


40.10c **40.10d**

Pyridine (0.70 mL, 8.6 mmol) and AcCl (0.31 mL, 4.296 mmol) were added dropwise to a stirred and cooled (0 °C) solution of **40.10c** (740 mg, 2.15 mmol) and DMAP (39 mg, 0.32 mmol) in CH_2Cl_2 (10 mL). Stirring at 0 °C was continued for 2 h and the mixture was quenched with water (35 mL), followed by hydrochloric acid (10%, 2 mL). The mixture was extracted with CH_2Cl_2 (3 x 15 mL) and the combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 20% EtOAc-hexane, gave **40.10d** (736 mg, 89%) as a viscous oil which was an inseparable (1:1) mixture of diastereoisomers which must differ in stereochemistry only at the acetoxy-bearing carbon: FTIR (CH_2Cl_2) 2951, 1742, 1633, 1369, 1235, 957 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.27-1.31 (m, 3 H), 1.34-1.48 (m, 1.5 H), 1.52-1.83 (m, 7 H), 1.95-1.99 (m, 0.5 H), 2.06 (s, 1.5 H), 2.07 (s, 1.5 H), 2.94-2.98 (m, 1 H), 3.09 (s, 1.5 H), 3.12 (s, 1.5 H), 3.17 (s, 1.5 H), 3.18 (s, 1.5 H), 3.648 (s, 1.5 H), 3.65 (s, 1.5 H), 4.15-4.27 (m, 2 H), 5.68-5.72 (m, 2 H), 6.23-6.25 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1 (q), 14.13 (q), 21.1 (q), 25.5 (t), 25.6 (t), 26.3 (t), 27.5 (t), 30.5 (d), 30.7 (d), 33.9 (t), 35.2 (t), 41.5 (t), 41.7 (t), 44.6 (d), 44.9 (d), 47.1 (q), 47.2 (q), 47.77 (q), 47.80 (q), 51.4 (q), 60.9 (t), 69.9 (d), 69.95 (d), 100.2 (s), 100.3 (s), 124.3 (s), 124.5 (s), 140.95 (t), 140.99

(t), 165.1 (s), 169.83 (s), 169.89 (s), 172.8 (s); exact mass (electrospray) *m/z* calcd for $C_{19}H_{30}NaO_8$ 409.1833, found 409.1835.

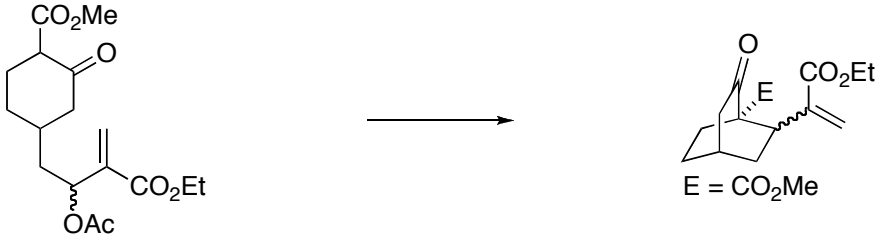
4-(2-Acetoxy-3-ethoxycarbonylbut-3-enyl)-2-oxocyclohexanecarboxylic Acid Ethyl Ester (40.10e).[†]



40.10d **40.10e**

A mixture of **40.10d** (700 mg, 1.81 mmol) and Amberlyst-15 (1.5 g) in acetone (reagent grade, 10 mL) was stirred at room temperature for 1.5 h and then filtered through a pad of silica gel (2 x 4 cm), using EtOAc (30 mL). Evaporation of the filtrate and flash chromatography of the residue over silica gel (2 x 20 cm), using 20% EtOAc-hexane, gave **40.10e** (605 mg, 98%) as an equilibrium mixture of keto-enol tautomers: FTIR (CH_2Cl_2) 2983, 2938, 1745, 1716, 1659, 1621, 1443, 1222, 1027, cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.26-1.34 (m, 3 H), 1.64-2.66 (m, 11 H), 3.33-3.38 (m, 0.4 H), 3.70-3.77 (m, 3 H), 4.11-4.30 (m, 2 H), 5.61-5.81 (m, 2 H), 6.26-6.33 (m, 1 H), 12.08 (s, 0.25 H), 12.09 (s, 0.25 H); exact mass (electrospray) *m/z* calcd for $C_{17}H_{24}NaO_7$ 363.1414, found 363.1412.

2-(1-Ethoxycarbonylvinyl)-6-oxobicyclo[2.2.2]octane-1-carboxylic Acid Methyl Ester (51.17a,a').[†]

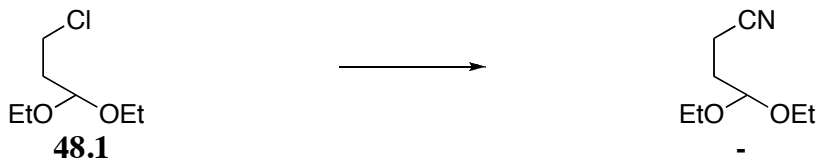


40.10e **51.17a,a'**

DBU (0.10 mL, 0.68 mmol) was added dropwise to a stirred solution of **40.10e** (116 mg, 0.34 mmol) in MeCN (5 mL). Stirring was continued for 1 h and the mixture was then filtered through a pad of silica gel (2 x 2 cm), using 60% EtOAc-hexane (60 mL). Evaporation of the filtrate and flash chromatography of the residue over silica gel (2 x 20 cm), using 10% EtOAc-hexane, gave **51.17a** (12 mg, 13%) and **51.17a'** (66 mg, 69%) as viscous oils. Compound **51.17a'** had: FTIR (CH_2Cl_2) 2951, 2876, 1721, 1626, 1262, cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.29 (t, *J* = 7.5 Hz, 3 H), 1.66 (ddt, *J* = 13.5, 8.0, 2.0 Hz, 1 H), 1.74-1.80 (m, 2 H), 2.11-2.25 (m, 4 H), 2.38 (dt, *J* = 19.0, 3.0 Hz, 1 H), 2.48 (dt, *J* = 18.5, 3.0 Hz, 1 H), 3.31 (dd, *J* = 11.0, 7.5 Hz, 1 H), 3.63 (s, 3 H), 4.14-4.25 (m, 2 H), 5.38 (s, 1 H), 6.10 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.2 (q), 23.8 (t), 27.6 (d), 29.1 (t), 34.6 (t), 41.8 (d), 44.6 (t), 51.7 (q), 57.9 (s), 60.7 (t), 123.9 (s), 143.7 (t), 166.6 (s), 170.9 (s), 208.2 (s); exact mass (electrospray) *m/z* calcd for $C_{15}H_{20}NaO_5$ 303.1203, found 303.1203.

The minor isomer (**51.17a**) was not obtained pure.

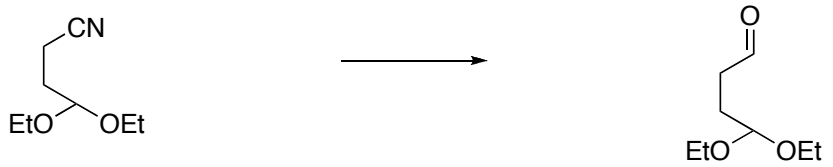
4,4-Diethoxybutyronitrile.[64]



48.1 **-**

A solution of **48.1** (2.00 g, 12.0 mmol) in dry DMSO (3 mL) was added to a stirred mixture of NaCN (2.94 mg, 60.0 mmol) and Bu_4NI (443.0 mg, 1.20 mmol) in DMSO (30 mL), and the resulting mixture was stirred at 50 °C for 15 h, cooled to room temperature, diluted with water (120 mL) and extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (4 x 15 cm), using 8:25 EtOAc-hexane, gave 4,4-diethoxybutyronitrile (1.76 g, 94%) as a liquid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.22 (t, *J* = 7.2 Hz, 6 H), 1.95 (td, *J* = 7.2, 4.2 Hz, 2 H), 2.44 (t, *J* = 7.2 Hz, 2 H), 3.53 (dq, *J* = 9.6, 7.2 Hz, 2 H), 3.69 (dq, *J* = 9. 6, 7.2 Hz, 2 H), 4.59 (t, *J* = 5.6 Hz, 1 H; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.5 (t), 15.2 (q), 29.6 (t), 62.4 (t), 100.8 (d), 119.5 (s).

4,4-Diethoxybutyraldehyde (40.11a).[63]

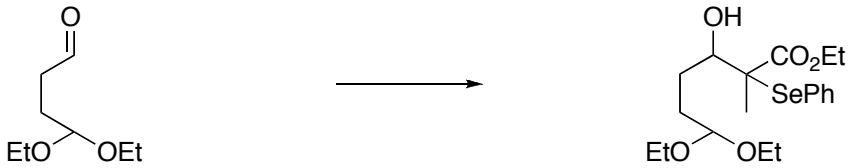


- **40.11a**

DIBAL (1.0 M in CH_2Cl_2, 1.93 mL, 1.93 mmol) was added dropwise to stirred and cooled (-78 °C, dry ice, acetone) solution of 4,4-diethoxybutyronitrile (202.0 mg, 1.29 mmol) in CH_2Cl_2. The dry-ice (but not the acetone) was removed from the cold bath, and stirring was continued for 1 h, by which time the mixture had reached room temperature. Acetone (0.3 mL), EtOAc (0.3 mL) and pH 7.0 buffer (0.3 mL) were added sequentially, and the mixture was stirred vigorously for 20 min. Na_2SO_4 was added and stirring was continued for 3 h. The solid was filtered off, and the solvent was evaporated. Flash chromatography of the residue over silica gel (1.5 x 15 cm), using 1:4 EtOAc-hexane, gave **40.11a** (140 mg, 68%) as a liquid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.16 (t, *J* = 7.2 Hz, 6 H), 1.93 (td, *J* = 7.2, 5.6 Hz, 2 H), 2.49 (td, *J* = 7.2, 1.6 Hz, 2 H), 3.45 (dq, *J* = 9.6, 7.2 Hz,

2 H), 3.62 (dq, *J* = 9.6, 7.2 Hz, 2 H), 4.47 (t, *J* = 5.6 Hz, 1 H), 9.74 (t, *J* = 1.6 Hz, 1 H).

6,6-Diethoxy-3-hydroxy-2-methyl-2-(phenylseleno)hexanoic Acid Ethyl Ester (40.11b,b').



40.11a **40.11b,b'**

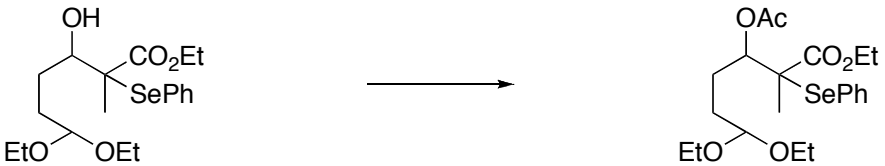
n-BuLi (1.5 M in hexane, 0.65 mL, 0.98 mmol) was added dropwise to a stirred and cooled (0 °C) solution of *i*-Pr_2NH (98.7 mg, 0.98 mmol) in THF (5 mL). Stirring at 0 °C was continued for 15 min, the mixture was cooled to -78 °C, and a solution of **38.1** (252 mg, 0.98 mmol) in THF (3 mL) was added dropwise. Stirring at -78 °C was continued for 1 h, and a solution of **40.11a** (120 mg, 0.75 mmol) in THF (2 mL) was added dropwise. Stirring at -78 °C was continued for 40 min, and the mixture was quenched with saturated aqueous NH_4Cl (5 mL). The cold bath was removed, stirring was continued for 15 min and the mixture was diluted with water (40 mL). The aqueous phase was extracted with EtOAc (3 x 20 mL) and the combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 13:50 EtOAc-hexane, gave **40.11b** (less polar isomer) (64 mg, 21%) as a viscous oil and **40.11b'** (more polar isomer) (132 mg, 42%) as a viscous oil.

Compound **40.11b** had: FTIR (CH_2Cl_2 cast) 3505, 3058, 2976, 2931, 2877, 1720, 1476, 1439 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.13 (t, *J* = 7.1 Hz, 3 H), 1.18 (t, *J* = 7.1 Hz, 3 H), 1.18 (t, *J* = 7.0 Hz, 3 H), 1.42 (s, 3 H), 1.42-1.50 (m, 1 H), 1.53-1.63 (m, 1 H), 1.65-1.73 (m, 1 H), 1.91 (dddd, *J* = 14.3, 9.0, 5.4, 5.4 Hz, 1 H), 3.21 (s, 1 H), 3.47 (dq, *J* = 9.4, 7.1 Hz, 2 H), 3.62 (dqd, *J* = 10.1, 7.1, 3.1 Hz, 2 H), 3.91 (dd, *J* = 9.9, 2.2 Hz, 1 H), 3.94-4.10 (m, 2 H), 4.49 (dd, *J* = 5.5,

5.5 Hz, 1 H), 7.28-7.32 (m, 2 H), 7.37-7.41 (m, 1 H), 7.59-7.62 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.8 (q), 15.3 (q), 17.1 (q), 27.0 (t), 31.0 (t), 57.3 (s), 61.0 (t), 61.1 (t), 61.2 (t), 73.1 (d), 102.6 (d), 126.6 (s), 128.8 (d), 129.4 (d), 138.1 (d), 173.1 (s); exact mass *m/z* calcd for $C_{19}H_{30}O_5{}^{80}Se$ 418.1259, found 418.1246.

Compound **40.11b'** had: FTIR (CH_2Cl_2 cast) 3492, 3058, 2976, 2932, 2878, 1724, 1579, 1477, 1439 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.18-1.23 (m, 9 H), 1.42 (s, 3 H), 1.44-1.50 (m, 1 H), 1.66-1.74 (m, 1 H), 1.93 (dddd, *J* = 9.7, 9.7, 5.2, 5.2 Hz, 1 H), 1.96-2.05 (m, 1 H), 2.99 (s, 1 H), 3.51 (dq, *J* = 9.4, 7.1 Hz, 2 H), 3.66 (dq, *J* = 9.4, 7.1 Hz, 2 H), 3.89 (dd, *J* = 10.7, 1.1 Hz, 1 H), 4.10 (q, *J* = 7.1 Hz, 2 H), 4.54 (dd, *J* = 5.4, 5.4 Hz, 1 H), 7.28-7.32 (m, 2 H), 7.37-7.41 (m, 1 H), 7.57-7.59 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.9 (q), 15.3 (q), 18.2 (q), 26.6 (t), 30.9 (t), 54.7 (s), 61.0 (t), 61.2 (t), 61.3 (t), 73.3 (d), 102.7 (d), 126.7 (s), 128.8 (d), 129.4 (d), 138.1 (d), 174.0 (s); exact mass *m/z* calcd for $C_{19}H_{30}O_5{}^{80}Se$ 418.1259, found 418.1255.

3-Acetoxy-6,6-diethoxy-2-methyl-2-(phenylseleno)hexanoic Acid Ethyl Ester (40.11c).

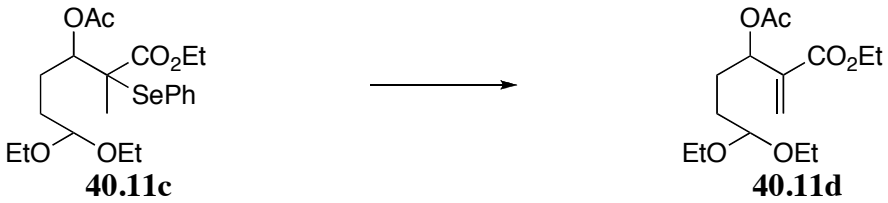


40.11b' **40.11c**

Pyridine (500 mg, 6.33 mmol) and AcCl (249 mg, 3.17 mmol) were added sequentially to a stirred and cooled (-10 °C, ice-acetone bath) solution of **40.11b'** (440 mg, 1.06 mmol) and DMAP (13 mg, 0.11 mmol) in CH_2Cl_2 (3 mL). The cold bath was left in place but not recharged and stirring was continued for 6 h, by which time the temperature had risen to room temperature. The mixture was diluted with water (10 mL), acidified with saturated aqueous NH_4Cl (5 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue

over silica gel (2.5 x 15 cm), using 11:50 EtOAc-hexane, gave **40.11c** (400 mg, 82%) as an oil: FTIR (CH_2Cl_2 cast) 3058, 2977, 2933, 2877, 1747, 1727, 1578, 1477, 1439 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.08 (t, *J* = 7.1 Hz, 3 H), 1.221 (t, *J* = 7.1 Hz, 3 H), 1.222 (t, *J* = 7.1 Hz, 3 H), 1.50 (s, 3 H), 1.59-1.71 (m, 3 H), 1.93 (s, 3 H), 2.18-2.28 (m, 1 H), 3.51 (dqd, *J* = 9.4, 7.0, 4.8 Hz, 2 H), 3.66 (dq, *J* = 9.4, 7.1 Hz, 2 H), 3.88 (dq, *J* = 10.7, 7.1 Hz, 1 H), 4.01 (dq, *J* = 10.7, 7.1 Hz, 1 H), 4.53 (dd, *J* = 5.3, 5.3 Hz, 1 H), 5.43-5.45 (m, 1 H), 7.29-7.32 (m, 2 H), 7.37-7.41 (m, 1 H), 7.59-7.61 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.8 (q), 15.3 (q), 17.8 (q), 20.9 (q), 25.5 (t), 30.5 (t), 53.0 (s), 61.1 (t), 61.2 (t), 61.3 (t), 75.6 (d), 102.4 (d), 126.3 (s), 128.9 (d), 129.5 (d), 138.0 (d), 169.6 (s), 172.1 (s); exact mass *m/z* calcd for $C_{21}H_{32}O_6{}^{80}Se$ 460.1364, found 460.1361.

2-(1-Acetoxy-4,4-diethoxybutyl)acrylic Acid Ethyl Ester (40.11d).

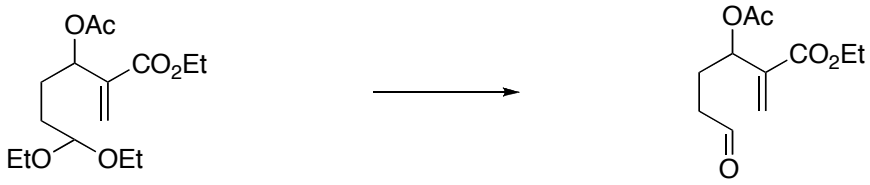


40.11c **40.11d**

H_2O_2 (30%, 0.95 mL, 9.3 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **40.11c** (421 mg, 0.92 mmol) in CH_2Cl_2 (5 mL). Stirring was continued at 0 °C for 40 min and the mixture was quenched with saturated aqueous $Na_2S_2O_3$ (4 mL). The mixture was stirred at 0 °C for 5 min, the ice bath was removed, stirring was continued for 5 min and the mixture was diluted with water (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 15 cm), using 23:100 EtOAc-hexane, gave **40.11d** (260 mg, 94%) as a oil: FTIR ($CDCl_3$ cast) 2977, 2933, 2878, 1747, 1719, 1633, 1446 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.18 (t, *J* = 7.1 Hz, 6 H), 1.29 (t, *J* = 7.1 Hz, 3 H), 1.58-1.77 (m, 3 H), 1.82-1.90 (m, 1 H), 2.06 (s, 3 H), 3.47 (dq, *J* = 9.4, 7.1 Hz, 2 H), 3.61 (dqd, *J* =

9.3, 7.0, 0.6 Hz, 2 H), 4.16-4.27 (m, 2 H), 4.47 (dd, *J* = 5.6, 5.6 Hz, 1 H), 5.63 (ddd, *J* = 7.7, 4.5, 0.8 Hz, 1 H), 5.74 (dd, *J* = 1.1, 1.1 Hz, 1 H), 6.27 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1 (q), 15.3 (q), 21.0 (q), 29.2 (t), 29.3 (t), 60.9 (t), 61.11 (t), 61.14 (t), 71.4 (d), 102.4 (d), 125.0 (t), 140.1 (s), 165.2 (s), 169.8 (s); exact mass (electrospray) *m*/*z* calcd for $C_{15}H_{26}NaO_6$ 325.1622, found 325.1620.

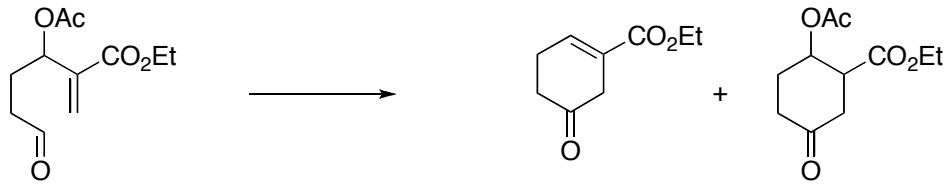
2-(1-Acetoxy-4-oxobutyl)acrylic Acid Ethyl Ester (40.11e).



40.11d **40.11e**

Hydrochloric acid (4 M, 0.11 mL, 0.42 mmol) was added to a stirred solution of **40.11d** (128 mg, 0.42 mmol) in acetone (4 mL), and stirring was continued at room temperature for 1.5 h. The mixture was diluted with water (20 mL) and the aqueous phase was extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 2:5 EtOAc-hexane, gave **40.11e** (90 mg, 94%) as a liquid: FTIR (CH_2Cl_2 cast) 2983, 2939, 2830, 2728, 1745, 1723, 1634, 1446 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.31 (t, *J* = 7.1 Hz, 3 H), 2.04 (dddd, *J* = 14.7, 14.7, 7.5, 7.5 Hz, 1 H), 2.07 (s, 3 H), 2.17 (dddd, *J* = 11.7, 7.4, 7.3, 4.4 Hz, 1 H), 2.50 (td, *J* = 7.5, 1.4 Hz, 2 H), 4.18-4.29 (m, 2 H), 5.65 (ddd, *J* = 7.6, 4.4, 1.2 Hz, 1 H), 5.76 (t, *J* = 1.0, 1.0 Hz, 1 H), 6.32 (s, 1 H), 7.53 (t, *J* = 1.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1 (q), 21.0 (q), 26.5 (t), 39.6 (t), 61.1 (t), 70.8 (d), 125.4 (t), 139.5 (s), 164.9 (s), 169.6 (s), 201.0 (d); exact mass (electrospray) *m*/*z* calcd for $C_{11}H_{16}NaO_5$ 251.0890, found 251.0888.

5-Oxocyclohex-1-enecarboxylic Acid Ethyl Ester (51.18) and 2-Acetoxy-5-oxocyclohexanecarboxylic Acid Ethyl Ester (51.18').



40.11e **51.18** **51.18'**

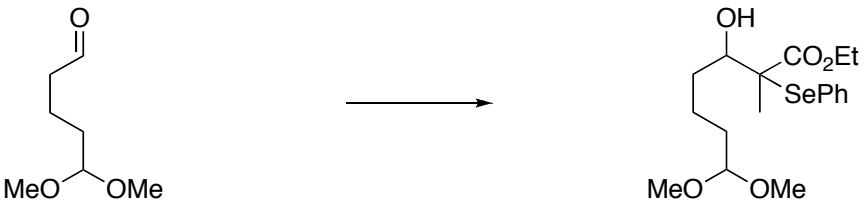
Et_3N (26.6 mg, 0.263 mmol) was added to a solution of **40.11e** (40 mg, 0.18 mmol) and 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride (**51a**) (4.7 mg, 0.018 mmol) in 1,4-dioxane (0.4 mL) contained in a thick-walled vial. The vial was closed with a Teflon-lined screw-on cap and the mixture was stirred at 70 °C for 10 h, cooled to room temperature, diluted with water (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (0.7 x 15 cm), using 1:4 EtOAc-hexane, gave a 2:3 mixture of **51.18** and **51.18'** (25 mg, 86%) as an oil.

DBU (61.1 mg, 0.4 mmol) was added to a solution of the above 2:3 mixture in MeCN (0.5 ml). The mixture was stirred at 50 °C overnight, cooled to room temperature, diluted with water (5 mL) and acidified with hydrochloric acid (1 M, 1 mL). The aqueous phase was extracted with EtOAc (3 x 5 mL) and the combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (0.7 x 7 cm), using 1:4 EtOAc-hexane, gave the acetate **51.18'** (ca 1 mg, 3.5%) as an oil (and no **51.18**): FTIR ($CHCl_3$ cast) 2985, 2942, 1739, 1720, 1655, 1448 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.24-1.28 (m, 5 H), 1.93-2.06 (m, 1 H), 2.08 (s, 3 H), 2.36-2.51 (m, 4 H), 4.11-4.27 (m, 2 H), 5.65-5.69 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.49 (q), 13.99 (q), 20.71 (d), 26.06 (t), 35.30 (t), 60.05 (t), 61.87 (t), 76.54 (d), 170.01 (s), 170.14 (s), 211.60 (s); exact mass (electrospray) *m/z* calcd for $C_{11}H_{16}NaO_5$ 251.0890, found 251.0891.

The above experiment was done in an attempt to establish if **51.18** is derived from **51.18'**; it appears, however, that **51.18** is not stable for a prolonged time under these conditions, and all we accomplished by this experiment was the isolation of pure **51.18'**.

By subtracting the signals of **51.18'** from the NMR spectrum of the mixture of **51.18** and **51.18'**, it was possible to identify the NMR signals of **51.18**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.29 (td, *J* = 7.1, 0.5 Hz, 3 H), 2.37-2.50 (m, 2 H), 2.61-2.66 (m, 2 H), 3.14 (dd, *J* = 2.1, 2.1 Hz, 2 H), 4.08-4.24 (m, 2 H), 7.16 (dddd, *J* = 4.0, 4.0, 1.9, 1.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2 (q), 25.1 (t), 37.3 (t), 39.0 (t), 60.8 (t), 128.7 (s), 137.9 (d), 165.7 (s), 208.2 (s).

3-Hydroxy-7,7-dimethoxy-2-methyl-2-(phenylseleno)heptanoic Acid Ethyl Ester (41.12b).[†]

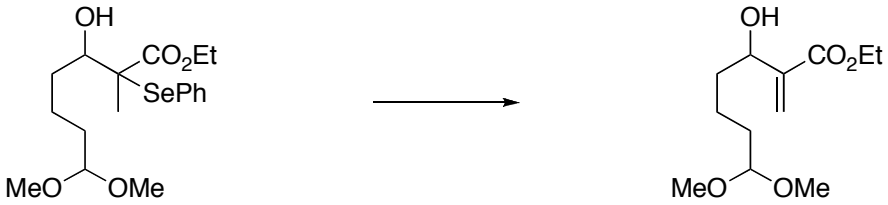


41.12a **40.12b**

n-BuLi (2.5 M in hexane, 9.03 mL, 22.6 mmol) was added dropwise over 5 min to a stirred and cooled (-78 °C) solution of *i*-Pr_2NH (3.47 mL, 24.6 mmol) in THF (50 mL). Stirring was continued for 45 min and a solution of **38.1** (6.07 g, 23.6 mmol) in THF (15 mL plus 2 mL as a rinse) was added over 10 min. Stirring at -78 °C was continued for 3 h and a solution of **41.12a**[65] (3.0 g, 21 mmol) in THF (15 mL plus 2 mL as a rinse) was added dropwise over 10 min. The mixture was stirred for 1.5 h, and quenched with water (10 mL) and saturated aqueous NH_4Cl (15 mL). The cold bath was removed, stirring was continued for 10 min and the mixture was diluted with water (100 mL) and extracted with EtOAc (3 x 25 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (3 x 20 cm),

using 20% EtOAc-hexane, gave **41.12b** (8.02 g, 97%) as a viscous oil which was a 60:40 mixture of diastereoisomers: FTIR (CH_2Cl_2 cast) 3477, 2980, 2947, 2830, 1721, 1250, 1129, 744 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.14 (t, *J* = 7.0 Hz, 1.2 H), 1.21 (t, *J* = 7.0 Hz, 1.8 H), 1.32-1.44 (m, 5.4 H), 1.52-1.71 (m, 4 H), 1.87-1.92 (m, 0.6 H), 2.82 (d, *J* = 7.0 Hz, 0.6 H), 2.97 (dd, *J* = 3.0, 1.5 Hz, 0.4 H), 3.30-3.33 (m, 6 H), 3.85-3.90 (m, 1 H), 3.96-4.14 (m, 2 H), 4.33-4.40 (m, 1 H), 7.29-7.33 (m, 2 H), 7.38-7.42 (m, 1 H), 7.56-7.60 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.8 (q), 14.0 (q), 17.0 (q), 18.2 (q), 21.99 (t), 22.01 (t), 31.2 (t), 31.6 (t), 32.27 (t), 32.34 (t), 52.64 (q), 52.69 (q), 52.74 (q), 52.81 (q), 54.8 (s), 57.5 (s), 61.0 (t), 61.2 (t), 72.8 (d), 75.2 (d), 104.48 (d), 104.53 (d), 126.5 (s), 126.6 (s), 128.77 (d), 128.83 (d), 129.36 (d), 129.44 (d), 138.04 (d), 138.07 (d), 173.1 (s), 174.0 (s); exact mass (electrospray) *m/z* calcd for $C_{18}H_{28}NaO_5{}^{80}Se$ 427.0994, found 427.0997.

2-(1-Hydroxy-5,5-dimethoxypentyl)acrylic Acid Ethyl Ester (41.12c).[†]

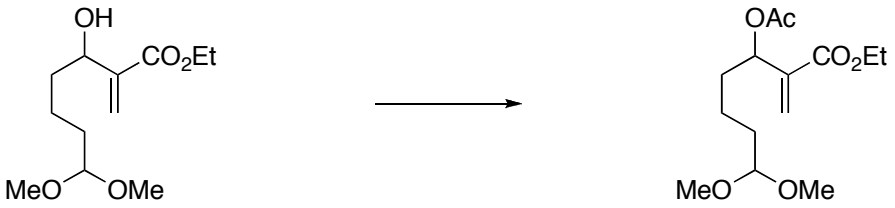


41.12b **41.12c**

H_2O_2 (30%, 5 mL, 49 mmol) was added dropwise over 2 min to a stirred and cooled (-10 °C) solution of **41.12b** (2.0 g, 4.958 mmol) in CH_2Cl_2 (20 mL). Stirring at -10 °C was continued for 1 h and the mixture was quenched with saturated aqueous $NaHCO_3$ (8 mL), followed by dropwise addition of saturated aqueous $Na_2S_2O_3$ (8 mL). The cold bath was removed after 10 min, stirring was continued for 5 min and the mixture was diluted with water (30 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 18 cm), using 15% EtOAc-hexane, gave **41.12c** (1.2 g, 98%) as a viscous oil: FTIR

(CH_2Cl_2 cast) 3454, 2983, 2948, 2832, 1714, 1629, 1128, 954 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.31 (t, *J* = 7.2 Hz, 3 H), 1.36-1.73 (m, 6 H), 2.68 (d, *J* = 6.8 Hz, 1 H), 3.304 (s, 3 H), 3.307 (s, 3 H), 4.23 (q, *J* = 7.2 Hz, 2 H), 4.36 (t, *J* = 5.6 Hz, 1 H), 4.36-4.41 (m, 1 H), 4.778-4.783 (m, 1 H), 6.22 (d, *J* = 0.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.0 (q), 20.9 (t), 32.1 (t), 35.8 (t), 52.6 (q), 52.7 (q), 60.7 (t), 71.5 (d), 104.4 (d), 124.6 (s), 142.5 (t), 166.4 (s); exact mass (electrospray) *m*/*z* calcd for $C_{12}H_{22}NaO_5$ 269.1359, found 269.1356.

2-(1-Acetoxy-5,5-dimethoxypentyl)acrylic Acid Ethyl Ester (40.12d).[†]

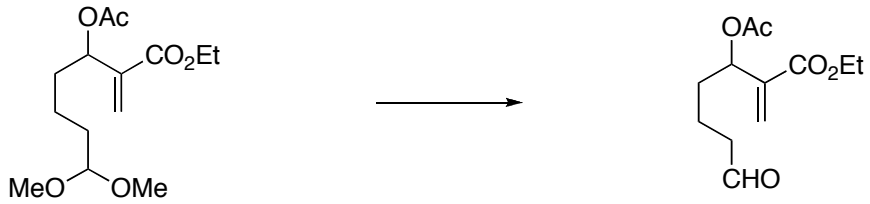


40.12c **40.12d**

Pyridine (1.56 mL, 19.3 mmol) and AcCl (0.51 mL, 7.2 mmol) were added dropwise over ca 5 min to a stirred and cooled (0 °C) solution of **40.12c** (1.19 g, 4.83 mmol) and DMAP (90 mg, 0.73 mmol) in CH_2Cl_2 (20 mL). Stirring at 0 °C was continued for 1 h and the mixture was quenched with water (5 mL). The cold bath was removed, stirring was continued for 10 min and the mixture was diluted with water (15 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (3 x 16 cm), using 20% EtOAc-hexane, gave **40.12d** (1.292 g, 93%) as a viscous oil: FTIR (CH_2Cl_2 cast) 2983, 2947, 2831, 1746, 1719, 1633, 1240, 956 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.31 (t, *J* = 7.2 Hz, 3 H), 1.34-1.47 (m, 2 H), 1.54-1.84 (m, 4 H), 2.08 (s, 3 H), 3.309 (s, 3 H), 3.311 (s, 3 H), 4.18-4.29 (m, 2 H), 4.34 (t, *J* = 5.6 Hz, 1 H), 5.62 (dd, *J* = 8.0, 4.4 Hz, 1 H), 5.74-5.75 (m, 1 H), 6.281-6.283 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.1 (q), 20.4 (t), 21.1 (q), 32.1 (t), 34.0 (t), 52.7 (q), 52.8

(q), 60.9 (t), 71.7 (d), 104.3 (s), 124.8 (s), 140.2 (t), 165.2 (s), 169.9 (s); exact mass (electrospray) *m*/*z* calcd for $C_{14}H_{24}NaO_6$ 311.1465, found 311.1460.

2-(1-Acetoxy-5-oxopentyl)acrylic Acid Ethyl Ester (40.12e).[†]

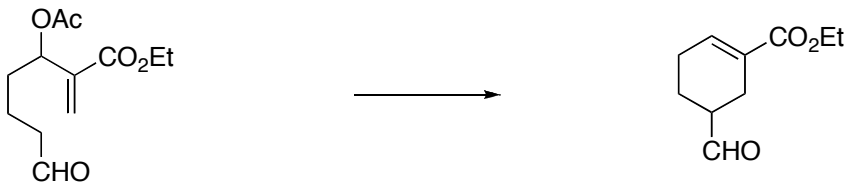


40.12d **40.12e**

Hydrochloric acid (10%, 4 mL) was added to a stirred and cooled (0 °C) solution of **40.12d** (650 mg, 2.25 mmol) in THF (12 mL). The ice bath was removed after 2 h, stirring was continued for 3 h and the mixture was diluted with water (30 mL) and extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 2 cm), using 50% EtOAc-hexane (80 mL), gave **40.12e** (525 mg, 96%) as a colorless liquid: FTIR (CH_2Cl_2 cast) 2941, 1743, 1372, 1235, 1029 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.29 (t, *J* = 7.2 Hz, 3 H), 1.56-1.83 (m, 4 H), 2.07 (s, 3 H), 2.40-2.53 (m, 2 H), 4.15-4.27 (m, 2 H), 5.59-5.62 (m, 1 H), 5.75 (t, *J* = 1.2 Hz, 1 H), 6.27 (t, *J* = 0.4 Hz, 1 H), 9.74 (t, *J* = 1.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1 (q), 17.8 (t), 21.0 (q), 33.5 (t), 43.2 (t), 60.9 (t), 71.2 (d), 125.0 (s), 139.9 (t), 165.1 (s), 169.8 (s), 201.7 (d); exact mass (electrospray) *m*/*z* calcd for $C_{12}H_{18}NaO_5$ 265.1047, found 265.1045.

5-Formylcyclohex-1-enecarboxylic Acid Ethyl Ester (51.19).[†]

(a) Use of pyrrolidine



40.12e **51.19**

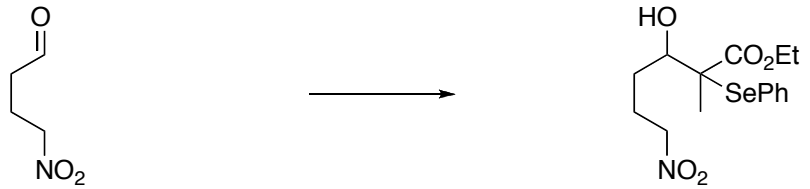
A solution of pyrrolidine (4 mg, 0.06 mmol) in PhH (2 mL) was added over 1 min to a stirred solution of **40.12e** (150 mg, 0.619 mmol) in PhH (1 mL). The reaction flask was lowered into a preheated oil bath and the mixture was refluxed for 18 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (0.5 x 8 cm), using 20% EtOAc-hexane, gave **51.19** (36 mg, 32%) as a viscous liquid: FTIR (CH_2Cl_2 cast) 2982, 2933, 2714, 1711, 1651, 1251, 1089, 720 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.29 (t, *J* = 7.5 Hz, 3 H), 1.63-1.7 (m, 1 H), 1.95-2.01 (m, 1 H), 2.22-2.37 (m, 2 H), 2.42-2.61 (m, 3 H), 4.20 (q, *J* = 7.5 Hz, 2 H), 6.98-7.0 (m, 1 H), 9.72 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2 (q), 21.0 (t), 23.4 (t), 24.2 (t), 45.6 (d), 60.4 (t), 128.5 (s), 138.9 (d), 166.7 (s), 203.2 (d); exact mass (electrospray) *m/z* calcd for $C_{10}H_{14}NaO_3$ 205.0835, found 205.0836.

(b) Use of proline-derived catalyst 51b.

A solution of the proline-derived catalyst **51b**[73] (15 mg, 0.046 mmol) in dry MeCN (3 mL) was added to a stirred solution of **40.12e** (68 mg, 0.28 mmol) in MeCN (1 mL). The reaction flask was lowered into a preheated oil bath and the mixture was refluxed for 15 h, cooled to room temperature and filtered through a pad of silica gel (2 x 2 cm), using 60% EtOAc-hexane (60 mL). Evaporation of the solvent and flash chromatography of the residue over silica gel (0.5 x 8 cm), using 10% EtOAc-hexane, gave **51.19** (27 mg, 53%, 69% after correction for recovered **40.12e**) as a viscous liquid and **40.12e** (16 mg, 24%) as

pure (^{1}H NMR) viscous oils. Compound **51.19** had: $[\alpha]_D$ -0.64 (CH_2Cl_2, c 0.5 g/100).

3-Hydroxy-2-methyl-6-nitro-2-(phenylseleno)hexanoic Acid Ethyl Ester (40.7b,b').



40.7a **40.7b,b'**

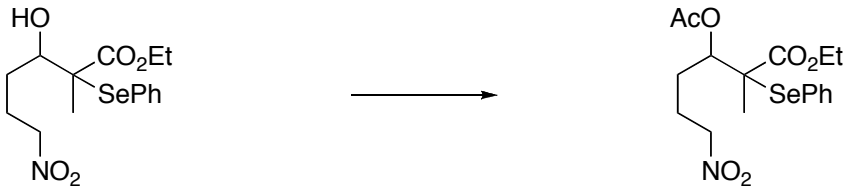
n-BuLi (1.6 M in hexane, 1.04 mL, 1.67 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of *i*-Pr_2NH (168.7 mg, 1.67 mmol) in THF (8 mL). Stirring at -78 °C was continued for 1 h, and a solution of **38.1** (429.0 mg, 1.67 mmol) in THF (1 mL) was then added dropwise. Stirring at -78 °C was continued for 85 min, and a solution of **40.7a**[66] (150 mg, 1.28 mmol) in THF (1 mL) was added dropwise. Stirring at -78 °C was continued for 40 min, and the mixture was quenched with saturated aqueous NH_4Cl (10 mL). The cold bath was removed, stirring was continued for 15 min, the mixture was diluted with water (30 mL) and the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2.5 x 15 cm), using 1:2 EtOAc-hexane, gave **40.7b** (less polar isomer) (91 mg, 19%) as a viscous oil and **40.7b'** (more polar isomer) (160 mg, 33%) as a viscous oil.

Compound **40.7b** had: FTIR ($CDCl_3$ cast) 3508, 3059, 2980, 2935, 1717, 1552, 1476, 1438 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.15 (dd, *J* = 7.1, 7.1 Hz, 3 H), 1.37 (s, 3 H), 1.46-1.52 (m, 1 H), 1.64 (dddd, *J* = 14.2, 10.2, 8.5, 5.8 Hz, 1 H), 2.08-2.16 (m, 1 H), 2.24-2.32 (m, 1 H), 3.19 (dd, *J* = 2.3, 2.3 Hz, 1 H), 3.87 (td, *J* = 10.2, 2.3 Hz, 1 H), 4.02 (dq, *J* = 10.8, 7.1 Hz, 1 H), 4.09 (dq, *J* = 10.8, 7.1 Hz, 1 H), 4.37-4.48 (m, 2 H), 7.31-7.35 (m, 2 H), 7.40-7.44 (m, 1 H), 7.57-7.59 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.8 (q), 17.1 (q), 24.8 (t), 28.1 (t), 56.9 (s),

61.3 (t), 72.2 (d), 75.3 (t), 126.0 (s), 129.0 (d), 129.7 (d), 138.0 (d), 173.1 (s); exact mass *m/z* calcd for $C_{15}H_{21}NO_5{}^{80}Se$ 375.0580, found 375.0584.

Compound **40.7b'** had: FTIR ($CDCl_3$ cast) 3509, 2980, 2938, 1717, 1551, 1476, 1438 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.22 (t, *J* = 7.2 Hz, 3 H), 1.41 (s, 3 H), 1.44-1.52 (m, 1 H), 2.01-2.15 (m, 2 H), 2.23-2.32 (m, 1 H), 2.93 (dd, *J* = 6.6, 1.0 Hz, 1 H), 3.86 (ddd, *J* = 10.7, 6.6, 1.7 Hz, 1 H), 4.12 (q, *J* = 7.2 Hz, 1 H), 4.13 (q, *J* = 7.2 Hz, 1 H), 4.40-4.51 (m, 2 H), 7.31-7.34 (m, 2 H), 7.39-7.43 (m, 1 H), 7.55-7.57 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.9 (q), 17.9 (q), 24.9 (t), 27.9 (t), 54.0 (s), 61.5 (t), 74.6 (d), 75.4 (t), 126.2 (s), 128.9 (d), 129.6 (d), 138.0 (d), 174.0 (s); exact mass *m/z* calcd for $C_{15}H_{21}NO_5{}^{80}Se$ 375.0580, found 375.0580.

3-Acetoxy-2-methyl-6-nitro-2-(phenylseleno)hexanoic Acid Ethyl Ester (40.7c).

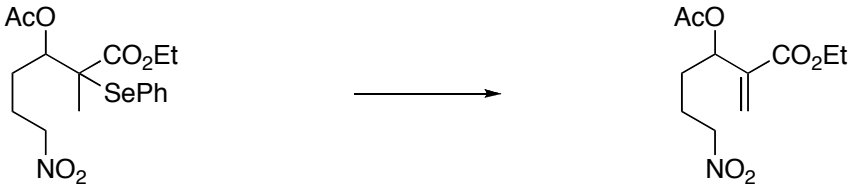


40.7b' **40.7c**

Pyridine (187.9 mg, 2.38 mmol) and AcCl (93.3 mg, 1.19 mmol) were added sequentially to a stirred and cooled (-10 °C, ice-acetone bath) solution of **40.7b'** (148 mg, 0.40 mmol) and DMAP (4.8 mg, 0.040 mmol) in CH_2Cl_2 (3 mL). The cold bath was left in place but not recharged and stirring was continued for 13 h, by which time the temperature had risen to room temperature. The mixture was diluted with water (5 mL), acidified with hydrochloric acid (1 M, 2 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 15 cm), using 19:50 EtOAc-hexane, gave **40.7c** (127 mg, 77%) as an oil: FTIR ($CDCl_3$ cast) 3058, 2982, 2936, 1743, 1725, 1669, 1552, 1477, 1439 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.09 (t, *J* = 7.2 Hz, 3 H), 1.49 (s, 3 H), 1.68 (dddd, *J* = 14.1, 10.5, 9.3, 4.8 Hz, 1 H), 1.96 (s, 3 H), 1.96-2.11 (m, 2

H), 2.23-2.30 (m, 1 H), 3.90 (dq, *J* = 10.8, 7.2 Hz, 1 H), 4.03 (dq, *J* = 10.8, 7.2 Hz, 1 H), 4.43 (dd, *J* = 6.7, 6.6 Hz, 2 H), 5.41 (dd, *J* = 10.6, 1.7 Hz, 1 H), 7.31-7.34 (m, 2 H), 7.39-7.43 (m, 1 H), 7.56-7.59 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.8 (q), 17.6 (q), 20.8 (q), 24.1 (t), 27.3 (t), 52.4 (s), 61.3 (s), 74.5 (d), 74.9 (t), 126.0 (s), 129.0 (d), 129.8 (d), 137.9 (d), 169.9 (s), 171.8 (s); exact mass *m*/*z* calcd for $C_{17}H_{23}NO_6{}^{80}Se$ 417.0691, found 417.0692.

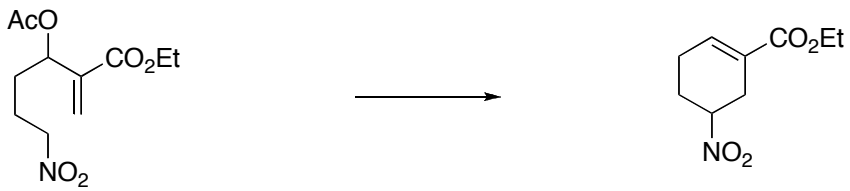
2-(1-Acetoxy-4-nitrobutyl)acrylic Acid Ethyl Ester (40.7d).



40.7c **40.7d**

H_2O_2 (30%, 0.36 mL, 3.52 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **40.7c** (123 mg, 0.30 mmol) in CH_2Cl_2 (3 mL). Stirring was continued at 0 °C for 70 min and the mixture was quenched with saturated aqueous $Na_2S_2O_3$ (2.0 mL). The mixture was stirred at 0 °C for 5 min, the ice bath was removed, stirring was continued for 30 min, and water (10 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 7:20 EtOAc-hexane, gave **40.7d** (60 mg, 78%) as a viscous oil: FTIR ($CDCl_3$ cast) 2983, 2940, 1743, 1633, 1553, 1436 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.30 (t, *J* = 7.1 Hz, 3 H), 1.75-1.82 (m, 1 H), 1.88 (dddd, *J* = 14.0, 10.0, 6.1, 4.2 Hz, 1 H), 1.99-2.09 (m, 2 H), 2.09 (s, 3 H), 4.18-4.27 (m, 2 H), 4.40 (dd, *J* = 7.0, 6.9 Hz, 2 H), 5.64 (dd, *J* = 7.7, 4.1 Hz, 1 H), 5.77 (s, 1 H), 6.31 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1 (q), 20.9 (q), 23.2 (t), 30.7 (t), 61.1 (t), 70.6 (d), 74.9 (t), 125.4 (t), 139.4 (s), 164.9 (s), 169.7 (s); exact mass (electrospray) *m*/*z* calcd for $C_{11}H_{17}NNaO_6$ 282.0948, found 282.0947.

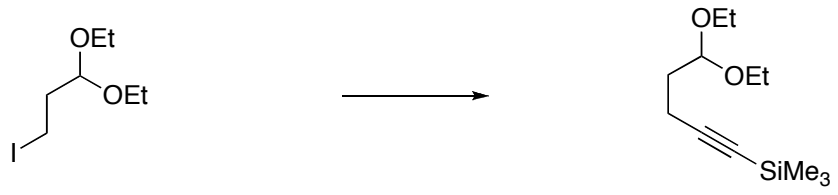
5-Nitrocyclohex-1-enecarboxylic Acid Ethyl Ester (51.12).



40.7d **51.12**

Cs_2CO_3 (66.2 mg, 0.203 mmol) was added to a stirred solution of **40.7d** (26.3 mg, 0.102 mmol) in THF (1 mL), and stirring at room temperature was continued for 4.5 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (0.7 x 7 cm), using 1:2 EtOAc-hexane, gave **51.12** (15 mg, 75%) as a colorless viscous oil: FTIR ($CDCl_3$ cast) 2982, 2938, 2907, 1712, 1655, 1548, 1462, 1445, 1430 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.30 (t, *J* = 7.2 Hz, 3 H), 2.14-2.49 (m, 4 H), 2.84-2.98 (m, 2 H), 4.21 (q, *J* = 7.2 Hz, 2 H), 4.67 (dddd, *J* = 9.6, 8.0, 6.0, 4.0 Hz, 1 H), 7.00 (dddd, *J* = 3.6, 3.6, 1.8, 1.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2 (q), 23.6 (t), 25.8 (t), 28.2 (t), 60.1 (t), 80.4 (d), 126.9 (s), 137.8 (d), 165.9 (s); exact mass *m/z* calcd for $C_9H_{13}NO_4$ 199.0845, found 199.0846.

(5,5-Diethoxypent-1-ynyl)trimethylsilane (49.3).[77]

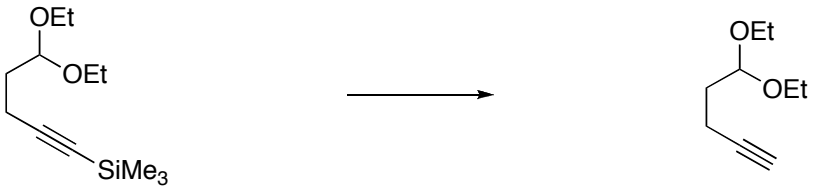


49.2 **49.3**

n-BuLi (1.3 M, 5.8 mL, 7.57 mmol) was added to a stirred and cooled (-78 °C) solution of trimethylsilylacetylene (0.744 g, 7.57 mmol) in THF (35 mL). The mixture was stirred at 0 °C for 10 min and then recooled to -78 °C. A solution of HMPA (7.4 g, 41.3 mmol) in THF (7 mL) was added, stirring was continued for 10 min, and a solution of **49.2** (1.78 g, 6.9 mmol) in THF (10 mL)

was added dropwise. The cold bath was left in place but not recharged and stirring was continued overnight. The mixture was quenched with saturated aqueous NH_4Cl (30 mL) and diluted with water (200 mL). The aqueous phase was extracted with Et_2O (3 x 60 mL) and the combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (4 x 15 cm), using 0.9:25 EtOAc-hexane, gave **49.3** (1.104 mg, 70%) as a colorless liquid.

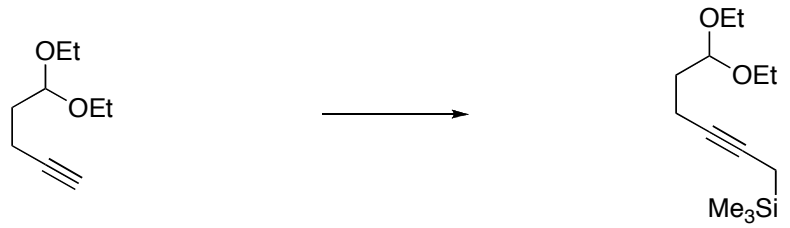
4-Pentynyl Diethyl Acetal (49.4).[77]



49.3 **49.4**

K_2CO_3 (2.67 g, 19.4 mmol) was added to a stirred solution of **49.3** (1.104 g, 4.84 mmol) in anhydrous MeOH (100 mL) (N_2 atmosphere). Stirring at room temperature was continued for 2.5 h. The mixture was concentrated to 50 mL and diluted with water (250 mL). The aqueous phase was extracted with Et_2O (3 x 60 mL) and the combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated to give **49.4** as a liquid (669 mg, 89%).

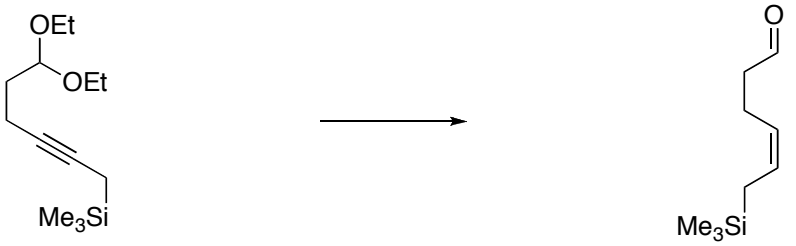
(6,6-Diethoxyhex-2-ynyl)trimethylsilane (49.5).[78]



49.4 **49.5**

n-BuLi (1.3 M, 4.5 mL, 5.85 mmol) was added to a stirred and cooled (-78 °C) solution of **49.4** (760 mg, 4.87 mmol) in THF (20 mL). The mixture was stirred at 0 °C for 15 min and HMPA (5.1 mL) was added. The mixture was cooled to -78 °C and iodomethyltrimethylsilane (1.25 g, 5.85 mmol) was added dropwise. The cold bath was left in place but not recharged and stirring was continued overnight. The mixture was quenched with saturated aqueous NH_4Cl (20 mL) and diluted with water (150 mL). The aqueous phase was extracted with Et_2O (3 x 30 mL) and the combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 1:20 EtOAc-hexane, gave **49.5** (852 mg, 72%) as a colorless liquid: FTIR (CH_2Cl_2 cast) 2975, 2960, 2933, 2901, 2881, 2222, 2177 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ -0.09 (s, 9 H), 1.21 (t, *J* = 5.8 Hz, 6 H), 1.41 (t, *J* = 2.7 Hz, 2 H), 1.77 (td, *J* = 7.2, 5.8 Hz, 2 H), 2.22 (tt, *J* = 7.2, 2.7 Hz, 2 H), 3.51 (dq, *J* = 9.5, 7.1 Hz, 2 H), 3.66 (dq, *J* = 9.5, 7.1 Hz, 2 H), 4.61 (t, *J* = 5.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ -2.1 (q), 6.9 (t), 14.6 (t), 15.4 (q), 33.5 (t), 61.5 (t), 77.7 (s), 77.8 (s), 102.0 (d); exact mass (electrospray) *m/z* calcd for $C_{13}H_{26}NaO_2Si$ 265.1594, found 265.1594.

(*Z*)-6-(Trimethylsilyl)hex-4-enal (40.13a).[79]



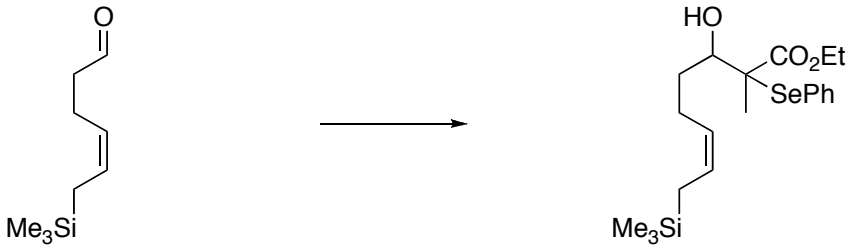
49.5 **40.13a**

N_2 was bubbled through a solution of **49.5** (256 mg, 1.06 mmol) in MeOH (1 mL) for 10 min, and then 10% Pd/$BaSO_4$ (5.8 mg) and quinoline (5.8 mg, 0.48 mmol) were added. Stirring at room temperature was continued for 5 min, and the mixture was purged with a stream of H_2 for 10 sec. The flask was connected

to a sloping manifold apparatus filled with H_2. The flask was removed when rapid absorption of H_2 stopped (a little more than the calculated amount), and the solid was filtered off through a pad of Celite, using Et_2O as a rinse. Evaporation of the filtrate gave the crude product (251 mg, 97%).

The above crude product was dissolved in acetone (2 mL), and hydrochloric acid (1 M, 1.1 mL) was added. The solution was stirred at room temperature for 2 h, diluted with water (20 mL), and extracted with Et_2O (3 x 15 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$) and evaporated, to give crude **40.13a** (157 mg, 87% over two steps), which was used directly in the next step: ^{1}H NMR ($CDCl_3$, 300 MHz) δ -0.01 (s, 9 H), 1.47-1.51 (m, 2 H), 2.31-2.37 (m, 2 H), 2.45-2.51 (m, 2 H), 5.23 (dtt, *J* = 10.5, 6.9, 1.5 Hz, 1 H), 5.47 (dtt, *J* = 10.5, 8.7, 1.5 Hz, 1 H), 9.78 (t, *J* = 1.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ -1.9 (q), 18.5 (t), 19.8 (t), 43.8 (t), 124.7 (d), 127.3 (d), 202.3 (d).

(*Z*)-3-Hydroxy-2-methyl-2-(phenylseleno)-8-(trimethylsilyl)oct-6-enoic Acid Ethyl Ester (40.13b,b').



40.13a **40.13b,b'**

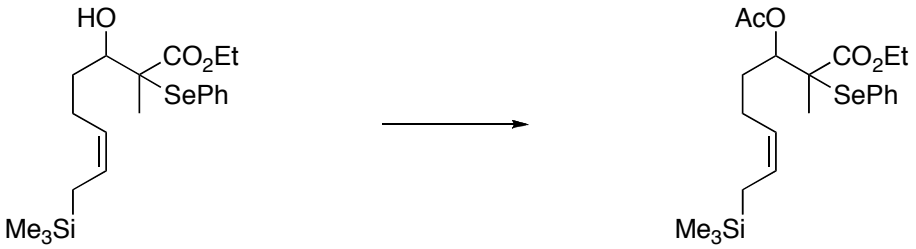
n-BuLi (1.3 M in hexane, 1.07 mL, 1.39 mmol) was added dropwise to a stirred and cooled (0 °C) solution of *i*-Pr_2NH (141 mg, 1.39 mmol) in THF (6 mL). Stirring at 0 °C was continued for 10 min, the mixture was cooled to -78 °C, and a solution of **38.1** (357.2 mg, 1.39 mmol) in THF (1 mL) was then added dropwise. Stirring at -78 °C was continued for 30 min, and a solution of **40.13a** (157 mg, 0.92 mmol) in THF (1.5 mL) was added dropwise. Stirring at -78 °C

was continued for 50 min, and the mixture was quenched with saturated aqueous NH_4Cl (5 mL). The cold bath was removed, stirring was continued for 15 min, the mixture was diluted with water (25 mL) and the aqueous phase was extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2.5 x 15 cm), using successively 1:20 EtOAc-hexane, 8% EtOAc-hexane, and 10% EtOAc-hexane, gave **40.13b** (less polar isomer) (80 mg, 20%) as a viscous oil and **40.13b'** (more polar isomer) (133 mg, 34%) as a viscous oil.

Compound **40.13b** had: FTIR ($CDCl_3$ cast) 3515, 3058, 2953, 1721, 1476, 1438 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ -0.01 (s, 9 H), 1.12 (t, *J* = 7.5 Hz, 3 H), 1.33-1.41 (m, 4 H), 1.47 (dddd, *J* = 13.7, 13.7, 13.6, 8.5 Hz, 2 H), 1.59 (dddd, *J* = 23.4, 19.9, 17.1, 10.7 Hz, 1 H), 2.06-2.14 (m, 1 H), 2.20-2.27 (m, 1 H), 2.96 (dd, *J* = 2.7, 1.7 Hz, 1 H), 3.93 (ddd, *J* = 9.8, 2.8, 1.9 Hz, 1 H), 3.95-4.09 (m, 2 H), 5.20-5.25 (m, 1 H), 5.40 (ddddd, *J* = 10.1, 8.7, 8.7, 1.4, 1.4 Hz, 1 H), 7.29-7.32 (m, 2 H), 7.37-7.41 (m, 1 H), 7.59-7.61 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ -1.8 (q), 13.8 (q), 17.1 (q), 18.4 (t), 24.2 (t), 31.9 (t), 57.5 (s), 61.0 (t), 72.6 (d), 126.3 (d), 126.48 (d), 126.54 (s), 128.8 (d), 129.4 (d), 138.0 (d), 173.1 (s); exact mass (electrospray) *m/z* calcd for $C_{20}H_{32}NaO_3{}^{80}SeSi$ 451.1178, found 451.1176.

Compound **40.13b'** had: FTIR ($CDCl_3$ cast) 3507, 3059, 3002, 2953, 1704, 1476, 1438 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.01 (s, 9 H), 1.19 (t, *J* = 7.5 Hz, 3 H), 1.41 (s, 3 H), 1.44-1.55 (m, 3 H), 1.90 (dddd, *J* = 13.6, 8.9, 7.3, 1.5 Hz, 1 H), 2.11 (ddddd, *J* = 14.6, 8.7, 7.3, 7.2, 1.5 Hz, 1 H), 2.24-2.31 (m, 1 H), 2.82 (d, *J* = 6.0 Hz, 1 H), 3.90 (ddd, *J* = 10.4, 6.8, 1.3 Hz, 1 H), 4.06-4.13 (m, 2 H), 5.26-5.31 (m, 1 H), 5.45 (ddddd, *J* = 10.2, 8.6, 8.6, 1.5, 1.5 Hz, 1 H), 7.28-7.32 (m, 2 H), 7.37-7.40 (m, 1 H), 7.56-7.59 m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ -1.8 (q), 13.9 (q), 18.3 (q), 18.5 (t), 24.2 (t), 31.6 (t), 54.7 (s), 61.2 (t), 75.0 (d), 126.4 (d), 126.5 (d), 126.7 (s), 128.7 (d), 129.3 (d), 138.1 (d), 174.0 (s); exact mass (electrospray) *m/z* calcd for $C_{20}H_{32}NaO_3{}^{80}SeSi$ 451.1178, found 451.1181.

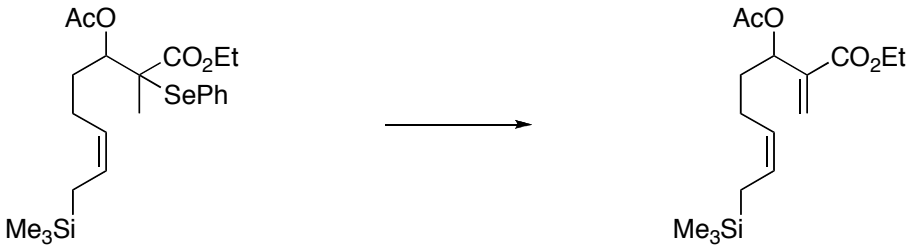
(*Z*)-3-Acetoxy-2-methyl-2-(phenylseleno)-8-(trimethylsilyl)oct-6-enoic Acid Ethyl Ester (40.13c).



40.13b **40.13c**

Pyridine (88.6 mg, 1.12 mmol) and AcCl (44.1 mg, 0.56 mmol) were added sequentially to a stirred and cooled (-10 °C, ice-acetone bath) solution of **40.13b** (80 mg, 0.19 mmol) and DMAP (2.3 mg, 0.018 mmol) in CH_2Cl_2 (1.5 mL). Stirring at -10 °C was continued for 30 min, the cold bath was removed and stirring was continued for 2.5 h. The mixture was quenched with hydrochloric acid (1 M, 3 mL) and diluted with water (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 1.3:20 EtOAc-hexane, gave **40.13c** (74 mg, 84%) as an oil: FTIR ($CDCl_3$ cast) 2954, 1745, 1727, 1439 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ -0.02 (s, 9 H), 1.07 (t, *J* = 7.5 Hz, 3 H), 1.37-1.50 (m, 3 H), 1.52 (s, 3 H), 1.65 (dddd, *J* = 15.0, 9.9, 7.4, 7.4 Hz, 1 H), 1.99 (ddd, *J* = 7.4, 7.3, 7.3 Hz, 2 H), 2.16 (s, 3 H), 3.83 (dq, *J* = 10.8, 7.2 Hz, 1 H), 3.97 (dq, *J* = 10.8, 7.2 Hz, 1 H), 5.18-5.23 (m, 1 H), 5.37-7.43 (m, 1 H), 5.58 (dd, *J* = 10.0, 1.2 Hz, 1 H), 7.29-7.32 (m, 2 H), 7.37-7.40 (m, 1 H), 7.61-7.63 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ -1.8 (q), 13.7 (q), 17.9 (q), 18.4 (t), 21.1 (q), 24.0 (t), 31.9 (t), 54.8 (s), 61.0 (t), 74.7 (d), 125.8 (d), 126.4 (d), 126.9 (s), 128.7 (d), 129.4 (d), 138.0 (d), 170.5 (s), 171.3 (s); exact mass (electrospray) *m/z* calcd for $C_{22}H_{34}NaO_4{}^{80}SeSi$ 493.1284, found 493.1289.

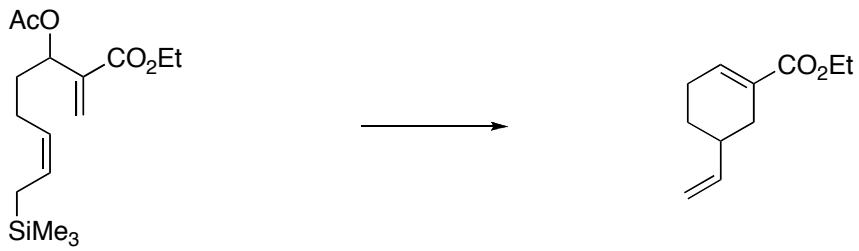
(*Z*)-3-Acetoxy-2-methylene-8-(trimethylsilyl)oct-6-enoic Acid Ethyl Ester (40.13d).



40.13c **40.13d**

H_2O_2 (30%, 127.6 mg, 1.13 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **40.13c** (44 mg, 0.094 mmol) in CH_2Cl_2 (1 mL). Stirring was continued at 0 °C for 1.3 h and the mixture was quenched with saturated aqueous $Na_2S_2O_3$ (2 mL). The mixture was stirred at 0 °C for 20 min, the ice bath was removed, stirring was continued for 5 min and the mixture was diluted with water (10 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 x 8 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (0.7 x 15 cm), using 7:100 EtOAc-hexane, gave **40.13d** (25.2 mg, 86%) as an oil: FTIR ($CDCl_3$ cast) 2955, 1749, 1721, 1632 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ -0.02 (s, 9 H), 1.30 (t, *J* = 7.2 Hz, 3 H), 1.43 (d, *J* = 8.4 Hz, 2 H), 1.72 (ddd, *J* = 14.2, 14.0, 6.9 Hz, 1 H), 1.77-1.85 (m, 1 H), 2.03 (ddd, *J* = 7.7, 7.7, 7.3 Hz, 2 H), 3.08 (s, 3 H), 4.17 (m, 2 H), 5.19-5.26 (m, 1 H), 5.41 (ddddd, *J* = 10.2, 8.7, 8.7, 1.5, 1.5 Hz, 1 H), 5.62 (dd, *J* = 8.0, 4.4 Hz, 1 H), 5.74 (dd, *J* = 0.8, 0.8 Hz, 1 H), 6.27 (dd, *J* = 0.8, 0.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ -1.8 (q), 14.1 (q), 18.4 (t), 21.1 (q), 23.0 (t), 34.3 (t), 60.8 (t), 71.6 (d), 124.7 (s), 125.8 (d), 126.5 (d), 140.4 (t), 165.2 (s), 169.9 (s); exact mass (electrospray) *m/z* calcd for $C_{16}H_{28}NaO_4Si$ 335.1649, found 335.1645.

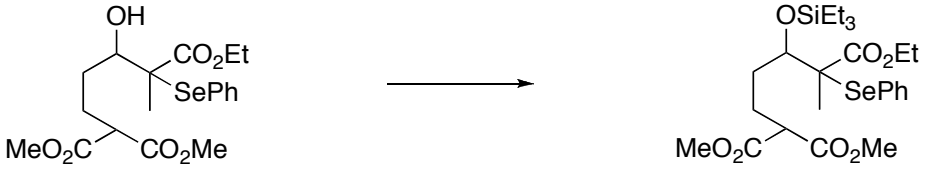
5-Vinylcyclohex-1-enecarboxylic Acid Ethyl Ester (51.20).



40.13d **51.20**

$TiCl_4$ (14.5 mg, 0.076 mmol) that had been frozen (-78 °C), placed under vacuum, allowed to melt under N_2, and subjected to this freeze-thaw cycle three times, was added to a stirred and cooled (-40 °C) solution of **40.13d** (19.8 mg, 0.063 mmol) in CH_2Cl_2 (0.6 mL). Stirring at -40 °C was continued for 5 min. The mixture was quenched with water (5 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO4) and evaporated. Flash chromatography of the residue over silica gel (0.7 x 7 cm), using 3:100 EtOAc-hexane, gave **51.20** (10.3 mg, 90%) as a colorless liquid: FTIR ($CDCl_3$ cast) 3081, 2980, 2930, 1711, 1651, 1434 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.29 (t, *J* = 7.6 Hz, 3 H), 1.33-1.41 (m, 1 H), 1.77-1.84 (m, 1 H), 1.98-2.06 (m, 1 H), 2.18-2.35 (m, 3 H), (ddddd, *J* = 17.5, 5.1, 2.7, 2.6, 1.3 Hz, 1 H), 1.19 (q, *J* = 7.6 Hz, 2 H), 5.03 (dddd, *J* = 23.4, 10.4, 1.5, 1.5 Hz, 2 H), 5.85 (ddd, *J* = 17.1, 0.4, 6.4 Hz, 1 H), 6.96-7.00 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.3 (q), 25.4 (t), 27.3 (t), 29.7 (t), 37.1 (d), 60.2 (t), 113.1 (t), 129.7 (s), 139.0 (d), 142.7 (d), 167.4 (s); exact mass *m/z* calcd for $C_{11}H_{16}O_2$ 180.1150, found 180.1151.

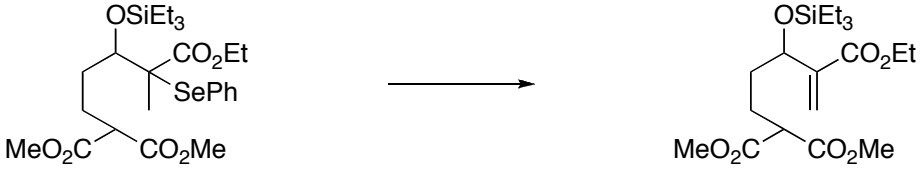
6-Methoxycarbonyl-2-methyl-2-(phenylseleno)-3-[(triethylsilyl)oxy]-heptanedioic Acid 1-Ethyl Ester 7-Methyl Ester.[†]



40.1b' **-**

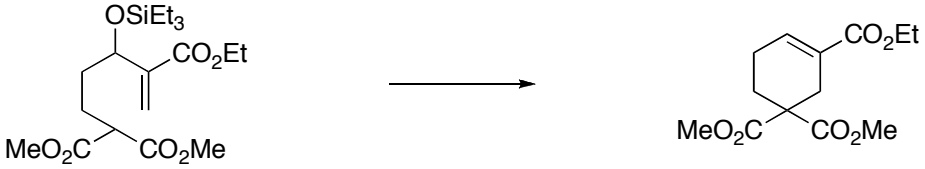
$Et_3SiOSO_2CF_3$ (0.5 mL, 2.14 mmol) was added dropwise over ca 2 min to a stirred and cooled (-78 °C) solution of **40.1b'** (530 mg, 1.19 mmol) and 2,6-lutidine (0.42 mL, 3.57 mmol) in CH_2Cl_2 (10 mL). Stirring at -78 °C was continued for 2 h and the mixture was quenched with water (5 mL) and saturated aqueous $NaHCO_3$ (3 mL). The cold bath was removed, stirring was continued for 10 min and the mixture was diluted with water (5 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 16 cm), using 15% EtOAc-hexane, gave 6-methoxycarbonyl-2-methyl-2-(phenylseleno)-3-[(triethyl-silyl)oxy]heptanedioic acid 1-ethyl ester 7-methyl ester (658 mg, 99%) as a colorless oil: FTIR (CH_2Cl_2 cast) 2954, 2916, 2876, 1754, 1737, 1437, 1242, 741 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.54 (q, *J* = 8.0 Hz, 6 H), 0.88 (t, *J* = 8.0 Hz, 9 H), 1.12 (t, *J* = 7.2 Hz, 3 H), 1.42-1.51 (m, 1 H), 1.49 (s, 3 H), 1.84-1.92 (m, 1 H), 2.06-2.20 (m, 2 H), 3.40 (t, *J* = 7.2 Hz, 1 H), 3.77 (s, 3 H), 3.79 (s, 3 H), 3.87-4.03 (m, 2 H), 4.21 (br d, *J* = 8.4 Hz, 1 H), 7.27-7.32 (m, 2 H), 7.37-7.40 (m, 1 H), 7.56-7.59 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 5.3 (t), 6.8 (q), 13.6 (q), 16.3 (q), 26.6 (t), 30.8 (t), 51.7 (d), 52.4 (q), 52.43 (q), 55.7 (s), 60.8 (t), 75.0 (d), 126.6 (s), 128.6 (d), 129.2 (d), 137.8 (d), 169.5 (s), 169.6 (s), 172.6 (s); exact mass (electrospray) *m/z* calcd for $C_{25}H_{40}NaO_7{}^{80}SeSi$ 583.1601, found 583.1590.

6-Methoxycarbonyl-2-methylene-3-[(triethylsilyl)oxy]heptanedioic Acid 1-Ethyl Ester 7-Methyl Ester (57.1).[†]



H_2O_2 (30%, 1.25 mL, 12.2 mmol) was added dropwise over 2 min to a stirred and cooled (-10 °C, ice-acetone cold bath) solution of 6-methoxycarbonyl-2-methyl-2-(phenylseleno)-3-[(triethylsilyl)oxy]heptanedioic acid 1-ethyl ester 7-methyl ester (655 mg, 1.17 mmol) in CH_2Cl_2 (10 mL). Stirring was continued for 1 h and the mixture was quenched with saturated aqueous $NaHCO_3$ (3 mL), followed by dropwise addition of saturated $Na_2S_2O_3$ (5 mL). The cold bath was removed after 10 min, stirring was continued for 10 min and the mixture was diluted with water (25 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 18 cm), using 5% EtOAc-hexane, gave **57.1** (453 mg, 96%) as a colorless oil: FTIR (CH_2Cl_2 cast) 2956, 2878, 1756, 1739, 1714, 1631, 1095, 743 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.59 (q, *J* = 7.6 Hz, 6 H), 0.94 (t, *J* = 7.6 Hz, 9 H), 1.30 (t, *J* = 7.2 Hz, 3 H), 1.50-1.59 (m, 1 H), 1.63-1.71 (m, 1 H), 1.89-1.99 (m, 2 H), 3.37 (t, *J* = 7.6 Hz, 1 H), 3.719 (s, 3 H), 3.722 (s, 3 H), 4.15-4.26 (m, 2 H), 4.66 (dd, *J* = 5.6, 4.4 Hz, 1 H), 5.93 (t, *J* = 1.6 Hz, 1 H), 6.27 (dd, *J* = 1.6, 0.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 4.6 (t), 6.7 (q), 14.0 (q), 24.0 (t), 34.6 (t), 51.4 (d), 52.26 (q), 52.28 (q), 60.5 (t), 69.4 (d), 124.8 (s), 143.2 (t), 165.9 (s), 169.62 (s), 169.7 (s); exact mass (electrospray) *m/z* calcd for $C_{19}H_{34}NaO_7Si$ 425.1966, found 425.1969.

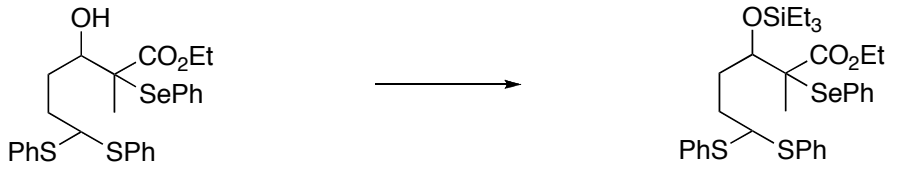
Cyclohex-3-ene-1,1,3-tricarboxylic Acid 3-Ethyl Ester 1,1-Dimethyl Ester (51.1) from 57.1.[†]



57.1 **51.1**

DBU (0.040 mL, 0.25 mmol) was added dropwise to a stirred solution of **57.1** (50 mg, 0.12 mmol) in MeCN (2 mL). The mixture was stirred for 1.5 h and then filtered through a pad of silica gel (2 x 2 cm), using 50% EtOAc-hexane (25 mL). Evaporation of the filtrate and flash chromatography of the residue over silica gel (0.5 x 8 cm), using 20% EtOAc-hexane, gave **51.1** (32 mg, 96%) as a viscous oil.

2-Methyl-2-(phenylseleno)-6,6-bis(phenylthio)-3-[(triethylsilyl)oxy]-hexanoic Acid Ethyl Ester.

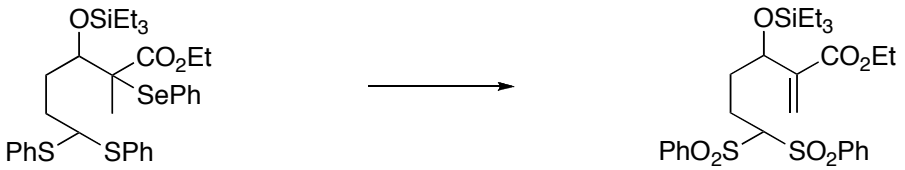


40.4b' **-**

$Me_3SiOSO_2CF_3$ (291 mg, 1.1 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of **40.4b'** (326 mg, o.6 mmol) and 2,6-lutidine (192.9 mg, 1.8 mmol) in dry CH_2Cl_2 (3 mL). Stirring at -78 °C was continued for 1.5 h and the mixture was quenched with water (5 mL) and saturated aqueous $NaHCO_3$ (3 mL). The cold bath was removed and stirring was continued for 15 min. The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2.4 x 15 cm), using 1:20 EtOAc-hexane, gave 2-methyl-2-

(phenylseleno)-6,6-bis(phenylthio)-3-[(triethylsilyl)oxy]hexanoic acid ethyl ester (338 mg, 85%) as an oil: FTIR ($CDCl_3$ cast) 3073, 3058, 2955, 2911, 2875, 1720, 1583, 1475, 1439 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.61-0.75 (m, 6 H), 0.99 (t, *J* = 8.0 Hz, 9 H), 1.02 (t, *J* = 7.0 Hz, 3 H), 1.57 (s, 3 H), 1.73-1.81 (m, 3 H), 1.97-2.05 (m, 1 H), 3.72-3.84 (m, 2 H), 4.33- 4.37 (m, 2 H), 7.27-7.33 (m, 8 H), 7.35-7.38 (m, 1 H), 7.45-7.48 (m, 4 H), 7.58-7.60 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 5.6 (t), 7.1 (q), 13.8 (q), 18.2 (q), 32.9 (t), 33.5 (t), 58.4 (s), 58.5 (d), 60.7 (t), 76.1 (d), 127.6 (s), 127.76 (d), 127.78 (d), 128.6 (d), 128.89 (d), 128.90 (d), 129.0 (d), 132.8 (d), 132.9 (d), 133.9 (s), 134.1 (s), 138.0 (d), 171.9 (s); exact mass (electrospray) *m/z* calcd for $C_{33}H_{44}NaO_3S_2{}^{80}SeSi$ 683.1559, found 683.1558.

2-[4,4-Bis(benzenesulfonyl)-1-[(triethylsilyl)oxy]butyl]acrylic Acid Ethyl Ester (57.2).

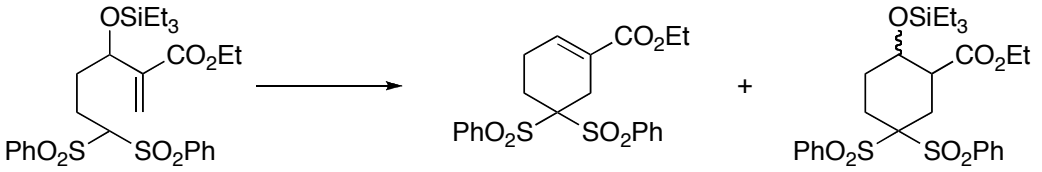


- **57.2**

$NaHCO_3$ (706 mg, 8.4 mmol) was added to a stirred and cooled (0 °C) solution of 2-methyl-2-(phenylseleno)-6,6-bis(phenylthio)-3-[(triethylsilyl)oxy]-hexanoic acid ethyl ester (231 mg, 0.35 mmol) in CH_2Cl_2 (3 mL), followed by *m*-CPBA (70%, 1.04 g, 4.2 mmol). Stirring at 0 °C was continued for 5 min and the cold bath was removed. Stirring was continued for 30 min and the mixture was quenched with saturated aqueous $NaHCO_3$ (5 mL) and saturated aqueous $Na_2S_2O_3$ (5 mL). The mixture was extracted with CH_2Cl_2 (3 x 10 mL), and the combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 1:5 EtOAc-hexane and then 1:3 EtOAc-hexane, gave **57.2** (175 mg, 88%) as an oil: FTIR ($CDCl_3$ cast) 3066, 2957, 2912, 2877, 1712, 1631, 1585, 1448 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.55 (q, *J* = 8.0 Hz, 6 H), 0.91 (t, *J* = 8.0 Hz, 9 H), 1.31 (t, *J* = 7.0 Hz, 3 H), 1.87

(ddt, *J* = 13.5, 11.0, 5.0 Hz, 1 H), 1.99-2.06 (m, 1 H), 2.09-2.32 (m, 2 H), 4.17-4.26 (m, 2 H), 4.49 (dd, *J* = 6.5, 5.0 Hz, 1 H), 4.66 (t, *J* = 10.0 Hz, 1 H), 5.84 (t, *J* = 1.5 Hz, 1 H), 6.25 (dd, *J* = 1.5, 1.0 Hz, 1 H), 7.54-7.59 (m, 4 H), 7.67-7.71 (m, 2 H), 7.94-7.97 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 4.7 (t), 6.8 (q), 14.1 (q), 21.0 (t), 34.8 (t), 60.7 (t), 69.3 (d), 83.7 (d), 125.3 (s), 128.96 (d), 128.99 (d), 129.7 (d), 134.39 (d), 134.41 (d), 137.9 (s), 142.6 (t), 165.7 (s); exact mass (electrospray) *m*/*z* calcd for $C_{27}H_{38}NaO_7S_2Si$ 589.1721, found 589.1723.

5,5-Bis(benzenesulfonyl)-2-[(triethylsilyl)oxy]cyclohexanecarboxylic Acid Ethyl Ester (59.2 and 59.2').



57.2 **51.8** **59.2** and **59.2'**

DBU (38.7 mg, 0.25 mmol) was added dropwise to a stirred solution of **57.2** (72 mg, 0.13 mmol) in dry MeCN (2.5 mL). Stirring at room temperature was continued for 40 min and the mixture was filtered through a pad (ca 5 cm) of silica gel in a Pasteur pipette, using 4:5 EtOAc-hexane. The filtrate was evaporated and preparative TLC of the residue, using CH_2Cl_2, gave **51.8** (15 mg, 27%), **59.2** (the less polar isomer, *trans*) (32 mg, 44%) as an oil and **59.2'** (the more polar isomer, *cis*) (4 mg, 5.6%) as an oil.

Compound **59.2** had: FTIR ($CDCl_3$ cast) 3067, 2955, 2876, 1734, 1584, 1448 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.58 (q, *J* = 8.0 Hz, 6 H), 0.94 (t, *J* = 8.0 Hz, 9 H), 1.28 (t, *J* = 7.0 Hz, 3 H), 1.94 (dddd, *J* = 12.5, 5.0, 5.0, 3.5 Hz, 1 H), 2.23 (dddd, *J* = 13.5, 13.5, 9.0, 4.5 Hz, 1 H), 2.32-2.38 (m, 2 H), 2.47 (ddd, *J* = 15.5, 13.5, 5.0 Hz, 1 H), 2.63 (dd, *J* = 15.5, 13.0 Hz, 1 H), 3.30 (ddd, *J* = 13.0, 9.5, 3.0 Hz, 1 H), 3.90 (ddd, *J* = 10.5, 10.5, 4.5 Hz, 1 H), 4.09-4.18 (m, 2 H), 7.59-7.64 (m, 4 H), 7.70-7.75 (m, 2 H), 8.01-8.03 (m, 2 H), 8.12-8.14 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 4.9 (t), 6.7 (q), 14.1 (q), 25.4 (t), 28.6 (t), 30.0 (t),

47.0 (d), 60.8 (t), 70.4 (d), 86.2 (s), 128.58 (d), 128.63 (d), 131.2 (d), 131.6 (d), 134.6 (d), 134.7 (d), 136.0 (s), 136.1 (s), 173.4 (s); exact mass (electrospray) *m*/*z* calcd for $C_{27}H_{38}NaO_7S_2Si$ 589.1721, found 589.1721.

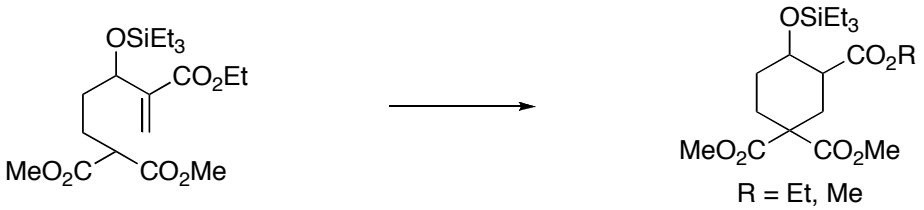
Compound **59.2'** had: FTIR ($CDCl_3$ cast) 3066, 2956, 2911, 2877, 1735, 1584, 1448 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.40 (q, *J* = 8.0 Hz, 6 H), 0.81 (t, *J* = 8.0 Hz, 9 H), 1.28 (t, *J* = 7.0 Hz, 3 H), 1.77 (dddd, *J* = 13.5, 4.0, 4.0, 2.5 Hz, 1 H), 2.28 (dddd, *J* = 14.5, 4.0, 2.5, 2.0 Hz, 1 H), 2.36 (dddd, *J* = 13.5, 13.5, 4.0, 1.5 Hz, 1 H), 2.48 (ddd, *J* = 14.0, 14.0, 4.5 Hz, 1 H), 2.57 (ddd, *J* = 15.0, 4.5, 2.0 Hz, 1 H), 2.71 (dd, *J* = 15.0, 12.5 Hz, 1 H), 3.42 (ddd, *J* = 12.5, 4.5, 2.5 Hz, 1 H), 4.06 (dq, *J* = 11.0, 7.0 Hz, 1 H), 4.21 (dq, *J* = 11.0, 7.0 Hz, 1 H), 4.49 (ddd, *J* = 4.0, 2.0, 2.0 Hz, 1 H), 7.55- 7.64 (m, 4 H), 7.67-7.70 (m, 1 H), 7.72-7.75 (m, 1 H), 7.96-7.98 (m, 2 H), 8.09-8.12 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 4.7 (t), 6.7 (q), 14.1 (q), 20.2 (t), 22.7 (t), 29.4 (t), 44.1 (d), 60.8 (t), 65.7 (d), 87.2 (s), 128.6 (d), 128.7 (d), 131.2 (d), 131.4 (d), 134.4 (d), 134.6 (d), 135.9 (s), 137.0 (s), 172.0 (s); exact mass (electrospray) *m*/*z* calcd for $C_{27}H_{38}NaO_7S_2Si$ 589.1721, found 589.1723.

Stability of 59.2 and 59.2' to DBU.

DBU (4.0 mg, 0.026 mmol) was added to a solution of **59.2** (7.5 mg, 0.013 mmol) in CD_3CN (0.7 mL) in an NMR tube. No change was observed after 45 min (^1H NMR, 400 MHz).

DBU (2.15 mg, 0.014 mmol) was added to a solution of **59.2'** (4 mg, 0.007 mmol) in CD_3CN (0.7 mL) in an NMR tube. No change was observed after 45 min (^1H NMR, 500 MHz).

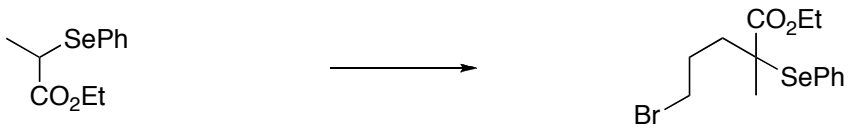
4-[(Triethylsilyl)oxy]cyclohexane-1,1,3-tricarboxylic Acid 3-Ethyl Ester 1,1-Dimethyl Ester (59.1, R = Et) and 4-[(Triethylsilyl)oxy]cyclohexane-1,1,3-tricarboxylic Acid Trimethyl Ester (59.1, R = Me).



57.1 **59.1**

DBU (10.8 mg, 0.071 mmol) was added into a stirred solution of **57.1** (14.3 mg, 0.036 mmol) in MeOH (0.1 mL). Stirring at room temperature was continued for 34.5 h and the mixture was filtered through a pad (ca 5 cm) of silica gel in a Pasteur pipette, using EtOAc. Evaporation of the filtrate and flash chromatography of the residue over silica gel (0.7 x 7 cm), using 1:6 EtOAc-hexane and then 1:3 EtOAc-hexane, gave **59.1** as an inseparable 7.6:2.4 mixture of 3-ethyl 1,1-dimethyl and trimethyl esters, respectively (4 mg, 28%) as an oil: FTIR ($CDCl_3$ cast) 2955, 2914, 2878, 1736, 1435 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.85-0.93 (m, 6 H), 1.25-1.29 (m, 9 H), 1.61 (t, *J* = 7.0 Hz, 2.6 H), 1.88 (dddd, *J* = 14.0, 14.0, 4.5, 2.0 Hz, 1 H), 2.09 (dddd, *J* = 14.5, 3.5, 3.5, 3.5 Hz, 1 H), 2.43 (dddd, *J* = 13.5, 4.5, 3.0, 3.0 Hz, 1 H), 2.50 (ddd, *J* = 14.0, 13.5, 4.0 Hz, 1 H), 2.61 (ddd, *J* = 13.5, 13.5, 2.5 Hz, 1 H), 2.71 (dddd, *J* = 14.0, 3.5, 3.5, 3.5 Hz, 1 H), 2.94 (dddd, *J* = 13.0, 13.0, 4.0, 2.5 Hz, 1 H), 4.02 (s, 1 H), 4.06 (s, 3 H), 4.07 (s, 3 H), 4.40 (dq, *J* = 11.0, 7.0 Hz, 1 H), 4.52 (dq, *J* = 11.0, 7.0 Hz, 1 H), 4.73-4.77 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 4.85 (t), 4.89 (t), 6.75 (q), 6.78 (q), 14.1 (q), 24.27 (t), 24.29 (t), 26.2 (t), 30.40 (t), 30.43 (t), 45.1 (d), 45.2 (d), 51.5 (q), 52.5 (q), 52.7 (q), 54.3 (s), 60.5 (t), 66.6 (d), 66.7 (d), 171.5 (s), 172.17 (s), 172.23 (s), 172.6 (s), 173.0 (s); exact mass (electrospray) *m*/*z* calcd for $C_{19}H_{34}NaO_7Si$ (**59.1**, R = Et) 425.1966, found 425.1966; *m*/*z* calcd for $C_{18}H_{32}NaO_7Si$ (**59.1**, R = Me) 411.1810, found 411. 1810.

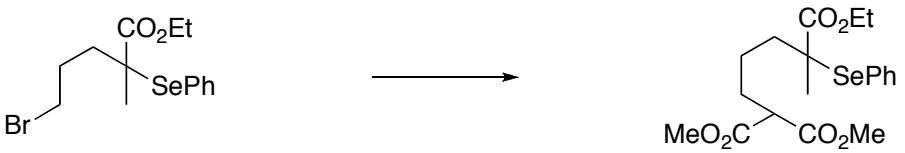
5-Bromo-2-methyl-2-(phenylseleno)pentanoic Acid Ethyl Ester (58.1).[†]



38.1 **58.1**

n-BuLi (2.5 M in hexane, 1.76 mL, 4.4 mmol) was added dropwise over ca 2 min to a stirred and cooled (-78 °C) solution of *i*-Pr_2NH (0.68 mL, 4.8 mmol) in THF (8 mL). Stirring at -78 °C was continued for 45 min and a solution of **38.1** (1.028 g, 4.0 mmol) in THF (3 mL plus 1 mL as a rinse) was added over 5 min. Stirring was continued for 1.5 h at -78 °C and a solution of 1,3-dibromopropane (1.615 g, 8.0 mmol) in a mixture of THF (3 mL) and HMPA (1 mL) was added over 5 min. The mixture was stirred at -78 °C for 2 h, the cold bath was removed and stirring was continued for 2 h. The mixture was recooled to 0 °C and quenched with water (1 mL) and saturated aqueous NH_4Cl (5 mL). The cold bath was removed, stirring was continued for 10 min and the mixture was diluted with water (50 mL) and extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (3 x 20 cm), using 4% EtOAc-hexane, gave **58.1** (1.27 g, 84%) as a viscous oil: FTIR (CH_2Cl_2 cast) 2978, 2932, 1720, 1244, 1155, 742 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.19 (t, *J* = 7.2 Hz, 3 H), 1.51 (s, 3 H), 1.79-1.93 (m, 2 H), 1.97-2.09 (m, 2 H), 3.34-3.39 (m, 2 H), 4.03-4.15 (m, 2 H), 7.29-7.34 (m, 2 H), 7.37-7.42 (m, 1 H), 7.57-7.60 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.9 (q), 22.8 (q), 29.0 (t), 33.0 (t), 37.2 (t), 49.1 (s), 61.0 (t), 127.0 (s), 128.7 (d), 129.2 (d), 137.9 (d), 173.5 (s); exact mass (electrospray) *m/z* calcd for $C_{14}H_{19}{}^{79}BrNaO_2{}^{80}Se$ 400.9626, found 400.9624.

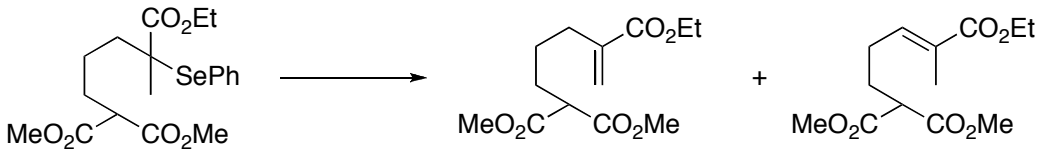
6-Methoxycarbonyl-2-methyl-2-(phenylseleno)heptanedioic Acid 1-Ethyl Ester 7-Methyl Ester (58.2).[†]



58.1 **58.2**

A solution of dimethyl malonate (0.5 ml, 4.23 mmol) in THF (8 mL) was added dropwise over ca 10 min to a stirred suspension of NaH (95%w/w, 100 mg, 3.966 mmol) in THF (10 mL). Stirring at room temperature was continued for 1.5 h and a solution of **58.1** (1.0 g, 2.644 mmol) in THF (10 mL plus 2 mL as a rinse) was added dropwise over ca 5 min. The mixture was refluxed for 16 h, cooled to room temperature and then to 0 °C, and quenched with water (5 mL) and saturated aqueous NH_4Cl (5 mL). The mixture was stirred at room temperature for 10 min and diluted with water (25 mL). The aqueous phase was extracted with EtOAc (3 x 15 mL) and the combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 18 cm), using 15% EtOAc-hexane, gave **58.2** (955 mg, 84%) as a viscous oil: FTIR (CH_2Cl_2) 2954, 1753, 1736, 1721, 1438, 1157 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.17 (t, *J* = 7.2 Hz, 3 H) 1.2-1.31 (m, 1 H), 1.43-1.53 (m, 1 H), 1.47 (s, 3 H), 1.75 (ddd, *J* = 13.6, 12.0, 4.4 Hz, 1 H), 1.84-1.97 (m, 3 H), 3.34 (t, *J* = 7.4 Hz, 1 H), 3.71 (s, 3 H), 3.72 (s, 3 H), 4.0-4.13 (m, 2 H), 7.27-7.32 (m, 2 H), 7.36-7.40 (m, 1 H), 7.55-7.57 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.0 (q), 22.7 (q), 23.5 (t), 28.8 (t), 38.0 (t), 49.6 (s), 51.4 (d), 52.5 (q), 61.0 (t), 127.2 (s), 128.7 (d), 129.2 (d), 137.9 (d), 169.6 (s), 173.7 (s); exact mass (electrospray) *m/z* calcd for $C_{19}H_{26}NaO_6{}^{80}Se$ 453.0787, found 453.0794.

2-Methoxycarbonyl-6-methyleneheptanedioic Acid 7-Ethyl Ester 1-Methyl Ester (57.3) and 6-Methoxycarbonyl-2-methylhept-2-enedioic Acid 1-Ethyl Ester 7-Methyl Ester (58.3).[†]

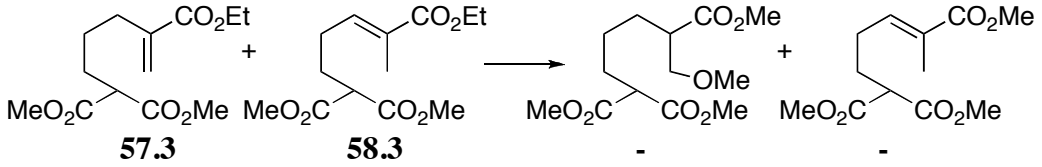


58.2 **57.3** **58.3**

H_2O_2 (30%, 0.25 mL, 2.45 mmol) was added dropwise over 2 min to a stirred and cooled (-10 °C, ice-acetone bath) solution of **58.2** (100 mg, 0.23 mmol) in CH_2Cl_2 (5 mL). Stirring at -10 °C was continued for 1 h and the mixture was quenched with saturated aqueous $NaHCO_3$ (2 mL), followed by dropwise addition of $Na_2S_2O_3$ (3 mL). The cold bath was removed after 10 min, stirring was continued for 10 min and the mixture was diluted with water (10 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (0.5 x 8 cm), using 15% EtOAc-hexane, gave an inseparable 1:3 mixture of **58.3** (minor isomer) and **57.3** (59 mg, 94% in total): FTIR (CH_2Cl_2 cast) 2956, 1754, 1737, 1715, 1632, 1437, 1156 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.26-1.30 (m, 3 H), 1.46-1.53 (m, 1.5 H), 1.795-1.80 (m, 0.75 H), 1.88-1.94 (m, 1.5 H), 2.02-2.07 (m, 0.5 H), 2.19-2.25 (m, 0.5 H), 2.30-2.33 (m, 1.5 H), 3.36 (t, J = 7.4 Hz, 1 H), 3.72 (s, 4.5 H), 3.73 (s, 1.5 H), 4.14-4.21 (m, 2 H), 5.51-5.52 (m, 0.75 H), 6.135-6.138 (m, 0.75 H), 6.65-6.69 (m, 0.25 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.3 (q), 14.15 (q), 14.23 (q), 26.0 (t), 26.2 (t), 27.6 (t), 28.3 (t), 31.4 (t), 50.9 (d), 51.4 (q), 52.4 (q), 52.5 (d), 60.5 (t), 60.6 (t), 124.9 (s), 129.3 (s), 139.5 (d), 140.0 (t), 167.0 (s), 167.8 (s), 169.4 (s), 169.7 (s); exact mass (electrospray) m/z calcd for (**57.3** and **58.3**) $C_{13}H_{20}NaO_6$ 295.1152, found 295.1153.

Compound **58.3** probably has *E* geometry, based on the chemical shift of the vinyl H (δ 6.7).

6-Methoxycarbonyl-2-(methoxymethyl)heptanedioic Acid Dimethyl Ester and 6-Methoxycarbonyl-2-methylhept-2-enedioic Acid Dimethyl Ester.

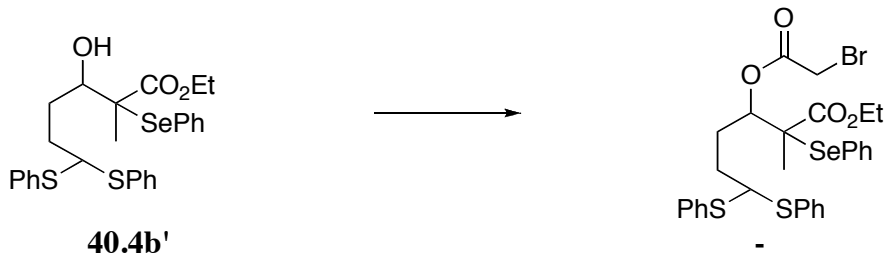


57.3 **58.3** - -

DBU (22.6 mg, 0.15 mmol) was added into a stirred solution of **57.3** and **58.3** (3:1, 20.2 mg, 0.074 mmol) in MeOH (0.2 mL). Stirring at room temperature was continued for 41 h and the mixture was filtered through a pad (ca 5 cm) of silica gel in a Pasteur pipette, using EtOAc. Evaporation of the filtrate and flash chromatography of the residue over silica gel (0.7 x 7 cm), using 1:5 EtOAc-hexane and then 4:5 EtOAc-hexane, gave 6-methoxycarbonyl-2-(methoxymethyl)-heptanedioic acid dimethyl ester (ca 2.4 mg, 11%) and what we assume [^{1}H NMR on the ester exchanged (OMe in place of OEt) starting materials] to be 6-methoxycarbonyl-2-methylhept-2-enedioic acid dimethyl ester (8 mg, 42%) as an oil:

6-Methoxycarbonyl-2-(methoxymethyl)heptanedioic acid dimethyl ester had: FTIR ($CDCl_3$ cast) 2955, 2870, 1737, 1436 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.33 (quintet J = 8.0 Hz, 2 H), 1.49-1.67 (m, 2 H), 1.87-1.94 (m, 2 H), 2.66 (dddd, J = 5.4, 5.4 2.6, 2.6 Hz, 1 H), 3.32 (s, 3 H), 3.35 (t, J = 7.6 Hz, 1 H), 3.43 (dd, J = 9.2, 5.2 Hz, 1 H), 3.57 (dd, J = 9.2, 8.0 Hz, 1 H), 3.70 (s, 3 H), 3.74 (s, 6 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 25.0 (t), 28.4 (t), 28.6 (t), 45.7 (d), 51.4 (q), 51.7 (d), 52.5 (q), 59.0 (q), 73.3 (t), 169.7 (s), 174.7 (s); exact mass (electrospray) m/z calcd for $C_{13}H_{22}NaO_7$ 313.1258, found 313.1258.

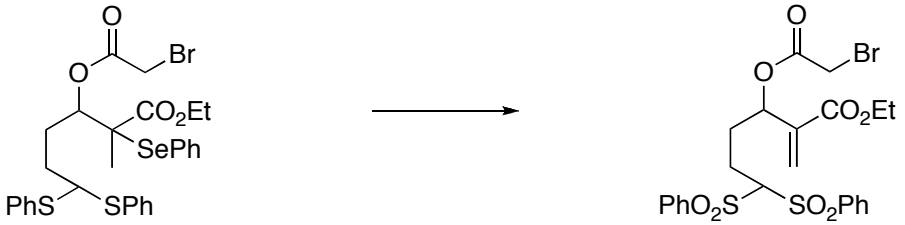
3-Bromoacetoxy-2-methyl-2-(phenylseleno)-6,6-bis(phenylthio)hexanoic Acid Ethyl Ester.



40.4b' **-**

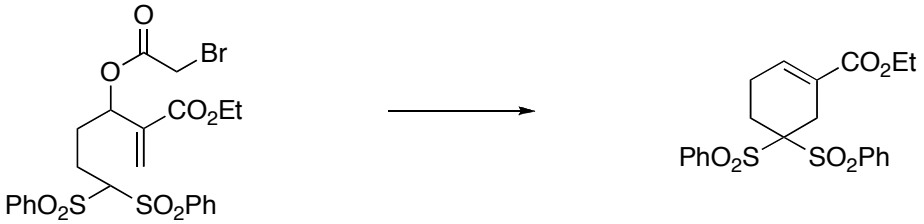
Pyridine (20.6 mg, 0.26 mmol) and $BrCH_2COBr$ (44.4 mg, 0.22 mmol) were added sequentially to a stirred and cooled (0 °C) solution of **40.4b'** (40 mg, 0.073 mmol) in CH_2Cl_2 (1 mL). Stirring at 0 °C was continued for 10 min, the cold bath was removed and stirring was continued for 3 h. The mixture was diluted with water (5 mL) and acidified with hydrochloric acid (1 M, 1 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (0.7 x 15 cm), using 1:6 EtOAc-hexane, gave 3-bromoacetoxy-2-methyl-2-(phenylseleno)-6,6-bis(phenylthio)-hexanoic acid ethyl ester (28.3 mg, 58%) as an oil: FTIR (CH_2Cl_2 cast) 3057, 2981, 2934, 1726, 1582, 1476, 1439 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.05 (t, *J* = 7.2 Hz, 3 H), 1.54 (s, 3 H), 1.82-1.98 (m, 3 H), 2.62-2.68 (m, 1 H), 3.56 (AB q, *J* = 12.5 Hz, $\Delta\nu_{AB}$ = 12.1 Hz, 2 H), 3.86 (dq, *J* = 10.7, 7.1 Hz, 1 H), 4.00 (dq, *J* = 10.7, 7.1 Hz, 1 H), 4.50 (dd, *J* = 6.1, 6.1 Hz, 1 H), 5.40 (dd, *J* = 10.0, 2.0 Hz, 1 H), 7.25-7.41 (m, 10 H), 7.50-7.57 (m, 5 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.7 (q), 17.4 (q), 25.4 (d), 27.6 (d), 32.2 (d), 52.4 (s), 57.7 (d), 61.4 (t), 77.1 (d), 126.0 (s), 127.87 (d), 127.93 (d), 129.0 (d), 129.8 (d), 132.9 (d), 133.0 (d), 133.8 (s), 138.0 (d), 165.8 (s), 171.5 (s); exact mass (electrospray) *m/z* calcd for $C_{29}H_{31}{}^{79}BrNaO_4S_2{}^{80}Se$ 688.9905, found 688.9908.

2-[4,4-Bis(benzenesulfonyl)-1-(bromoacetoxy)butyl]acrylic Acid Ethyl Ester (49).



m-CPBA (70-75%, 60.3 mg, 0.25 mmol) was added to a stirred solution of 3-bromoacetoxy-2-methyl-2-(phenylseleno)-6,6-bis(phenylthio)hexanoic acid ethyl ester (16.3 mg, 0.025 mmol) in CH_2Cl_2 (1 mL), and the mixture was stirred at 40 °C for 24 h, cooled to room temperature and evaporated. Flash chromatography of the residue over silica gel (0.7 x 7 cm), using 1:2 EtOAc-hexane, gave **57.4** (5.3 mg, 52%) as a viscous oil: FTIR ($CDCl_3$ cast) 3066, 2982, 2928, 1721, 1634, 1584, 1448 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.32 (t, *J* = 7.2 Hz, 3 H), 2.04-2.15 (m, 1 H), 2.22-2.32 (m, 3 H), 3.83 (AB q, *J* = 12.2 Hz, $\Delta\nu_{AB}$ = 14.1 Hz, 2 H), 4.248 (q, *J* = 7.2 Hz, 1 H), 4.253 (q, *J* = 7.2 Hz, 1 H), 4.53 (dd, *J* = 5.6, 5.6 Hz, 1 H), 5.64 (dd, *J* = 8.0, 2.8 Hz, 1 H), 5.83 (s, 1 H), 6.34 (s, 1 H), 7.56-7.60 (m, 4 H), 7.68-7.72 (m, 2 H), 7.94-7.96 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1 (q), 21.4 (t), 25.5 (t), 31.7 (t), 61.3 (t), 76.5 (d), 82.5 (d), 125.9 (s), 129.1 (d), 129.6 (d), 134.6 (d), 137.6 (s), 137.7 (s), 138.3 (t), 164.6 (s), 166.0 (s); exact mass (electrospray) *m/z* calcd for $C_{23}H_{25}{}^{79}BrNaO_8S_2$ 595.0066, found 595.0064.

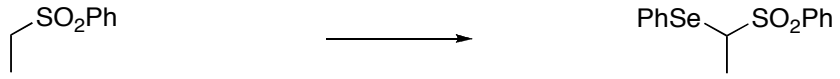
5,5-Bis(benzenesulfonyl)cyclohex-1-enecarboxylic Acid Ethyl Ester (51.8) from 57.4.



57.4 **51.8**

Cs_2CO_3 (3.3 mg, 0.01 mmol) was added to a stirred solution of **57.4** (2.9 mg, 0.005 mmol) in THF (0.5 mL). Stirring at room temperature was continued for 1 h, the solid was filtered off through a pad of Celite, using CH_2Cl_2 as a rinse, and the filtrate was evaporated. The ^1H NMR spectrum of the residue showed only unreacted **57.4** and the ICD product **51.8** in a 1:2 ratio.

[[1-(Phenylseleno)ethyl]sulfonyl]benzene (39.5).[50]

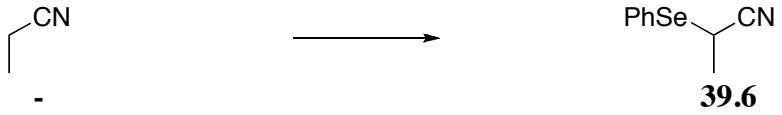


- **39.5**

n-BuLi (1.6 M in hexane, 9.3 mL, 14.89 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of (ethanesulfonyl)benzene (2.53 g, 14.89 mmol) in THF (150 mL). Stirring at -78 °C was continued for 1 h, and a solution of PhSeCl (1.34 g, 7.00 mmol) in THF (20 mL) was added rapidly in one portion. Stirring at -78 °C was continued for 3 h and the mixture was quenched with saturated aqueous NH_4Cl (40 mL). The cold bath was removed, stirring was continued for 15 min and the mixture was diluted with water (100 mL) and extracted with EtOAc (3 x 40 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (3 x 15 cm), using 3:20 EtOAc-hexane, gave **39.5** (1.91 g,

85%) as an oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.67 (d, *J* = 7.2 Hz, 3 H), 4.26 (q, *J* = 7.2 Hz, 1 H), 7.22-7.27 (m, 2 H), 7.30-7.34 (m, 1 H), 7.51-7.55 (m, 4 H), 7.62-7.66 (m, 1 H), 7.91-7.93 (m, 2 H).

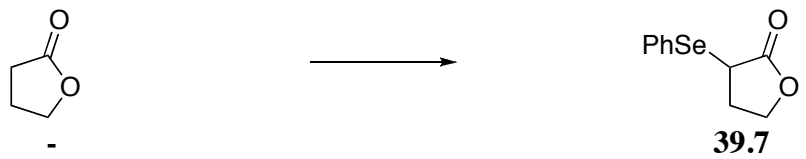
2-(Phenylseleno)propionitrile (39.6).[51]



- **39.6**

n-BuLi (1.6 M in hexane, 8.9 mL, 14.3 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of *i*-Pr_2NH (1.52 g, 15.0 mmol) in THF (150). Stirring at -78 °C was continued for 45 min, and EtCN (826.0 mg, 15.0 mmol) was added dropwise. Stirring at -78 °C was continued for 1 h, and a solution of PhSeCl (1.27 g, 6.6 mmol) in THF (10 mL) was added rapidly in one portion. Stirring at -78 °C was continued for 1.5 h, and the mixture was quenched with hydrochloric acid (1 M, 10 mL). The cold bath was removed, stirring was continued for 15 min and the mixture was diluted with water (250 mL) and extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2.5 x 12 cm), using 7:100 EtOAc-hexane, gave **39.6** (830 mg, 60%) as a oil: FTIR ($CHCl_3$ cast) 3058, 2927, 2931, 2870, 2233, 1578, 1477, 1448 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.66 (d, *J* = 7.2 Hz, 3 H), 3.71 (q, *J* = 7.2 Hz, 1 H), 7.35-7.40 (m, 2 H), 7.44 (tt, *J* = 7.2, 1.2 Hz, 1 H), 7.71-7.75 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.2 (q), 19.4 (d), 120.7 (s), 125.8 (s), 129.4 (d), 129.6 (d), 136.4 (d); exact mass *m/z* calcd for $C_{16}H_9N^{80}Se$ 210.9900, found 210.9896.

3-(Phenylseleno)dihydrofuran-2-one (39.7).[52]



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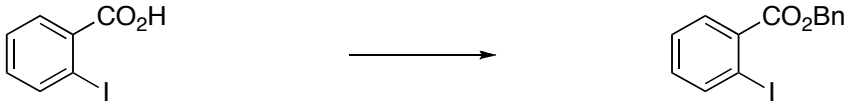
39.7

n-BuLi (1.6 M in hexane, 3.9 mL, 6.27 mmol) was added dropwise to a stirred and cooled (0 °C) solution of *i*-Pr_2NH (634.0 mg, 6.27 mmol) in THF (60). Stirring at 0 °C was continued for 15 min, the mixture was cooled to -78 °C and γ-butyrolactone (540.0 mg, 6.27 mmol) was added dropwise. Stirring at -78 °C was continued for 1 h, a solution of PhSeCl (600 mg, 3.13 mmol) in THF (5 mL) was added rapidly in one portion. Stirring at -78 °C was continued for 1 h, and the mixture was quenched with saturated aqueous NH_4Cl (5 mL). The cold bath was removed, stirring was continued for 15 min and the mixture was diluted with water (200 mL) and extracted with EtOAc (3 x 60 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2.5 x 12 cm), using 1:5 EtOAc-hexane, gave **39.7** (580 mg, 77%) as a oil: FTIR ($CHCl_3$ cast) 3056, 2989, 2912, 1765, 1578, 1478, 1438 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.28 (dddd, *J* = 13.9, 7.2, 4.4, 4.0 Hz, 1 H), 2.71 (dddd, *J* = 13.8, 8.5, 8.3, 8.3 Hz, 1 H), 3.93 (dd, *J* = 8.5, 4.4 Hz, 1 H), 4.12 (ddd, *J* = 9.2, 8.3, 7.2 Hz, 1 H), 4.26 (ddd, *J* = 9.2, 8.4, 4.0 Hz, 1 H), 7.31-7.41 (m, 3 H), 7.67-7.70 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 30.5 (t), 35.8 (d), 66.8 (t), 126.5 (s), 129.1 (d), 129.3 (d), 135.8 (d), 176.0 (s); exact mass *m/z* calcd for $C_{10}H_{10}O_2{}^{80}Se$ 241.9846, found 241.9843.

2-Iodobenzoic Acid Benzyl Ester.[80]



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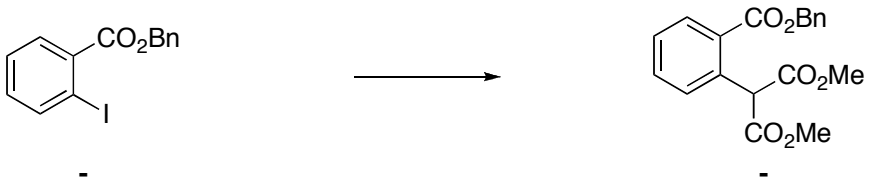
K_2CO_3 (8.90 g, 64.5 mmol) was added to a stirred solution of BnCl (4.90 g, 38.7 mmol), 2-iodobenzoic acid (8.0 g, 32.3 mmol) and Bu_4NI (1.19 g, 3.23 mmol) in THF (180 mL), and the mixture was refluxed for 6 h. The mixture was cooled to room temperature and the solid was filtered off. The filtrate was diluted with water (200 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were washed with aqueous $Na_2S_2O_3$ (5%, 30 mL) and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (5 x 15 cm), using 1:20 EtOAc-hexane, gave 2-iodobenzoic acid benzyl ester (10.81 g, 99%) as a liquid: FTIR ($CDCl_3$ cast) 3064, 3033, 2953, 2890, 1727, 1583, 1562, 1498, 1455, 1429 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.83 (s, 2 H), 7.15 (td, *J* = 7.7, 1.7 Hz, 1 H), 7.33-7.42 (m, 4 H), 7.46-7.49 (m, 2 H), 7.82 (dd, *J* = 7.8, 1.7 Hz, 1 H), 7.99 (dd, *J* = 7.9, 1.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 67.4 (t), 94.2 (s), 127.9 (d), 128.4 (d), 128.5 (d), 128.6 (d), 131.0 (d), 132.7 (d), 135.0 (s), 135.5 (s), 141.3 (d), 166.3 (s); exact mass *m/z* calcd for $C_{14}H_{11}IO_2$ 337.9804, found 337.9802.

2-[(2-Benzyloxycarbonyl)phenyl])malonic Acid Dimethyl Ester.



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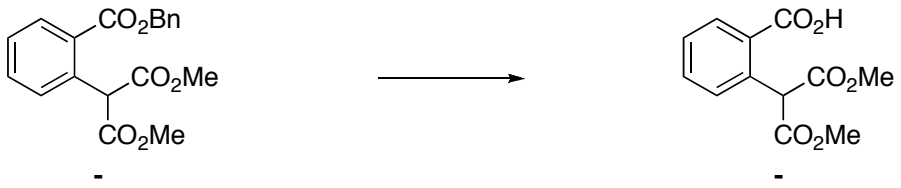
Dimethyl malonate (2.34 g, 17.8 mmol) was added slowly to a stirred suspension of NaH (0.71 g, 17.8 mmol) in 1,4-dioxane (80 mL) (N_2 atmosphere). Stirring at room temperature was continued for 15 min, and CuBr (4.24 g, 29.6 mmol) was added. Stirring at room temperature was continued for 15 min, and a solution of 2-iodobenzoic acid benzyl ester (5.0 g, 14.8 mmol) in 1,4-dioxane (20 mL) was added dropwise. The mixture was refluxed for 48 h, cooled to room temperature, acidified with hydrochloric acid (1 M, 20 mL) and diluted with water (200 mL). The aqueous phase was extracted with EtOAc (3 x 80 mL) and the

combined organic extracts were washed brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (3 x 15 cm), using 1:3 EtOAc-hexane, gave 2-[(2-benzyloxycarbonyl)phenyl])malonic acid dimethyl ester (1.18 g, 73%) as a white solid: mp 71-72 °C; FTIR ($CDCl_3$ cast) 3034, 3004, 2954, 2844, 1758, 1738, 1716, 1602, 1680, 1498, 1455, 1436 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.76 (s, 6 H), 5.35 (s, 2 H), 5.84 (s, 1 H), 7.33-7.47 (m, 7 H), 7.55 (td, *J* = 7.6, 1.4 Hz, 1 H), 8.08 (dd, *J* = 7.9, 1.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 52.7 (q), 54.5 (d), 66.8 (t), 128.0 (d), 128.1 (d), 128.2 (d), 128.4 (d), 129.2 (s), 129.9 (d), 130.9 (d), 132.5 (d), 134.2 (s), 135.5 (s), 166.4 (s), 168.7 (s); exact mass (electrospray) *m/z* calcd for $C_{19}H_{18}NaO_6$ 365.0996, found 365.0998.

2-(2-Carboxyphenyl)malonic Acid Dimethyl Ester.[55]



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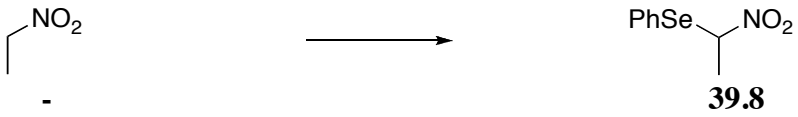
Pd/C (10%, 0.32 g) was added to a solution of 2-[(2-benzyloxycarbonyl)phenyl])malonic acid dimethyl ester (3.23 g, 9.44 mmol) in THF (35 mL) (N_2 atmosphere). The flask was capped with a septum and the solution was degassed by being placed under house vacuum, and the flask was then filled with H_2. This process was repeated three times, and the mixture was stirred under H_2 (balloon) at room temperature for 24 h, and then filtered through a pad of Celite, using CH_2Cl_2 (100 mL) as a rinse. Evaporation of the filtrate gave pure (^1H NMR) 2-(2-carboxyphenyl)malonic acid dimethyl ester (2.38 g, 100%) as a white solid: mp 115-118 °C; FTIR ($CDCl_3$ cast) 3400-2500, 3007, 2956, 1737, 1602, 1780, 1493, 1437,1411 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.79 (s, 6 H), 5.85 (s, 1 H), 7.44-7.48 (m, 2 H), 7.61 (td, *J* = 7.9, 1.5 Hz, 1 H), 8.16 (dd *J* = 8.1, 1.5 Hz, 1 H), ^{13}C NMR ($CDCl_3$, 100 MHz) δ 52.9 (q), 54.6 (d), 128.1 (s),

128.3 (d), 130.3 (d), 132.0 (d), 133.5 (d), 135.0 (s), 168.9 (s), 171.6 (s); exact mass *m*/*z* calcd for $C_{12}H_{12}O_6$ 252.0634, found 252.0631.

[(1-Nitroethyl)seleno]benzene (39.8).[53]



- **39.8**

n-BuLi (1.6 M in hexane, 8.3 mL, 13.2 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of $EtNO_2$ (1.02 g, 13.6 mmol) in THF (120 mL). Stirring at -78 °C was continued for 1 h, and a solution of PhSeCl (1.2 g, 6.3 mmol) in THF (20 mL) was added rapidly in one portion. Stirring at -78 °C was continued for 2 h and the mixture was quenched with saturated aqueous NH_4Cl (20 mL). The cold bath was removed, stirring was continued for 15 min and the mixture was diluted with water (100 mL) and extracted with EtOAc (3 x 40 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (4 x 15 cm), using 1:20 EtOAc-hexane, gave **39.8** (1.17 g, 81%) as a liquid: FTIR ($CDCl_3$ cast) 3059, 2959, 2932, 2885, 1548, 1477, 1439 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.82 (d, *J* = 6.9 Hz, 3 H), 5.69 (q, *J* = 6.9 Hz, 1 H), 7.34-7.38 (m, 2 H), 7.41-7.46 (m, 1 H), 760-7.63 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.6 (q), 78.7 (d), 125.8 (s), 129.4 (d), 129.8 (d), 136.2 (d); exact mass *m*/*z* calcd for $C_8H_9NO_2{}^{78}Se$ 228.9806, found 228.9813.

5. Notes and References

† The experiments were done by a previous group member Dr. Prabhudas B. (see our coauthored paper: Wang, L.; Prabhudas, B.; Clive, D. L. J. *J. Am. Chem. Soc.* **2009**, *131*, 6003-6012; and also his communication paper: Prabhudas, B.; Clive, D. L. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 9295.). For completeness of the study of ICD reactions for carbocycles, I included those experiments in this thesis.

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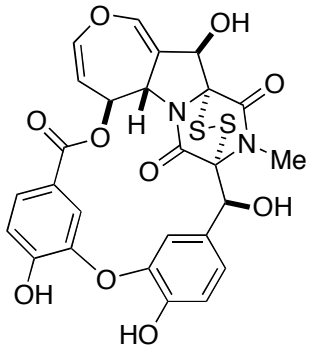
Chapter 2

Studies towards the total synthesis of MPC1001

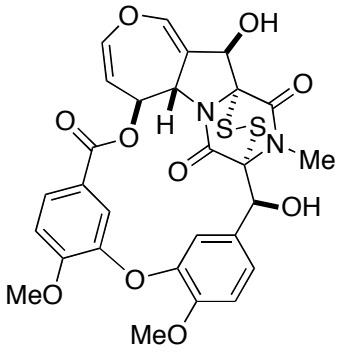
1. Introduction

1.1. Isolation and properties of MPC1001

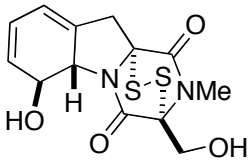
MPC1001 (**1.2**) is an epidithiodioxopiperazine (ETP), a member of a small class of mycotoxins. There are at least 14 ETPs isolated and characterized — much more if derivatives, epipolythio and epimonothiodioxopiperazines, and desulfurized ETPs are counted — all of them produced by ascomycetes.[1] The conspicuous characteristic of the main compounds is the disulfur bridge on a cyclic dipeptide, and among such compounds gliotoxin was the first to be characterized and it has been studied extensively. MPC1001 is an *O*-methyl derivative of emestrin (**1.1**) and was first isolated from a microorganism *Cladorrhinum* sp. KY4922, which was obtained from a soil sample collected in Indonesia;[2] the compound was also extracted from a fungus isolated from Musk Ox dung collected in Alaska.[3]



emestrin (**1.1**)



MPC1001 (**1.2**)



gliotoxin (**1.3**)

Scheme 1

The structure of MPC1001 was elucidated by multiple NMR experiments, and the stereochemistry was determined based on NMR data and comparisons of

the CD spectra of MPC1001 and emestrin,[2b] whose structure had been established by X-ray crystallography.[4]

Preliminary examination showed that MPC1001 exhibited antimicrobial activity against Gram-positive bacteria and weak activity against Gram-negative bacteria.[2c] It also suppressed proliferation of a human prostate cancer cell line (DU145) with an IC_{50} value of 9.3 nM, about 2- to 40-fold more potent than adriamycin, mitomycin C or etoposide.

Scientists in the Merck Research Laboratories Rahway also found that MPC1001 and several other ETPs inhibit the binding of monocyte chemoattractant protein MCP-1 to chemokine receptor CCR2.[3] This observation was made during screening for small molecule non-peptide antagonists to suppress the MCP-1-CCR2 complex, as this complex is associated with some autoimmune disorders such as rheumatoid arthritis, atherosclerosis and infectious diseases, and it is known that neutralization of CCR2 can effectively suppress or prevent the joint swelling in rodent models of rheumatoid arthritis.[5] The group at Merck has found that both the disulfur bridge and the macrocycle of the emestrins are essential for their agonist role; increasing the sulfur number to four results in a slightly lower activity and breaking the macrocycle renders the compound ten times less active.

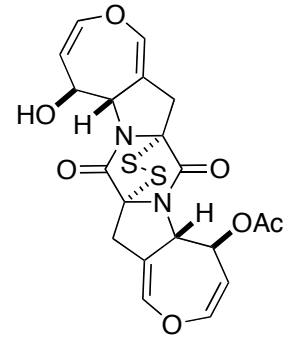
Other ETPs also display important biological characteristics including activity against viruses,[6] fungi,[4] bacteria,[7] and inhibition of both epidermal growth factor[8] and histamine release.[9]

All ETPs are toxic secondary metabolites, and the disulfur bridge is essential for many of their biological properties; desulfurization of gliotoxin or sporidesmin abrogates their antibacterial activity[10] and removal or conversion of the disulfide to two methylthio groups completely shuts down the antiviral activity.[11]

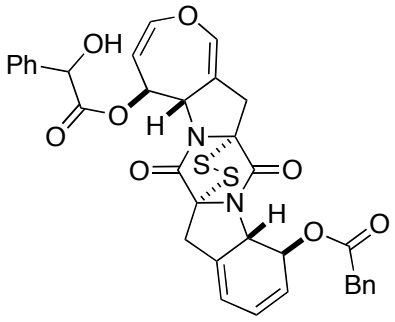
Two possible mechanisms are involved in ETP toxicity. The first mechanism is formation of mixed disulfide bonds between the ETP moiety and a thiol group on a protein.[10-12] ETPs have no specific protein targets. For some proteins the cysteine residues participate in the mixed disulfide bond formation;

for example, in a 1:1 covalent complex of gliotoxin with alcohol dehydrogenase, gliotoxin was found linked to cysteine residue 281 or 282.[13] Complete abolition of gliotoxin's ability to inhibit viral RNA synthesis was observed in the presence of a large excess of dithiothreitol (10^3 fold excess over gliotoxin), which reduces the disulfur bridge of gliotoxin to a dithiol.[14] The second mechanism is generation of deleterious reactive oxygen species such as superoxide ($O_2^{-\cdot}$) or hydrogen peroxide during the redox cycle when an ETP-derived dithiol autoxidizes to the disulfide bridge.[15]

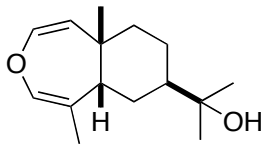
Besides the ETP core, MPC1001 also possess a dihydrooxepin ring, a feature shared by several other metabolites such as aranotin and emethallicin (Scheme 2). However, this theme is not confined to the realm of ETP natural products, as it is also found in some simple terpenoids such as occedinol,[16] dictyoxepin,[17] miscandenin[18] and compound **2.6**[19] (Scheme 2).



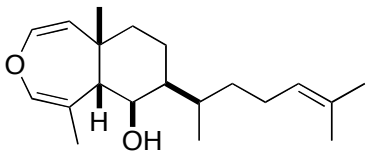
aranotin (**2.1**)



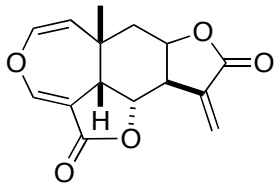
emethallicin (**2.2**)



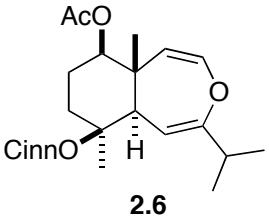
occedinol (**2.3**)



dictyoxepin (**2.4**)



miscandenin (**2.5**)

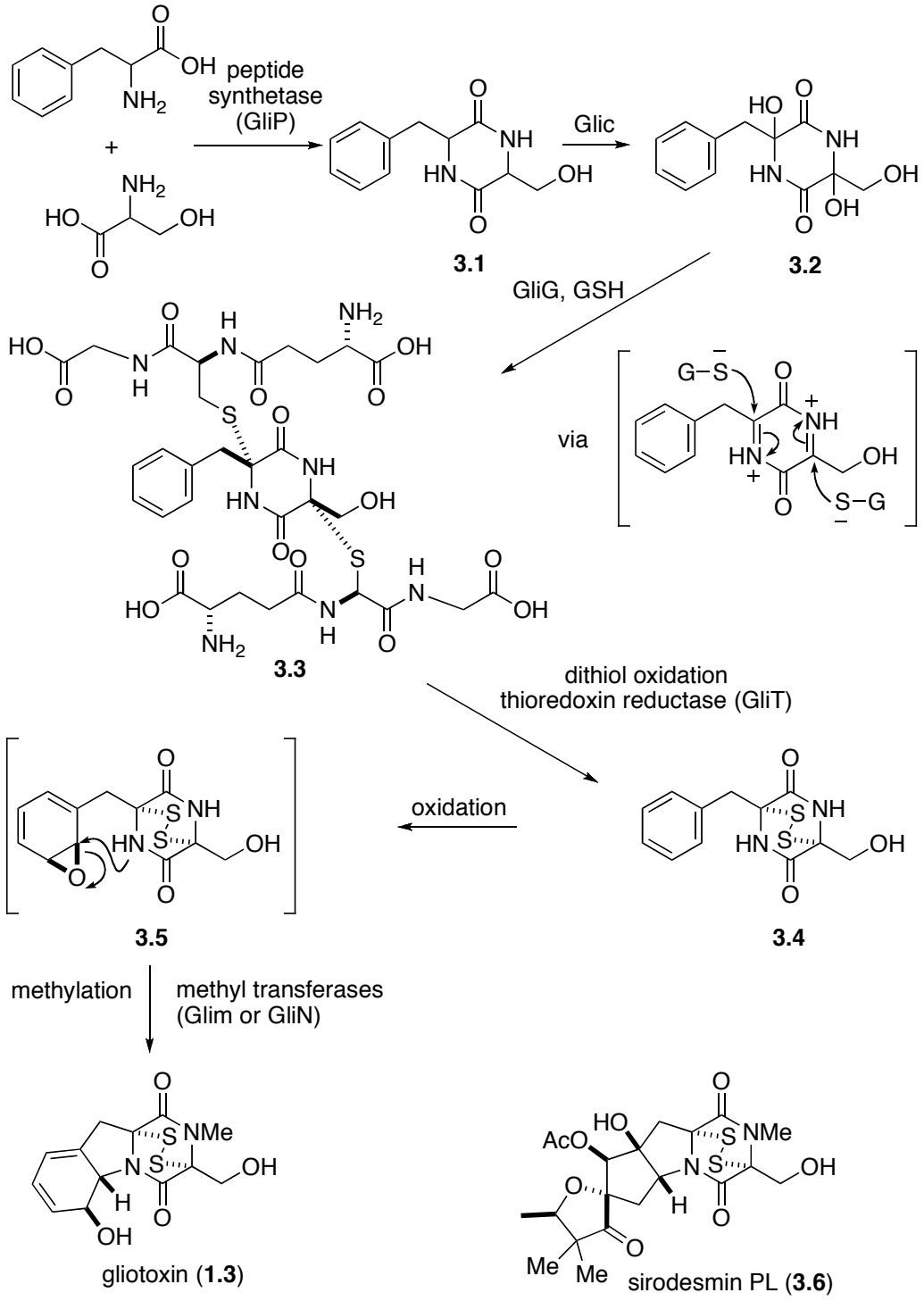


2.6

Scheme 2

1.2. Biosynthesis of MPC1001

No research has been done on the biosynthesis of emestrins (of course, including MPC1001), despite a comment by the authors who isolated the first



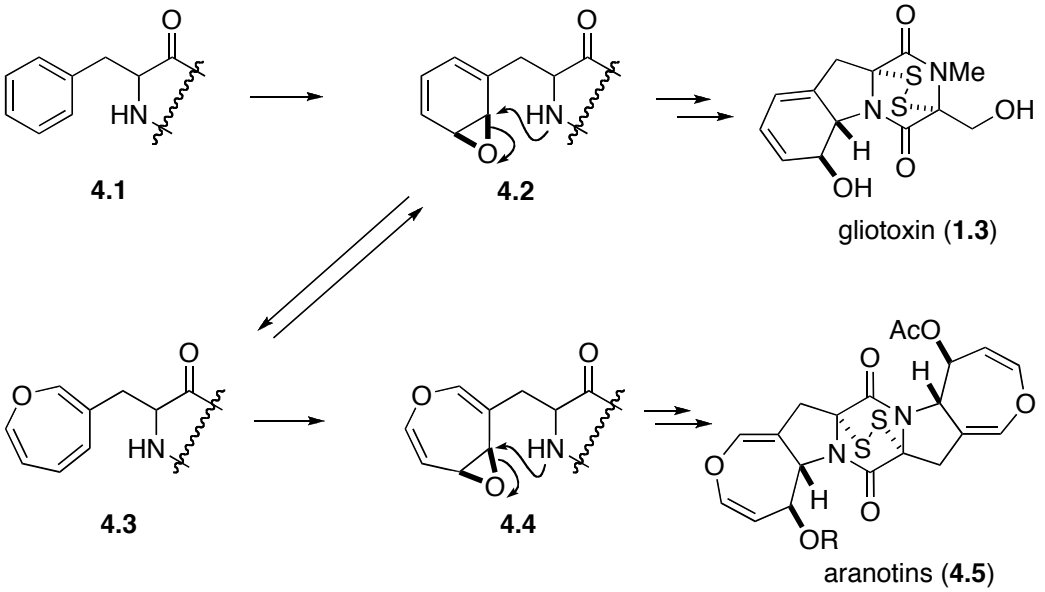
Scheme 3[a]

[a]Intermediates in brackets are putative and have not been isolated.

emestrin, to the effect that it "is biogenetically derived from the combination of one molecule of benzoic acid with the epidithiodioxopiperazine structure formed from two molecules of phenylalanine."[4] Other speculations also predicted the origin of the ETP core from one molecule of phenylalanine and one of tyrosine.[1a] The biosynthesis of some earlier isolated ETPs has been investigated. Feeding and labeling experiments showed that gliotoxin is derived from the condensation of serine and phenylalanine;[20] and sirodesmin PL (**3.6**) from serine and tyrosine.[21]

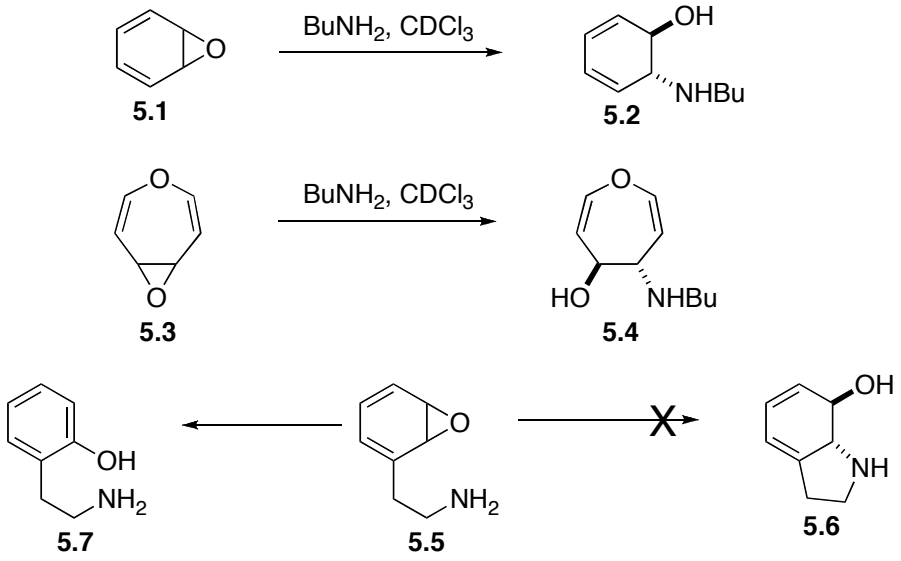
More recently, genes that encode enzymes involved in the biosynthesis of sirodesmin PL[22] and gliotoxin[1a,23] were identified and a possible route to gliotoxin is summarized in Scheme 3; earlier labeling experiments also showed that cystine is the sulfur source.[24]

The biosynthesis of the dihydrooxepin ring in aranotins (**4.5**, Scheme 4) and the diydroarene ring in gliotoxin was proposed to stem from an arene oxide intermediate **4.2**.[20a,25] Epoxide opening by nucleophilic attack of the amide nitrogen in **4.2** can afford the dihydroarene subunit in gliotoxin; rearrangement of **4.2** to **4.3**, followed by a second oxidation, provides the oxepin oxide **4.4**, and epoxide opening will then lead to the dihydrooxepin subunit in aranotins (and other ETPs including MPC1001). However, this proposal has never been



Scheme 4

validated by experiment. Rastetter *et al*. tried to mimic the biosynthetic pathway to dihydroarene and dihydrooxepin subunits, using benzene oxide **5.1** and oxepin oxide **5.3**, respectively (Scheme 5), but only intermolecular reaction with a nitrogen nucleophile could be realized, while attempts to perform the intramolecular version using **5.7** afforded only phenol via rearrangement.[26]



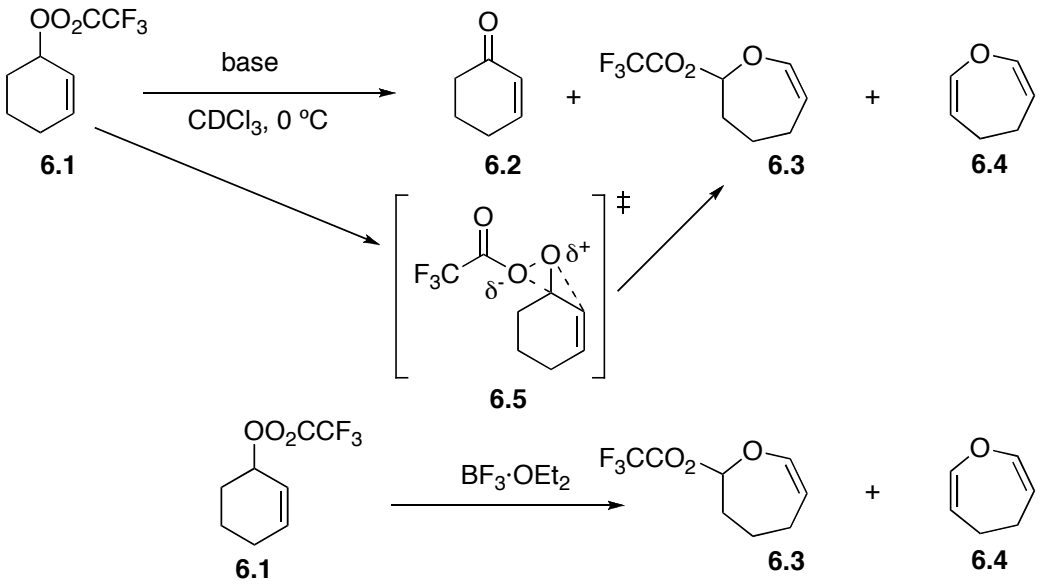
Scheme 5

1.3. Synthesis of dihydrooxepins reported in the literature

As described below, a few methods have been reported for the preparation of dihydrooxepins via rearrangement of acetates of allylic hydroperoxides,[19,27] Cope rearrangement of 2,3-divinyl epoxides,[28] retro [2+2] cycloaddition of strained cyclobutene epoxides,[29] ring-closing metathesis,[30] benzene oxide rearrangement, followed by epoxidation and epoxide opening with a nucleophile,[26] and a selenoxide elimination strategy reported from this laboratory.[31] No ETP containing a dihydrooxepin has been synthesized.

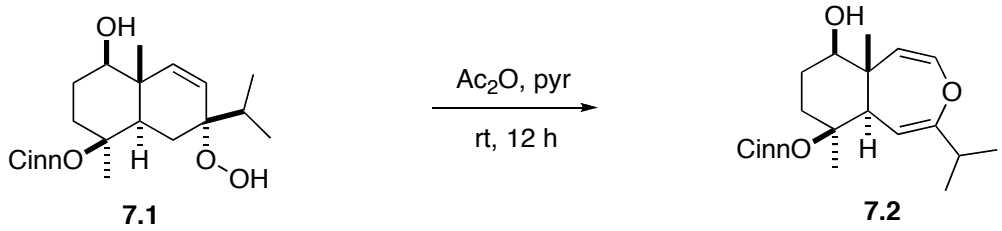
Goodman *et al*.[27] observed that exposure of peroxide **6.1** to a base afforded three products, elimination product **6.2**, cyclic ether **6.3**, possibly via transition state **6.5** (Criegee rearrangement), and dihydrooxepin **6.4** from further elimination of **6.3** (Scheme 6). The ratio of **6.2** to rearrangement products (**6.3** + **6.4**) is

influenced by the nature of the base used in the reaction; however, without a base, the rearrangement still occurs and gives only **6.3**, while under the action of a Lewis acid ($BF_3{\cdot}OEt_2$), both **6.3** and **6.4** were formed but no enone **6.2**.



Scheme 6

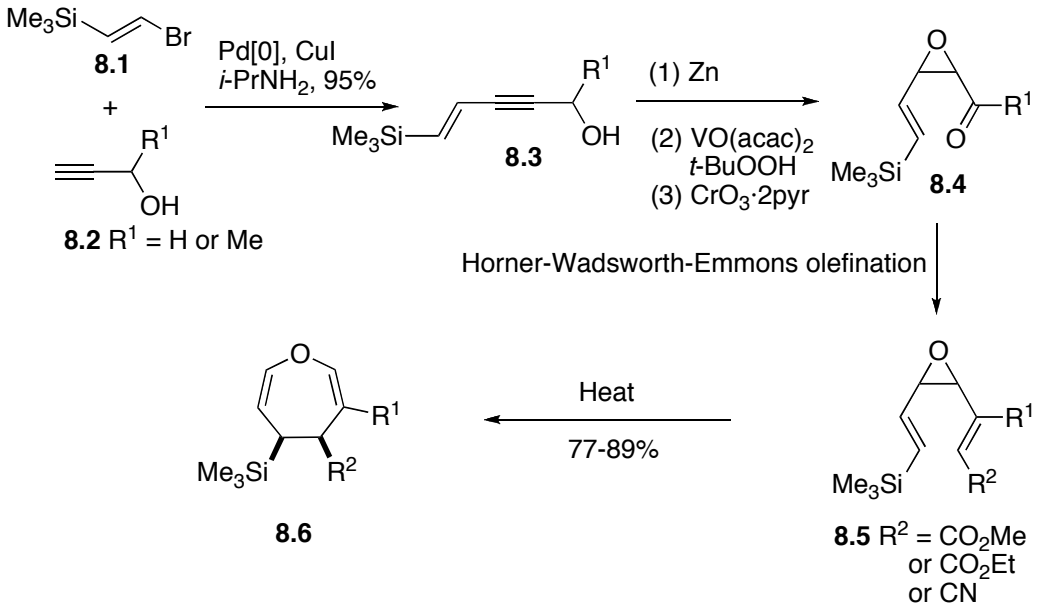
The rearrangement (cf **6.1→6.4**) was also observed by Lu *et al*.[19] and helped in their identification of the hydroperoxide group in sesquiterpene **7.1**. Thus treatment of **7.1** with Ac_2O and pyridine at room temperature produced dihydrooxepin **7.2** (Scheme 7).[19]



Scheme 7

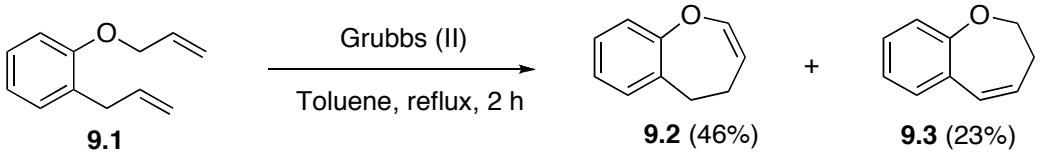
Cope rearrangement seems to have been regarded as a very attractive way of constructing the dihydrooxepin ring.[28] One representative example was reported by White's group, as shown in Scheme 8.[28e] The Cope rearrangement

precursor **8.5** was prepared by the route outlined in Scheme 8 from the simple starting materials vinyl bromide **8.1** and propargyl alcohol **8.2**. Heating the epoxides **8.5** at 95-135 ºC (depending on the substrate) in CCl_4 gave the desired *syn* product **8.6** stereospecifically and in good yields; the *anti* diastereomers could also be formed using precursors with the appropriate double bond geometry.



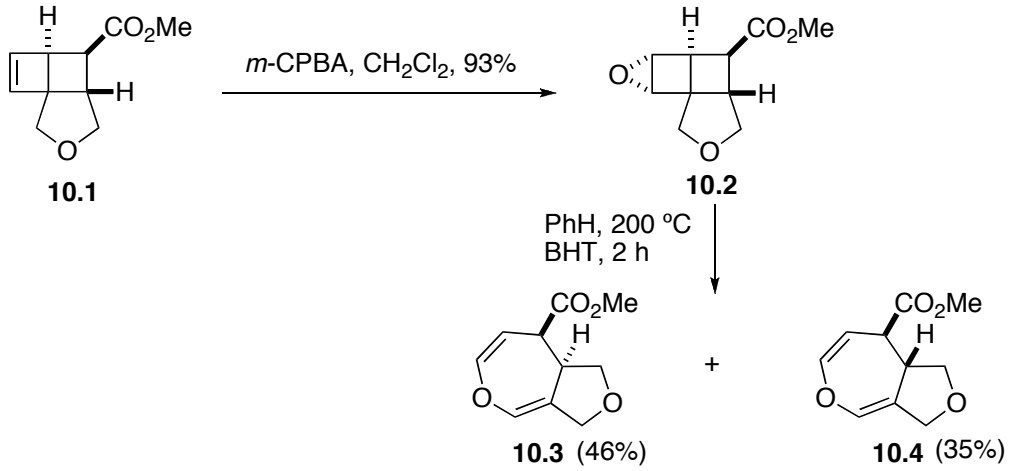
Scheme 8

Fustero *et al*. reported isolation of the benzo-fused dihydrooxepin **9.2** from diene **9.1** via a sequence of ring closing-metathesis and double bond migration (Scheme 9).[30] The yield was low as isomer **9.3** was also formed.



Scheme 9

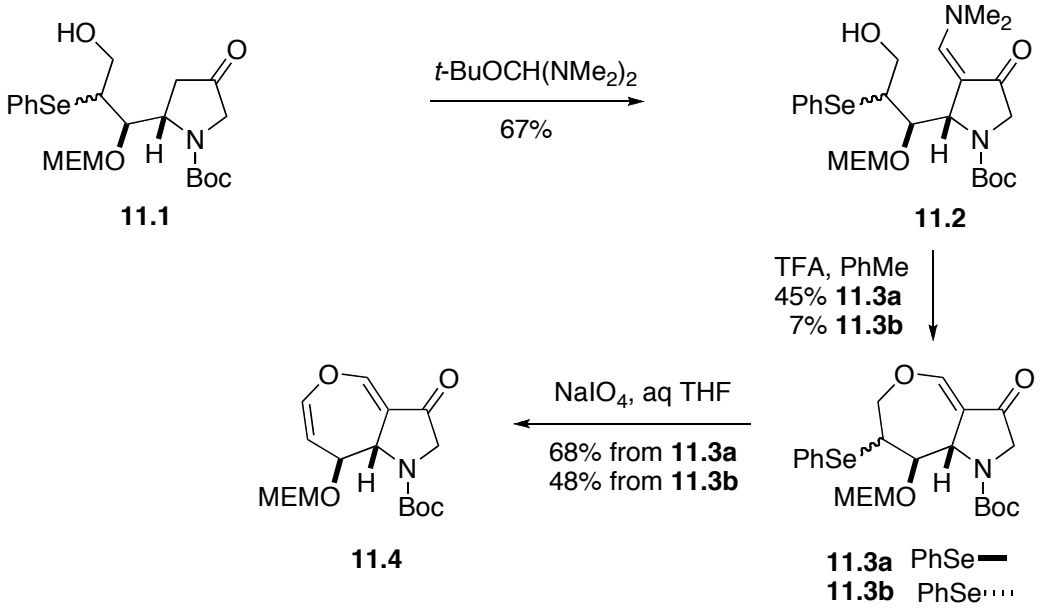
Snapper's group reported generation of tetrahydrofuran-fused dihydrooxepin bicyclic compounds **10.3** and **10.4** from cyclobutene oxide **10.2** (Scheme 10), which itself was obtained by *m*-CPBA oxidation of cyclobutene



Scheme 10

10.1.[29] Using the same method, a series of similar bicyclic dihydrooxepins were synthesized in 55-81% yield, but efforts to improve the diastereoselectivity of the reaction were unfruitful.[29]

Last, but not the least, a selenoxide elimination strategy was developed in this group, aiming at the total synthesis of MPC1001.[31] The route is depicted in Scheme 11. Treatment of ketone **11.1** with *t*-BuOCH(NMe$_2$)$_2$ gave vinylogous amide **11.2** which, under acidic conditions (TFA in toluene), cyclized to give



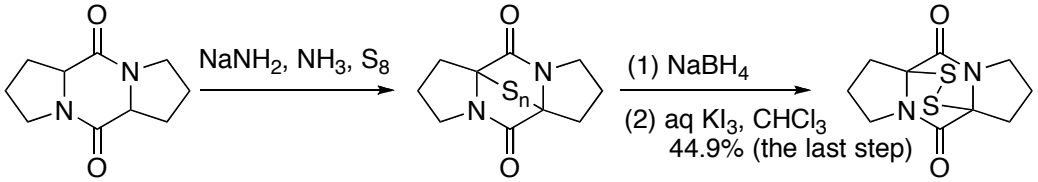
Scheme 11

cyclic ethers **11.3a**,**b**, and, in the last step, oxidation of the phenylselenium group using $NaIO_4$ in aqueous THF afforded the desired bicyclic dihydrooxepin compound **11.4**.[31b]

1.4. Synthesis of ETPs reported in the literature

Generally, there are two strategies for installing sulfurs onto a diketopiperazine (DKP) ring: using a nucleophilic carbon on the DKP and an electrophilic sulfur source, or *vice versa*. Two reviews have been published on the synthesis of ETPs.[32]

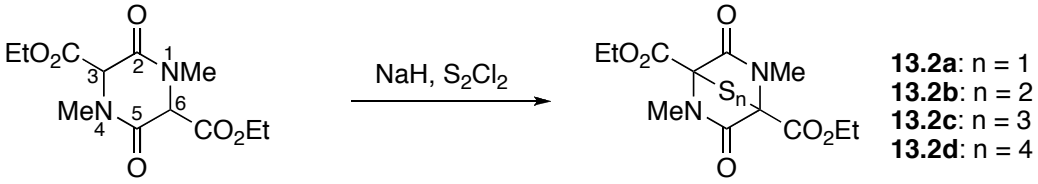
Schmidt *et al*.[33] were the first to make the ETP structure. They used carbanions generated from **12.1** with a strong base ($NaNH_2$) and an electrophilic sulfur reagent (S_8) to give **12.2** which, after reduction with $NaBH_4$ and oxidation with KI_3, gave symmetric ETP **12.3**.



12.1 **12.2** **12.3**

Scheme 12

Using the same starting material **12.1**, Hino *et al*.[34] found that NaH in benzene or toluene is not a strong enough base to deprotonate the substrate, as quenching the reaction mixture with S_2Cl_2 only resulted in recovery of compound

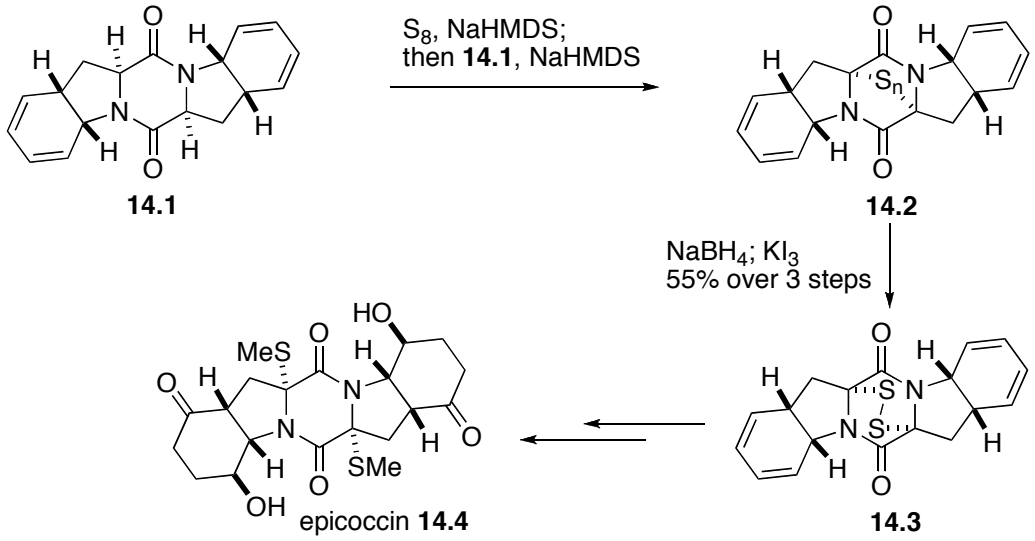


13.1 **13.2a-c**

Scheme 13

12.1. They then turned to substrate **13.1**, but treatment with NaH and S_2Cl_2 gave only a 17% yield of the desired disulfide **13.2b**, plus tetrasulfide **13.2d** and mono- and trisulfides (Scheme 13).[34] The authors also found that the action of $NaBH_4$–MeOH on **13.2b-c** delivered desthio compound **13.1** instead of the expected bisthiol compound. It seems that the ester groups at C3 and C6 (see compound **13.1**) are responsible for this special reactivity, as epidithio or epipolythiodioxopiperazines can generally be reduced to the corresponding bisthiol compounds without incident.[33,35] However, it is reported that treatment of epidithio- (or polythio-) dioxopiperazines with excess Ph_3P results in gradual desulfurization to epimonothiodioxopiperazine,[34,36] but there is some debate about the mechanism and the stereochemistry of the products (retention or inversion at C3 and C6).[37] Besides $NaBH_4$, an excess of MeSH has also been used to quickly reduce ETPs to dithiols.[37b,38]

Recently, Nicolaou's group adopted a similar approach to that of Schmidt *et al*. in order to synthesize ETP **14.3**,[39] a key structure towards the total synthesis of epicoccin **14.4** (Scheme 14).

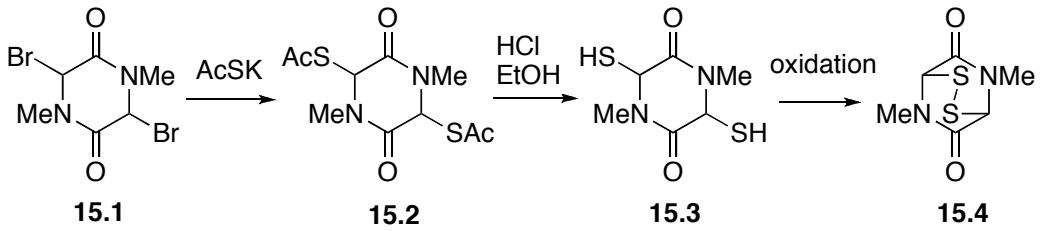


Scheme 14

The second strategy for introducing sulfurs onto a DKP ring is to render the C3 and C6 positions electrophilic and use a nucleophilic sulfur reagent. One

common method is nucleophilic displacement of a bromine at C3 and C6 by RSH (or RS^-). This approach was first developed by Trown *et al*. for making the very simple ETP **15.4**, as outlined in Scheme 15.[40]

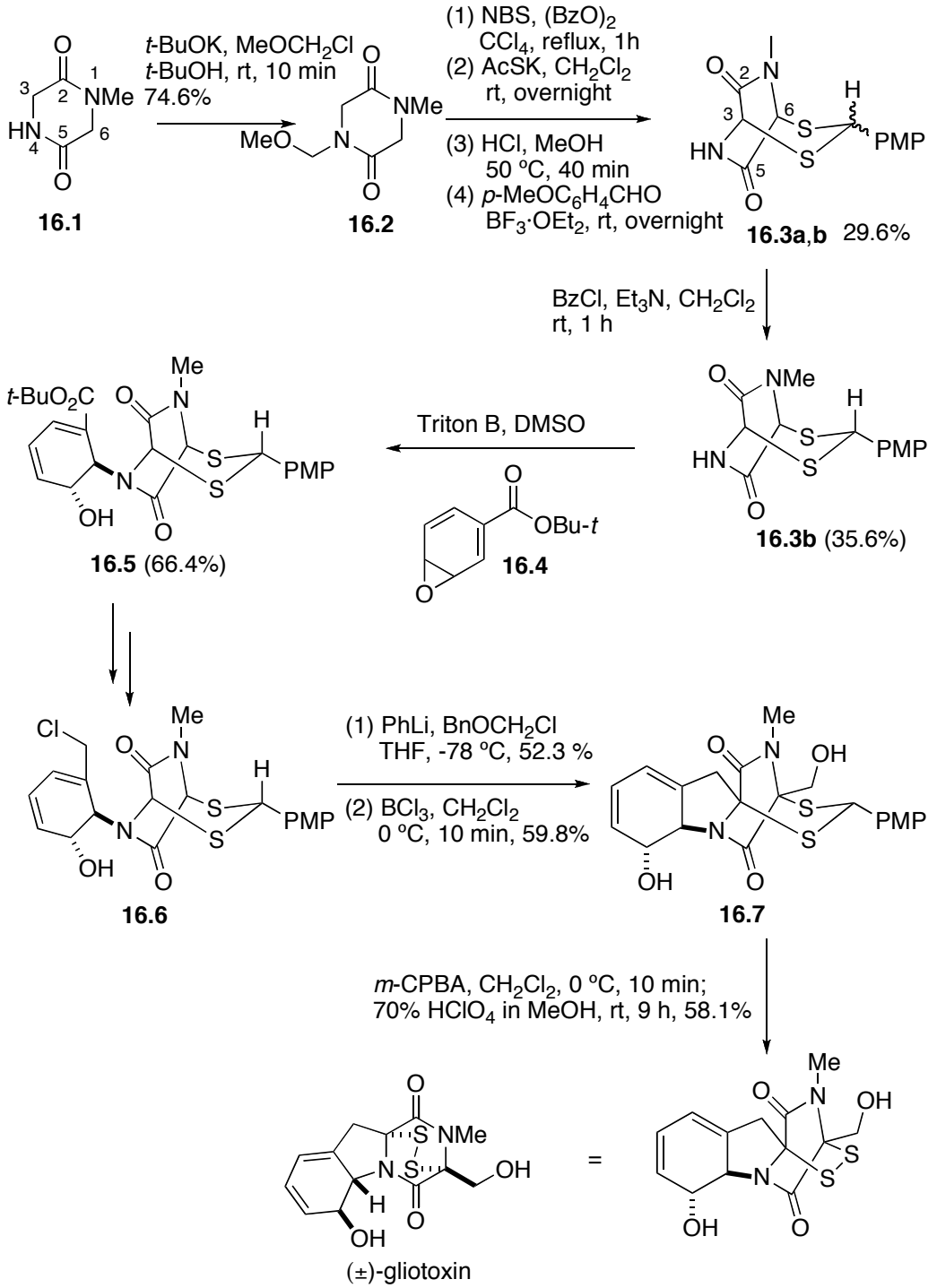
Kishi *et al*.[27,41] also used this bromination–S_N2 displacement sequence for installing sulfurs onto DKP rings, and moreover, they developed an ingenious way of protecting the thiol groups on simple DKPs such as **15.3**, which is not only robust enough to withstand further transformations at C3 and C6 but also allows deprotection and oxidation to the desired ETP structure at a late stage.



Scheme 15

One example using this method for the total synthesis of gliotoxin is illustrated in Scheme 16.[41f] After protection of the nitrogen on the starting material **16.1** with an $MeOCH_2$ group, a four-step sequence with only one purification converted **16.2** to dithiol acetal **16.3a**,**b** as an inseparable mixture in 29.6% overall yield [with the *para*-methoxyphenyl (PMP) group pointing either up (**16.3a**) or down (**16.3b**)]. Separation of **16.3a** and **16.3b** was then achieved by selectively converting **16.3a** to its imide by exposure to a mixture of BzCl and Et_3N in CH_2Cl_2 for 1 h. The reason for this kinetically different behavior of the two compounds is obscure.

Following isolation of **16.3b**, it was then coupled with benzene oxide **16.4** in the presence of Triton B in DMSO, affording **16.5** in 66.4%. Functional group manipulation then led to **16.6**. Both inter- and intramolecular alkylations occurred in one step when a mixture of **16.6** and $BnOCH_2Cl$ were treated with PhLi. Debenzylation using BCl_3 then yielded the dithioacetal of gliotoxin (**16.7**). One equivalent of *m*-CPBA oxidized one of the two sulfurs to a sulfoxide, and



Scheme 16

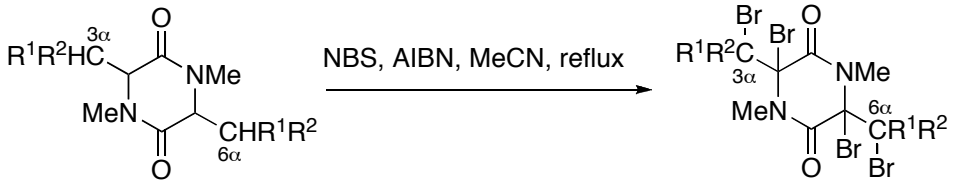
treatment of the crude mixture with aqueous $HClO_4$ in MeOH gave the final product, (±)-gliotoxin in 58.1% over two steps. The authors mentioned that the

PMP group on the thioacetal was essential for successful deprotection; presumably, it stabilizes the carbocation developed during deprotection.[41a,41f]

Using the same protection-alkylation-deprotection strategy, Kishi's group synthesized other ETP compounds including (±)-sporidesmin[41c,d] and (±)-dehydrogliotoxin.[41b]

Besides AcS^- as the nucleophile, a number of bidentate sulfur reagents have been used for installing two sulfurs in a *cis* stereocontrolled manner, such as Na_2CS_3,[35d] Na_2S_4,[35d] $Na_2S_2C{=}O$,[35d,42] etc,[42] (deprotection difficulties were encountered for some of them)[42]; although for simple DKPs bearing an SR group on each carbon (C3 and C6) the *cis* geometry seems to be more stable than the *trans* and is normally formed preferably or exclusively.[35d,43]

Bromination on DKPs with substituents on C3 and C6 seems to be not as smooth as on simple DKPs such as **16.2**. Matsunari's group reported that bromination not only occurred at the desired C3 and C6 positions but also readily

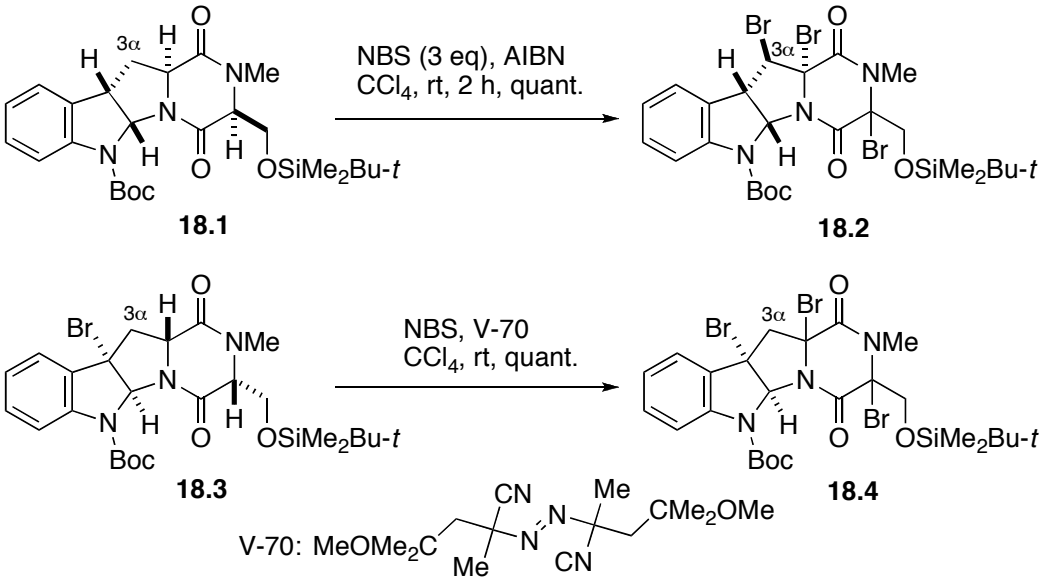


17.1 R^1, R^2 = H or alkyl **17.2**

Scheme 17

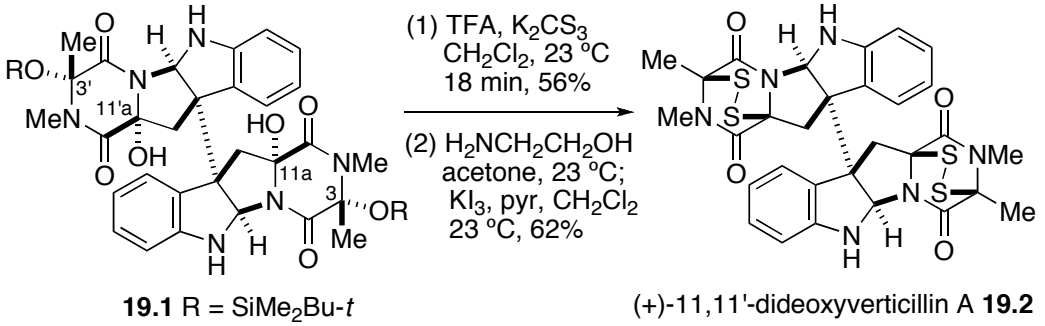
at positions 3α and 6α, as shown in Scheme 17.[44] A similar problem was observed recently by Iwasa *et al*. during bromination of the model substrate **18.1** for the total synthesis of (+)-chaetocin (Scheme 18).[45] Tribromination was the major pathway even when the amount of NBS was reduced. However, when substrate **18.3** was treated under similar conditions, no bromination of C3α was detected. The authors reasoned that the bulky bromine atom at the benzylic position might help prevent over-bromination.[45]

Instead of bromide precursors, DKPs with OH or OR groups at C3 and C6 can be converted into ETPs by treatment with an acid and H_2S (or RSH), followed by oxidation (or deprotection and oxidation). Movassaghi's group synthesized



Scheme 18

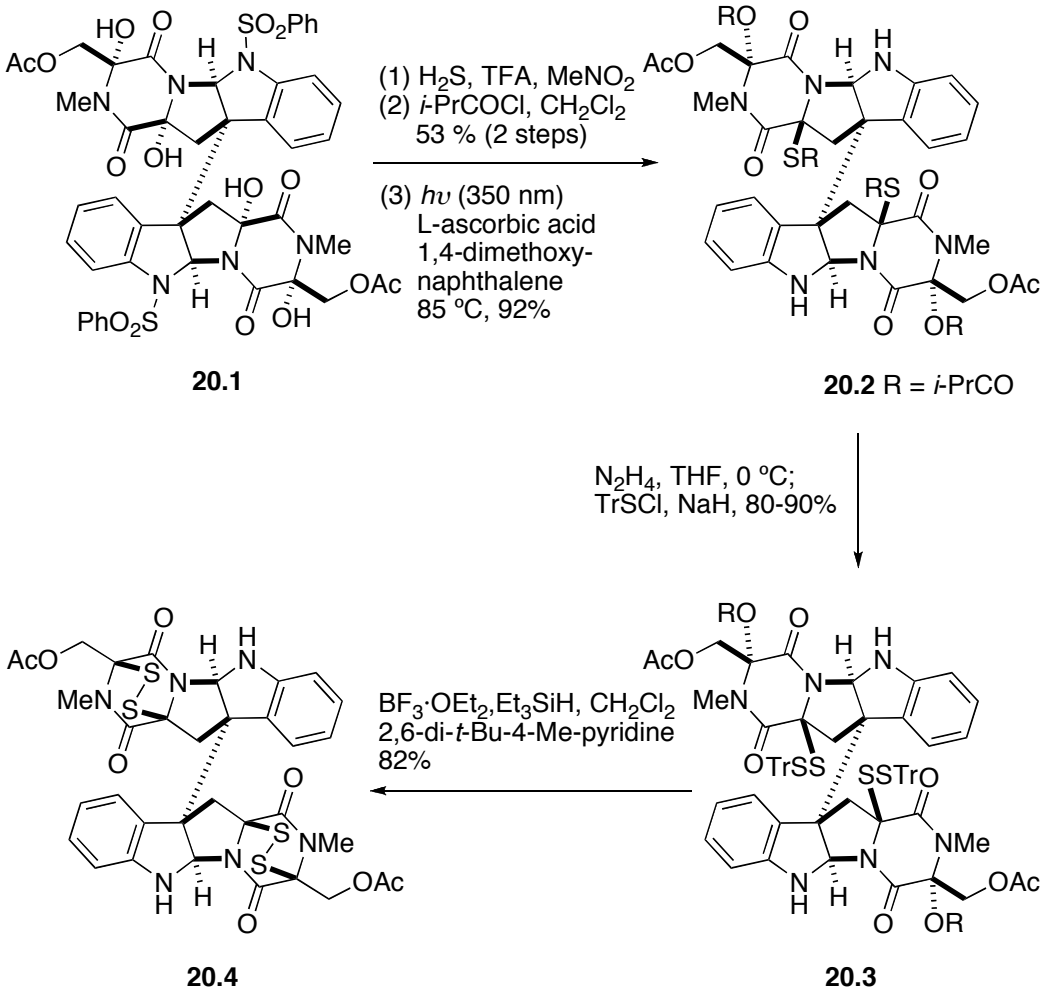
(+)-11,11'-dideoxyverticillin A by treatment of the advanced intermediate **19.1** with TFA and K_2CS_3 to install the sulfurs with the required *cis* geometry, followed by deprotection with ethanolamine and oxidation of the resulting dithiol (Scheme 19).[46] The oxygen groups at C3, C3', C11a and C11a' of **19.1** were introduced by oxidation of C-H bonds with pyr_2AgMnO_4.[46]



Scheme 19

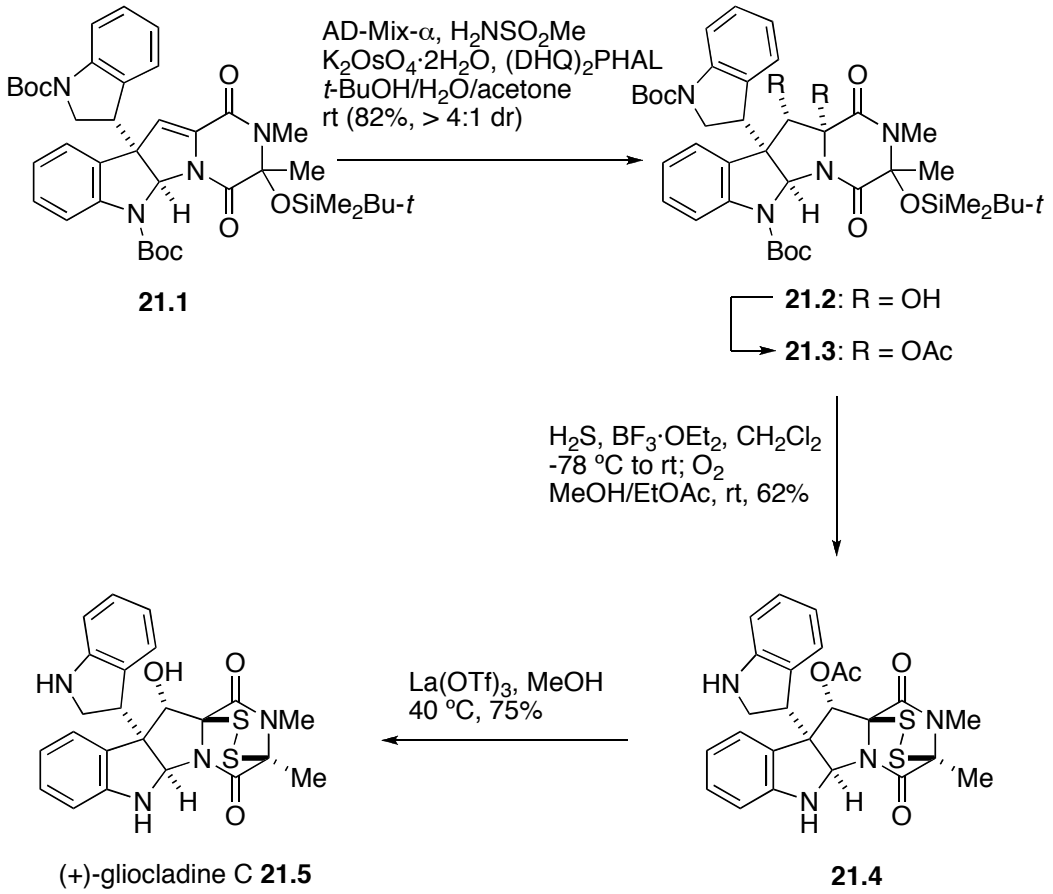
Using intramolecular sulfur delivery, Movassaghi's group also developed a method for making epidithiodioxopiperazines and epipolythiodioxopiperazines.[47] As shown in Scheme 20, tetrahydroxy compound **20.1** was converted to bis-sulfide **20.2** by treatment with H_2S and TFA in $MeNO_2$, followed by a universal

protection of both SH and OH groups and removal of sulfonamide groups by UV irradiation. Selective deprotection of the thioesters and sulfenylation with Ph_3CSCl and NaH provided the precursor **20.3** for intramolecular sulfur delivery. The key transformation was performed using the Lewis acid $BF_3{\cdot}OEt$, Et_3SiH and a substituted pyridine as the base to give ETP **20.4** in 82% yield.[47] By using Ph_3CSSCl and $Ph_3CSSSCl$ polythio ETPs could be constructed. This method enabled the authors to make (+)-chaetocin A (an epidithiodioxopiperazine), (+)-chaetocin C (an epitrithiodioxopiperazine) and (+)-12,12'-dideoxychetracin A (an epitetrathiodioxopiperazine).[47]



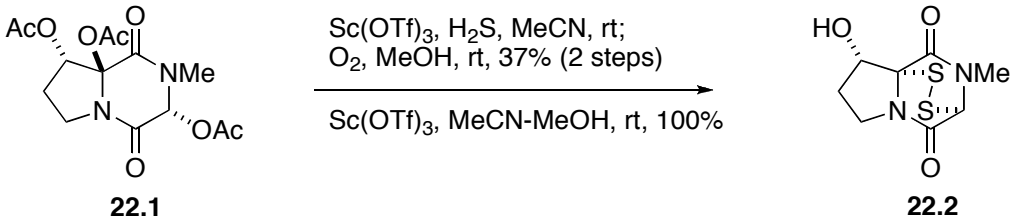
Scheme 20

Overman's group synthesized (+)-gliocladine C (**21.5**) by substitution of OR groups in **21.3** with H_2S in the presence of a Lewis acid ($BF_3{\cdot}OEt_2$), followed by oxidation with oxygen and hydrolysis of the remaining acetate group (Scheme 21).[48] Compound **21.2**, a precursor to **21.3**, was synthesized by dihydroxylation of **21.1**.



Scheme 21

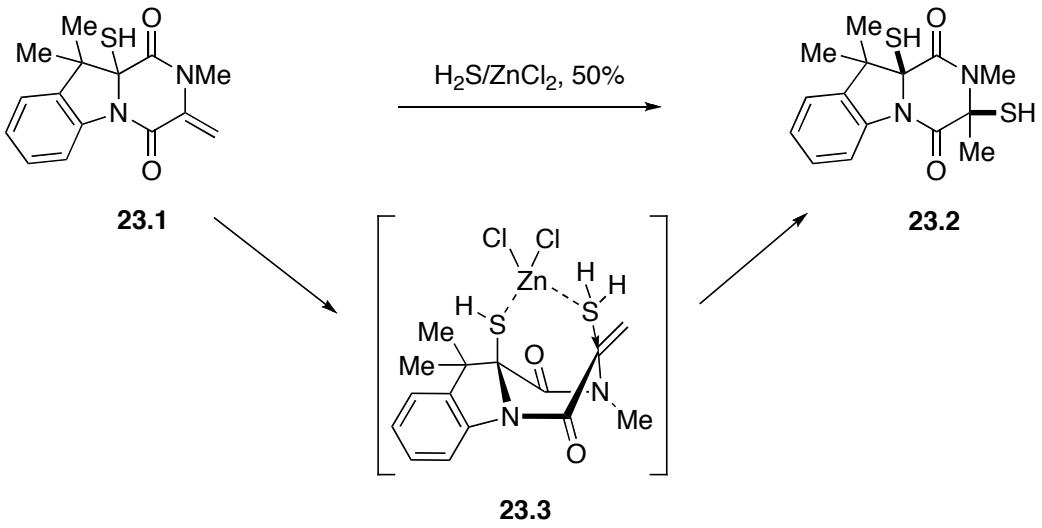
Previous to the above total synthesis, Overman's group used a similar approach for making the simpler ETP **22.2**, as outlined in Scheme 22.[49] The authors adopted Woerpel's model for reactions between a five-membered oxocarbenium ion and a nucleophile to explain the observed 1,2-*cis* relationship between the hydroxyl group and the adjacent sulfur in **22.2**,[49] which seems to be contradictory to the observation on **21.4**, although the latter is more complex. The authors did not explain why the two thio groups prefer to adopt the *syn* geometry



Scheme 22

on the DKP ring during the substitution reaction while in principle 4 isomers could be generated in both cases.

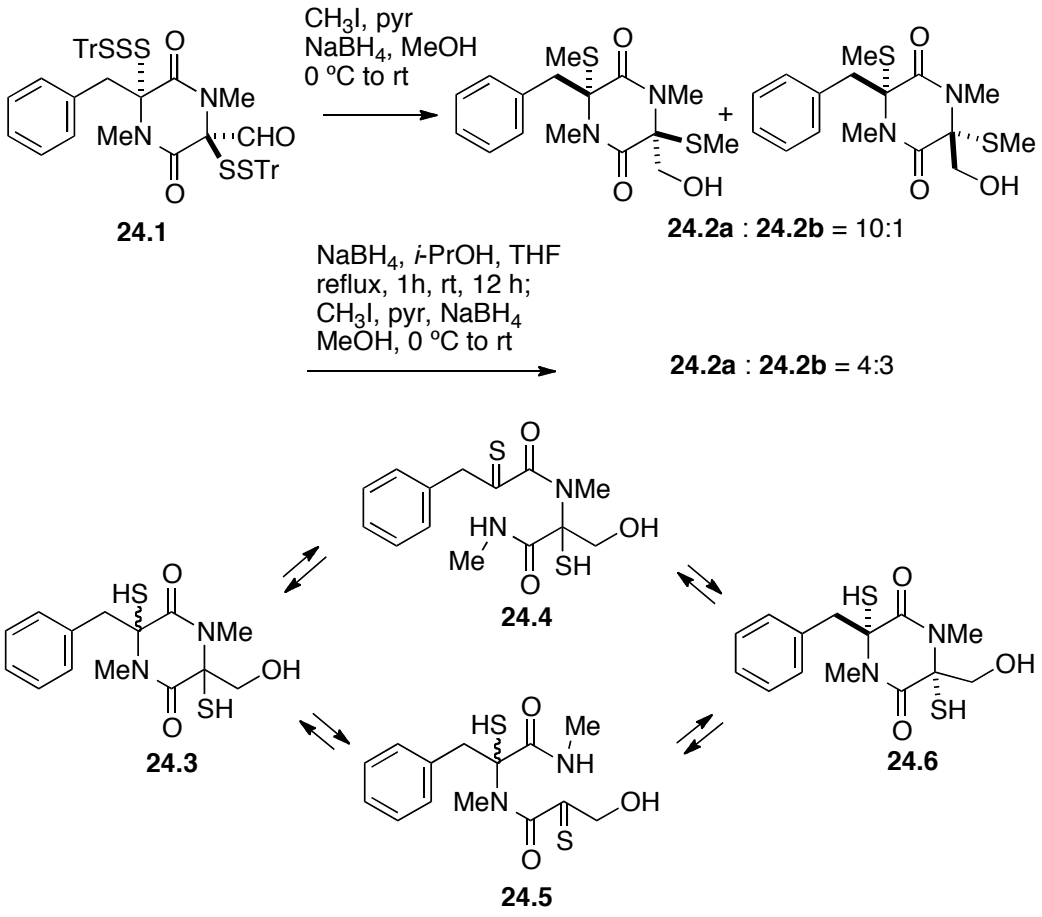
Ottenheijm *et al*.[36a] provided a tentative explanation for the *syn* preference of the thiol groups on a DKP ring installed under Lewis acid conditions. When mono-thiol **23.1** was treated with H_2S and $ZnCl_2$, *cis* dithiol **23.2** was formed in 50% yield (Scheme 23). The authors rationalized the stereoselectivity by invoking the ligated intermediate **23.3** that allows delivery of the second sulfur in a *syn* manner.[36a]



Scheme 23

Williams *et al*.[50] disclosed the possibility of equilibration between *syn* and *anti* isomers during the synthesis of the fungal metabolites (±)-gliovictin and (±)-hyalodendrin. The evidence for equilibration is that reductive methylation of the starting material **24.1** (Scheme 24) with *trans* stereochemistry, using a mixture of

MeI, pyridine and $NaBH_4$ in cold MeOH, afforded both *trans* and *cis* products in a ratio of 10:1; this ratio was lowered to 4:3 when the reduction was done at an elevated temperature (reflux and then room temperature) before the methylation under the same conditions. Based on these results, Williams *et al*. proposed an equilibration via the open form **24.4** or **24.5** to account for their observations.[50]

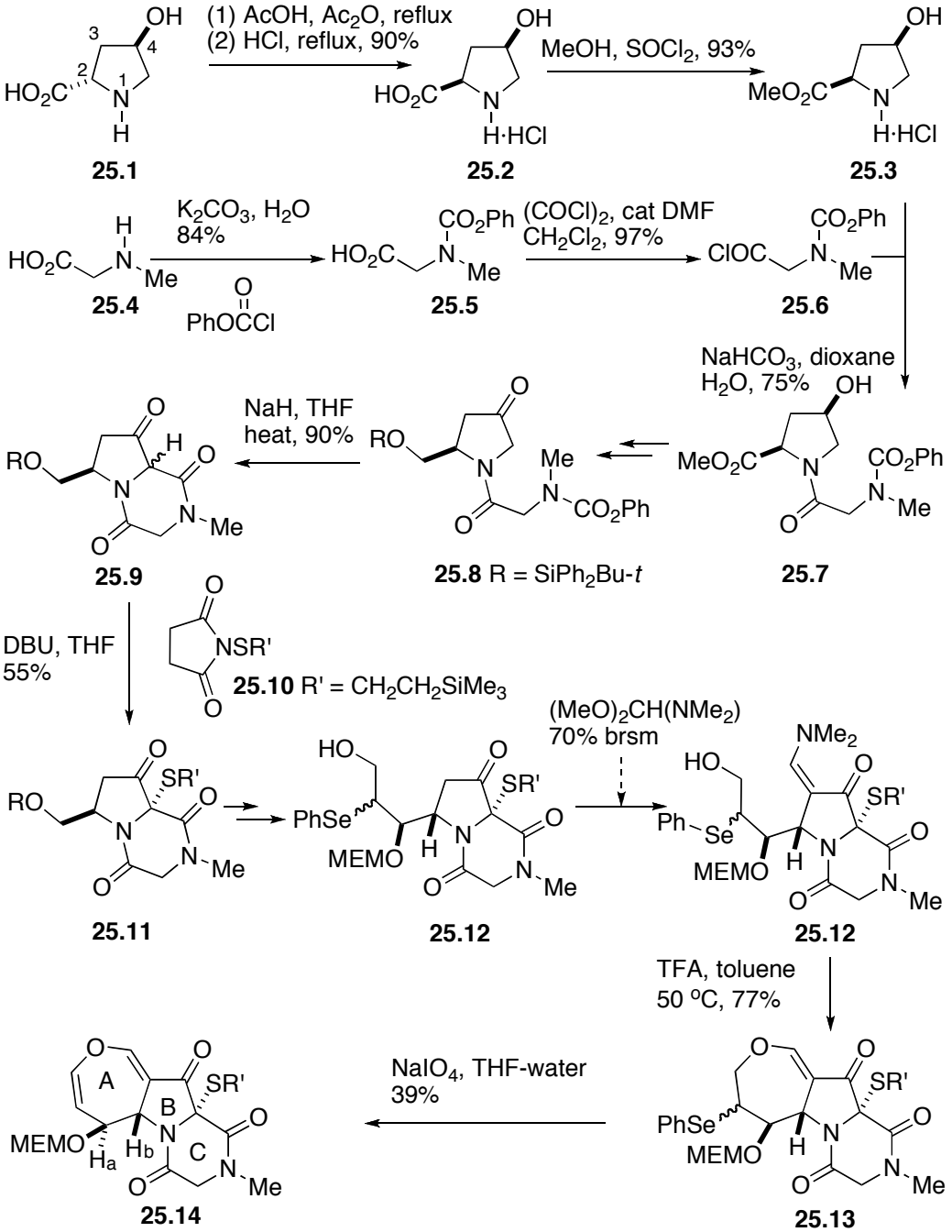


Scheme 24

2. Results and Discussion

2.1. Previous synthetic studies in this laboratory

The tricyclic core structure **25.14** of MPC1001 without the disulfur bridge



Scheme 25

was made by Dr. Jianbiao Peng, and the route is summarized in Scheme 25.[31a,51] The synthesis started with epimerization at C2 of optically pure *trans*-4-hydroxy-L-proline (**25.1**), using a three-step literature sequence.[52] Coupling of the amine salt **25.3** and the carboxyl chloride **25.6** gave amide **25.7** smoothly, and further manipulations led to ketone **25.8**. A Dieckmann type condensation, mediated by NaH in refluxing THF, afforded **25.9**. Sulfenylation and a short series of further transformations on the left part of the substrate provided **25.12**, a precursor to the tricyclic structure. At this point, an oxy-Michael addition and concomitant elimination of $HNMe_2$ afforded **25.13**, and subsequent selenoxide elimination delivered the tricyclic core structure **25.14**.

During the above synthesis Dr. Peng found that the protecting group ($CH_2CH_2SiMe_3$) on sulfur could not be removed[51] by treatment with Bu_4NF or by a reported method using 2-nitrobenzenesulfenyl chloride.[53] Consequently, finding a suitable protecting group for the sulfur became an urgent priority in order to continue the synthesis.

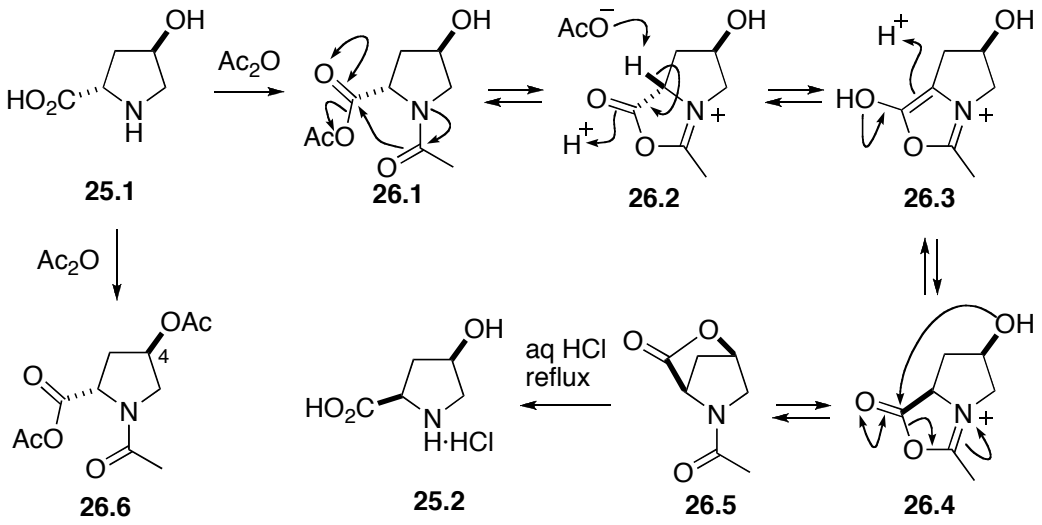
2.2. Synthetic studies towards the epidithiodioxopiperazine core of MPC1001

2.2.1. A practical preparation of large quantities of optically pure cis-4-hydroxy-D-proline

After I took over the project, it was soon realized that the *cis*-4-hydroxy-D-proline hydrochloride **25.2** prepared by epimerization of optically pure *trans*-4-hydroxy-L-proline, using the literature method (see Scheme 25),[52] was not optically pure, as two sets of peaks could be clearly seen in the ^{13}C NMR spectrum for both the acid **25.2** and the ester **25.3**. Later, after optically pure ester **25.3** had been prepared, a comparison of the optical rotation values of **25.8** made from the two sources revealed that the ee of **25.8** made from the optically impure **25.3** was only ca 70%.

The mechanism of epimerization is sketched in Scheme 26.[54] Working up the reaction after treatment with Ac_2O allowed isolation of pure crystalline solid **26.5**, albeit in a low yield (ca 50%). After exposure to refluxing aqueous HCl, the

bicyclic solid **26.5** was converted to optically pure **25.2**, which has a much higher $[\alpha]_D$ value (10.64 vs 6.5[52a], MeOH, *c* = 1.0) than that obtained by directly subjecting crude (as opposed to recrystallized) **26.5** to aqueous HCl.[54] It is highly possible that during the first step some of the starting material undergoes esterification of the hydroxyl group to give **26.6**, which then could not be converted into the bicyclic lactone **26.5** (or very slowly as cleavage of the C4 acetate to regenerate the hydroxyl group is required).

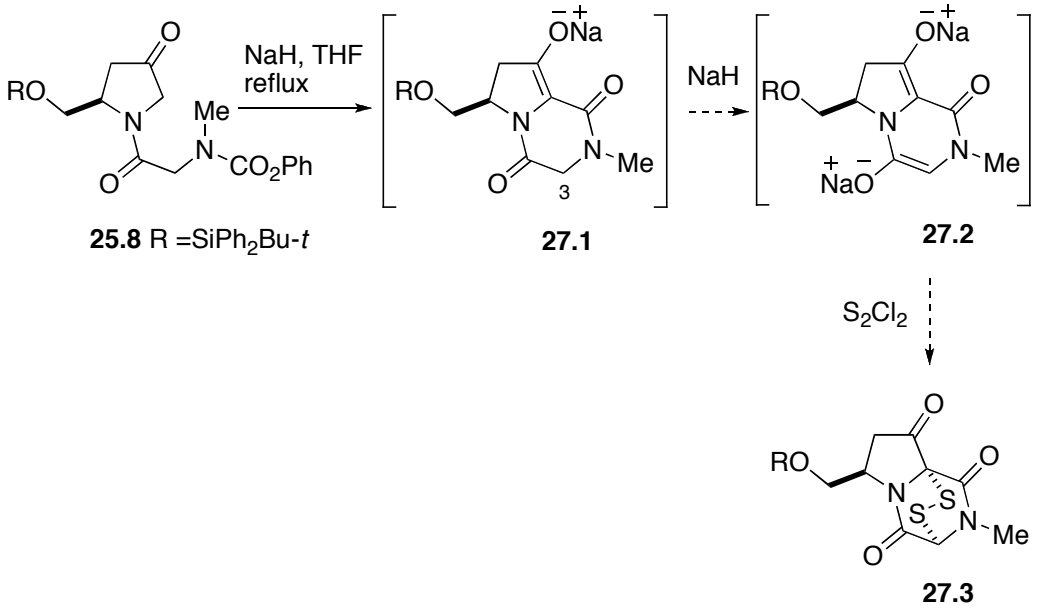


Scheme 26

However, isolation of **26.5** on a big scale (>10 g) was difficult, not only because a large amount of base is needed to neutralize the residual Ac_2O and AcOH in the crude material before recrystallization, but also because of the fact that **26.5**, as a strained lactone, is quite unstable in either acidic or basic aqueous solution (it also decomposed on silica gel). Moreover, **26.5** is very soluble in the aqueous layer and complete extraction is difficult (although continuous extraction was not tried). Later, it was gratifying to find that a single recrystallization of crude **25.2** [produced by direct treatment of crude **26.5** with refluxing aqueous HCl (2 N) after evaporation of Ac_2O and AcOH] from a hot mixture of ethanol and hexanes provided optically pure **25.2** in a very good yield (87%, ca 35 g scale) with the same $[\alpha]_D$ as that produced from pure **26.5**.

2.2.2. Attempts to form the disulfur bridge directly

We envisaged that, following Dieckmann cyclization, treatment of the enolate **27.1** with more NaH would probably generate dianion **27.2**, and quenching the dianion with S_2Cl_2 would lead to the epidithiodioxopiperazine **27.3** (Scheme 27). However, a single experiment along these lines gave only a complex mixture.



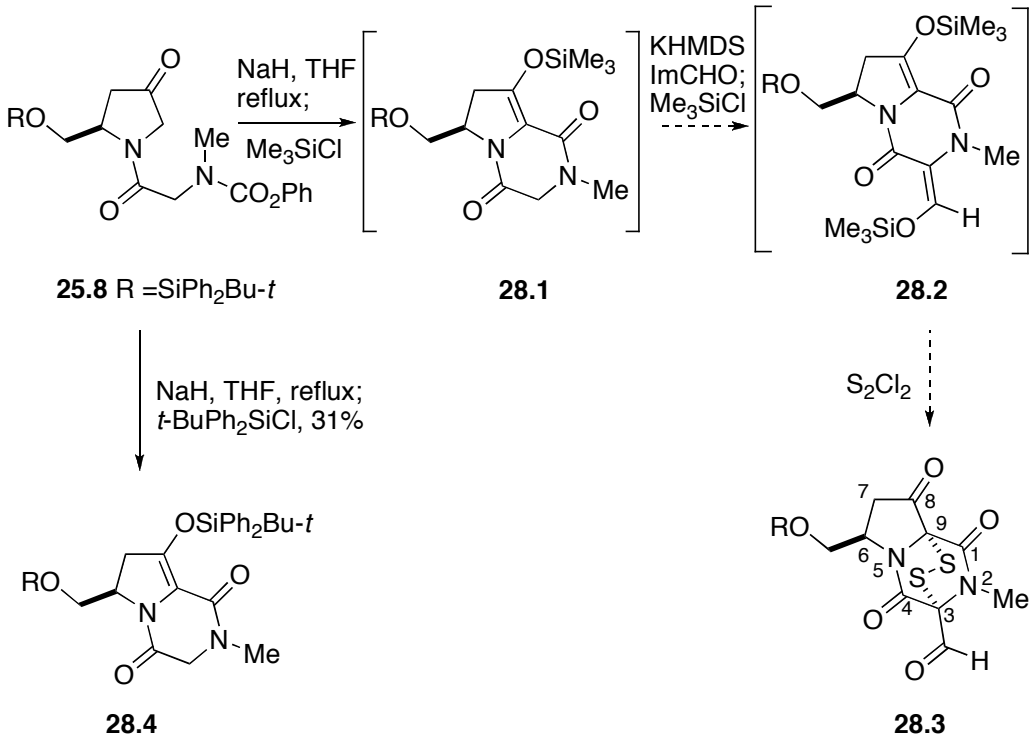
25.8 R =$SiPh_2Bu$-*t* **27.1** **27.2** **27.3**

Scheme 27

Based on an early report by Hino *et al*.,[34] we considered that NaH is not a strong enough base to deprotonate **27.1** at C3. They also found that treatment of a DKP dianion generally leads to a poor yield of the desired disulfide bridge. We then turned to sulfenylation of dienol ether **28.2** which would be generated *in situ* by formylation of **28.1** (Scheme 28), followed by quenching the resulting enolate with Me_3SiCl. Subsequent treatment with S_2Cl_2, again, gave only a complex mixture.

Further experimentation showed that enol ether **28.1** is probably unstable when treated with a strong base, as the action of KHMDS at –78 ºC on a similar compound, **28.4** (compound **28.1** itself was unstable and could not be isolated), led to severe decomposition within a short time (ca 20 min).

As attempts at simultaneous disulfenylation to install the disulfur bridge were not promising we turned our attention back to the original strategy, which was to attach the sulfur at C9 (see **28.3** in Scheme 28) stereoselectively first and to then use this sulfur to direct the facial selectivity of the sulfenylation during introduction of the second sulfur at C3.



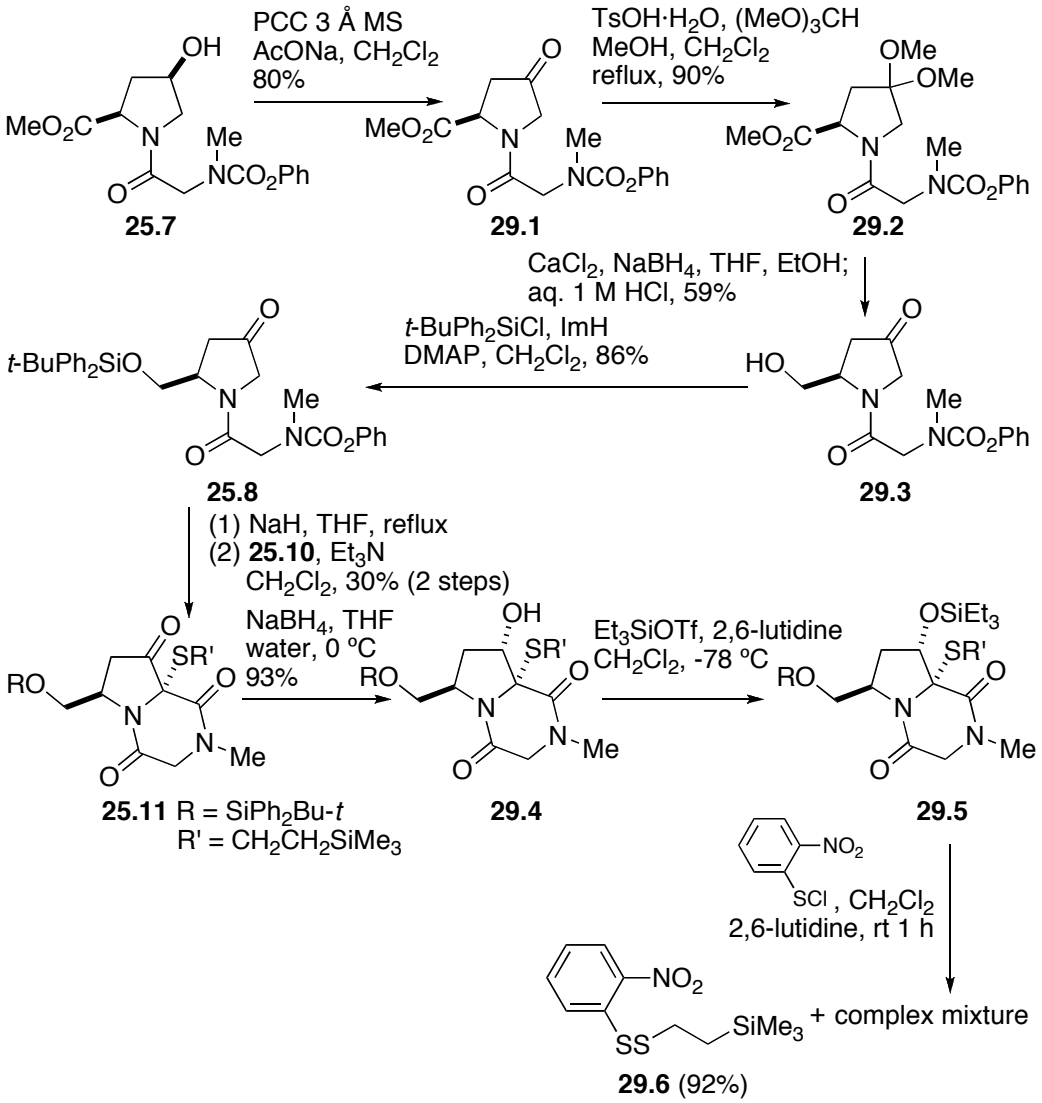
25.8 R =$SiPh_2Bu$-*t* **28.1** **28.2**

28.4 **28.3**

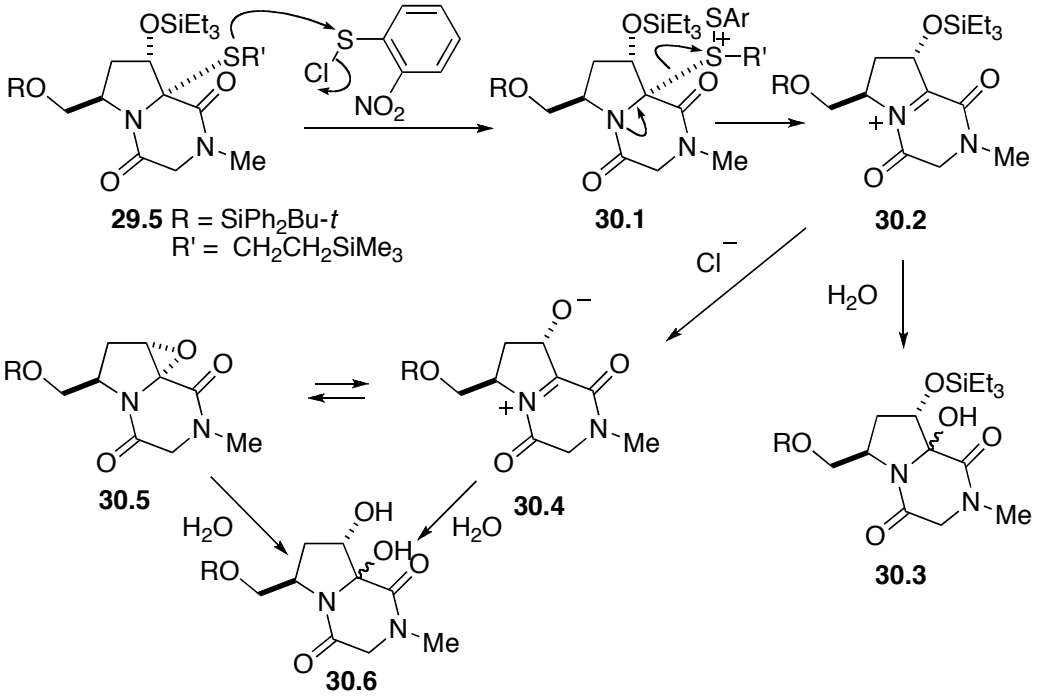
Scheme 28

2.2.3. Problems in removing the sulfur protecting group

As mentioned earlier, Dr. Peng[51] found that the $CH_2CH_2SiMe_3$ could not be removed from the sulfur with 2-nitrobenzenesulfenyl chloride (a deprotection method reported by Gerland *et al*.[53]). To reexamine the reaction, compound **29.5** was prepared. In this series, Dr. Peng's route to **29.4** was used with small modifications[31a,51] (Scheme 29). Treatment of **29.5** with purified 2-nitrobenzene-sulfenyl chloride resulted in a complex mixture. Among the components, disulfide **29.6** was isolated in 92% yield, plus two impure side products **30.3** and



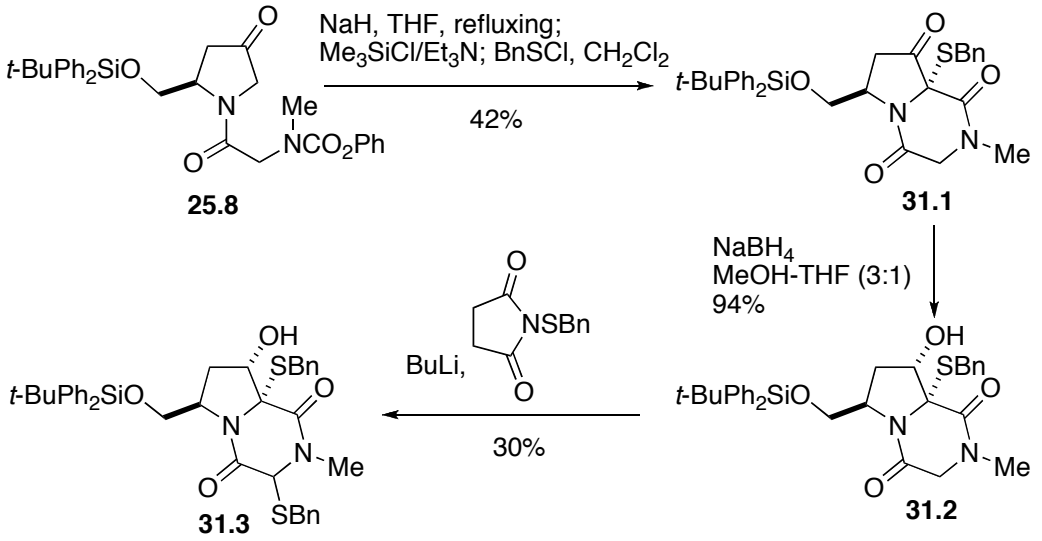
Scheme 29



Scheme 30

30.6 (characterized only by high resolution mass spectrometry) as shown in Scheme 30. A plausible mechanism is proposed in Scheme 30 to account for the formation of these products: after sulfenylation with 2-nitrobenzenesulfenyl chloride, the sulfur group is expelled by the lone pair electrons of the nitrogen to give iminium cation **30.2**, which is trapped by water during workup. Attack of chloride on the Et_3Si group of **30.2** will result in the deprotection product **30.4**. Both **30.4** and epoxide **30.5** are converted to the dihydroxy compound **30.6** after workup.

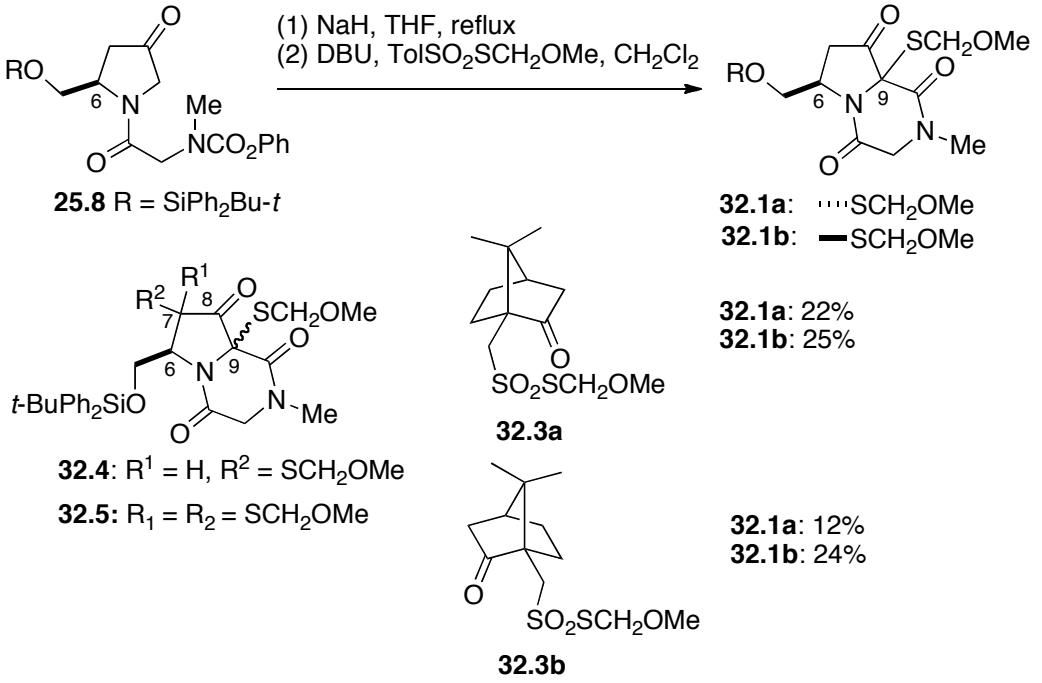
The next protecting group we tested was a benzyl group. The required substrates were prepared as shown in Scheme 31. It is worth noting that **31.1** was prepared by a sequence of 3 steps in one pot, thus avoiding handling the sensitive ketone **25.9**, which decomposes partially at room temperature overnight or on silica gel. However, this method of sulfenylation limits the range of protecting groups on sulfur as some reagents of the type RSCl could not be made, including $MeOCH_2SCl$ and PmbSCl. Treatment of either **31.2** or **31.3** with Li/NH_3 gave only a complex mixture, as did treatment with the Lewis acid BBr_3. It is known



Scheme 31

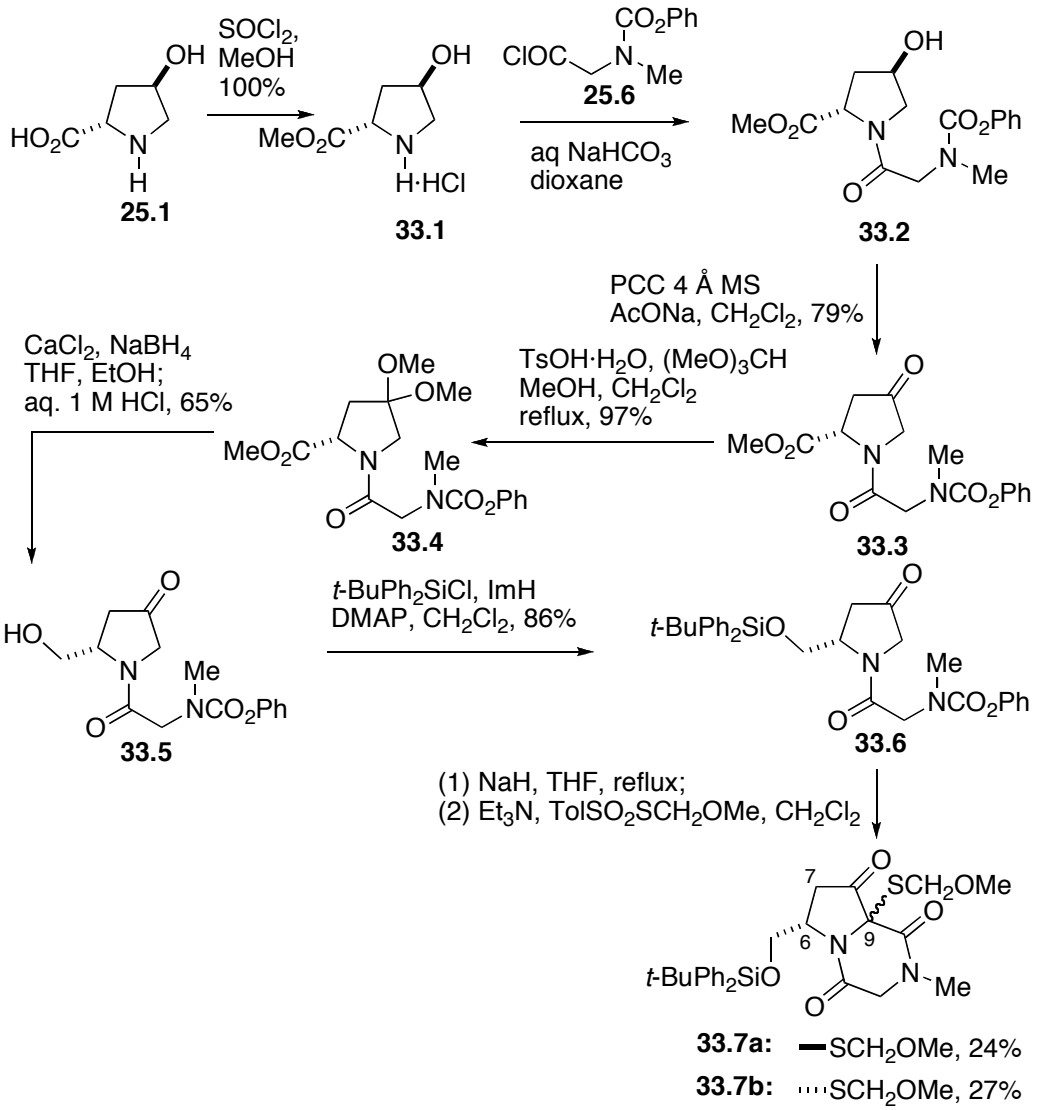
that a benzyl group on sulfur is much more difficult to remove than a benzyl group on oxygen.[55]

We next turned to a $MeOCH_2$ group for sulfur protection, as deprotection had been demonstrated in Kishi's work using BCl_3 in CH_2Cl_2.[41f] In contrast to the



Scheme 32

reasonable facial selectivity in the preparation of **25.11** (ca 4:1 in favor of the desired product) (Scheme 25),[31a,51] very poor selectivity (ca 1:1) was observed when $TolSO_2SCH_2OMe$[56] was used as the sulfenylation agent (Scheme 32). Increasing the bulkiness of the sulfone leaving group (using camphor derivatives **32.3a**,**b**, which were prepared from camphor thiosulfonate sodium salt[57] and $MeOCH_2Cl$, by the same method as for the preparation of $TolSO_2SCH_2OMe$) gave no obvious improvement in selectivity. As in this case the stereochemistry at C6 (Scheme 32) has no influence on the C9 stereochemistry, we decided to use compound **33.7b** (Scheme 33) which has the desired stereochemistry at both C6

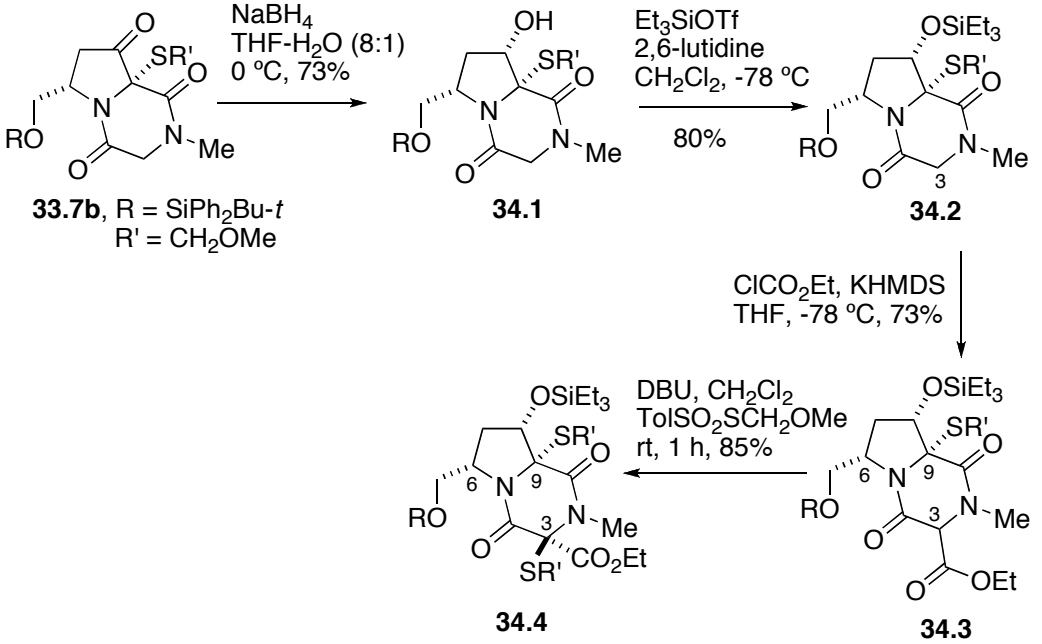


Scheme 33

and C9, thus avoiding epimerization steps. The preparation of **33.7a**,**b** was carried out as outlined in Scheme 33, using the same methods as for **32.1a**,**b**.

It is interesting to note that after the Dieckmann cyclization using NaH in refluxing THF, if the resulting enolate **27.1** (see Scheme 27) was directly treated with $TolSO_2SCH_2OMe$ or $MeSO_2SCH_2OMe$ at 0 ºC, no desired products (**33.7a**,**b**) were observed, and instead over-sulfenylation products **32.4** and **32.5** were obtained (Scheme 32). Compound **32.5** was also isolated when 2 equivalents of DBU (or fast addition of 1 equivalent of DBU) was used for sulfenylation of crude **25.9**. It is possible that the presence of three electron-withdrawing groups at C9 renders the proton at C7 very acidic. Pyridine tends to give a slow and incomplete reaction in the sulfenylation, and later we found that Et_3N is better in terms of a reasonable reaction rate and minimization of over sulfenylation (**33.6→33.7a**,**b**, Scheme 33).

Ketone **33.7b** was carried forwards to **34.2** by $NaBH_4$ reduction and protection of the resulting hydroxyl with Et_3SiOTf (Scheme 34). Attempts to introduce the second sulfur group at C3 of **34.2** using a strong base (LDA or KHMDS) followed by addition of $TolSO_2SCH_2OMe$ were fruitless, as compound

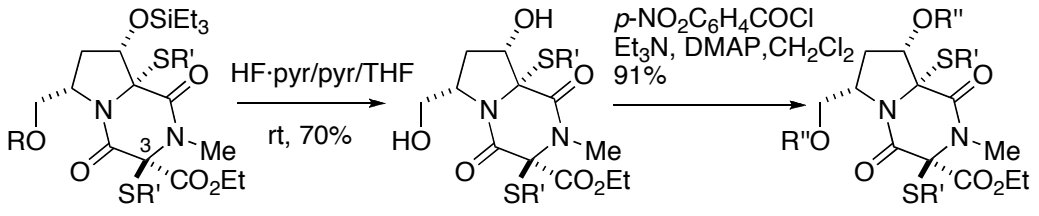


Scheme 34

34.2 decomposed quickly after addition of the base, (which resulted in formation of a deep blue solution). Addition of the base to a mixture of **34.2** and $TolSO_2SCH_2OMe$ resulted in disulfenylation at C3. However, ethoxycarbonylation was successfully performed by addition of KHMDS to a mixture of **34.2** and $ClCO_2Et$ in THF at -78 ºC (Scheme 34), and sulfenylation of the resulting 1,3-dicarbonyl compound **34.3** was carried out using DBU and $TolSO_2SCH_2OMe$. At this stage the C3 stereochemistry was unknown, but was later shown to be as indicated in Scheme 34.

As the stereochemistry at C3 in **34.4** could not be defined by NMR experiments and crystals suitable for X-ray crystallographic analysis could not be obtained by recrystallization of **34.4**, the *para*-nitrobenzoyl derivative **35.2** was made in two steps from **34.4** by desilylation with HF·pyr, followed by esterification using *para*-nitrobenzoyl chloride, Et_3N and DMAP in CH_2Cl_2. Unfortunately, the X-ray crystallographic analysis of **35.2** (Figure 1) showed that the stereochemistry at C3 was opposite to the desired stereochemistry (the sulfur group at C3 in **35.2** is *anti* to that at C9). The X-ray measurements were made on the enantiomer of the structure shown in Figure 1. As we had compounds from both the 6*R* and 6*S* series (see Scheme 34 for numbering), we sometimes did exploratory experiments with compounds of the 6*R* series. For the actual MPC1001 synthesis we would need to use compounds with 6S stereochemistry.

At this point we wanted to find out the factors that determine the stereochemical outcome during sulfenylation at C3 and we wondered if the C6 or



34.4 R = $SiPh_2Bu$-*t*
R' = CH_2OMe

35.1

35.2
R'' = *p*-$NO_2C_6H_4CO$

Scheme 35

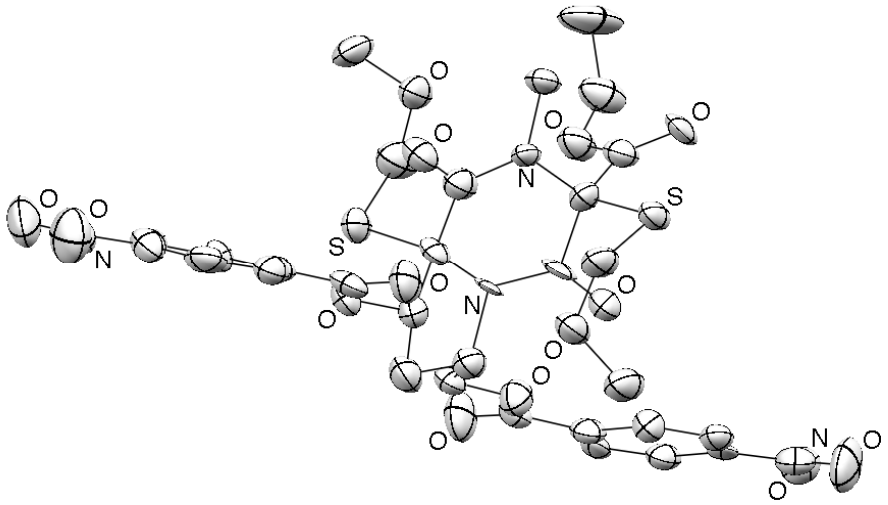
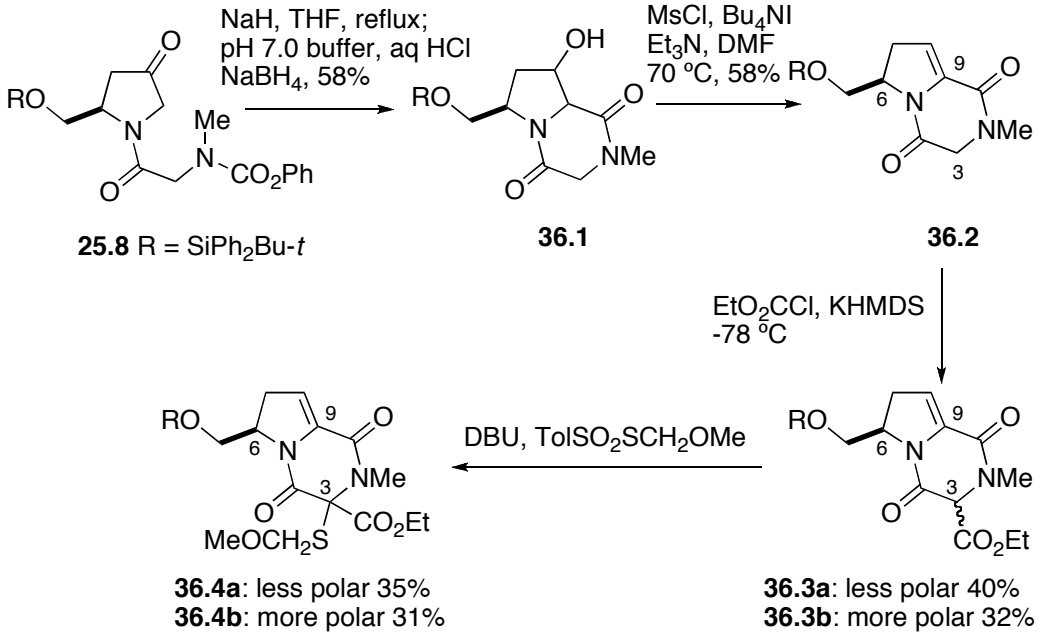


Figure 1. ORTEP diagram of compound 35.2.

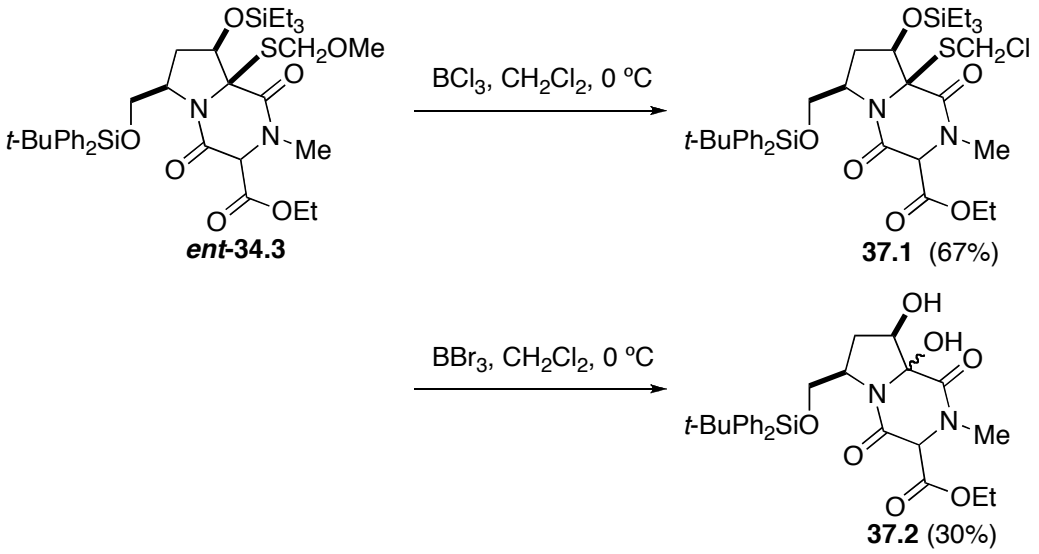
C9 centers, or both, were deciding factors. In order to establish which one is the dominating factor, compound **36.2** was prepared in two steps from **25.8** which has C6 as the only stereogenic center (Scheme 36). Ethoxyarbonylation using $ClCO_2Et$ and KHMDS provided the two diastereomers **36.3a** and **36.3b**.



Scheme 36

Treatment of the less polar isomer **36.3a** under the same sulfenylation conditions as that for **34.3** (DBU and $TolSO_2SCH_2OMe$ in CH_2Cl_2) produced two diastereomers in almost the same yields, indicating that C6 exerts no effect on the stereochemical outcome at C3 during sulfenylation — at least when C9 is sp^2 hybridized.

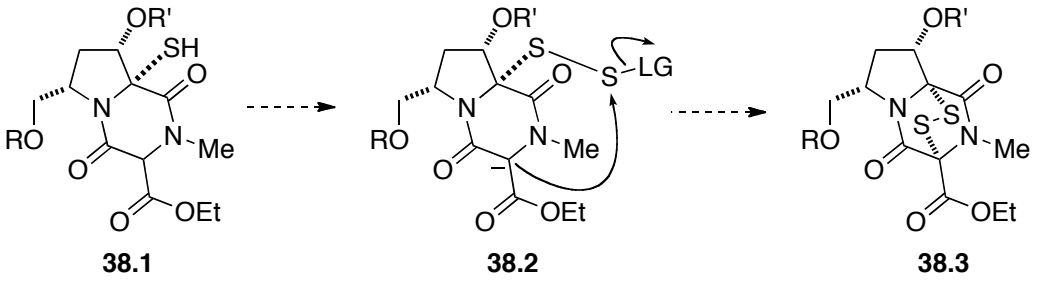
Meanwhile another problem emerged when deprotection of the CH_2OMe on sulfur was attempted. In contrast to smooth deprotection reported by Kishi's group,[41f] treatment of *ent*-**34.3** (enantiomer of **34.3** prepared from **32.1b** using the same method as outlined in Scheme 34) with BCl_3 in CH_2Cl_2 at 0 ºC yielded only chloride **37.1** in 67% yield, and switching to a stronger Lewis acid led to formation of the desulfurization and desilylation product **37.2** in 30% yield. Brønsted acidic conditions [conc. HCl in EtOH (3.6 M) at room temperature] only removed the $SiEt_3$ group, and a combination of Me_3SiCl/EtOH in refluxing EtOH generated a complex mixture.



Scheme 37

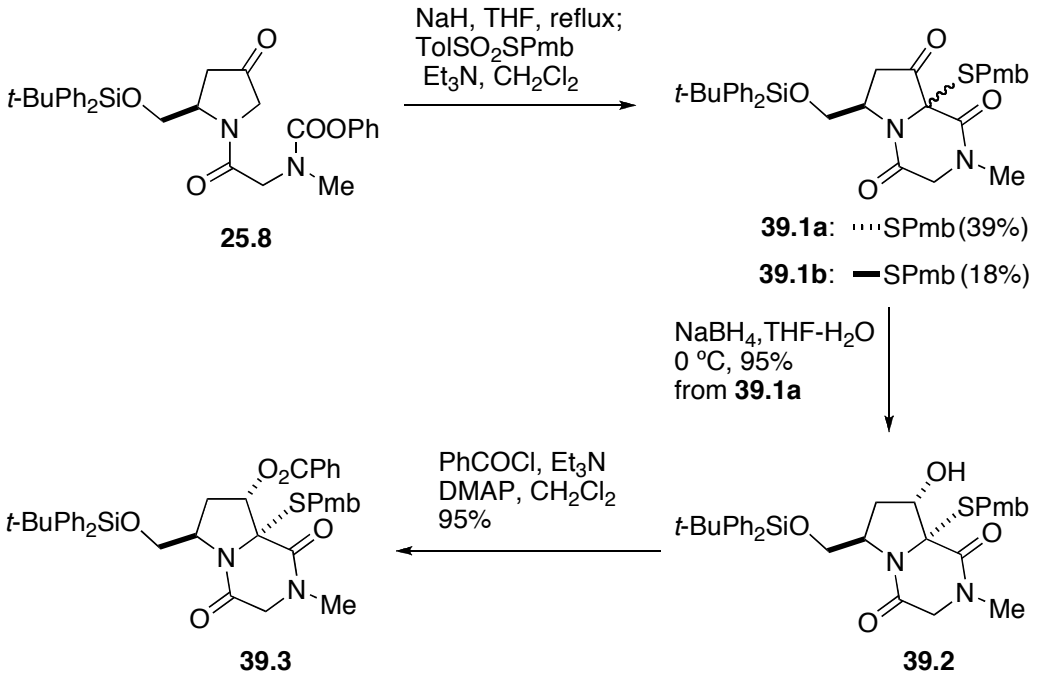
It seems that a protecting group that requires strong acidic conditions (either Lewis acid or Brønsted acid) for deprotection is unsuitable in our case. In addition, setting up the right stereochemistry at C3 in compound **34.4** (Scheme

34), seems to require an intramolecular sulfur delivery, as illustrated in Scheme 38 (for the 6*S* series).



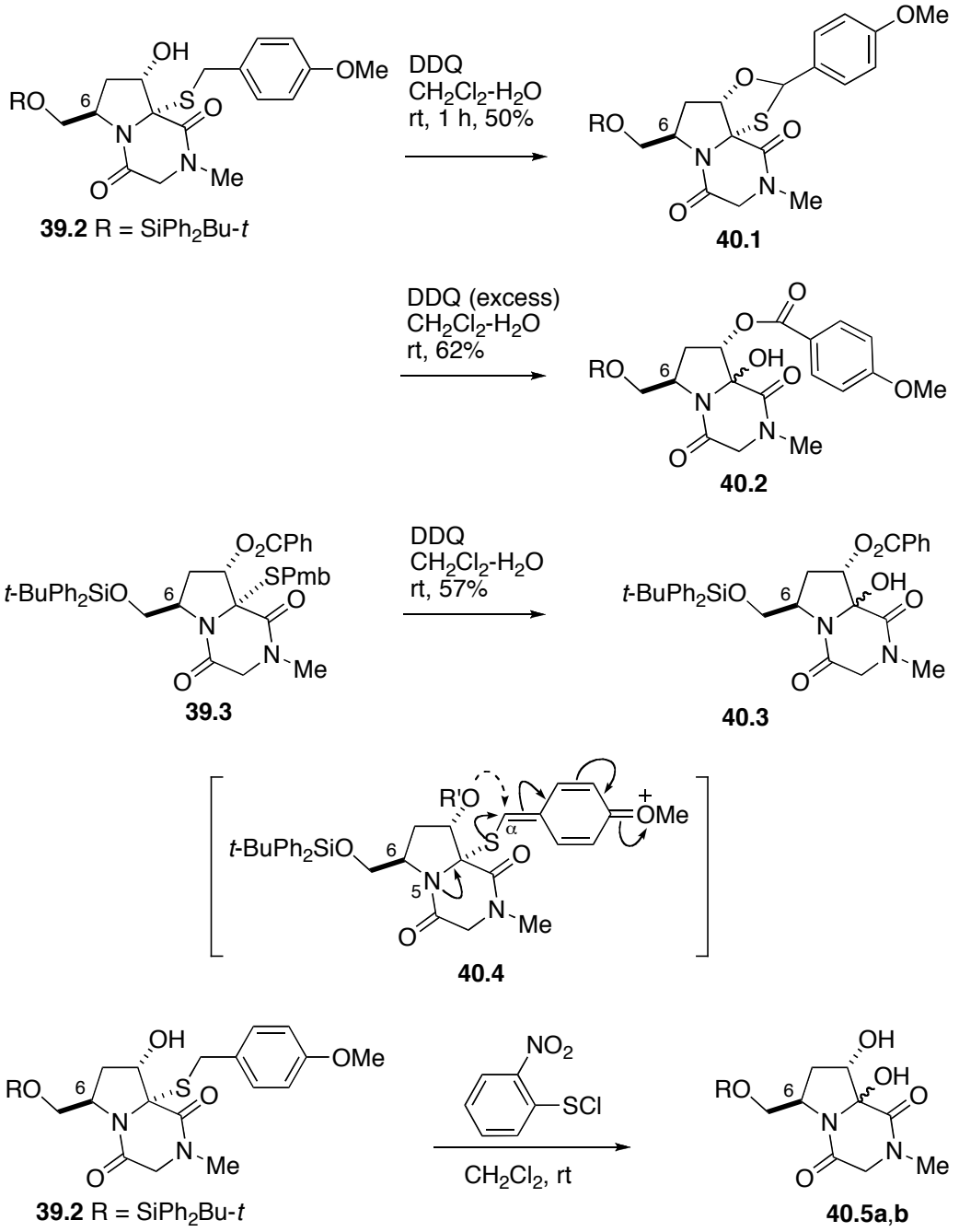
Scheme 38

We than envisioned that a *para*-methoxybenzyl group might be a proper choice as mild conditions could then be used for its deprotection such as TFA,[58] $Hg(O_2CCF_3)_2$,[59] or DDQ.[60] Compounds **39.1a**,**b**, **39.2** and **39.3** (Scheme 39) were prepared for testing the Pmb group. The facial selectivity of sulfenylation using $TolSO_2SPmb$ was a little better than $TolSO_2SCH_2OMe$.



Scheme 39

However, the Pmb protecting group could not be removed using a variety of conditions: treatment of **39.1a** with TFA and anisole at room temperature removed only the *t*-$BuPh_2Si$ group, and refluxing the solution gave a complex mixture. Use of TFA, anisole, dithiothreitol and $Hg(O_2CCF_3)_2$ together at room temperature also generated a complex mixtures. Oxidative conditions applied to

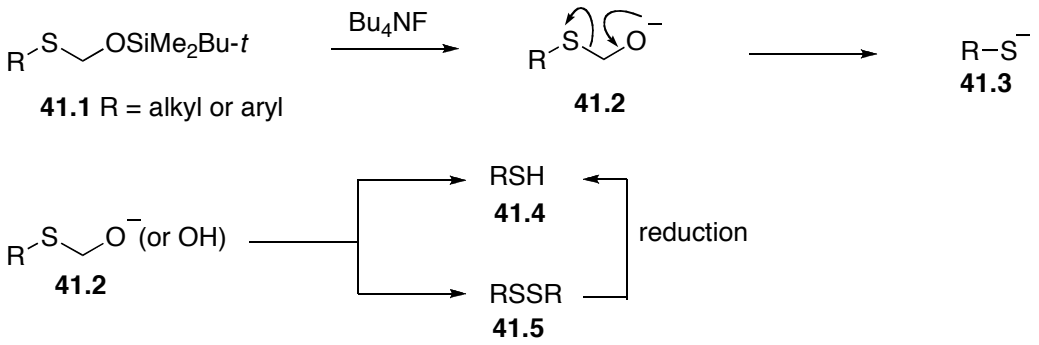


Scheme 40

39.2 (DDQ in a mixture of CH_2Cl_2 and water) led to formation of the tricyclic compound **40.1**, or desulfurization if excess DDQ was used (Scheme 40; note that all the structures shown represent the enantiomers of the compounds actually used. For consistency with Scheme 39, the C6 stereochemistry has been depicted as 6*R* throughout Scheme 40). Treatment of ester **39.3** with DDQ also produced only the desulfurization product **40.3**. Obviously, the expected nucleophilic attack of water on Cα (see **40.4**) did not occur after generation of the cationic species **40.4**; an intramolecular nucleophilic attack of the hydroxy group led to formation of the oxathiolane **40.1** and, when an excess of DDQ was used, further oxidation and generation of a cationic species similar to **40.4** resulted in expulsion of the sulfur by *N*5 (see compound **40.4**). The same mechanism accounts for the desulfurization when ester **39.3** was treated with DDQ. Treatment of **39.2** with 2-$NO_2C_6H_4SCl$ also gave only separable desulfurization products **40.5a**,**b**.

2.2.4. Designing a new thiol protecting Group (CH_2OSiMe_2Bu-t)

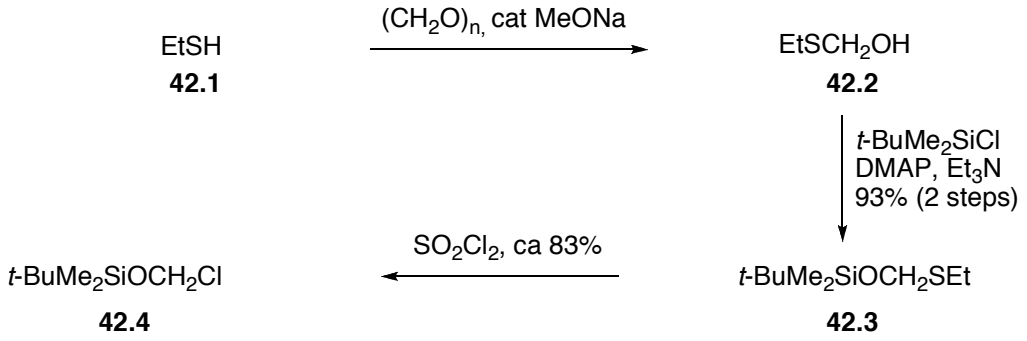
As all the above protecting groups could not be removed with retention of the sulfur atom on the substrate, we were forced to design a new thiol protecting group. After a literature survey, we were led to consider CH_2OSiMe_2Bu-*t* as a potential candidate, which could probably be removed by Bu_4NF or mild Lewis acid. Surprisingly, our literature search showed that this group has never been used for thiol protection, while its applications to hydroxyl groups is not uncommon.[61] One reason could be that, unlike hemiacetals, $RSCH_2OH$ is a stable



Scheme 41

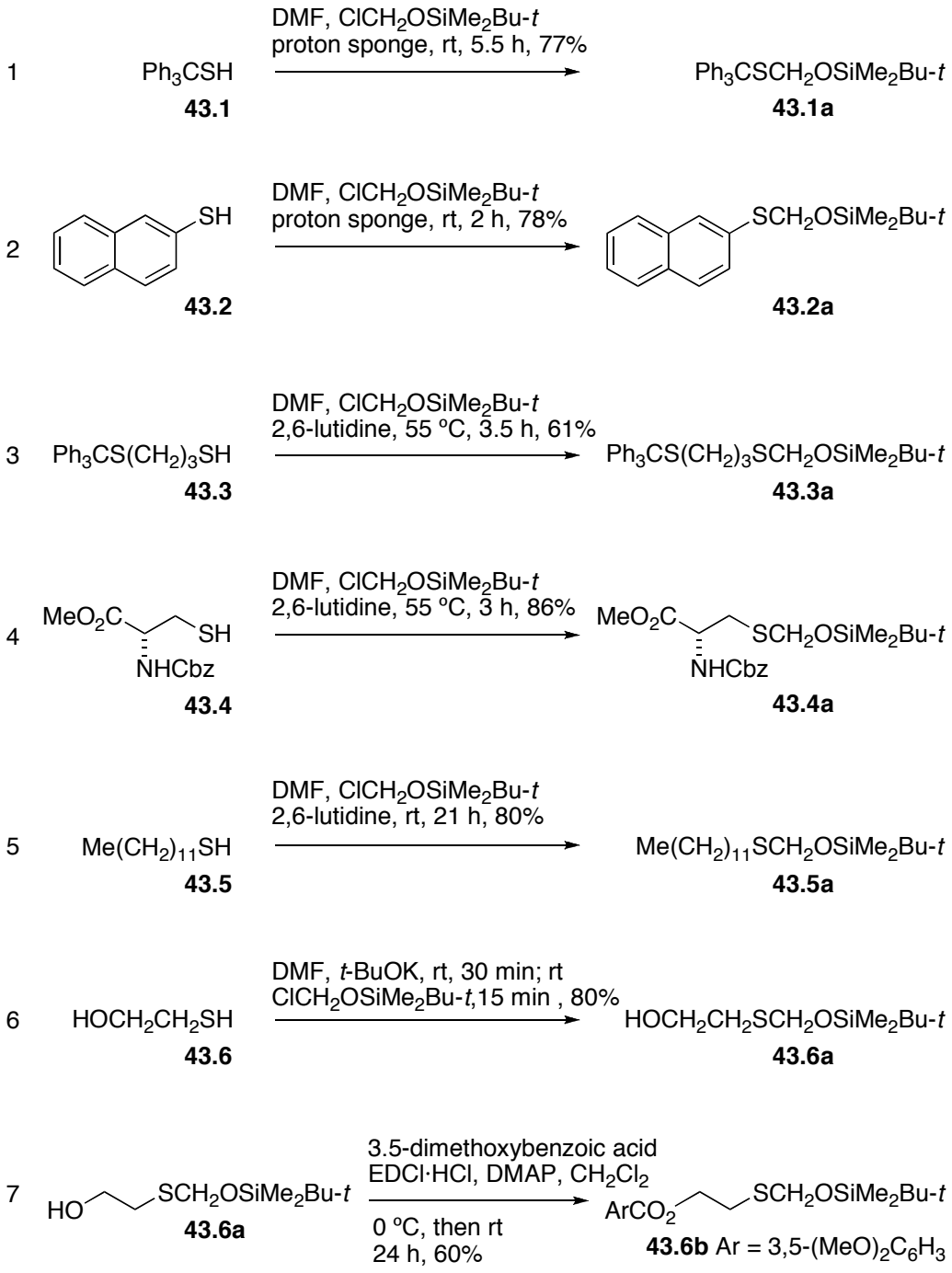
and isolable compound; however, under proper conditions, this type of compound does undergo fragmentation to release the thiol.[60,62] We envisioned that the anionic species **41.2** (Scheme 41), generated by treatment of compound **41.1** with Bu_4NF, would fragment *in situ* to give **41.3**; alternatively, collapse of **41.2** might be achieved by conversion to disulfide **41.5**, which could easily be reduced to thiol **41.4**.

To validate the above ideas, we first had to gain access to compounds **41.1** (Scheme 41). As the chloride **42.4** could easily be prepared in three steps according to the literature method (Scheme 42),[63] displacement of the chloride with a thiol should allow easy acquisition of compounds of type **41.1**.



Scheme 42

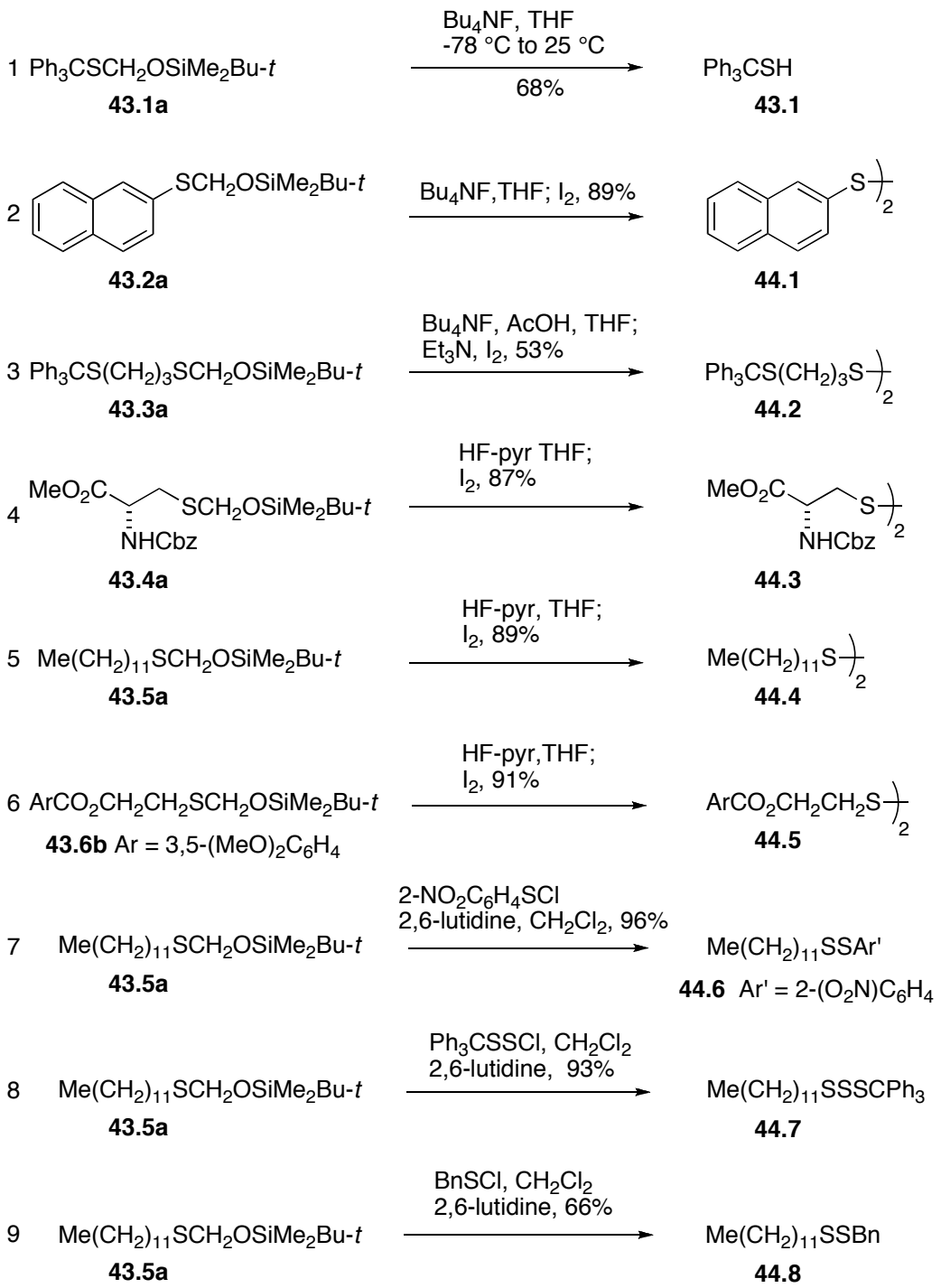
A number of simple thiols were protected in this way, as summarized in Scheme 43. However, this seemingly straightforward conversion was not trivial at all, and the conditions used in Scheme 43 were found only after careful screening. Among common amine bases, 2,6-lutidine and proton sponge perform better than others, including DBU, Hünig's base, Et_3N, and DMAP, while for entry 6, *t*-BuOK gives a better yield than both 2,6-lutidine and proton sponge. DMF as the solvent offers fast reactions and better yields than less polar solvents. The most common side product is the disulfide formed by oxidation of the starting thiol by adventitious oxygen.



Scheme 43

With some *S*-protected compounds in hand, we next examined the deprotection using Bu_4NF and found that usually a mixture of thiol (**41.4**) and alcohol (**41.2**) was generated, with the ratio depending on the nature of the substrate; HF·pyr gave alcohol almost exclusively. However, treatment of the

crude product *in situ* with I_2 resulted in formation of the corresponding disulfide. Thus for entries 2-6 (Scheme 44) the F^-/I_2 combination was used to form the symmetrical disulfides.



Scheme 44

It is sometimes more convenient to generate unsymmetrical disulfides from which the original thiol can be regenerated by reduction,[55,61] and we were pleased to find that conversion of the *S*-protected compounds to the corresponding unsymmetrical disulfides could be performed smoothly using a sulfenyl chloride RSCl (entries 7 and 9); a trisulfide could also be produced by using Ph_3CSSCl[64] (entry 8).

The stability of the protecting group was tested briefly by exposure of **43.5a** to a variety of conditions that are summarized in Table 1. This protecting group is quite labile to acid catalyzed solvolysis (entries 12 and 13), strong acidic conditions (entries 11 and 15) and common oxidizing reagents (entries 17-20); it is robust enough to withstand reduction conditions such as $NaBH_4$ (entry 4), $LiAlH_4$ (entry 5), H_2-Pd/C (or H_2-Rh/Al_2O_3, entries 1 and 2, respectively) and DIBAL (entry 6). It is also reasonably stable when treated with a Grignard reagent (entry 8), BuLi (entry 9), or LDA (entry 7). This protecting group is also compatible with the conditions for removal of a Troc group using Zn/AcOH (entry 3), Fmoc group deprotection using piperidine (entry 10) and conversion of a hydroxyl group to a bromide with CBr_4/Ph_3P.

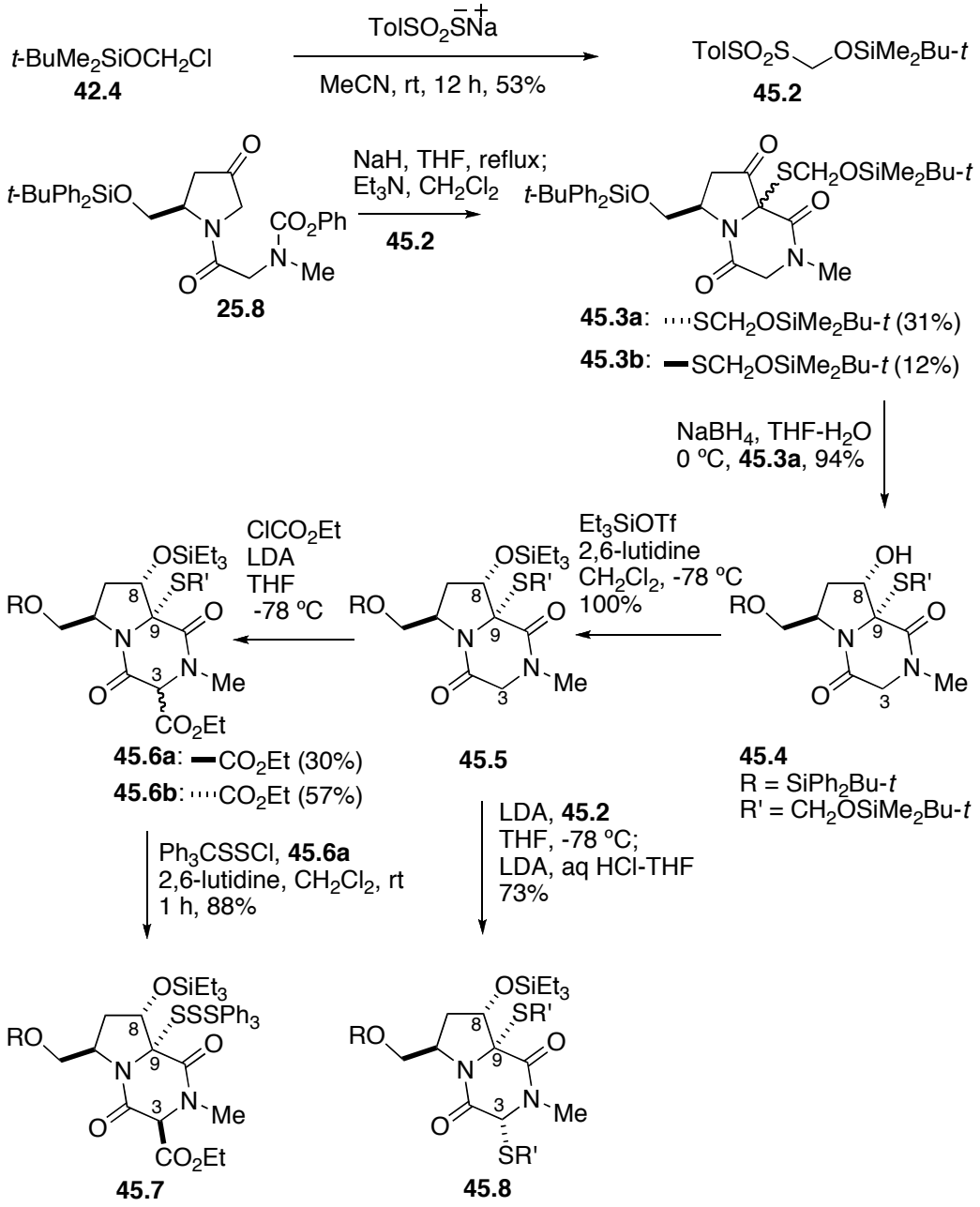
Table 1. Stability tests

	Reagent	Solvent	Temp	Time	Decomposition of 43.5a
1	H_2, Pd/C	MeOH-CH_2Cl_2[a]	rt	5.5 h	0%
2	H_2, Rh/Al_2O_3	EtOAc	rt	4 h	0%
3	Zn dust	AcOH-Et_2O (1:2)[b]	rt	1 h	3%
4	$NaBH_4$	THF-H_2O (8:1)	0 °C	1 h	0%
5	$LiAlH_4$	THF	rt	1 h	7%
6	DIBAL	CH_2Cl_2	-78 °C	1 h	3%
7	LDA	THF	-78 °C	45 min	10%
8	EtMgBr	THF	0 °C	1 h	7%
9	BuLi[c]	THF	-78 °C	15 min	4%
10	piperidine[d]	CH_2Cl_2	rt	20 min	0%
11	CF_3CO_2H[e]	CH_2Cl_2	0 °C	30 min	100%
12	TsOH·H_2O	CH_2Cl_2	rt	4.5 h	94%
13	PPTS[f]	MeOH	rt	4.7 h	47%
14	PPTS	CH_2Cl_2	rt	4.5 h	2%
15	BF_3·Et_2O	CH_2Cl_2	0 °C	1 h	100%
16	CBr_4/Ph_3P[g]	CH_2Cl_2	0 °C	30 min	7%
17	PCC[h]	CH_2Cl_2	rt	40 min	100%
18	Dess-Martin	CH_2Cl_2	rt	2 h	100%
19	IBX[i]	DMSO	rt	2 h	10%
20	Swern	CH_2Cl_2	[j]		100%
21	Et_3SiOTf[k]	CH_2Cl_2	-78 °C	25 min	5%

[a]Minimal amount of CH_2Cl_2 was used to dissolve **43.5a**; using 2:3 MeOH-CH_2Cl_2 at room temperature for 40 min in the presence of [2-(2-bromophenyl)ethoxy]-triethylsilane the Et_3Si group was removed.[65] [b]Conditions for Troc removal.[66] [c]In the presence of $(PhS)_2CH_2$; after quenching the mixture with D_2O all the dithioketal was converted into $(PhS)_2CHD$. [d]Piperidine:CH_2Cl_2 = 1:4 by vol. In the presence of Fmoc-Pro-OMe the Fmoc group was removed.[67] [e]CF_3CO_2H:CH_2Cl_2 = 1:2 by vol.; conditions for Boc removal.[68] [f]*O*-$SiMe_2Bu$-*t* groups are desilylated.[69] [g]In the presence of 2-(2-bromophenyl)ethanol; all of the alcohol was converted into the corresponding bromide. [h]Oxidation of a secondary alcohol in the presence of a methylthiomethyl ether is known.[70] [i]A hydroxyl can be oxidized in the presence of a sulfide.[71] [j]Standard Swern procedure. [k]In the presence of 2-(2-bromophenyl)ethanol and 2,6-lutidine; after 25 min 50% of the alcohol had been silylated.

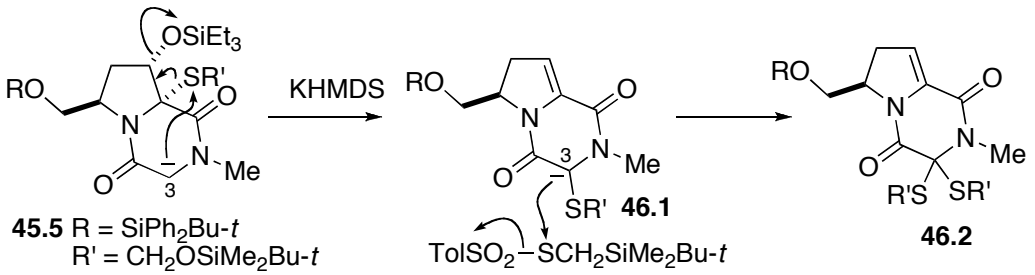
2.2.5. Application of the new protecting group to studies on MPC1001

To apply the new protecting group in our MPC1001 work, compound **45.2** was prepared as the sulfenylating agent, and the sulfenylation was conducted using the previous method, as shown in Scheme 45. Reduction of **45.3a** with $NaBH_4$ in THF-water as the cosolvent, followed by silylation of the resulting



Scheme 45

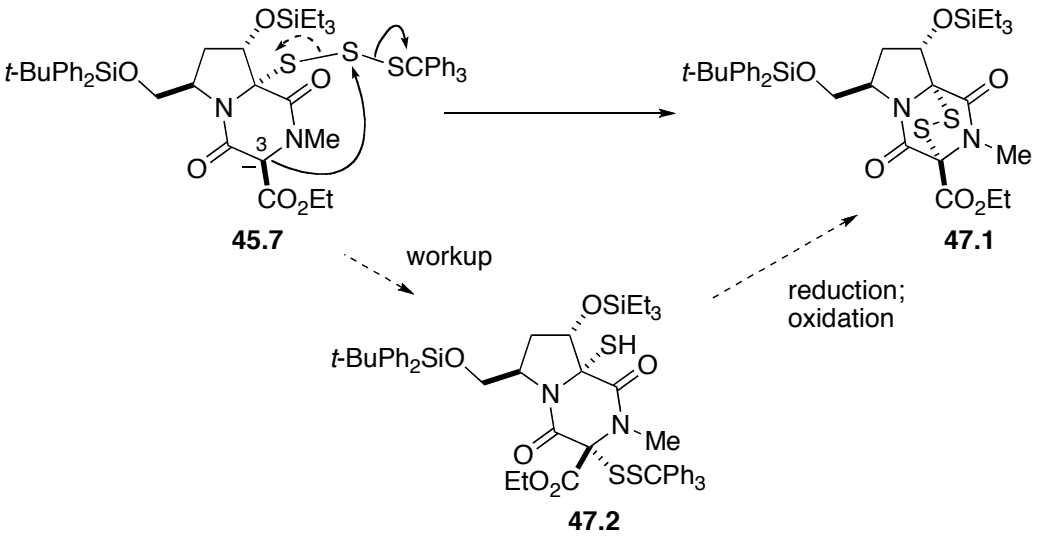
hydroxyl group with Et_3SiOTf and 2,6-lutidine in CH_2Cl_2 afforded compound **45.5** smoothly (Scheme 45). Further manipulation at C3 of **45.5** requires deprotonation with a strong base. Ethoxycarbonylation could be carried out by addition of LDA to a mixture of **45.5** and $ClCO_2Et$ in THF at -78 ºC, generating two isomers. The relative stereochemistry at C3 was tentatively assigned based on observations in the next step (*vide infra*); in contrast, KHMDS gave a much lower yield (20%) and the products were impure. The different behavior of the two bases was also observed for sulfenylation at C3 (**45.5→45.8**): addition of $TolSO_2SCH_2OSiMe_2Bu$-*t* shortly after treatment of **45.5** with LDA (LDA was quickly added and then stirred for 1 min, longer times result in significant decomposition) gave the desired product in good yield (73%, after epimerization by treatment with LDA and quenching with aqueous HCl-THF), while the same procedure using KHMDS led to decomposition of the starting material and a small amount of **46.2** was isolated, which was possibly formed via the mechanism depicted in Scheme 46.



Scheme 46

With **45.6a** and **45.6b** in hand (Scheme 45), we next examined the deprotection step using Ph_3CSSCl, which would also serve as the sulfur source for a second sulfenylation via internal delivery, as shown in Scheme 47, viz. the carbanion can attack the middle sulfur of **45.7** to give either **47.1** or **47.2**, and the latter could be converted to the former by reduction and oxidation. Although **45.6a** reacted smoothly with Ph_3CSSCl, the other diastereomer **45.6b** remained unchanged even at an elevated temperature ($ClCH_2CH_2Cl$, 80 ºC) for 44 h. As the only difference between the two isomers is the stereochemistry at C3, it is

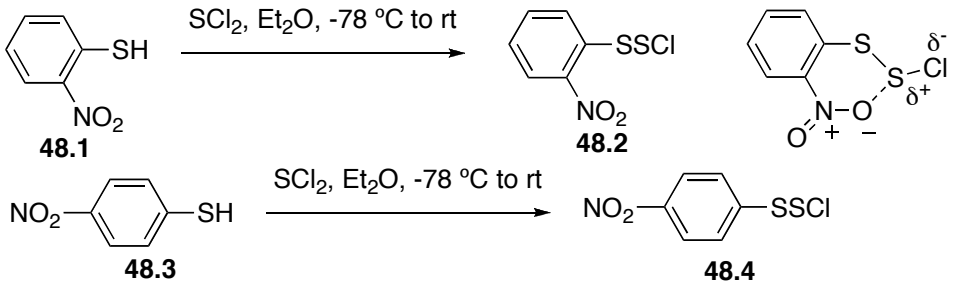
reasonable to assign the relative stereochemistries of the two as shown in Scheme 45, and the suppressed reactivity of **45.6b** was attributed to the increased steric hindrance at sulfur imposed by the ester group at C3.



Scheme 47

It was disappointing that treatment of **45.7** with a base (DBU in CH_2Cl_2 at room temperature or *t*-BuOK in THF at room temperature) only resulted in a complex mixture. We reasoned that it is probable that the bulky CPh_3 group inhibits the desired nucleophilic attack on the middle sulfur by the C3 carbanion. Presumably, a smaller group would not impose such hindrance, and would allow formation of **47.1** if the group could also stabilize a sulfur anion. With these considerations in mind, we chose the two sulfenylating agents **48.2** and **48.4** shown in Scheme 48. Both reagents could be prepared by treatment of the corresponding thiols with freshly distilled SCl_2 in Et_2O, using a modified literature procedure.[72]

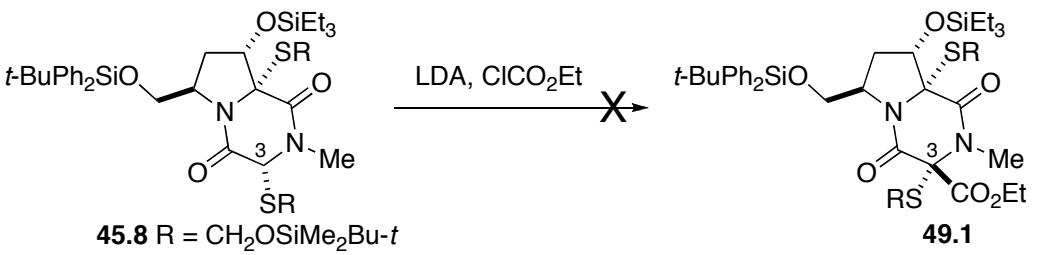
It was surprising that **48.2** did not react with **45.6b** at all. The reason could be that **48.2** is not reactive enough, due to the fact that the partial positive charge on the sulfur is stabilized by the oxygen of the nitro group (Scheme 48).[73] However, **48.4** also did not behave the way we expected as its reaction with **45.6a** gave a complex mixture containing *p*-$NO_2C_6H_4SSSCH_2OSiMe_2Bu$-*t*.



Scheme 48

The tendency of the sulfur at C9 (see Scheme 45) to be removed by an electrophile led us to suspect that this problem was probably caused by steric congestion between the C9 sulfur group and the adjacent C8 protected oxygen. We tried to invert the C8 stereochemistry of **45.4**; however, all our efforts failed, using either a Mitsunobu reaction or an S_N2 displacement strategy. The Mitsunobu reaction, with either benzoic acid[74] or *p*-nitrobenzoic acid,[75] gave only unchanged starting material; converting the hydroxy group of **45.4** into a leaving group such as a mesylate or triflate, followed by treatment with an oxygen nucleophile including AcO^-, $PhCO_2^-$, CHO_2^-, NO_2^-, and the sodium salt of allyl alcohol in DMSO (or DMF) at room temperature or at 80 ºC gave either starting material or decomposition. In some cases, I was able to isolate from the resulting complex mixtures the elimination compound **36.2** (See Scheme 36 for the structure) in ca 17% yield. Such an elimination process is reported in the literature.[76]

We also tried to introduce a carbonyl group at C3 of **45.8** (Scheme 49), but this apparently simple process did not proceed at all and the reaction (LDA, THF



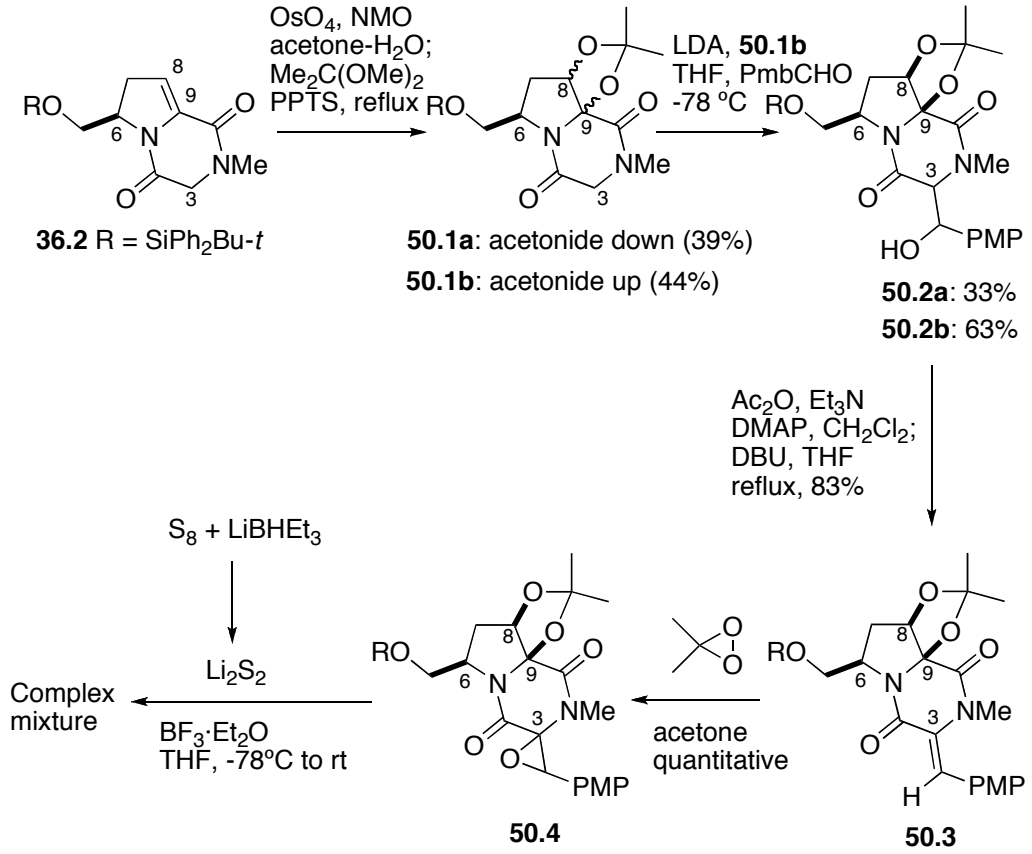
45.8 R = CH_2OSiMe_2Bu-*t* **49.1**

Scheme 49

and $ClCO_2Et$) gave a complex mixture after 25 min at -78 ºC. The difficulty of introducing the carbonyl group at C3 in a similar compound was encountered in the previous study.[51]

2.2.6. A second approach to the disulfide bridge

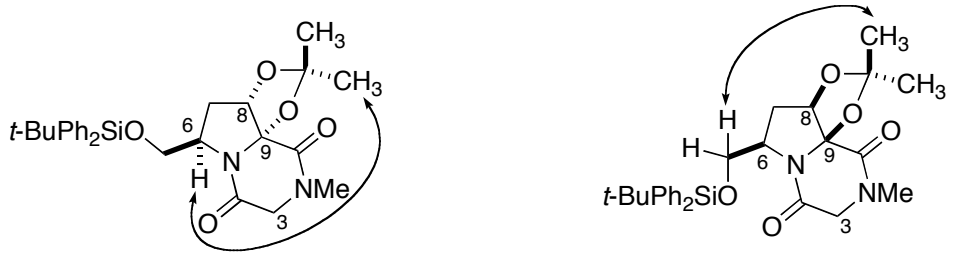
As we could not install the disulfide bridge using the methods discussed above, we started to think of other routes. We envisioned that treatment of **50.4** with a strong Lewis acid in the presence of Li_2S_2 might enable us to install the disulfide bridge (Scheme 50), in a manner in which the stereochemistry might be controlled by the C8 oxygen group.



Scheme 50

The preparation of **50.4** started by dihydroxylation of compound **36.2** (Scheme 50). Attempts to introduce the hydroxy groups in a stereocontrolled manner by the standard Sharpless asymmetric dihydroxylation procedure (using

commercial AB-mix-α or AB-mix-β) failed, as the starting material was recovered after 1 day. However, the dihydroxylation was successfully performed with a catalytic amount of OsO_4 in the presence of NMO in acetone-water, yielding a pair of inseparable diastereomers. The two diastereomers were then protected as acetonides, which were separable and the stereochemistry of each diastereomer was established based on TROESY measurement (Figure 2). Isomer **50.1b** was carried forward to **50.2a**,**b** using an aldol reaction. After acetylation and elimination, both **50.2a** and **50.2b** gave the same product **50.3**, whose double bond geometry was established by NMR measurements. The double bond of **50.3** was inert to dihydroxylation conditions using OsO_4 and NMO, but could be epoxidized with dimethyldioxirane in acetone, giving a mixture of two diastereomers in a ca 1:1 ratio. However, the anticipated substitution of the angular oxygen groups in **50.4** with *in situ* generated Li_2S_2, mediated by $BF_3{\cdot}OEt_2$ gave only a complex mixture.



50.1a **50.1b**

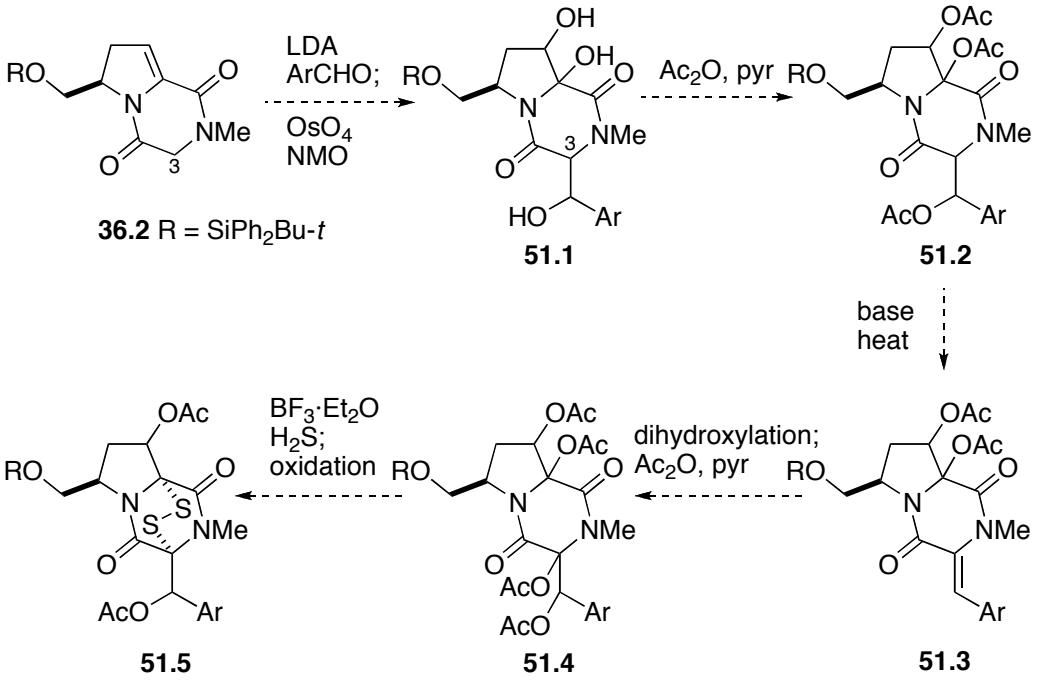
Figure 2. TROESY measurements for 50.1a,b.

The failure of the reaction between **50.4** and Li_2S_2 could be due to the high stability of the acetonide unit of **50.4**, as common deprotection conditions (such as PPTS in THF-water, TFA, or PTSA in THF-water) did not remove the acetonide group — sometimes the $SiPh_2Bu$-*t* was lost.

2.2.7. Further plans for the second approach to the disulfur bridge

As the acetonide protecting group seems to be too stable to undergo the desired substitution by sulfur reagents or to be deprotected, it is probably more

appropriate to use ester groups instead of an acetonide. A plausible route is depicted in Scheme 51, using **36.2** as the starting material. The plan starts with an aldol reaction, followed by dihydroxylation of the double bond to give compound **51.1**. Esterification, followed by elimination, using a similar process to that for the conversion of **50.2a**,**b** to **50.3** (Scheme 50), will, in principle, afford substrate **51.3**. Another dihydroxylation and esterification would then furnish tetraacetate **51.4**, setting the stage for installing the sulfurs. We hope that the literature method of displacement, mediated by a Lewis acid (see the introduction section, Schemes 19-22), followed by oxidation, will allow us to get access to the disulfur bridge core structure **51.5**.



Scheme 51

3. Conclusion

Different protecting groups for a thiol were tried during studies on the total synthesis of MPC1001, and difficulties were encountered for the deprotection.

A new thiol protecting group (CH_2OSiMe_2Bu-*t*) was designed which could be deprotected by either treatment with F^-/I_2 or a sulfenylating agent (RSCl). In synthetic studies on MPC1001, this protecting could be removed by the action of Ph_3SSCl (but not 2-$NO_2C_6H_4SSCl$ or 4-$NO_2C_6H_4SSCl$), but subsequent attempts at internal sulfur delivery gave complex mixtures.

We also started a new route for making the disulfide bridge, and the feasibility was tested very briefly.

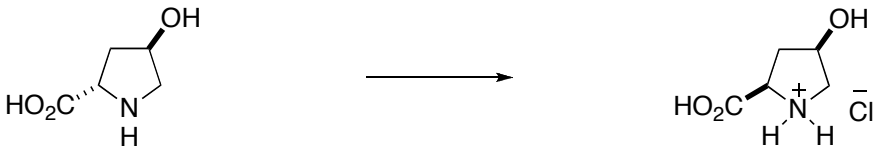
4. Experimental Section

Unless specified, reactions were carried out under a slight static pressure of Ar or N_2 that had been purified by passage through a column (3.5 × 42 cm) of R-311 catalyst and then through a similar column of Drierite. Solvents for reactions were dried as described below. Glassware was dried in an oven (140 °C) overnight before use and either cooled in a desiccator over Drierite, or assembled quickly, sealed with rubber septa, and allowed to cool under a light static pressure of Ar or N_2.

Solvents used for chromatography were distilled before use. Commercial thin layer chromatography plates (silica gel, Merck 60F-254 was used. Silica gel for flash chromatography was Merck type 60 (230-400 mesh). Dry solvents were prepared under an inert atmosphere and transferred by syringe or cannula. Dry THF and Et_2O were distilled from sodium and benzophenone ketyl. Dry MeCN, Et_3N and pyridine were distilled from CaH_2.

The symbols s, d, t and q used for ^{13}C NMR spectra indicate zero, one, two, or three attached hydrogens, respectively, the assignments being made by from APT and HSQC spectra.

(4*R*)-*4*-Hydroxy-D-proline hydrochloride (25.2).

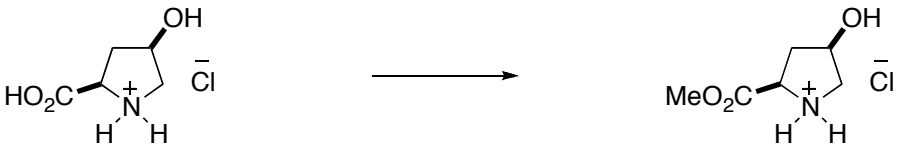


25.1 **25.2**

A mixture of **25.1** (30.0 g, 228.8 mmol) in Ac_2O (220 mL) was heated at 95 °C (oil bath temperature) for 16 h, cooled to room temperature, and evaporated. The residue was dissolved in hydrochloric acid (2 N, 450 mL) and the mixture was refluxed for 16 hand cooled to room temperature. The solvent was evaporated and the resulting solid was dried under oil pump vacuum

overnight. The solid was dissolved in EtOH (ca 140 mL) under reflux, the bath temperature was lowered to 90 °C and hexane was added slowly so as to maintain refluxing until the mixture started to become cloudy. The mixture was cooled to room temperature and then in ice water. The resulting product was filtered and dried under oil pump vacuum to give **25.2** (33.48 g, 87%) as a white solid: mp 138-143 °C; $[\alpha]_D$ = 10.64 (*c* 1.00, MeOH); FTIR (MeOH, cast) 2100-3400 (br), 1715, 1587, 1376 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 2.13 (ddt, *J* = 13.6, 3.7, 1.9 Hz, 1 H), 2.29 (ddd, *J* = 13.7, 9.6, 4.3 Hz, 1 H), 3.13 (dt, *J* = 11.8, 1.5 Hz, 1 H), 3.19 (dd, *J* = 11.8, 4.1 Hz, 1 H), 3.73 (s, 3 H), 4.33-4.37 (m, 1 H), 4.47 (dd, *J* = 9.7, 3.8 Hz, 1 H), 5.47 (d, *J* = 2.2 Hz, 1 H), 9.79 (br, s, 1 H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 37.0 (t), 52.9 (t), 53.0 (d), 57.3 (d), 68.1 (d), 169.6; exact mass (electrospray) *m*/*z* calcd for $C_5H_{10}NO_3$ 132.0655, found 132.0655.

(4*R*)-4-Hydroxy-D-proline hydrochloride methyl ester (25.3).

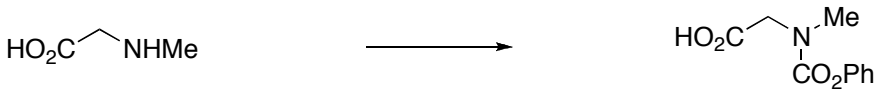


25.2 **25.3**

$SOCl_2$ (12.8 g, 0.107 mol) was added dropwise to a stirred and cooled (0 °C) solution of **25.2** (15.0 g, 0.090 mol) in dry MeOH (180 mL). Stirring at 0 °C was continued for 30 min, the cooling bath was removed, and stirring was continued for 16 h. The mixture was evaporated and the resulting solid was dissolved in a minimal amount of MeOH with heating. The solution was slowly poured into stirred and cooled (0°C) Et_2O (ca 350 mL). The product was filtered and dried under oil pump vacuum to give **25.3** (13.25 g, 81%) as a white solid: mp 165-168 °C; $[\alpha]_D$ =10.16 (*c* 1.75, MeOH); FTIR (MeOH, cast) 3291, 3005, 2976, 2936, 2200-3500 (br), 1737, 1568, 1448, 1437 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 2.13 (ddt, *J* = 13.6, 3.7, 1.9 Hz, 1 H), 2.29 (ddd, *J* = 13.7, 9.6, 4.3 Hz, 1 H), 3.13 (dt, *J* = 11.8, 1.5 Hz, 1 H), 3.19 (dd, *J* = 11.8, 4.1 Hz, 1 H), 3.73 (s, 3

H), 4.33-4.37 (m, 1 H), 4.47 (dd, *J* = 9.7, 3.8 Hz, 1 H), 5.47 (d, *J* = 2.2 Hz, 1 H), 9.79 (br, s, 1 H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 37.0 (t), 52.9 (t), 53.0 (d), 57.3 (d), 68.1 (d), 169.6 (s); exact mass *m/z* calcd for $C_6H_{11}NO_3$ (M-HCl) 145.0739, found 145.0737.

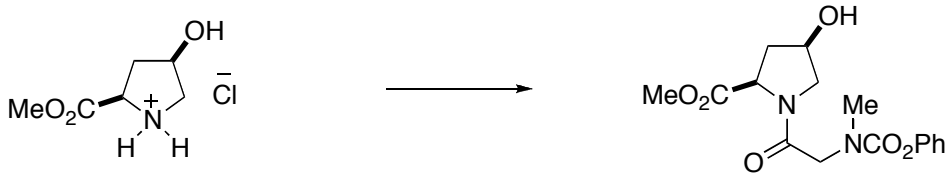
2-[Methyl(phenoxycarbonyl)amino]acetic acid (25.5).



25.4 **25.5**

K_2CO_3 (19.4 g, 140.3 mmol) was added to a stirred and cooled (0 °C) solution of **25.4** (10 g, 112.2 mmol) in water (120 mL) and $PhCO_2Cl$ (20.2 g, 128.9 mmol) was added over 15 min. The ice bath was left in place but not recharged and stirring was continued for 24 h. The mixture was washed with Et_2O (3 times) and the aqueous layer was acidified with concentrated hydrochloric acid to pH 1.0 and extracted with CH_2Cl_2 (4 times). The combined organic extracts were washed with brine and dried ($MgSO_4$). Evaporation of the solvent gave **25.5** (20.0 g, 85%) as a viscous oil: FTIR ($CDCl_3$, cast) 2500-3500 (br), 1723, 1477, 1456, 1398 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.07 (s, 1.5 H), 3.17 (s, 1.5 H), 4.14 (s, 1 H), 4.19 (s, 1 H), 7.07-7.10 (m, 1 H), 7.13-7.16 (m, 1 H), 7.17-7.22 (m, 1 H), 7.32-7.39 (m, 2 H), 11.29 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 35.9 (q), 36.2 (q), 50.7 (t), 121.6 (d), 121.7 (d), 125.55 (d), 125.58 (d), 129.3 (d), 151.1 (s), 151.2 (s), 154.8 (s), 155.6 (s), 174.5 (s), 174.6 (s); exact mass (electrospray) *m/z* calcd for $C_{10}H_{11}NNaO_4$ 232.0580, found 232.0581.

Methyl (2*R*,4*R*)-4-hydroxy-1-{2-[methyl(phenoxycarbonyl)amino]-acetyl}pyrrolidine-2-carboxylate (25.7).

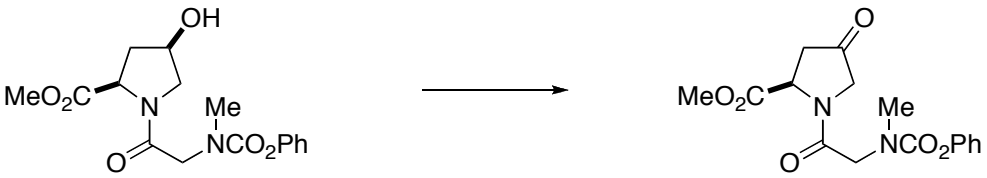


25.3 **25.7**

$(COCl)_2$ (12.8 g, 100.6 mmol) was added to a stirred and cooled (0 °C) solution of **25.5** (18.3 g, 87.5 mmol) and DMF (511.6 mg, 7.0 mmol) in dry CH_2Cl_2 (145 mL). The cooling bath was left in place but not recharged and stirring was continued for 4 h. A small aliquot of the mixture was evaporated and the ^1H NMR spectrum showed that the reaction was complete. The mixture was evaporated (protection from moisture), and the residue was diluted with dry THF (10 mL) and evaporated again. The resulting residue wad diluted with dry THF (15 mL) and added over 1 h to a stirred and cooled (0 °C) mixture of **25.3** (13.25 g, 72.95 mmol) and $NaHCO_3$ (27.6 g, 328.3 mmol) in a mixture of dioxane (160 mL) and water (160 mL). The cooling bath was left in place but not recharged and stirring was continued for 20 h. The dioxane was evaporated, CH_2Cl_2 was added to the residue and some precipitate was filtered off. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3 times). The combined organic extracts were washed and dried ($MgSO_4$). Evaporation of the filtrate and flash chromatography of the residue over silica gel (5.9 x 15 cm), using 3:1 EtOAc–hexane (500 mL), 6:1 EtOAc–hexane (500 mL), 10:1 EtOAc–hexane (500 mL), EtOAc (1500 mL), 1:20 MeOH–EtOAc (1000 mL) and 1:10 MeOH-EtOAc (800 mL), gave **25.7** (21.26 g, 87%) as a foam: $[\alpha]_D$ = 49.46 (*c* 0.45, CH_2Cl_2); FTIR (CH_2Cl_2, cast) 3443, 2952, 1726, 1657, 1594, 1455, 1398 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.02-2.08 (m, 0.78 H), 2.21-2.29 (m, 1 H), 2.36-2.42 (m, 0.22 H), 3.03 (s, 1.2 H), 3.17 (s, 1.4 H), 3.20 (s, 0.4 H), 3.56-4.22 (m, 7 H), 4.32-4.42 (m, 1 H), 4.54-4.58 (m, 1 H), 7.06-7.11 (m, 2 H), 7.15-7.18 (m, 1 H), 7.29-7.35 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 36.1 (q), 36.37 (q),

36.41 (q), 36.6 (t), 39.4 (t), 39.5 (t), 51.18 (t), 51.21 (t), 51.3 (t), 51.4 (t), 52.77 (q), 52.84 (q), 54.9 (t), 55.0 (t), 55.6 (t), 55.7 (t), 57.5 (d), 57.7 (d), 57.9 (d), 58.0 (d), 68.2 (d), 68.4 (d), 71.10 (d), 71.15 (d), 121.65 (d), 121.71 (d), 121.8 (d), 125.3 (d), 125.4 (d), 129.17 (d), 129.20 (d), 151.29 (s), 151.32 (s), 154.9 (s), 155.0 (s), 155.4 (s), 155.5 (s), 167.3 (s), 167.5 (s), 167.6 (s), 168.0 (s), 172.4 (s), 172.8 (s), 174.2 (s), 174.3 (s); exact mass (electrospray) *m*/*z* calcd for $C_{16}H_{20}N_2NaO_6$ 359.1214, found 359.1213.

Methyl (2*R*)-1-{2-[methyl(phenoxycarbonyl)amino]acetyl}-4-oxo-pyrrolidine-2-carboxylate (29.1).

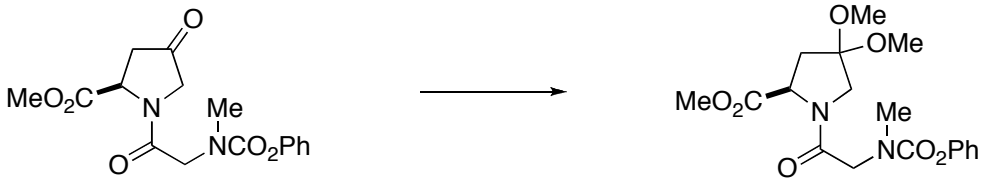


25.7 **29.1**

Molecular sieves (3Å, 31.6 g) and NaOAc (7.8 g, 94.8 mmol) were added to a stirred solution of **25.7** (21. 26 g, 63.2 mmol) in dry CH_2Cl_2 (210 mL). The mixture was stirred at room temperature for 5 min and then cooled to 0 °C. Pulverized PCC (40.87 g, 189.6 mmol) was added over ca 10 sec, stirring at 0 °C was continued for 15 min, the cooling bath was removed and stirring was continued for 30 min. Florisil was added and the mixture was filtered through a column of Florisil (5 x 15 cm), using EtOAc and then 1:20 MeOH-EtOAc. Evaporation of the filtrate and flash chromatography of the residue over silica gel (5 x 15 cm), using 1:1 EtOAc–hexane, 2:1 EtOAc–hexane, 3:1 EtOAc–hexane and 5:1 EtOAc–hexane, gave **29.1** (16.91 g, 80 %) as a foam: $[\alpha]_D$ = 23.78 (*c* 1.00, $CHCl_3$); FTIR ($CHCl_3$, cast) 2956, 1767, 1726, 1673, 1594, 1477, 1455, 1435 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.51 (ddd, 0.8 H, *J* = 18.9, 9.0, 2.8 Hz), 2.64 (m, 0.2 H), 2.81-2.96 (m, 1 H), 2.99 (s, 1.1 H), 3.13-3.14 (m, 1.9 H), 3.65-4.31 (m, 7 H), 4.79-4.83 (m, 0.1 H), 4.96-4.99 (m, 0.9 H), 7.03-7.10 (m, 2 H), 7.14 (q, *J* = 7.3 Hz, 1 H), 7.28-7.32 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 35.9

(q), 36.0 (q), 36.2 (q), 39.4 (t), 41.1 (t), 41.2 (t), 50.3 (t), 50.5 (t), 51.3 (t), 51.5 (t), 51.6 (t), 51.7 (t), 52.6 (q), 53.0 (q), 55.3 (d), 55.4 (d), 55.9 (d), 56.1 (d), 121.5 (d), 121.6 (d), 125.25 (d), 125.30 (d), 129.1 (d), 151.1 (s), 151.2 (s), 154.6 (s), 155.2 (s), 167.4 (s), 167.59 (s), 167.64 (s), 170.4 (s), 170.7 (s), 171.3 (s), 171.4 (s), 206.2 (s), 206.4 (s), 206.6 (s); exact mass (electrospray) *m/z* calcd for $C_{16}H_{18}N_2NaO_6$ 357.1057, found 357.1052.

Methyl (2*R*)-4,4-dimethoxy-1-{2-[methyl(phenoxycarbonyl)amino]-acetyl}pyrrolidine-2-carboxylate (29.2).



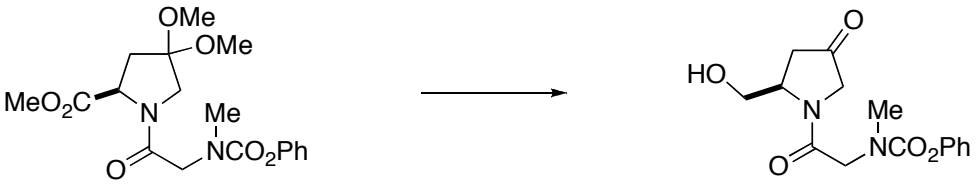
29.1 **29.2**

$TsOH{\cdot}H_2O$ (0.96 g, 5.06 mmol) was added to a stirred solution of **29.1** (16.91 g, 50.58 mmol) and $(MeO)_3CH$ (26.8 g, 252.9 mmol) in CH_2Cl_2 (29 mL) and anhydrous MeOH (145 mL). The mixture was refluxed for 24 h, cooled to room temperature and evaporated. The residue was diluted with saturated aqueous $NaHCO_3$ and extracted with EtOAc (3 times). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. The resulting **29.2** (19.33 g, 100%), which was obtained as a foam was used for next step.

In another experiment (27.65 g scale) the crude product was subjected to flash chromatography over silica gel (5.9 x 15 cm), using 2:1 EtOAc–hexane and then 3:1 EtOAc–hexane, to obtain **29.2** (28.34 g, 90%) as a white foam: $[\alpha]_D$ = 78.96 (*c* 1.00, $CHCl_3$); FTIR (CH_2Cl_2, cast) 2951, 2837, 1728, 1668, 1954, 1455, 1436, 1396 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.19-2.24 (m, 0.7 H), 2.30-2.40 (m, 1 H), 2.55-2.60 (m, 0.3 H), 3.17-3.26 (m, 9 H), 3.60-3.78 (m, 5 H), 3.92-3.97 (m, 0.6), 4.14-4.31 (m, 1.4 H), 4.46-4.48 (m, 0.1 H), 4.60-4.66 (m, 0.9 H), 7.08-7.13 (m, 2 H), 7.15-7.19 (m, 1 H), 7.31-7.36 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 35.69, 35.71, 35.9, 36.18, 36.22, 36.3, 37.8, 38.0, 49.0, 49.2, 49.7, 49.8,

49.9, 50.0, 50.4, 50.49, 50.51, 50.6, 51.0, 51.2, 51.8, 51.98, 52.05, 52.1, 52.3, 52.7, 57.3, 57.4, 57.5, 57.8, 105.3, 105.4, 107.07, 107.15, 121.59, 121.62, 121.67, 121.70, 125.2, 129.08, 129.12, 151.3, 154.7, 154.8, 155.3, 155.4, 166.8, 167.0, 167.5, 167.8, 171.0, 171.16, 171.23, 171.3; exact mass (electrospray) *m*/*z* calcd for $C_{18}H_{24}N_2NaO_7$ 403.1476, found 403.1470.

Phenyl *N*-{2-[(2*R*)-2-(hydroxymethyl)-4-oxopyrrolidin-1-yl]-2-oxo-ethyl}-*N*-methylcarbamate (29.3).

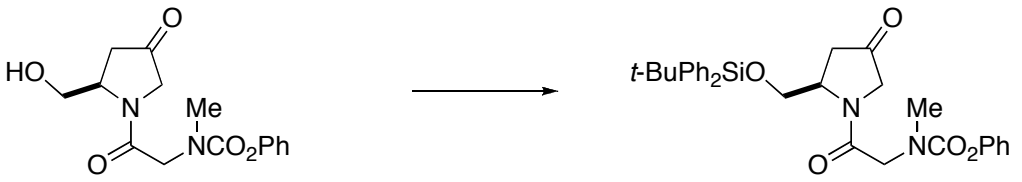


29.2 **29.3**

$CaCl_2$ (9.92 g, 89.4 mmol) was added to a stirred and cooled (0 °C) solution of **29.2** (28.34 g, 74.50 mmol) in a mixture of EtOH (80 mL) and dry THF (93 mL). Stirring at 0 °C was continued for ca 15 min (most of the $CaCl_2$ dissolved) and $NaBH_4$ (6.77 g, 178.8 mmol) was added in portions over ca 1 min. Stirring at 0 °C was continued for 10 h (the reaction had to be monitored by TLC) and the mixture was carefully quenched and acidified to pH 1 with hydrochloric acid (2 M, ca 250 mL). Stirring was continued overnight and the mixture was extracted with CH_2Cl_2 (3-4 times, the extraction being monitored by TLC). The combined organic extracts were washed with brine and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (5.4 x 15 cm), using EtOAc and then 1:20 MeOH–EtOAc, gave **29.3** (22.82 g, 59%) as a foam: $[\alpha]_D$ = -22.02 (*c* 1.00, CH_2Cl_2); FTIR (CH_2Cl_2, cast) 3432, 2925, 1763, 1722, 1656, 1594, 1456, 1400 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.33-2.51 (m, 1 H), 2.62-2.81 (m, 1 H), 3.04-3.24 (m, 3 H), 3.50-4.18 (m, 5.8 H), 4.30-4.37 (m, 0.28 H), 4.42-4.47 (m, 0.17 H), 4.67-4.77 (m, 0.73 H), 7.07-7.13 (m, 2 H), 7.17-7.22 (m, 1 H), 7.32-7.38 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 36.6, 36.8, 39.3, 39.4, 40.8, 50.6, 51.8, 52.2, 52.8, 53.1, 55.9, 56.1, 56.4, 64.2, 64.6,

65.1, 121.7, 121.8, 125.5, 125.6, 129.31, 129.32, 151.26, 151.29, 155.0, 155.8, 167.48, 167.51, 167.8, 208.5, 208.6, 208.7; exact mass (electrospray) *m*/*z* calcd for $C_{15}H_{18}N_2NaO_5$ 329.1108, found 329.1109.

Phenyl *N*-{2-[(2*R*)-2-{[(*tert*-butyldiphenylsilyl)oxy]methyl}-4-oxo-pyrrolidin-1-yl]-2-oxoethyl}-*N*-methylcarbamate (25.8).

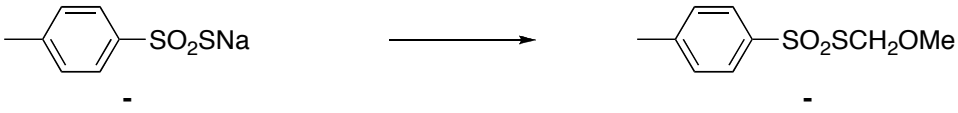


29.3 **25.8**

t-$BuPh_2SiCl$ (13.3 g, 48.3 mmol) was added to a stirred solution of **29.3** (13.44 g, 43.88 mmol), imidazole (4.48 g, 65.8 mmol) and DMAP (0.536 g, 4.4 mmol) in dry CH_2Cl_2 (145 mL) and stirring at room temperature was continued for 7 h. The mixture was washed with aqueous $NaHSO_4$ (1 M, 100 mL) and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were washed with brine and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (5.9 x 15 cm), using 1:2 EtOAc–hexane and then 4:5 EtOAc–hexane, gave **25.8** (20.47 g, 86%) as a foam: $[\alpha]_D$ = -6.48 (*c* 1.00, CH_2Cl_2); FTIR (CH_2Cl_2, cast) 3072, 3048, 2956, 2931, 2859, 1766, 1726, 1667, 1593, 1473, 1449, 1428 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.48-2.56 (m, 1 H), 2.68 (dd, 0.7 H, *J* = 18.0, 9.7 Hz), 2.77-2.84 (m, 0.3 H), 2.99 (s, 0.2 H), 3.07 (s, 0.7 H), 3.16 (s, 0.6 H), 3.21 (s, 1.3 H), 3.57-3.62 (m, 1.2 H), 3.74-4.01 (m, 2.8 H), 4.14-4.38 (m, 2.1 H), 4.52-4.54 (m, 0.2 H), 4.76-4.80 (m, 0.7 H), 7.00-7.09 (m, 1 H), 7.13-7.22 (m, 2 H), 7.29-7.46 (m, 8 H), 7.50-7.63 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.07, 19.12, 26.69, 26.72, 26.8, 36.2, 36.4, 36.5, 36.6, 39.5, 41.0, 41.1, 50.1, 50.2, 51.6, 51.7, 52.8, 53.1, 53.3, 55.2, 55.3, 55.8, 56.1, 65.7, 65.8, 66.6, 66.9, 121.67, 121.72, 121.78, 121.82, 125.38, 125.41, 125.43, 127.8, 127.987

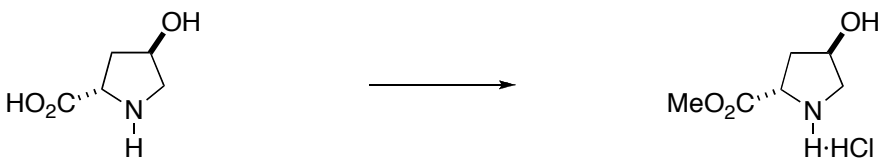
127.89, 128.03, 128.05, 129.2, 129.3, 129.9, 130.96, 130.03, 130.06, 130.13, 130.2, 130.3, 132.0, 132.1, 132.16, 132.17, 132.4, 132.5, 132.59, 132.64, 135.3, 135.4, 135.56, 135.61, 135.62, 151.27, 151.31, 151.33, 151.4, 154.8, 154.9, 155.39, 155.44, 166.4, 166.7, 167.3, 208.2, 208.4, 208.56, 208.62; exact mass (electrospray) *m*/*z* calcd for $C_{31}H_{37}N_2O_5Si$ (M+H), 545.2466, found 545.2466.

4-Methylbenzenesulfonothioic acid *S*-(methoxymethyl) ester.



MeOCH_2Cl (421.7 mg, 5.23 mmol) was added to a mixture of dry K_2CO_3 (ca 45 mg, 0.33 mmol) in CH_2Cl_2 (1 mL), and the mixture was swirled for 1 min. The resulting supernatant was taken up into a syringe, using dry CH_2Cl_2 (1 mL) as a rinse, and the total supernatant was added to a stirred suspension of TolSO_2Na (1.0 g, 4.76 mmol) in dry MeCN (8 mL). Stirring at room temperature was continued for 7 h, and the mixture was diluted with 1:1 Et_2O–hexane (50 mL) and filtered through a pad of Celite, using 1:1 Et_2O–hexane as a rinse. Evaporation of the filtrate gave 4-Methylbenzenesulfonothioic acid *S*-(methoxymethyl) ester (0.988 g, 90%) as a colorless oil: FTIR (CH_2Cl_2, cast) 3064, 2998, 2930, 2827, 1594, 1492, 1450, 1421 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.44 (s, 3 H), 3.19 (s, 3 H), 5.25 (s, 2 H), 7.28-7.36 (m, 2 H), 7.77–7.93 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.9 (q), 57.1 (q), 80.0 (t), 127.2 (d), 129.9 (d), 143.6 (s), 144.9 (s); exact mass (electrospray) *m*/*z* calcd for $C_9H_{12}NaO_3S_2$ 255.0120, found 255.0117.

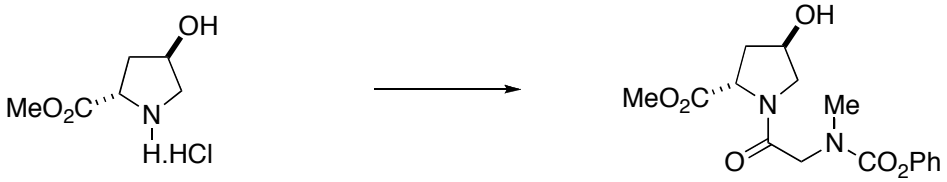
(4*R*)-*4*-Hydroxy-L-proline hydrochloride (33.1).



25.1 **33.1**

$SOCl_2$ (10.6 g, 89.1 mmol) was added dropwise to a stirred and cooled (0 °C) mixture of **25.1** (10.0 g, 76.3 mmol) in dry MeOH (76 mL). The cooling bath was removed and stirring was continued for 30 min. The mixture was then refluxed for 30 h, cooled to room temperature and evaporated to give **33.1** (13.89 g, 100%) as a white solid: mp 165-168 °C; $[\alpha]_D$ = -23.50 (*c* 1.00, MeOH); FTIR (MeOH, cast film) 3327 (br), 2200-3500 (br), 2956, 2884, 2706, 2604, 2569, 1745, 1635, 1593, 1443 cm^{-1}; ^1H NMR (CD_3OD, 500 MHz) δ 2.21 (ddd, *J* = 13.6, 10.8, 4.3 Hz, 1 H), 2.41 (ddt, *J* = 13.6, 7.6, 1.8 Hz, 1 H), 3.30-3.33 (m, 1 H), 3.46 (dd, *J* = 12.1, 3.6 Hz, 1 H), 3.85 (s, 3 H), 4.58-4.62 (m, 2 H); ^{13}C NMR (CD_3OD, 125 MHz) δ 38.5 (t), 54.0 (d), 55.0 (t), 59.4 (d), 70.6 (q), 170.6 (s); exact mass (electrospray) *m/z* calcd for $C_6H_{12}NO_3$ (M+H) 146.0812, found 146.0812.

Methyl (2*S*,4*R*)-4-hydroxy-1-{2-[methyl(phenoxycarbonyl)amino]-acetyl}pyrrolidine-2-carboxylate (33.2).

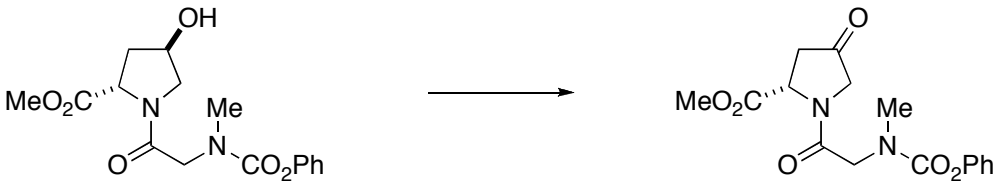


33.1 **33.2**

$(COCl)_2$ (13.98 g, 110.16 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **25.5** (19.2 g, 91.8 mmol) and DMF (0.54 g, 7.34 mmol) in dry CH_2Cl_2 (150 mL). The cooling bath was left in place but not recharged and stirring was continued for 5.5 h. A small aliquot of the mixture was evaporated and the ^1H NMR spectrum showed that the reaction was complete. The mixture was evaporated (protected from moisture) and the residue was dissolved in CH_2Cl_2 and evaporated again. The residue was dissolved in dry THF (25 mL) and added over 1 h to a stirred and cooled (0 °C) solution of **33.1** (13.89 g, 76.5 mmol) and $NaHCO_3$ (28.92 g, 344.25 mmol) in a mixture of dioxane (150 mL) and water (150 mL). The cooling bath was left in place but not recharged and stirring was continued for 21 h. Most of dioxane was evaporated, the residue was

diluted with water and the aqueous phase was extracted with CH_2Cl_2 (4 times). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (5.9 x 15 cm), using EtOAc and then 1:20 MeOH–EtOAc, gave **33.2** (24.88 g, 97%) as a foam: $[\alpha]_D$ = -14.72 (*c* 0.83, $CHCl_3$); FTIR ($CHCl_3$, cast) 3435 (br), 2952, 1727, 1653, 1595, 1456, 1437, 1398 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.02-2.08 (m, 0.78 H), 2.21-2.29 (m, 1 H), 2.36-2.42 (m, 0.22 H), 3.03 (s, 1.2 H), 3.17 (s, 1.4 H), 3.20 (s, 0.4 H), 3.56-4.22 (m, 7 H), 4.32-4.42 (m, 1 H), 4.54-4.58 (m, 1 H), 7.06-7.11 (m, 2 H), 7.15-7.18 (m, 1 H), 7.29-7.35 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 36.1 (q), 36.37 (q), 36.41 (q), 36.6 (t), 39.4 (t), 39.5 (t), 51.18 (t), 51.21 (t), 51.3 (t), 51.4 (t), 52.77 (q), 52.84 (q), 54.9 (t), 55.0 (t), 55.6 (t), 55.7 (t), 57.5 (d), 57.7 (d), 57.9 (d), 58.0 (d), 68.2 (d), 68.4 (d), 71.10 (d), 71.15 (d), 121.65 (d), 121.71 (d), 121.8 (d), 125.3 (d), 125.4 (d), 129.17 (d), 129.20 (d), 151.29 (s), 151.32 (s), 154.9 (s), 155.0 (s), 155.4 (s), 155.5 (s), 167.3 (s), 167.5 (s), 167.6 (s), 168.0 (s), 172.4 (s), 172.8 (s), 174.2 (s), 174.3 (s); exact mass (electrospray) *m/z* calcd for $C_{16}H_{20}N_2NaO_6$ 359.1214, 359.1211.

Methyl (2*S*)-1-{2-[methyl(phenoxycarbonyl)amino]acetyl}-4-oxo-pyrrolidine-2-carboxylate (33.3).

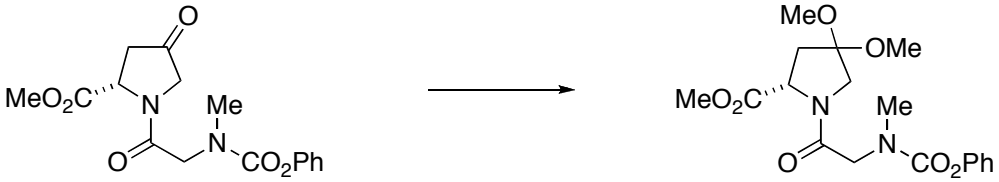


33.2 **33.3**

Molecular sieves (4Å, 33.9 g) and NaOAc (7.8 g, 94.8 mmol) were added to a stirred solution of **33.2** (22. 8 g, 67.8 mmol) in dry CH_2Cl_2 (220 mL). The mixture was stirred at room temperature for 5 min and then cooled to 0 °C. Pulverized PCC (36.5 g, 169.5 mmol) was added portionwise, stirring at 0 °C was continued for 15 min, the cooling bath was removed and stirring was continued for 30 min. Florisil (ca 30 g) was added and the mixture was filtered through a

column of Florisil (5 x 10 cm), using EtOAc and then 1:20 MeOH-EtOAc. Evaporation of the filtrate and flash chromatography of the residue over silica gel (5.9 x 15 cm), using 1:1 EtOAc–hexane, 2:1 EtOAc–hexane, 3:1 EtOAc–hexane and 5:1 EtOAc–hexane, gave **33.3** (19.4 g, 79 %) as a foam: $[\alpha]_D$ = -39.75 (*c* 1.40, $CHCl_3$); FTIR ($CHCl_3$, cast) 2956, 1767, 1726, 1673, 1594, 1477, 1455, 1435 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.51 (ddd, 0.8 H, *J* = 18.9, 9.0, 2.8 Hz), 2.64 (m, 0.2 H), 2.81-2.96 (m, 1 H), 2.99 (s, 1.1 H), 3.13-3.14 (m, 1.9 H), 3.65-4.31 (m, 7 H), 4.79-4.83 (m, 0.1 H), 4.96-4.99 (m, 0.9 H), 7.03-7.10 (m, 2 H), 7.14 (q, *J* = 7.3 Hz, 1 H), 7.28-7.32 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 35.9 (q), 36.0 (q), 36.2 (q), 39.4 (t), 41.1 (t), 41.2 (t), 50.3 (t), 50.5 (t), 51.3 (t), 51.5 (t), 51.6 (t), 51.7 (t), 52.6 (q), 53.0 (q), 55.3 (d), 55.4 (d), 55.9 (d), 56.1 (d), 121.5 (d), 121.6 (d), 125.25 (d), 125.30 (d), 129.1 (d), 151.1 (s), 151.2 (s), 154.6 (s), 155.2 (s), 167.4 (s), 167.59 (s), 167.64 (s), 170.4 (s), 170.7 (s), 171.3 (s), 171.4 (s), 206.2 (s), 206.4 (s), 206.6 (s); exact mass (electrospray) *m/z* calcd for $C_{16}H_{18}N_2NaO_6$ 357.1057, found 357.1059.

Methyl (2*S*)-4,4-dimethoxy-1-{2-[methyl(phenoxycarbonyl)amino]-acetyl}pyrrolidine-2-carboxylate (33.4).

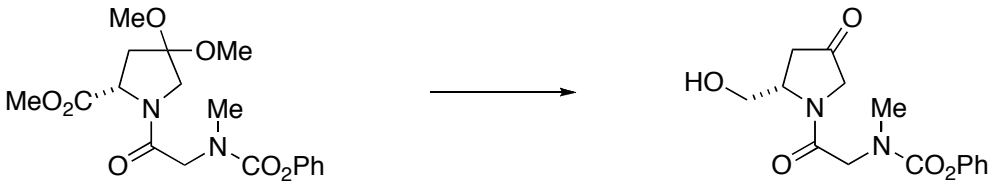


33.3 **33.4**

$TsOH \cdot H_2O$ (1.1 g, 5.8 mmol) was added to a stirred solution of **33.3** (19.38 g, 57.97 mmol) and $(MeO)_3CH$ (30.76 g, 289.85 mmol) in CH_2Cl_2 (32 mL) and anhydrous MeOH (160 mL). The mixture was refluxed for 24 h, cooled to room temperature and evaporated. The residue was diluted with saturated aqueous $NaHCO_3$ and extracted with EtOAc (3 times). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. The resulting **33.4** (21.37 g, 97%), which was obtained as a foam, was used for the next step:

$[\alpha]_D$ = -42.76 (*c* 1.85, $CHCl_3$); FTIR ($CHCl_3$, cast) 3000, 2953, 2837, 1729, 1669, 1955, 1455, 1436, 1396 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.19-2.24 (m, 0.7 H), 2.30-2.40 (m, 1 H), 2.55-2.60 (m, 0.3 H), 3.17-3.26 (m, 9 H), 3.60-3.78 (m, 5 H), 3.92-3.97 (m, 0.6), 4.14-4.31 (m, 1.4 H), 4.46-4.48 (m, 0.1 H), 4.60-4.66 (m, 0.9 H), 7.08-7.13 (m, 2 H), 7.15-7.19 (m, 1 H), 7.31-7.36 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 35.69, 35.71, 35.9, 36.18, 36.22, 36.3, 37.8, 38.0, 49.0, 49.2, 49.7, 49.8, 49.9, 50.0, 50.4, 50.49, 50.51, 50.6, 51.0, 51.2, 51.8, 51.98, 52.05, 52.1, 52.3, 52.7, 57.3, 57.4, 57.5, 57.8, 105.3, 105.4, 107.07, 107.15, 121.59, 121.62, 121.67, 121.70, 125.2, 129.08, 129.12, 151.3, 154.7, 154.8, 155.3, 155.4, 166.8, 167.0, 167.5, 167.8, 171.0, 171.16, 171.23, 171.3; exact mass (electrospray) *m/z* calcd for $C_{18}H_{24}N_2NaO_7$ 403.1476, found 403.1476.

Phenyl *N*-{2-[(2*S*)-2-(hydroxymethyl)-4-oxopyrrolidin-1-yl]-2-oxo-ethyl}-*N*-methylcarbamate (33.5).

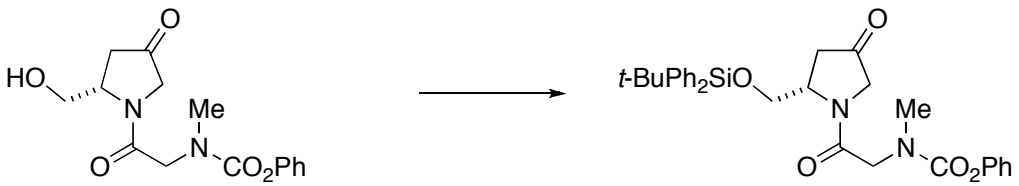


33.4 **33.5**

$CaCl_2$ (6.86 g, 61.8 mmol) was added to a stirred and cooled (0 °C) solution of **33.4** (21.37 g, 56.2 mmol) in a mixture of absolute EtOH (70 mL) and dry THF (70 mL). Stirring at 0 °C was continued for ca 15 min (most of the $CaCl_2$ dissolved) and $NaBH_4$ (4.68 g, 123.64 mmol) was added in portions over ca 1 min. Stirring at 0 °C was continued for 10 h (the reaction was monitored by TLC until the composition seemed constant) and the mixture was carefully quenched and acidified to pH 1 with hydrochloric acid (2 M, ca 130 mL). Stirring was continued overnight and the mixture was extracted with CH_2Cl_2 (3-4 times, the progress of extraction being monitored by TLC). The combined organic extracts were washed with brine and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (5.4 x 15 cm), using

EtOAc and then 1:20 MeOH–EtOAc, gave **33.5** (11.18 g, 65%) as a foam: $[\alpha]_D$ = 7.94 (*c* 1.11, MeOH); FTIR (CH_2Cl_2, cast) 3430, 2937, 1763, 1722, 1656, 1594, 1456, 1400 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.33-2.51 (m, 1 H), 2.62-2.81 (m, 1 H), 3.04-3.24 (m, 3 H), 3.50-4.18 (m, 5.8 H), 4.30-4.37 (m, 0.28 H), 4.42-4.47 (m, 0.17 H), 4.67-4.77 (m, 0.73 H), 7.07-7.13 (m, 2 H), 7.17-7.22 (m, 1 H), 7.32-7.38 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 36.6, 36.8, 39.3, 39.4, 40.8, 50.6, 51.8, 52.2, 52.8, 53.1, 55.9, 56.1, 56.4, 64.2, 64.6, 65.1, 121.7, 121.8, 125.5, 125.6, 129.31, 129.32, 151.26, 151.29, 155.0, 155.8, 167.48, 167.51, 167.8, 208.5, 208.6, 208.7; exact mass (electrospray) *m/z* calcd for $C_{15}H_{18}N_2NaO_5$ 329.1108, found 329.1109.

Phenyl *N*-{2-[(2*S*)-2-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-4-oxo-pyrrolidin-1-yl]-2-oxoethyl}-*N*-methylcarbamate (33.6).

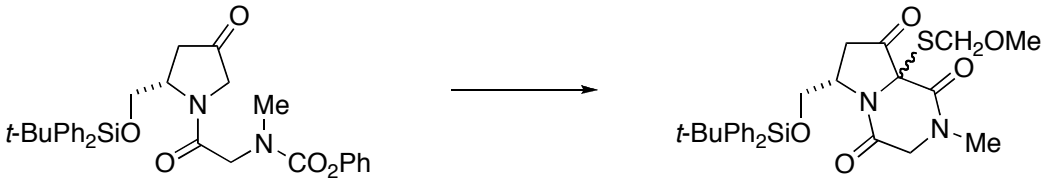


33.5 **33.6**

t-$BuPh_2SiCl$ (564.0 mg, 2.05 mmol) was added to a stirred solution of **33.5** (523.8 mg, 2.05 mmol), imidazole (174.6 mg, 65.8 mmol) and DMAP (20.9 mg, 0.17 mmol) in dry CH_2Cl_2 (6 mL) and stirring at room temperature was continued for 25 h. The mixture was washed with aqueous $NaHSO_4$ (1 M, 20 mL) and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were washed with brine and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (1.8 x 15 cm), using 1:2 EtOAc–hexane and then 4:5 EtOAc–hexane, gave **33.6** (696 mg, 75%) as a foam: $[\alpha]_D$ = 10.51 (*c* 1.13, CH_2Cl_2); FTIR (CH_2Cl_2, cast) 3072, 3048, 2956, 2931, 2859, 1766, 1726, 1667, 1593, 1473, 1449, 1428 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.48-2.56 (m, 1 H), 2.68 (dd, 0.7

H, *J* = 18.0, 9.7 Hz), 2.77-2.84 (m, 0.3 H), 2.99 (s, 0.2 H), 3.07 (s, 0.7 H), 3.16 (s, 0.6 H), 3.21 (s, 1.3 H), 3.57-3.62 (m, 1.2 H), 3.74-4.01 (m, 2.8 H), 4.14-4.38 (m, 2.1 H), 4.52-4.54 (m, 0.2 H), 4.76-4.80 (m, 0.7 H), 7.00-7.09 (m, 1 H), 7.13-7.22 (m, 2 H), 7.29-7.46 (m, 8 H), 7.50-7.63 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.07, 19.12, 26.69, 26.72, 26.8, 36.2, 36.4, 36.5, 36.6, 39.5, 41.0, 41.1, 50.1, 50.2, 51.6, 51.7, 52.8, 53.1, 53.3, 55.2, 55.3, 55.8, 56.1, 65.7, 65.8, 66.6, 66.9, 121.67, 121.72, 121.78, 121.82, 125.38, 125.41, 125.43, 127.8, 127.987 127.89, 128.03, 128.05, 129.2, 129.3, 129.9, 130.96, 130.03, 130.06, 130.13, 130.2, 130.3, 132.0, 132.1, 132.16, 132.17, 132.4, 132.5, 132.59, 132.64, 135.3, 135.4, 135.56, 135.61, 135.62, 151.27, 151.31, 151.33, 151.4, 154.8, 154.9, 155.39, 155.44, 166.4, 166.7, 167.3, 208.2, 208.4, 208.56, 208.62; exact mass (electrospray) *m/z* calcd for $C_{31}H_{36}N_2NaO_5Si$, 567.2286, found 567.2294.

(6*S*)-6-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-8a-[(methoxymethyl)-sulfanyl]-2-methyloctahydropyrrolo[1,2-*a*]piperazine-1,4,8-trione (33.7a,b).



33.6 **33.7a,b**

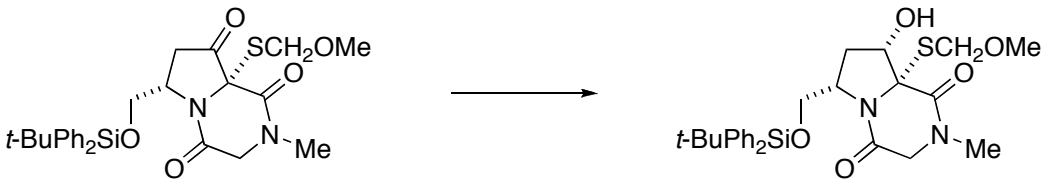
NaH (792.0 mg, 19.8 mmol) was added to a stirred solution of **33.6** (4.9 g, 9.0 mmol) in THF (90 mL). The mixture was refluxed for 1 h, cooled to 0 °C and quenched with pH 7.0 buffer (0.2 M, 90 mL) and aqueous HCl (1 M, 20 mL). The mixture was extracted with EtOAc (4 times), and the combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. The residue was dissolved in dry CH_2Cl_2 (45 mL) and a solution of $TolSO_2SCH_2OMe$ (1.67 g, 7.2 mmol) in CH_2Cl_2 (5 mL) was added in one portion, followed by Et_3N (1.09 g, 10.8 mmol) which was added at a fast dropwise rate. The mixture was swirled occasionally for 10 min and filtered through a pad silica gel (3 x 7 cm), using EtOAc. Evaporation of the filtrate and flash chromatography of the residue over

silica gel (3.8 x 15 cm), using 4:5 EtOAc–hexane, 6:5 EtOAc–hexane, 3:2 EtOAc–hexane, 2:1 EtOAc–hexane and 5:2 EtOAc–hexane, gave **33.7a** (1.11 g, 24%) as a foam and **33.7b** (1.30 g, 27%) as a foam.

33.7a: $[\alpha]_D$ = -11.71 (*c* 1.40, $CHCl_3$); FTIR ($CHCl_3$, cast) 3072, 3047, 2932, 2889, 2859, 1779, 1767, 1689, 1589, 1472, 1449, 1406 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.97 (s, 9 H), 2.64 (dd, *J* = 18.1, 3.3 Hz, 1 H), 2.98 (s, 3 H), 3.21 (dd, *J* = 18.1, 9.5 Hz, 1 H), 3.31 (s, 3 H), 3.53-3.57 (m, 1 H), 3.78 (d, *J* = 17.1 Hz, 1 H), 4.31-4.36 (m, 2 H), 4.40 (d, *J* = 17.1 Hz, 1 H), 4.73 (d, *J* = 12.0 Hz, 1 H), 5.08 (d, *J* = 12.0 Hz, 1 H), 7.35-7.45 (m, 6 H), 7.51-7.54 (m, 2 H), 7.54-7.58 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.1 (s), 26.6 (q), 33.9 (q), 36.6 (t), 53.2 (q), 53.4 (t), 57.0 (d), 62.1 (t), 63.1 (s), 74.1 (t), 127.7 (d), 127.8 (d), 129.9 (d), 130.0 (d), 132.6 (s), 135.5 (d), 135.6 (d), 161.1 (s), 165.7 (s), 196.7 (s); exact mass (electrospray) *m/z* calcd for $C_{27}H_{34}N_2NaO_5SSi$ 549.1850, found 549.1844.

33.7b: $[\alpha]_D$ = -3.63 (*c* 1.50, $CHCl_3$); FTIR ($CHCl_3$, cast) 3071, 3013, 2957, 2931, 2891, 2858, 1776, 1687, 1589, 1463, 1468, 1427, 1400 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.07 (s, 9 H), 2.73-2.81 (m, 1 H), 2.92 (dd, *J* = 19.1, 2.8 Hz, 1 H), 2.98 (s, 3 H), 3.26 (s, 3 H), 3.74-3.80 (m, 2 H), 3.98 (dd, *J* = 10.0, 4.7 Hz, 1 H), 4.40 (d, *J* = 16.6 Hz, 1 H), 4.56-4.62 (m, 1 H), 4.74 (d, *J* = 12.2 Hz, 1 H), 5.08 (d, *J* = 12.2 Hz, 1 H), 7.35-7.45 (m, 6 H), 7.61-7.68 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.3 (s), 26.9 (q), 34.4 (q), 37.5 (t), 52.8 (t), 52.9 (q), 56.8 (d), 63.7 (s), 63.8 (t), 74.2 (t), 127.8 (d), 127.9 (d), 129.9 (d), 130.0 (d), 132.88 (s), 132.91 (s), 135.62 (d), 135.63 (d), 161.1 (s), 164.7 (s), 199.6 (s); exact mass (electrospray) *m/z* calcd for $C_{27}H_{34}N_2NaO_5SSi$ 549.1850, found 549.1845.

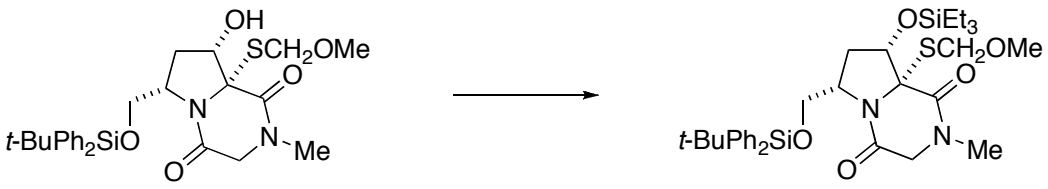
(6*S*,8*S*,8a*R*)-6-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-8-hydroxy-8a-[(methoxymethyl)sulfanyl]-2-methyloctahydropyrrolo[1,2-*a*]piperazine-1,4-dione (34.1).



33.7b **34.1**

$NaBH_4$ (35.9 mg, 0.95 mmol) was added to a stirred and cooled (0 °C) solution of **33.7b** (500.0 mg, 0.95 mmol) in a mixture of THF (6.5 mL) and water (0.8 mL). Stirring at 0 °C was continued for 20 min and the mixture was quenched with saturated aqueous NH_4Cl, diluted with water and extracted with EtOAc (3 times). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 15 cm), using 3:1 EtOAc–hexane and then 5:1 EtOAc–hexane, gave **34.1** (366 mg, 73%) as a foam: $[\alpha]_D$ = -114.01 (*c* 4.21, CH_2Cl_2); FTIR (CH_2Cl_2, cast) 3453 (br), 3071, 3050, 2932, 2888, 2858, 1672, 1589, 1472, 1462, 1428 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.07 (s, 9 H), 2.22-2.29 (m, 1 H), 2.51 (dt, *J* = 12.8, 7.4 Hz, 1 H), 2.92 (s, 3 H), 3.24 (s, 3 H), 3.61 (d, *J* = 1.7 Hz, 1 H), 3.65 (d, *J* = 16.8 Hz, 1 H), 3.75-3.78 (m, 1 H), 4.16-4.23 (m, 2 H), 4.30 (d, *J* = 16.8 Hz, 1 H), 4.35-4.41 (m, 2 H), 4.73 (d, *J* = 12.5 Hz, 1 H), 7.36-7.44 (m, 6 H), 7.64-7.68 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.3 (s), 26.9 (q), 31.9 (t), 33.6 (q), 52.9 (t), 56.0 (q), 56.1 (d), 64.6 (t), 72.2 (t), 73.2 (s), 75.8 (d), 127.7 (d), 127.8 (d), 129.7 (d), 129.8 (d), 133.27 (s), 133.31 (s), 135.60 (d), 135.64 (d), 164.0 (s), 167.2 (s); exact mass (electrospray) *m/z* calcd for $C_{27}H_{36}N_2NaO_5SSi$ 551.2006, found 551.2006.

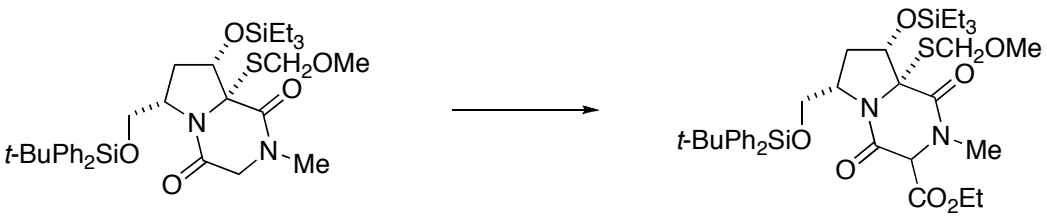
(6*S*,8*S*,8a*R*)-6-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-8a-[(methoxymethyl)sulfanyl]-2-methyl-8-[(triethylsilyl)oxy]octahydropyrrolo[1,2-*a*]piperazine-1,4-dione (34.2).



34.1 **34.2**

$Et_3SiOSO_2CF_3$ (202.0 mg, 0.76 mmol) was added to a stirred and cooled (-78 °C) solution of **34.1** (336.0 mg, 0.64 mmol) and 2,6-lutidine (157.7 mg, 1.47 mmol) in CH_2Cl_2 (4 mL). Stirring at -78 °C was continued for 30 min and the mixture was quenched with water (5 mL). The cooling bath was removed and the mixture was allowed to warm to room temperature (ca 5 min). Aqueous $NaHSO_4$ (1 M, 1 mL) and saturated aqueous $CuSO_4$ (10 mL) were added and the mixture was extracted twice with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 15 cm), using 2:5 EtOAc–hexane and then 3:5 EtOAc–hexane, gave **34.2** (328.0 mg, 80%) as a foam: $[\alpha]_D$ = -33.42 (*c* 2.07, CH_2Cl_2); FTIR (CH_2Cl_2, cast) 3071, 2954, 2934, 2877, 2859, 1679, 1488, 1463, 1448, 1427, 1419, 1400 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.64-0.76 (m, 6 H), 1.02 (t, *J* = 7.9 Hz, 9 H), 1.08 (s, 9 H), 2.19 (dt, *J* = 12.8, 9.6 Hz, 1 H), 2.35 (dt, *J* = 12.9, 7.6 Hz, 1 H), 2.92 (s, 3 H), 3.22 (s, 3 H), 3.62 (d, *J* = 16.4 Hz, 1 H), 3.77 (t, *J* = 8.6 Hz, 1 H), 4.04 (qd, *J* = 8.2, 3.9 Hz, 1 H), 4.16 (dd, *J* = 9.4, 4.0 Hz, 1 H), 4.37 (d, *J* = 16.5 Hz, 1 H), 4.50-4.56 (m, 2 H), 4.81 (d, *J* = 12.3 Hz, 1 H), 7.36-7.43 (m, 6 H), 7.65-7.68 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 5.0, 6.9, 19.4, 26.9, 34.0, 34.6, 53.1, 55.9, 56.1, 64.5, 72.6, 73.1, 75.3, 127.70, 127.71, 129.72, 129.74, 133.47, 133.51, 135.6, 135.7, 164.7, 165.8; exact mass (electrospray) *m/z* calcd for $C_{33}H_{50}N_2NaO_5SSi_2$ 665.2871, found 665.2866.

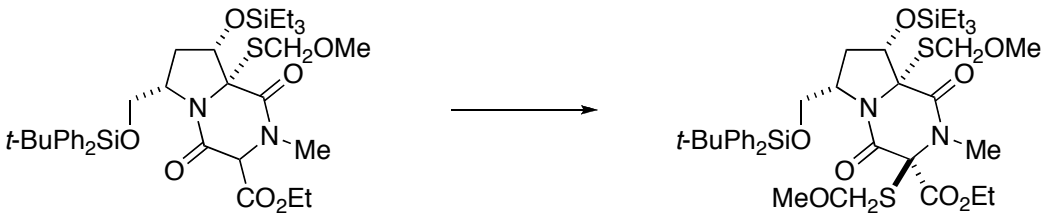
Ethyl (6*S*,8*S*,8a*R*)-6-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-8a-[(methoxymethyl)sulfanyl]-2-methyl-1,4-dioxo-8-[(triethylsilyl)oxy]octahydropyrrolo[1,2-*a*]piperazine-3-carboxylate (34.3).



34.2 **34.3**

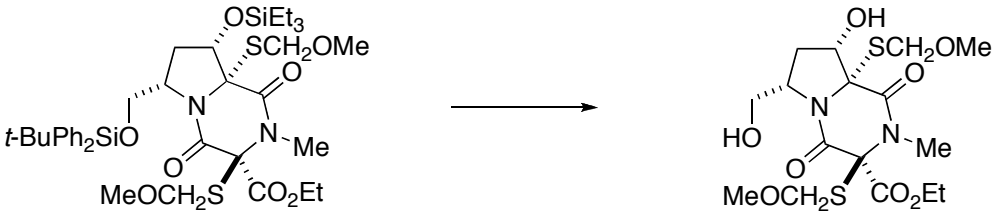
EtOCOCl (83.0 mg, 0.77) was added dropwise to a stirred and cooled (-78 °C) solution of **34.2** (328.0 mg, 0.51 mmol) in THF (9 mL), followed by $(Me_3Si)_2NK$ (1.0 M in THF, 1.2 mL, 1.2 mmol), which was added at a fast dropwise rate. Stirring at -78 °C was continued for 15 min and the mixture was quenched with saturated aqueous NH_4Cl. The cooling bath was removed and the mixture was allowed to warm to room temperature (ca 5 min). The mixture was diluted with water and extracted with EtOAc (3 times). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 15 cm), using 1:5 EtOAc–hexane and 2:5 EtOAc–hexane, gave **34.3** (265 mg, 73%) as a foam: $[\alpha]_D = 5.36$ (*c* 2.23, CH_2Cl_2); FTIR (CH_2Cl_2, cast) 3072, 3050, 2955, 2935, 2877, 2859, 1749, 1682, 1590, 1463, 1447, 1428, 1416 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.67-0.72 (m, 6 H), 1.02 (t, *J* = 7.9 Hz, 9 H), 1.08 (s, 9 H), 1.19 (t, *J* = 7.1 Hz, 3 H), 2.19-2.31 (m, 2 H), 3.15 (s, 3 H), 3.24 (s, 3 H), 3.74 (dd, *J* = 9.4, 7.8 Hz, 1 H), 3.94-4.00 (m, 1 H), 4.12-4.19 (m, 2 H), 4.26 (dq, *J* = 10.7, 7.1 Hz, 1 H), 4.41 (s, 1 H), 4.47 (dd, *J* = 10.4, 7.3 Hz, 1 H), 4.67 (d, *J* = 11.4 Hz, 1 H), 5.18 (d, *J* = 11.4 Hz, 1 H), 7.36-7.44 (m, 6 H), 7.65-7.68 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 4.9, 6.8, 13.8, 19.4, 26.9, 33.8, 35.0, 55.7, 56.7, 62.5, 64.1, 66.4, 70.4, 74.6, 75.4, 127.69, 127.72, 129.71, 129.74, 133.4, 133.5, 135.6, 135.7, 161.2, 165.4, 165.9; exact mass (electrospray) *m/z* calcd for $C_{36}H_{54}N_2NaO_7SSi_2$ 737.3082, found 737.3072.

Ethyl (3*R*,6*S*,8*S*,8a*R*)-6-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-3,8a-bis[(methoxymethyl)sulfanyl]-2-methyl-1,4-dioxo-8-[(triethylsilyl)oxy]octahydropyrrolo[1,2-*a*]piperazine-3-carboxylate (34.4).



DBU (42.5 mg, 0.28 mmol) was added to a stirred solution of **34.3** (133.0 mg, 0.19 mmol) and $TolSO_2SCH_2OMe$ (51.0 mg, 0.22 mmol) in CH_2Cl_2 (2 mL). The mixture was occasionally stirred at room temperature for 1 h. Evaporation and flash chromatography of the residue over silica gel (0.8 x 15 cm), using 1:10 EtOAc–hexane, 1:5 EtOAc–hexane and 3:10 EtOAc–hexane, gave **34.4** (124.9 mg, 85%) as a foam: $[\alpha]_D$ = 10.00 (*c* 1.59, $CHCl_3$); FTIR ($CHCl_3$, cast) 3072, 3050, 2954, 2933, 2877, 2858, 1750, 1680, 1590, 1463, 1447, 1428, 1410 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.63-0.74 (m, 6 H), 1.01 (t, *J* = 7.9 Hz, 9 H), 1.06 (s, 9 H), 1.25 (t, *J* = 7.1 Hz, 3 H), 2.09 (ddd, *J* = 12.8, 9.2, 8.7 Hz, 1 H), 2.39-2.46 (m, 1 H), 2.96 (s, 3 H), 3.11 (s, 3 H), 3.27 (s, 3 H), 3.75 (t, *J* = 9.3 Hz, 1 H), 4.08 (qd, *J* = 8.9, 4.8 Hz, 1 H), 4.22-4.33 (m, 3 H), 4.37 (d, *J* = 12.8 Hz, 1 H), 4.54 (dd, *J* = 9.4, 8.0 Hz, 1 H), 4.63 (d, *J* = 12.8 Hz, 1 H), 4.84 (q, *J* = 12.0 Hz, 2 H), 7.35-7.42 (m, 6 H), 7.65-7.68 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 4.9 (t), 6.8 (q), 13.8 (q), 19.4 (s), 26.9 (q), 32.3 (q), 35.2 (t), 56.0 (q), 56.6 (q), 57.7 (d), 64.0 (t), 65.9 (t), 72.5 (t), 73.2 (t), 73.3 (s), 75.2 (d), 78.7 (s), 127.69 (d), 127.73 (d), 129.6 (d), 129.7 (d), 133.6 (s), 133.7 (s), 135.6 (d), 135.7 (d), 161.5 (s), 165.1 (s), 165.9 (s); exact mass (electrospray) *m/z* calcd for $C_{38}H_{58}N_2NaO_8S_2Si_2$ 813.3065, found 813.3054.

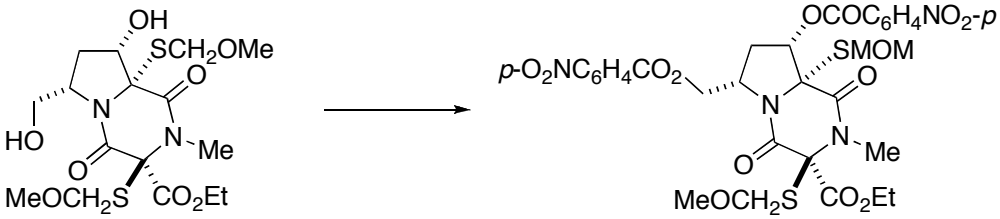
Ethyl (3*R*,6*S*,8*S*,8a*R*)-6-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-8-hydroxy-3,8a-bis[(methoxymethyl)sulfanyl]-2-methyl-1,4-dioxooctahydro-pyrrolo[1,2-*a*]piperazine-3-carboxylate (35.1).



34.4 **35.1**

HF·pyr/pyr/THF stock solution (1:2:5, HF·pyr/pyr/THF, 0.3 mL) was added to **34.4** (27.6 mg, 0.035 mmol) in a sample vial. The mixture was kept at room temperature for 19 h and quenched with Me_3SiOMe (0.1 mL). Evaporation of the solvent and flash chromatography of the residue over silica gel (0.5 x 7 cm), using 1:1 EtOAc–hexane and then 5:1 EtOAc–hexane, gave **35.1** (10.7 mg, 70%) as a foam: $[\alpha]_D$ = -27.69 (*c* 0.93, CH_2Cl_2); FTIR (CH_2Cl_2, cast) 3444 (br), 2984, 2931, 2824, 1748, 1664, 1446, 1420 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.35 (t, *J* = 7.1 Hz, 3 H), 1.89 (dt, *J* = 12.4, 10.1 Hz, 1 H), 2.44 (dt, *J* = 12.7, 7.8 Hz, 1 H), 3.02 (s, 3 H), 3.30 (s, 3 H), 3.33 (s, 3 H), 3.48 (d, *J* = 2.8 Hz, 1 H), 3.74 (ddd, *J* = 11.6, 8.2, 2.7 Hz, 1 H), 3.90 (ddd, *J* = 11.6, 8.6, 2.8 Hz, 1 H), 4.06 (qd, *J* = 8.9, 2.4 Hz, 1 H), 4.30 (dd, *J* = 8.2, 2.7 Hz, 1 H), 4.34 (d, *J* = 13.0 Hz, 1 H), 4.37 (q, *J* = 7.1 Hz, 2 H), 4.44 (ddd, *J* = 10.4, 7.6, 2.8 Hz, 1 H), 4.66 (d, *J* = 12.9 Hz, 1 H), 4.74 (d, *J* = 12.4 Hz, 1 H), 5.17 (d, *J* = 12.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.8 (q), 31.0 (t), 32.0 (q), 56.5 (q), 56.9 (q), 61.8 (d), 64.5 (t), 66.6 (t), 72.0 (t), 73.1 (t), 73.2 (s), 74.4 (d), 78.4 (s), 163.8 (s), 164.4 (s), 166.9 (s); exact mass (electrospray) *m/z* calcd for $C_{16}H_{26}N_2NaO_8S_2$ 461.1023, found 461.1017.

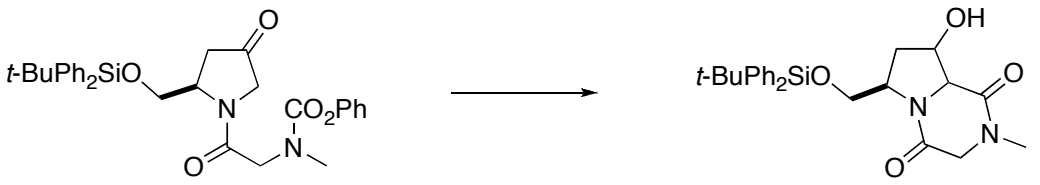
Ethyl (3*R*,6*S*,8*S*,8a*R*)-3,8a-Bis[(methoxymethyl)sulfanyl]-2-methyl-8-[(4-nitrophenyl)carbonyloxy]-6-{[(4-nitrophenyl)carbonyloxy]methyl}-1,4-dioxooctahydropyrrolo[1,2-*a*]piperazine-3-carboxylate (35.2).



35.1 **35.2**

p-$NO_2C_6H_4COCl$ (31.5 mg, 0.17 mmol) was added to a stirred solution of **35.1** (9.3 mg, 0.021 mmol), Et_3N (21.2 mg, 0.21 mmol) and DMAP (0.24 mg, 0.002 mmol) in CH_2Cl_2 (1 mL). Stirring at room temperature was continued for 15 min and the mixture was quenched with water (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 8 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (0.5 x 7 cm), using 3:10 EtOAc–hexane, 2:5 EtOAc–hexane, 1:2 EtOAc–hexane and 4:5 EtOAc–hexane, gave **35.2** (14.1 mg, 91%) as a foam: $[\alpha]_D$ = 54.19 (*c* 0.88, CH_2Cl_2); FTIR (CH_2Cl_2, cast) 3111, 3080, 2988, 2930, 1733, 1681, 1608, 1529, 1490, 1448, 1409 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.29 (t, *J* = 7.1 Hz, 3 H), 2.19 (ddd, *J* = 12.9, 9.6, 7.8 Hz, 1 H), 2.85 (dt, *J* = 12.9, 8.5 Hz, 1 H), 2.94 (s, 3 H), 3.33 (s, 3 H), 3.36 (s, 3 H), 4.26-4.36 (m, 2 H), 4.39 (d, *J* = 12.9 Hz, 1 H), 4.59-4.68 (m, 2 H), 4.74 (d, *J* = 13.0 Hz, 1 H), 4.83 (d, *J* = 12.9 Hz, 1 H), 4.87 (dd, *J* = 10.8, 7.4 Hz, 1 H), 5.36 (d, *J* = 12.6 Hz, 1 H), 5.97 (t, *J* = 9.0 Hz, 1 H), 8.20-8.23 (m, 2 H), 8.26-8.29 (m, 2 H), 8.31-8.35 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.8 (q), 30.4 (t), 32.2 (q), 55.7 (d), 56.8 (q), 56.9 (q), 64.5 (t), 67.0 (t), 72.0 (t), 72.5 (s), 73.0 (t), 74.3 (d), 78.7 (s), 123.5 (d), 123.7 (d), 131.0 (d), 131.3 (d), 134.9 (s), 135.3 (s), 150.7 (s), 150.9 (s), 162.4 (s), 163.6 (s), 164.5 (s), 164.6 (s), 165.1 (s); exact mass (electrospray) *m/z* calcd for $C_{30}H_{32}N_4NaO_{14}S_2$ 759.1249, found 759.1239.

(6*R*)-6-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-8-hydroxy-2-methyl-octahydropyrrolo[1,2-*a*]piperazine-1,4-dione (36.1).

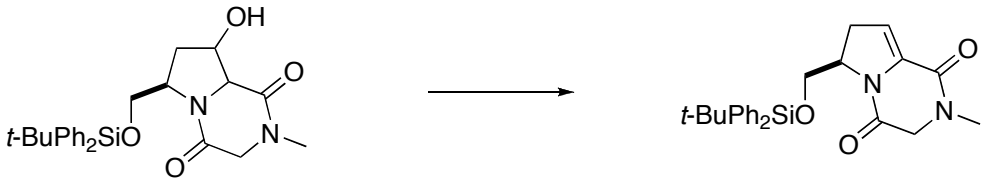


25.8 **36.1**

NaH (60% in mineral oil, 467.8 mg, 11.7 mmol) was added to a solution of **25.8** (2.90 g, 5.3 mmol) in dry THF (50 mL). The flask was lowed into a preheated oil bath (70 °C) and the mixture was heated for 25 min (i.e. 5 more min after vigorous bubbling ceased and the solution became clear, although some particles of NaH were still present). The mixture was cooled to 0 °C and poured into a stirred and cooled (0 °C) aqueous pH buffer (0.2 M, 100 mL), using dry THF (10 mL) as a rinse, followed by immediate addition of aqueous HCl (1 M, 11.7 mL to the mixture. While maintaining the temperature at 0 °C, $NaBH_4$ (301.9 mg, 8.0 mmol) was added portionwise (over ca 1 min, bubbling!). Stirring at 0 °C was continued for 20 min, and the mixture was diluted with water and extracted with CH_2Cl_2 (4 times). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (30 x 15 cm), using 2:1 EtOAc–hexane, EtOAc and then 1:50 MeOH–EtOAc, gave **36.1** (1.40 g, 58 %) as a foam: $[\alpha]_D$ = 83.44 (*c* 0.55, CH_2Cl_2); FTIR (CH_2Cl_2, cast) 3442 (br), 3071, 3049, 3013, 2955, 2931, 2858, 1663, 1459, 1428, 1399 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.08 (s, 9 H), 2.26 (ddd, *J* = 12.6, 9.7, 8.3 Hz, 1 H), 2.38 (dt, *J* = 12.6, 7.9 Hz, 1 H), 2.96 (s, 3 H), 3.60 (s, 1 H), 3.68 (d, *J* = 16.8 Hz, 1 H), 3.72 (dd, *J* = 10.5, 2.1 Hz, 1 H), 3.87 (d, *J* = 8.4 Hz, 1 H), 3.95 (dd, *J* = 16.7, 2.0 Hz, 1 H), 4.14-4.23 (m, 3 H), 7.36-7.44 (m, 6 H), 7.62 (dd, *J* = 7.9, 1.4 Hz, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.3 (s), 27.0 (q), 31.7 (t), 33.0 (q), 53.0 (t), 55.8 (d), 62.9 (d), 63.3 (t), 72.9 (d), 127.7 (d), 127.8 (d), 129.8 (d), 129.9 (d), 133.0 (s), 133.2 (s), 135.56 (d), 135.60 (d), 161.6

(s), 167.1 (s); exact mass (electrospray) *m*/*z* calcd for $C_{25}H_{32}N_2NaO_4Si$ 475.2024, found 475.2022.

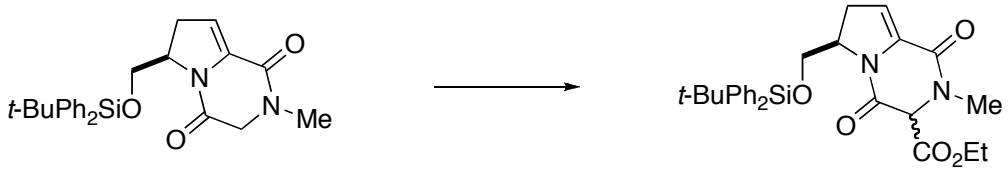
(6*R*)-6-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-2-methyl-1,2,3,4,6,7-hexahydropyrrolo[1,2-*a*]piperazine-1,4-dione (36.2).



36.1 **36.2**

Et_3N (2.27 g, 22.4 mmol) and MsCl (1.25 g, 10.9 mmol) were added to a stirred solution of **36.1** (2.89 g, 6.40 mmol) and Bu_4NI (236.4 mg, 0.64 mmol) in DMF (12 mL). The mixture was heated at 70 °C for 19 h, cooled to room temperature, diluted with water and extracted with EtOAc (3 times). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3.8 x 15 cm), using 3:1 EtOAc–hexane and 5:1 EtOAc–hexane, gave **36.2** (1.61 g, 58%) as a foam: FTIR (CH_2Cl_2, cast) 3071, 3050, 2931, 2858, 1679, 1648, 1500, 1444, 1428, 1404 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.03 (s, 9 H), 2.87 (dt, *J* = 6.1, 3.0 Hz, 2 H), 2.95 (s, 3 H), 3.78 (d, *J* = 18.0 Hz, 1 H), 3.86 (dd, *J* = 10.5, 3.0 Hz, 1 H), 3.92 (d, *J* = 18.0 Hz, 1 H), 4.10 (dd, *J* = 10.5, 4.8 Hz, 1 H), 4.58-4.63 (m, 1 H), 6.11 (t, *J* = 3.0 Hz, 1 H), 7.33-7.44 (m, 6 H), 7.58-7.62 (m, 4 H); ^{13}C NMR ($CDCl_3$, 500 MHz) δ 19.3 (s), 26.8 (q), 31.5 (t), 32.8 (q), 53.3 (t), 59.7 (d), 63.0 (t), 118.0 (d), 127.6 (d), 127.7 (d), 129.7 (d), 129.8 (d), 133.1 (s), 133.2 (s), 133.4 (s), 135.5 (d), 135.6 (d), 155.9 (s), 159.3 (s); exact mass (electrospray) *m*/*z* calcd for $C_{25}H_{30}N_2NaO_3Si$ 457.1918, found 457.1919.

Ethyl (6*R*)-6-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-2-methyl-1,4-dioxo-1,2,3,4,6,7-hexahydropyrrolo[1,2-*a*]piperazine-3-carboxylate (36.3a,b).



36.2 **36.3a,b**

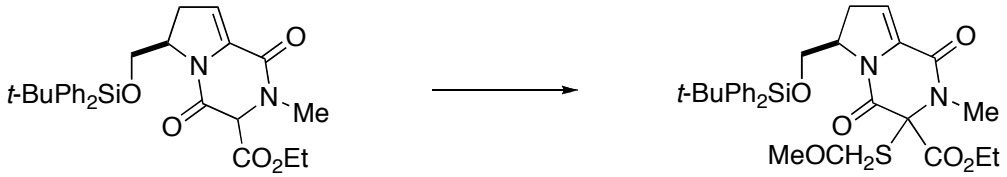
$ClCO_2Et$ (13.0 mg, 0.12 mmol) was added to a stirred and cooled (-78 °C) solution of **36.2** (48.5 mg, 0.11 mmol) in THF (0.7 mL), followed by $(Me_3Si)_2NK$ (0.5 M in THF, 0.45 mL, 0.22 mmol), which was added at a fast dropwise rate. Stirring at -78 °C was continued for 30 min and the mixture was quenched with saturated aqueous $NaHCO_3$. The cooling bath was removed and the mixture was allowed to warm to room temperature (ca 5 min). The mixture was extracted with EtOAc (3 times) and the combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (0.8 x 15 cm), using 3:10 EtOAc–hexane, 1:2 EtOAc–hexane, 4:5 EtOAc–hexane and 1:1 EtOAc–hexane, gave **36.3a** (22.0 mg, 40%) as a foam and **36.3b** (17.8 mg, 32%) as a foam.

36.3a: FTIR (CH_2Cl_2, cast) 3071, 2957, 2932, 2893, 2858, 1746, 1683, 1653, 1589, 1472, 1463, 1429, 1400 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.03 (s, 9 H), 1.29 (t, *J* = 7.1 Hz, 3 H), 2.82-2.95 (m, 5 H), 3.84 (dd, *J* = 10.5, 3.0 Hz, 1 H), 4.05 (dd, *J* = 10.5, 4.9 Hz, 1 H), 4.25 (q, *J* = 7.1 Hz, 2 H), 4.40 (s, 1 H), 4.58-4.63 (m, 1 H), 6.19 (t, *J* = 2.9 Hz, 1 H), 7.36 (q, *J* = 7.1 Hz, 4 H), 7.40-7.43 (m, 2 H), 7.57-7.61 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 4.1 (q), 19.3 (s), 26.8 (q), 31.6 (t), 32.3 (q), 60.1 (d), 63.00 (t), 63.03 (t), 67.5 (d), 119.4 (d), 127.71 (d), 127.73 (d), 129.76 (d), 129.81 (d), 132.5 (s), 133.21 (s), 133.25 (s), 135.5 (d), 135.6 (d), 156.2 (s), 156.8 (s), 166.2 (s); exact mass (electrospray) *m/z* calcd for $C_{28}H_{34}N_2NaO_5Si$ 529.2129, found 529.2124.

36.3b: FTIR (CH_2Cl_2, cast) 3072, 2958, 2932, 2893, 2858, 1748, 1682, 1652, 1589, 1472, 1463, 1429, 1401 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.03 (s,

9 H), 1.18 (t, *J* = 7.1 Hz, 3 H), 2.83 (dd, *J* = 7.8, 3.0 Hz, 2 H), 2.95 (s, 3 H), 3.81 (dd, *J* = 10.3, 3.0 Hz, 1 H), 4.09 (dd, *J* = 10.3, 5.4 Hz, 1 H), 4.12-4.26 (m, 2 H), 4.60-4.63 (m, 2 H), 4.60-4.63 (m, 2 H), 6.18 (t, *J* = 2.9 Hz, 1 H), 7.34-7.42 (m, 6 H), 7.57-7.62 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.0 (q), 19.3 (s), 26.8 (q), 31.8 (t), 32.2 (q), 60.6 (d), 62.1 (t), 62.9 (t), 67.9 (d), 119.2 (d), 127.77 (d), 127.82 (d), 129.8 (d), 129.9 (d), 132.6 (s), 133.13 (s), 133.14 (s), 135.5 (d), 135.6 (d), 156.0 (s), 156.3 (s), 165.9 (s); exact mass (electrospray) *m/z* calcd for $C_{28}H_{34}N_2NaO_5Si$ 529.2129, found 529.2133.

Ethyl (6*R*)-6-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-3-[(methoxymethyl)sulfanyl]-2-methyl-1,4-dioxo-1,2,3,4,6,7-hexahydropyrrolo[1,2-*a*]piperazine-3-carboxylate (36.4a,b).



36.3a **36.4a,b**

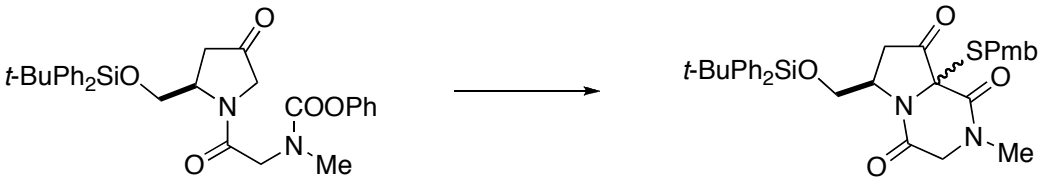
DBU (3.81 mg, 0.025 mmol) was added to a stirred solution of **36.3a** (11.5 mg, 0.023 mmol) and $TolSO_2SCH_2OMe$ (5.3 mg, 0.023 mmol) in dry CH_2Cl_2 (0.5 mL). Stirring at room temperature was continued for 10 min and the mixture was evaporated. Preparative TLC of the residue (silica gel, 0.25 mm, 5 x 7 cm), using 7:10 EtOAc–hexane, gave **36.4a** (4.6 mg, 35%) as an oil and **36.4b** (4.1 mg, 31%) as an oil.

36.4a: FTIR (CH_2Cl_2, cast) 3071, 2957, 2932, 2894, 2858, 1753, 1682, 1653, 1589, 1472, 1463, 1429 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.04 (s, 9 H), 1.28 (t, *J* = 7.1 Hz, 3 H), 2.85-2.88 (m, 2 H), 2.928 (s, 3 H), 2.932 (s, 3 H), 3.82 (dd, *J* = 10.1, 7.2 Hz, 1 H), 4.03 (dd, *J* = 10.1, 3.6 Hz, 1 H), 4.23-4.33 (m, 2 H), 4.37 (d, *J* = 12.7 Hz, 1 H), 4.58 (d, *J* = 12.7 Hz, 1 H), 4.68-4.73 (m, 1 H), 6.21 (t, *J* = 3.0 Hz, 1 H), 7.33-7.42 (m, 6 H), 7.57-7.62 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.0 (q), 19.4 (s), 27.0 (q), 30.3 (q), 31.9 (t), 56.3 (q), 60.8 (d), 62.0 (t),

64.0 (t), 73.1 (t), 80.1 (s), 119.9 (d), 127.86 (d), 127.91 (d), 129.88 (d), 129.94 (d), 131.8 (s), 133.0 (s), 133.3 (s), 135.5 (d), 135.6 (d), 155.9 (s), 158.0 (s), 165.2 (s).; exact mass (electrospray) *m/z* calcd for $C_{30}H_{38}N_2NaO_6SSi$ 605.2112, found 605.2106.

36.4b: FTIR (CH_2Cl_2, cast) 3071, 2956, 2931, 2857, 1752, 1682, 1654, 1589, 1472, 1437, 1429 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.04 (s, 9 H), 1.14 (t, *J* = 7.1 Hz, 3 H), 2.76-2.82 (m, 1 H), 2.86-2.93 (m, 1 H), 2.98 (s, 3 H), 3.28 (s, 3 H), 3.82 (dd, *J* = 10.3, 3.0 Hz, 1 H), 4.08 (dd, *J* = 10.3, 5.5 Hz, 1 H), 4.15 (dq, *J* = 10.7, 7.1 Hz, 1 H), 4.29 (dq, *J* = 10.7, 7.1 Hz, 1 H), 4.41 (d, *J* = 12.6 Hz, 1 H), 4.52-4.57 (m, 1 H), 4.64 (d, *J* = 12.6 Hz, 1 H), 6.22 (t, *J* = 3.0 Hz, 1 H), 7.34-7.44 (m, 6 H), 7.59-7.63 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.9 (q), 19.4 (s), 26.8 (q), 30.1 (q), 32.0 (t), 56.5 (q), 61.1 (d), 63.1 (t), 63.9 (t), 72.6 (t), 79.8 (s), 119.7 (d), 127.77 (d), 127.83 (d), 129.8 (d), 129.9 (d), 132.0 (s), 133.23 (s), 133.24 (s), 135.6 (d), 156.5 (s), 158.3 (s), 165.1 (s); exact mass (electrospray) *m/z* calcd for $C_{30}H_{38}N_2NaO_6SSi$ 605.2112, found 605.2102.

(6*R*)-6-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-8a-{[(4-methoxyphenyl)-methyl]sulfanyl}-2-methyloctahydropyrrolo[1,2-*a*]piperazine-1,4,8-trione (39.1a,b).



25.8 **39.1a,b**

NaH (60%w/w in mineral oil, 323.2 mg, 8.08 mmol) was added to a stirred solution of **25.8** (2.0 g, 3.67 mmol) in THF (37 ml). The mixture was lowered into a pre-heated oil bath (70 °C) and heated for 30 min. The mixture was cooled to 0 °C and quenched with pH 7.0 buffer (0.2 M, 35 mL) and hydrochloric acid (1 M, 8.1 mmol). The mixture was extracted with EtOAc (3

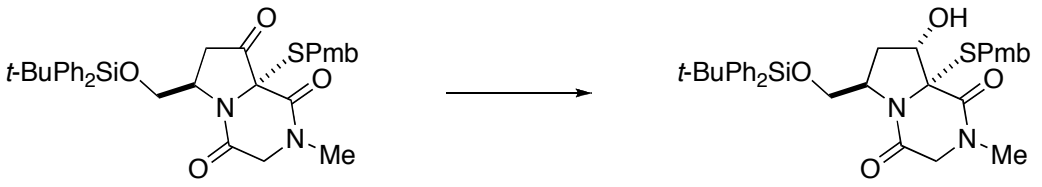
times) and the combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. The resulting residue was dissolved in dry CH_2Cl_2 (30 mL) and a solution of $TolSO_2SPmb$ (1.13 g, 3.67 mmol) in CH_2Cl_2 (4 mL) was added, followed by Et_3N (371.4 mg, 3.67 mmol). The mixture was swirled occasionally for 30 min and filtered through a pad of silica gel (2.2 x 7 cm), using 5:1 EtOAc–hexane. Evaporation of the solvent and flash chromatography of the residue over silica gel (2.7 x 15 cm), using 2:5 EtOAc–hexane, 1:2 EtOAc–hexane, 1:1 EtOAc–hexane and then 3:2 EtOAc–hexane, gave **39.1a** (865 mg, 39%) as a foam and **39.1b** (398 mg, 18%) as a foam.

39.1a: $[\alpha]_D$ = -28.57 (*c* 1.00, CH_2Cl_2); FTIR (CH_2Cl_2, cast) 3071, 3049, 2999, 2955, 2890, 2858, 1765, 1689, 1609, 1588, 1512, 1486, 1472 1427, 1409 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.98 (s, 9 H), 2.62 (dd, *J* = 18.0, 2.8 Hz, 1 H), 2.91 (s, 3 H), 3.37 (dd, *J* = 18.0, 9.8 Hz, 1 H), 3.53 (dd, *J* = 10.6, 1.7 Hz, 1 H), 3.71 (d, *J* = 17.0 Hz, 1 H), 3.76 (s, 3 H), 4.00 (ABq, $\Delta\nu_{AB}$ = 18.4 Hz, J_{AB} = 12.8 Hz, 2 H), 4.25 (dd, *J* = 10.6, 2.8 Hz, 1 H), 4.31-4.36 (m, 2 H), 6.79-6.82 (m, 2 H), 7.14-7.17 (m, 2 H), 7.34-7.44 (m, 6 H), 7.49-7.52 (m, 2 H), 7.55-7.57 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.1 (s), 26.6 (q), 33.7 (q), 35.0 (t), 36.2 (t), 52.7 (d), 53.2 (t), 55.3 (q), 62.3 (s), 62.5 (t), 114.1 (d), 127.2 (s), 127.76 (s), 127.85 (d), 129.9 (d), 130.0 (d), 130.4 (d), 132.6 (s), 135.5 (d), 135.7 (d), 159.0 (s), 160.7 (s), 165.4 (s), 195.0 (s); exact mass (electrospray) *m/z* calcd for $C_{33}H_{38}N_2NaO_5SSi$ 625.2163, found 625.2154.

39.1b: $[\alpha]_D$ = -18.23 (*c* 1.29, CH_2Cl_2); FTIR (CH_2Cl_2, cast) 3071, 3050, 2999, 2957, 2932, 2892, 2848, 1771, 1726, 1687, 1610, 1588, 1512, 1487, 1464, 1427, 1400 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.07 (s, 9 H), 2.79 (dd, *J* = 19.3, 9.6 Hz, 1 H), 2.92 (s, 3 H), 3.05 (dd, *J* = 19.3, 3.0 Hz, 1 H), 3.71 (d, *J* = 16.6 Hz, 1 H), 3.76-3.80 (m, 4 H), 4.01 (dd, *J* = 10.5, 4.0 Hz, 1 H), 4.07 (ABq, $\Delta\nu_{AB}$ = 21.7 Hz, *J* = 12.8 Hz, 2 H), 4.30 (d, *J* = 16.6 Hz, 1 H), 4.48-4.55 (m, 1 H), 6.79-6.83 (m, 2 H), 7.11-7.14 (m, 2 H), 7.35-7.45 (m, 6 H), 7.62-7.67 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.2 (s), 26.9 (q), 34.1 (q), 34.9 (t), 37.2 (t), 52.59 (d), 52.62 (t), 55.3 (q), 62.2 (s), 63.6 (t), 114.0 (d), 127.1 (s), 127.8 (d), 127.8 (s), 129.8 (d), 129.9 (d), 130.4 (d), 132.90 (s), 132.93 (s), 135.56 (d), 135.58 (d),

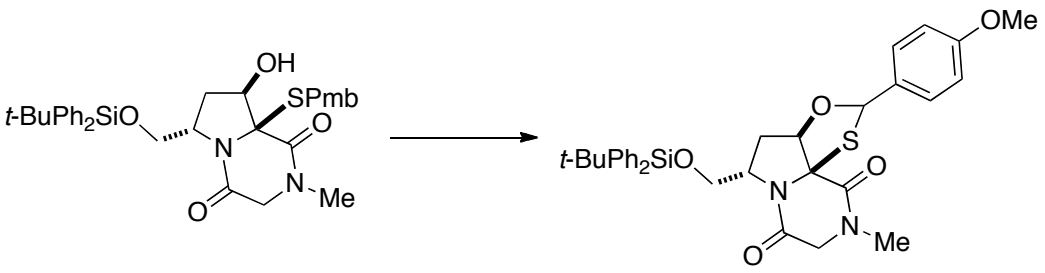
159.0 (s), 160.5 (s), 164.1 (s), 198.6 (s); exact mass (electrospray) *m/z* calcd for $C_{33}H_{38}N_2NaO_5SSi$ 603.2343, found 603.2332.

(6*R*,8*S*,8a*R*)-6-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-8-hydroxy-8a-{[(4-methoxyphenyl)methyl]sulfanyl}-2-methyloctahydropyrrolo[1,2-*a*]piperazine-1,4-dione (39.2).



$NaBH_4$ (54.4 mg, 1.44 mmol) was added to a stirred and cooled (0 °C) solution of **39.1a** (865 mg, 1.44 mmol) in a mixture of THF (15 mL) and water (2 mL). Stirring at 0 °C was continued for 10 min and the mixture was quenched with saturated aqueous NH_4Cl, diluted with water and extracted with EtOAc (3 times). The combined organic extracts were washed with brine and dried ($MgSO_4$). Evaporation of the solvent gave **39.2** (829 mg, 95%) as a foam: $[\alpha]_D$ = 1.00 (*c* 1.16, $CHCl_3$); FTIR ($CHCl_3$, cast) 3451 (br), 3000, 2955, 2932, 2890, 2858, 1676, 1610, 1512, 1427, 1400 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.02 (s, 9 H), 2.28 (dd, *J* = 12.3, 7.0 Hz, 1 H), 2.44 (q, *J* = 11.0 Hz, 1 H), 2.78 (s, 3 H), 3.18 (d, *J* = 4.4 Hz, 1 H), 3.57-3.63 (m, 2 H), 3.78 (s, 3 H), 3.86 (d, *J* = 13.4 Hz, 1 H), 4.02 (d, *J* = 13.5 Hz, 1 H), 4.06 (d, *J* = 10.2 Hz, 1 H), 4.10 (dd, *J* = 10.4, 3.8 Hz, 1 H), 4.18 (d, *J* = 17.1 Hz, 1 H), 5.00 (ddd, *J* = 11.2, 6.8, 4.4 Hz, 1 H), 6.83 (d, *J* = 8.6 Hz, 2 H), 7.21 (d, *J* = 8.6 Hz, 2 H), 7.34-7.44 (m, 6 H), 7.55-7.60 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.2 (s), 26.8 (q), 31.9 (t), 33.0 (q), 34.5 (t), 53.4 (t), 55.28 (q), 55.35 (d), 62.6 (t), 72.3 (s), 74.2 (d), 113.9 (d), 127.7 (d), 127.8 (d), 129.1 (s), 129.8 (d), 130.0 (d), 132.8 (s), 133.1 (s), 135.47 (d), 135.55 (d), 158.8 (s), 164.9 (s), 165.9 (s); exact mass (electrospray) *m/z* calcd for $C_{33}H_{40}N_2NaO_5SSi$ 627.2319, found 627.2313.

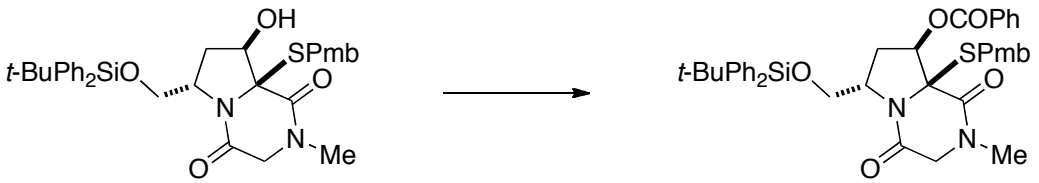
(1*S*,5*R*,7*S*)-7-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-3-(4-methoxyphenyl)-11-methyl-4-oxa-2-thia-8,11-diazatricyclo[6.4.0.0^{1,5}]dodecane-9,12-dione (*ent*-40.1).



***ent*-39.2** ***ent*-40.1**

DDQ (8.2 mg, 0.036 mmol) was added to a stirred mixture of ***ent*-39.2** (prepared from **33.6** by the same methods as were used for making **39.2**, 19.9 mg, 0.033 mmol) in CH_2Cl_2 (0.5 mmol) and water (28 μL). Stirring at room temperature was continued for 12 h and the mixture was filtered through a pad of silica gel, using 7:10 EtOAc–hexane. Evaporation of the solvent and flash chromatography of the residue over silica gel (0.5 x 7 cm), using 1:5 EtOAc–hexane, 1:3 EtOAc–hexane and 2:5 EtOAc–hexane, gave ***ent*-40.1** (10.4 mg, 52%) as a foam: $[\alpha]_D$ = 55.38 (*c* 0.46, CH_2Cl_2); FTIR (CH_2Cl_2, cast) 3071, 3050, 2999, 2956, 2931, 2895, 2857, 1686, 1612, 1588, 1515, 1488, 1472, 1463, 1427, 1401 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.03 (s, 9 H), 2.31-2.46 (m, 2 H), 3.05 (s, 3 H), 3.75 (d, *J* = 17.3 Hz, 1 H), 3.79-3.83 (m, 4 H), 4.19 (d, *J* = 17.3 Hz, 1 H), 4.31-4.38 (m, 1 H), 4.43 (dd, *J* = 10.5, 4.3 Hz, 1 H), 5.36 (dd, *J* = 5.8, 3.5 Hz, 1 H), 6.43 (s, 1 H), 6.87-6.92 (m, 2 H), 7.36-7.47 (m, 8 H), 7.60-7.64 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.3 (s), 26.8 (q), 34.0 (q), 34.4 (t), 53.9 (t), 55.4 (q), 60.2 (d), 61.4 (t), 84.3 (s), 86.0 (d), 90.3 (d), 114.1 (d), 127.2 (s), 127.77 (d), 127.83 (d), 128.7 (d), 129.8 (d), 129.9 (d), 132.9 (s), 133.2 (s), 135.6 (d), 135.7 (d), 160.7 (s), 164.9 (s), 166.4 (s); exact mass (electrospray) *m*/*z* calcd for $C_{33}H_{38}N_2NaO_5SSi$ 625.2163, found 625.2159.

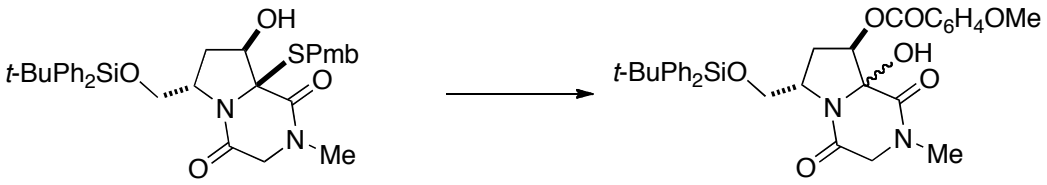
(6*S*,8*R*,8a*S*)-6-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-8a-{[(4-methoxyphenyl)methyl]sulfanyl}-2-methyl-1,4-dioxooctahydropyrrolo[1,2-*a*]piperazin-8-yl benzoate (*ent*-39.3).



***ent*-39.2** ***ent*-39.3**

Et_3N (30.4 mg, 0.3 mmol) and PhCOCl (31.4 mg, 0.22 mmol) were added to a stirred solution of ***ent*-39.2** (30.0 mg, 0.05 mmol) and DMAP (0.61 mg, 0.005 mmol) in CH_2Cl_2 (1 mL). The mixture was refluxed for 18 h, cooled to room temperature and diluted with CH_2Cl_2 (15 mL). The solution was washed with aqueous $NaHSO_4$ (1 M, 10 mL) and saturated aqueous $NaHCO_3$ (10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (0.5 x 7 cm), using 1:5 EtOAc–hexane, 3:10 EtOAc–hexane and 2:5 EtOAc–hexane, gave ***ent*-39.3** (33.6 mg, 95 %) as a white solid: mp 151-153 °C; $[\alpha]_D$ = -41.53 (*c* 0.87, CH_2Cl_2); FTIR (CH_2Cl_2, cast) 3071, 2998, 2955, 2932, 2858, 1726, 1682, 1607, 1585, 1512, 1471, 1451, 1411 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.06 (s, 9 H), 2.48-2.54 (m, 1 H), 2.65-2.68 (m, 4 H), 3.56 (dd, *J* = 10.6, 2.0 Hz, 1 H), 3.59 (d, *J* = 17.1 Hz, 1 H), 3.78 (s, 3 H), 3.94 (d, *J* = 13.9 Hz, 1 H), 4.04 (d, *J* = 13.8 Hz, 1 H), 4.10 (dd, *J* = 10.5, 3.7 Hz, 1 H), 4.17-4.19 (m, 1 H), 4.25 (d, *J* = 17.1 Hz, 1 H), 6.31 (dd, *J* = 10.7, 7.1 Hz, 1 H), 6.81-6.84 (m, 2 H), 7.17-7.21 (m, 2 H), 7.35-7.48 (m, 8 H), 7.56-7.60 (m, 3 H), 7.69-7.71 (m, 2 H), 8.15-8.17 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.1 (s), 26.7 (q), 30.9 (t), 33.2 (q), 34.8 (t), 53.5 (t), 55.4 (d), 55.8 (q), 62.6 (t), 71.1 (s), 74.6 (d), 113.9 (d), 127.77 (d), 127.84 (d), 128.5 (d), 129.3 (s), 129.83 (d), 129.86 (d), 129.91 (d), 130.0 (d), 130.2 (s), 132.8 (s), 132.9 (s), 133.1 (d), 135.7 (d), 135.8 (d), 158.9 (s), 164.1 (s), 165.2 (s), 165.3 (s); exact mass (electrospray) *m*/*z* calcd for $C_{40}H_{44}N_2NaO_6SSi$ 731.2582, found 731.2575.

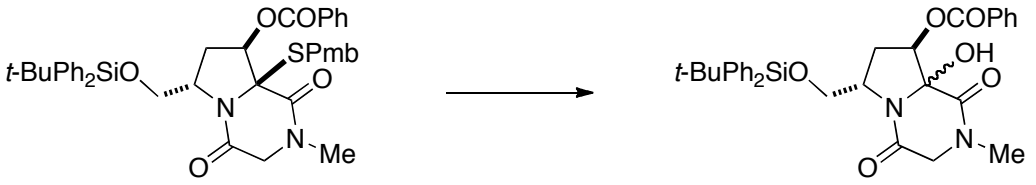
(6*S*,8*R*)-6-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-8a-hydroxy-2-methyl-1,4-dioxooctahydropyrrolo[1,2-*a*]piperazin-8-yl 4-methoxybenzoate (*ent*-40.2).



***ent*-39.2** ***ent*-40.2**

DDQ (46.5 mg, 0.21 mmol) was added to a stirred mixture of ***ent*-39.2** (27.5 mg, 0.046 mmol), CH_2Cl_2 (1 mL) and water (0.1 mL). Stirring at room temperature was continued for 19 h and the mixture was filtered through a pad of Celite, using CH_2Cl_2. Evaporation and preparative TLC of the residue (silica gel, 0.25 mm, 8 cm x 10 cm), using 2:1 EtOAc–hexane, gave ***ent*-40.2** (17.6 mg, 62%) as a thick oil: FTIR ($CHCl_3$, cast) 3331, 3072, 2999, 2957, 2931, 2894, 2858, 1719, 1684, 1607, 1513, 1428 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.07 (s, 7.6 H), 1.08 (s, 1.4 H), 2.25-2.32 (m, 1 H), 2.62-2.72 (m, 1 H), 2.98 (s, 2.5 H), 3.02 (s, 0.5 H), 3.56 (dd, *J* = 10.6, 1.8 Hz, 0.2 H), 3.61 (dd, *J* = 10.6, 2.0 Hz, 0.8 H), 3.69-3.74 (m, 1.8 H), 3.84 (s, 0.5 H), 3.85 (s, 2.5 H), 3.97 (d, *J* = 17.3 Hz, 0.2 H), 4.10 (dd, *J* = 10.6, 3.4 Hz, 0.8 H), 4.23 (dd, *J* = 10.7, 3.0 Hz, 0.2 H), 4.29-4.36 (m, 1.8 H), 4.55-4.59 (m, 0.2 H), 5.68 (d, *J* = 4.4 Hz, 0.2 H), 6.01 (dd, *J* = 10.6, 7.6 Hz, 0.8 H), 6.85-6.87 (m, 0.3 H), 6.89-6.92 (m, 1.7 H), 7.36-7.46 (m, 6 H), 7.58-7.61 (m, 2 H), 7.63-7.65 (m, 0.3 H), 7.67-7.69 (m, 1.7 H), 7.76-7.78 (m, 0.3 H), 7.99-8.02 (m, 1.7 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.1, 19.3, 26.8, 26.9, 29.7, 30.8, 33.3, 33.6, 52.9, 53.16, 53.20, 55.49, 55.53, 55.9, 58.0, 62.4, 63.0, 72.78, 72.81, 78.1, 84.8, 88.0, 113.7, 113.8, 121.9, 122.0, 127.77, 127.84, 128.0, 128.1, 129.8, 129.9, 130.2, 130.4, 131.7, 131.9, 132.9, 133.0, 135.5, 135.67, 135.73, 163.08, 163.12, 163.67, 163.69, 164.4, 164.5, 165.4, 165.7; exact mass (electrospray) *m*/*z* calcd for $C_{33}H_{38}N_2NaO_7Si$ 625.2340, found 625.2336.

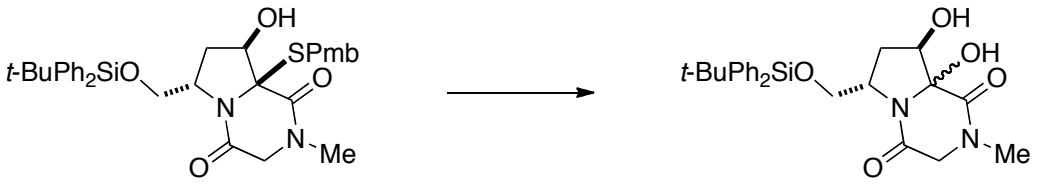
(6*S*,8*R*)-6-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-8a-hydroxy-2-methyl-1,4-dioxooctahydropyrrolo[1,2-*a*]piperazin-8-yl benzoate (*ent*-40.3).



***ent*-39.3** ***ent*-40.3**

DDQ (9.6 mg, 0.042 mmol) was added to a stirred mixture of ***ent*-39.3** (30 mg, 0.042 mmol) in CH_2Cl_2 (0.5 mL) and water (0.1 mL). Stirring at room temperature was continued for 3 h, more DDQ (9.6 mg, 0.042 mmol) was added and stirring was continued for 6 h. The mixture was filtered through a pad of Celite, using CH_2Cl_2. Evaporation of the solvent and flash chromatography of the residue over silica gel (0.5 x 7 cm), using 3:5 EtOAc–hexane, 1:1 EtOAc–hexane and 3:2 EtOAc–hexane, gave ***ent*-40.3** (14.1 mg, 57%) as a foam: FTIR (CH_2Cl_2, cast) 3324 (br), 3072, 2956, 2930, 2893, 2857, 1727, 1684, 1602, 1589, 1472, 1451, 1428, 1408 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.07 (s, 8 H), 1.09 (s, 1 H), 2.25-2.34 (m, 1 H), 2.71 (ddd, *J* = 12.5, 7.6, 0.9 Hz, 1 H), 2.98 (s, 2.7 H), 3.03 (s, 0.3 H), 3.54 (s, 1 H), 3.61 (dd, *J* = 10.7, 2.0 Hz, 1 H), 3.72 (d, *J* = 17.2 Hz, 1 H), 3.98 (d, *J* = 17.2 Hz, 0.1 H), 4.12 (dd, *J* = 10.7, 3.4 Hz, 0.9 H), 4.25 (dd, *J* = 10.6, 3.1 Hz, 0.1 H), 4.30-4.36 (m, 1.9 H), 5.71 (d, *J* = 4.5 Hz, 0.1 H), 6.05 (dd, *J* = 10.7, 7.6 Hz, 0.9 H), 7.36-7.48 (m, 8 H), 7.55-7.61 (m, 3 H), 7.63-7.66 (m, 0.2 H), 7.66-7.70 (m, 1.8 H), 7.81-7.84 (m, 0.2 H), 8.04-8.08 (m, 1.8 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.2 (s), 26.8 (q), 27.0 (q), 28.6 (t), 30.7 (t), 33.3 (q), 33.6 (q), 52.9 (t), 53.1 (t), 56.0 (d), 58.0 (d), 62.3 (t), 63.0 (t), 73.1 (d), 78.4 (d), 84.7 (s), 87.9 (s), 127.78 (d), 127.85 (d), 128.0 (d), 128.1 (d), 128.4 (d), 128.5 (d), 129.6 (s), 129.8 (d), 129.85 (d), 129.88 (d), 132.9 (s), 133.0 (s), 133.4 (d), 135.5 (d), 135.69 (d), 135.74 (d), 164.7 (s), 165.4 (s), 165.6 (s); exact mass (electrospray) *m*/*z* calcd for $C_{32}H_{36}N_2NaO_6Si$ 595.2235, found 595.2227.

(6*S*,8*R*)-6-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-8,8a-dihydroxy-2-methyloctahydropyrrolo[1,2-*a*]piperazine-1,4-dione (*ent*-40.5a,b).



***ent*-39.2** ***ent*-40.5a,b**

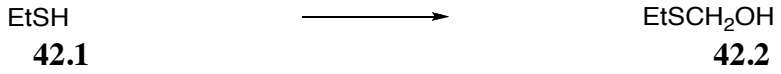
2-Nitrobenzenesulfenyl chloride (9.5 mg, 0.05 mmol) was added to a stirred and cooled (0 °C) solution of ***ent*-39.2** (25.3 mg, 0.042 mmol) in CH_2Cl_2 (1 mL). Stirring at 0 °C was continued for 70 min. The mixture was evaporated and the residue was dissolved in dry CH_2Cl_2 and evaporated again. The residue was left at room temperature for 3 h and flash chromatography of the mixture over silica gel (0.5 x 7 cm), using 1:2 EtOAc–hexane, 1:1 EtOAc–hexane, 2:1 EtOAc–hexane, 3:1 EtOAc–hexane, 6:1 EtOAc–hexane, 10:1 EtOAc–hexane and pure EtOAc, gave ***ent*-40.5a** (10.3 mg, 51%) as a foam and ***ent*-40.5b** (3.9 mg, 20%) as a foam.

***ent*-40.5a**: $[\alpha]_D$ = 19.92 (*c* 0.98, $CHCl_3$); FTIR ($CHCl_3$, cast) 3372 (br), 3072, 3049, 3014, 2957, 2931, 2858, 1667, 1589, 1471, 1428, 1404 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.02 (s, 9 H), 2.15 (ddd, *J* = 12.6, 10.9, 9.7 Hz, 1 H), 2.30 (ddd, *J* = 12.6, 7.6, 1.1 Hz, 1 H), 2.98 (s, 3 H), 3.30 (d, *J* = 2.3 Hz, 1 H), 3.64 (dd, *J* = 10.6, 2.2 Hz, 1 H), 3.68 (d, *J* = 17.2 Hz, 1 H), 4.08 (dd, *J* = 10.6, 3.7 Hz, 1 H), 4.15-4.18 (m, 1 H), 4.22 (s, 1 H), 4.30 (d, *J* = 17.2 Hz, 1 H), 4.83 (ddd, *J* = 10.4, 7.8, 2.2 Hz, 1 H), 7.34-7.39 (m, 4 H), 7.41-7.45 (m, 2 H), 7.54-7.56 (m, 2 H), 7.57-7.60 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.2 (s), 26.8 (q), 31.2 (t), 33.1 (q), 53.2 (t), 55.3 (d), 63.0 (t), 71.5 (d), 83.6 (s), 127.79 (d), 127.83 (d), 129.9 (d), 132.9 (s), 133.1 (s), 135.5 (d), 135.6 (d), 165.4 (s), 167.2 (s); exact mass (electrospray) *m/z* calcd for $C_{25}H_{32}N_2NaO_5Si$ 491.1973, found 491.1971.

***ent*-40.5b**: $[\alpha]_D$ = -86.44 (*c* 0.39, $CHCl_3$); FTIR ($CHCl_3$, cast) 3338 (br), 3072, 3050, 2958, 2932, 2888, 2858, 1654, 1590, 1472, 1463, 1442, 1429, 1407 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.07 (s, 9 H), 2.07 (dd, *J* = 14.3, 8.7 Hz, 1 H),

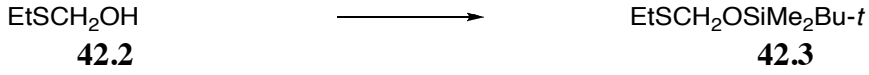
2.44 (dddd, *J* = 14.4, 7.5, 5.3, 2.1 Hz, 1 H), 2.85 (t, *J* = 2.2 Hz, 1 H), 3.05 (s, 3 H), 3.44 (dd, *J* = 10.6, 1.4 Hz, 1 H), 3.82 (d, *J* = 17.1 Hz, 1 H), 4.32 (d, *J* = 17.1 Hz, 1 H), 4.36 (dd, *J* = 10.6, 2.4 Hz, 1 H), 4.52-4.56 (m, 2 H), 4.57 (s, 1 H), 7.38-7.42 (m, 4 H), 7.43-7.48 (m, 2 H), 7.56-7.58 (m, 2 H), 7.61-7.63 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.3 (s), 27.0 (q), 29.2 (t), 33.5 (q), 53.0 (t), 58.4 (d), 61.9 (t), 76.7 (d), 89.6 (s), 128.0 (d), 128.1 (d), 130.3 (d), 130.4 (d), 131.8 (s), 131.9 (s), 135.5 (d), 135.7 (d), 163.6 (s), 164.8 (s); exact mass (electrospray) *m*/*z* calcd for $C_{25}H_{32}N_2NaO_5Si$ 491.1973, found 491.1969.

(Ethylthio)methanol (42.2).[63]



A solution of MeONa in MeOH (4.6 M, 0.03 mL) was added to a stirred mixture of EtSH (5.89 g, 94.5 mmol) and paraformaldehyde (2.83 g, 94.5 mmol). The reaction flask was lowered into a preheated oil bath (40 °C) and the mixture was refluxed for 30 min. During this time all the solid dissolved. The mixture was cooled to room temperature and the resulting crude material (**42.2**) was used for the next step: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.31 (t, *J* = 7.3 Hz, 3 H), 1.79 (br s, 1 H), 2.72 (q, *J* = 7.5 Hz, 2 H), 4.73 (s, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.1 (q), 24.6 (t), 65.7 (t).

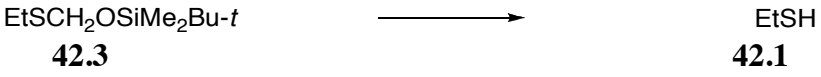
(1,1-Dimethylethyl)[(ethylthio)methoxy]dimethylsilane (42.3).[63]



Et_3N (5.37 g, 53.0 mmol) and *t*-$BuMe_2SiCl$ (7.3 g, 48.6 mmol) were added sequentially to a stirred and cooled (0 °C) solution of **42.2** (4.065 g, 44.2 mmol) and DMAP (216 mg, 1.77 mmol) in dry CH_2Cl_2 (45 mL). The mixture was stirred at 0 °C for 10 min, the cooling bath was removed, and stirring was continued for

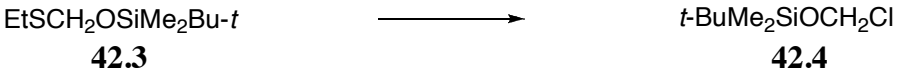
4 h. The mixture was diluted was CH_2Cl_2, and the organic phase was washed twice with water and twice with saturated aqueous NH_4Cl, dried ($MgSO_4$) and evaporated to give crude **42.3** (8.5 g, 93%), which could be used for the next step or distilled before use (bp 53–55 °C, 4.3 Torr): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.12 (s, 6 H), 0.91 (s, 9 H), 1.30 (t, *J* = 7.4 Hz, 3 H), 2.67 (q, *J* = 7.5 Hz, 2 H), 4.81 (s, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ -5.0 (q), 15.0 (q), 18.2 (s), 24.6 (t), 25.8 (q), 66.0 (t).

Ethanethiol (42.1) from 42.3.



Bu_4NF (1.0 M in THF, 0.13 mL, 0.13 mmol) was added to a solution of **42.3**(23.5 mg, 0.11 mmol) in CD_2Cl_2 (0.7 mL) in an NMR tube. The ^{1}H NMR spectrum showed that ca 76% of **42.3** was converted into **42.1** within 5 min, based on changes to the SCH_2O signal.

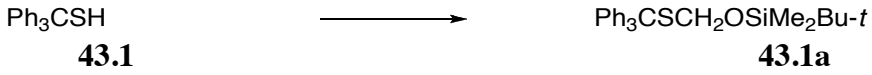
(Chloromethoxy)(1,1-dimethylethyl)dimethylsilane (42.4).[63]



A solution of SO_2Cl_2 (2.81 g, 20. 83 mmol) in CH_2Cl_2 (21 mL) was added dropwise to a stirred and cooled (0 °C) solution of **42.3** (4.29 g, 20.83 mmol) in dry CH_2Cl_2 (21 mL). Stirring at 0 °C was continued for 30 min, the cooling bath was removed, and stirring was continued for 10 min. The mixture was evaporated on a water bath at 22–25 °C (ca 100 Torr). The residue was diluted with dry CH_2Cl_2 and evaporated in the same way, and the process of dilution with CH_2Cl_2 and evaporation was repeated for 3–4 times until the ^{1}H NMR showed that the residue was pure and no CH_2Cl_2 remained. Compound **42.4** was a slightly yellow liquid (3.23 g, 86%). This compound is not stable, but it could be kept in a

freezer (–20 °C) for 1–2 days; the decomposition was evident as fine solid particles formed on the bottom of the flask (probably paraformaldehyde): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.20 (s, 6 H), 0.91 (s, 9 H), 5.60 (s, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ –5.2 (q), 17.8 (s), 25.5 (q), 76.5 (t).

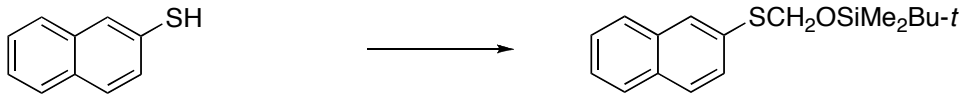
(1,1-Dimethylethyl)dimethyl[[(triphenylmethyl)thio]methoxy]silane (43.1a).



43.1 **43.1a**

Proton sponge (20.4 mg, 0.095 mmol) was added to a stirred solution of **43.1** (10.5 mg, 0.038 mmol) and *t*-$BuMe_2SiOCH_2Cl$ (8.2 mg, 0.046 mmol) in dry DMF (degassed using three freeze-pump-thaw cycles, 0.5 mL). Stirring at room temperature was continued for 5.5 h. The mixture was diluted with Et_2O (10 mL) and washed with water (5 mL), aqueous $NaHSO_4$ (1 M, 5 mL) and water (5 mL). The organic phase was dried ($MgSO_4$) and evaporated. Preparative TLC of the residue (silica gel, 0.25 mm, 10 cm x 10 cm), using 2.2% EtOAc in hexanes, gave **43.1a** (12.3 mg, 77%): mp 61–64 °C; FTIR (CH_2Cl_2, cast) 3058, 3031, 2954, 2929, 2885, 2856, 1492, 1471, 1463, 1444 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ -0.03 (s, 6 H), 0.86 (s, 9 H), 4.48 (s, 2 H), 7.21–7.26 (m, 3 H), 7.27–7.32 (m, 6 H), 7.38–7.44 (m, 6 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ –5.4 (q), 18.1 (s), 25.8 (q), 66.7 (t), 68.6 (s), 126.7 (d), 127.7 (d), 130.3 (d), 145.2 (s); exact mass (electrospray) *m/z* calcd for $C_{26}H_{32}NaOSSi$ 443.1835, found 443.1843.

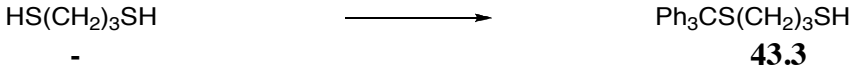
(1,1-Dimethylethyl)dimethyl[(2-naphthylthio)methoxy]silane (43.2a).



43.2 **43.2a**

Proton sponge (26.8 mg, 0.13 mmol) was added to a solution of **43.2** (8.0 mg, 0.05 mmol) and *t*-$BuMe_2SiOCH_2Cl$ (10.8 mg, 0.060 mmol) in dry DMF (degassed using three freeze-pump-thaw cycles, 0.6 mL). Stirring at room temperature was continued for 2 h and the mixture was diluted with Et_2O (10 mL). The mixture was washed with water (6 mL), aqueous $NaHSO_4$ (1 M, 6 mL) and water (6 mL), dried ($MgSO_4$) and evaporated. Preparative TLC of the residue (silica gel, 0.25 mm, 7 cm x 5 cm), using 2.2% EtOAc in hexane, gave **43.2a** (11.9 mg, 78%) as a viscous oil: FTIR ($CDCl_3$, cast) 3055, 2954, 2929, 2895, 2857, 1626, 1591, 1502, 1471, 1463, 1442 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.12 (s, 6 H), 0.92 (s, 9 H), 5.22 (s, 2 H), 7.40–7.52 (m, 2 H), 7.56 (dd, *J* = 8.5, 1.9 Hz, 1 H), 7.71–7.85 (m, 3 H), 7.94–8.03 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ -5.0 (q), 18.2 (s), 25.8 (q), 69.0 (t), 125.8 (d), 126.5 (d), 127.4 (d), 127.7 (d), 128.1 (d), 128.3 (d), 128.4 (d), 132.1 (s), 133.8 (s), 133.8 (s); exact mass *m/z* calcd for $C_{17}H_{24}OSSi$ 304.1317, found 304.1316.

3-[(Triphenylmethyl)thio]propane-1-thiol (43.3).

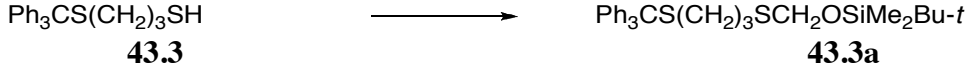


- **43.3**

Pyridine (226.2 mg, 2.86 mmol) was added to a stirred solution of propane-1,3-dithiol (1.55 g, 14.3 mmol) and Ph_3CCl (400 mg, 1.43 mmol) in dry DMF (20 mL). Stirring at room temperature was continued for 1.5 days. The mixture was diluted with Et_2O (60 mL) and washed with water (3 x 50 mL), and the organic phase was dried ($MgSO_4$) and evaporated. The excess of propane-1,3-dithiol was evaporated under high vacuum at room temperature. Dry flash chromatography[77] (which was arbitrarily tried instead of flash chromatography) of the residue over silica gel (4 x 5 cm), by gradient elution,[77] using hexane to 1:20 EtOAc–hexane, gave **43.3** (400 mg, 80%) containing some impurities: ^1H NMR ($CDCl_3$, 500 MHz) δ 1.18 (t, *J* = 8.1 Hz, 1 H), 1.64 (quintet, *J* = 7.1 Hz, 2 H),

2.27 (t, *J* = 7.1 Hz, 2 H), 2.45 (q, *J* = 7.5 Hz, 2 H), 7.17–7.24 (m, 3 H), 7.25–7.32 (m, 6 H), 7.35–7.49 (m, 6 H).

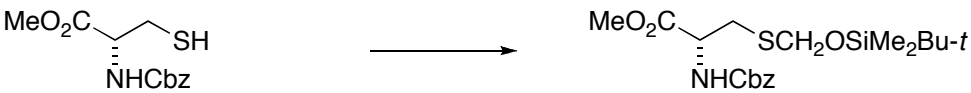
(1,1-Dimethylethyl)dimethyl[[[3-[(triphenylmethyl)thio]propyl]thio]-methoxy]silane (43.3a).



43.3 **43.3a**

t-BuMe$_2$SiOCH$_2$Cl (6.42 mg, 0.036 mmol) was added to a stirred solution of **43.3** (7.2 mg, 0.021 mmol) and 2,6-lutidine (7.73 mg, 0.072 mmol) in dry DMF (degassed using three freeze-pump-thaw cycles, 0.6 mL). The mixture was heated at 55 °C for 3.5 h, cooled to room temperature and diluted with Et$_2$O (10 mL). The mixture was washed with aqueous NaHSO$_4$ (1 M, 5 mL) and water (4 mL), dried (MgSO$_4$) and evaporated. Preparative TLC of the residue (silica gel, 0.25 mm, 7 cm x 5 cm), using 2.5% EtOAc in hexane, gave **43.3a** (6.2 mg, 61%) as a viscous oil: FTIR (CH$_2$Cl$_2$, cast) 3083, 3057, 2954, 2928, 2856, 1595, 1489, 1471, 1463, 1444 cm^{-1}; ^{1}H NMR (CDCl$_3$, 500 MHz) δ 0.12 (s, 6 H), 0.92 (s, 9 H), 1.72 (quintet, *J* = 7.3 Hz, 2 H), 2.30 (t, *J* = 7.2 Hz, 2 H), 2.62 (t, *J* = 7.3 Hz, 2 H), 4.73 (s, 2 H), 7.20–7.27 (m, 3 H), 7.27–7.35 (m, 6 H), 7.40–7.48 (m, 6 H); ^{13}C NMR (CDCl$_3$, 125 MHz) δ -5.0 (q), 18.2 (s), 25.8 (q), 28.9 (t), 29.8 (t), 31.1 (t), 66.3 (t), 66.6 (s), 126.6 (d), 127.9 (d), 129.6 (d), 145.0 (s); exact mass (electrospray) *m*/*z* calcd for C$_{29}$H$_{38}$NaOS$_2$Si 517.2026, found 517.2022.

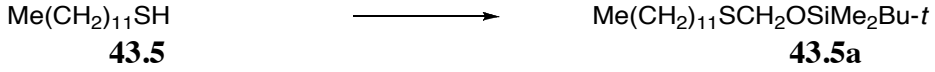
***S*-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]-*N*-[(phenyl-methoxy)carbonyl]-L-cysteine methyl ester (43.4a).**



43.4 **43.4a**

t-$BuMe_2SiOCH_2Cl$ (9.9 mg, 0.055 mmol) was added to a stirred solution of *N*-[(phenylmethoxy)carbonyl]-L-cysteine methyl ester (**43.4**)[78] (8.2 mg, 0.030 mmol) and 2,6-lutidine (11.3 mg, 0.11 mmol) in dry DMF (degassed using three freeze-pump-thaw cycles, 0.5 mL). The mixture was heated at 55 °C for 3 h, cooled to room temperature and diluted with Et_2O (10 mL). The mixture was washed with aqueous $NaHSO_4$ (1 M, 5 mL) and water (4 mL), dried ($MgSO_4$) and evaporated. Preparative TLC of the residue (silica gel, 0.25 mm, 10 cm x 10 cm), using 1:2 EtOAc–hexane, gave **43.4a** (10.7 mg, 86%) as a viscous oil: $[\alpha]_D$ = 5.85 (CH_2Cl_2, *c* 0.55); FTIR (CH_2Cl_2, cast) 3318, 3066, 2954, 2930, 2896, 2857, 1727,1529, 1472, 1464, 1456, 1437 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.09 (s, 3 H), 0.11 (s, 3 H), 0.87 (s, 9 H), 3.00 (dd, *J* = 14.5, 3.8 Hz, 1 H), 3.26 (dd, *J* = 14.5, 5.1 Hz, 1 H), 3.75 (s, 3 H), 4.69 (dd, *J* = 9.3, 4.8 Hz, 1 H), 4.72 (dd, *J* = 11.2, 0.7 Hz, 1 H), 4.7–4.85 (m, 1 H), 5.12 (s, 2 H), 6.33 (d, *J* = 8.2 Hz, 1 H), 7.27–7.44 (m, 5 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ -5.4 (q), -5.1 (q), 18.3 (s), 25.7 (q), 35.2 (t), 52.5 (q), 53.9 (d), 67.0 (t), 67.7 (t), 128.1 (d), 128.2 (d), 128.5 (d), 136.3 (s), 156.1 (s), 171.1 (s); exact mass (electrospray) *m/z* calcd for $C_{19}H_{31}NNaO_5SSi$ 436.1584, found 436.1577.

(1,1-Dimethylethyl)dimethyl[(dodecylthio)methoxy]silane (43.5a).



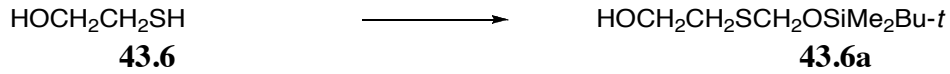
43.5 **43.5a**

t-$BuMe_2SiOCH_2Cl$ (12.5 mg, 0.069 mmol) was added to a stirred solution of **43.5** (10 mg, 0.049 mmol) and 2,6-lutidine (18.5 mg, 0.17 mmol) in dry DMF (degassed using three freeze-pump-thaw cycles, 0.5 mL). Stirring at room temperature was continued for 21 h and the mixture was diluted with hexane (10 mL). The mixture was washed with water (5 mL), aqueous $NaHSO_4$ (1 M. 5 mL) and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (0.7 x 7 cm), using 1:20 CH_2Cl_2–hexane and then 1:10 CH_2Cl_2–hexane, gave **43.5a** (13.6 mg, 80%) as a colorless oil: FTIR (CH_2Cl_2, cast) 2955,

2926, 2855, 1464 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.12 (s, 6 H), 0.88 (t, *J* = 7.0 Hz, 3 H), 0.91 (s, 9 H), 1.17–1.44 (m, 18 H), 1.62 (quintet, *J* = 7.5 Hz, 2 H), 2.64 (t, *J* = 7.3 Hz, 2 H), 4.79 (s, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ -5.0 (q), 14.2 (q), 18.2 (s), 22.7 (t), 25.9 (q), 29.0 (t), 29.3 (t), 29.4 (t), 29.6 (t), 29.67 (t), 29.69 (t), 29.71 (t), 29.9 (t), 30.8 (t), 32.0 (t), 66.5 (t); exact mass *m/z* calcd for $C_{15}H_{33}OSSi$ (M-C_4H_9) 289.2022, found 289.2023.

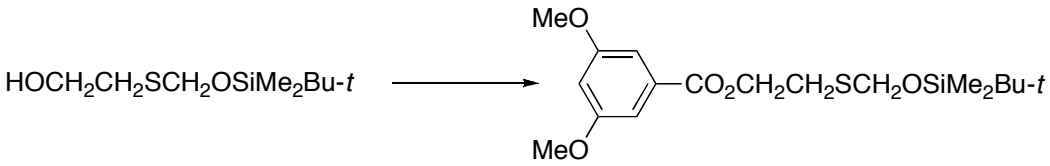
The reaction was also carried out using 0.600 g of the thiol and we obtained a yield of 84%.

2-[[[[(1,1-Dimethyl)ethyl)dimethylsilyl]oxy]methyl]thio]ethanol (43.6a).



Thiol **43.6** (56.3 mg, 0.72 mmol) was added to a stirred solution of *t*-BuOK (62.2 mg, 0.55 mmol) in dry DMF (degassed using three freeze-pump-thaw cycles, 5 mL). Stirring at room temperature was continued for 13 min and *t*-$BuMe_2SiOCH_2Cl$ (100 mg, 0.55 mmol) was added dropwise. Stirring at room temperature was continued for 15 min and the mixture was diluted with Et_2O (30 mL), washed with water (3 x 10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 15 cm), using 1:10 EtOAc–hexane and 1:5 EtOAc–hexane, gave **43.6a** (77.5 mg, 63%) as a colorless oil: FTIR (CH_2Cl_2, cast) 3382, 2955, 2930, 2886, 2858, 1472, 1464, 1443, 1410 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.15 (s, 6 H), 0.92 (s, 9 H), 2.86 (t, *J* = 5.3 Hz, 2 H), 3.42 (t, *J* = 6.6 Hz, 1 H), 3.78 (dt, *J* = 6.4, 5.3 Hz, 2 H), 4.80 (s, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ -5.2 (q), 18.2 (s), 25.7 (q), 37.1 (t), 62.5 (t), 67.6 (t); exact mass *m/z* calcd for $C_7H_{17}OSSi$ (M-C_2H_4OH) 177.0769, found 177.0769; exact mass (electrospray) *m/z* calcd for $C_9H_{22}NaO_2SSi$ 245.1002, found 245.1003.

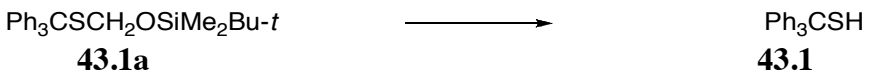
3,5-Dimethoxybenzoic acid 2-[[[[(1,1-Dimethyl)ethyl)dimethylsilyl]-oxy]methyl]thio]ethyl ester (21b).



43.6a **43.6b**

EDCI·HCl (16.0 mg, 0.082 mmol) was added to a stirred and cooled (0 °C) solution of **43.6a** (15.3 mg, 0.082 mmol), 3,5-dimethoxybenzoic acid (15 mg, 0.068 mmol) and DMAP (0.9 mg, 0.007 mmol) in dry CH_2Cl_2 (1.5 mL). Stirring at 0 °C was continued for 10 min, the cooling bath was removed and stirring was continued for 24 h. The mixture was diluted with CH_2Cl_2 (5 mL) and washed with aqueous $NaHSO_4$ (1 M, 5 mL), and the aqueous phase was extracted with CH_2Cl_2 (5 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (0.8 x 15 cm), using 1:20 EtOAc–hexane and 1:10 EtOAc–hexane, gave **43.6b** (19.0 mg, 60%) as a viscous oil: FTIR (CH_2Cl_2, cast) 3002, 2955, 2931, 2857, 1722, 1598, 1463, 1429 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.13 (s, 6 H), 0.91 (s, 9 H), 3.01 (t, J = 7.1 Hz, 2 H), 3.83 (s, 6 H), 4.52 (t, J = 7.1 Hz, 2 H), 4.85 (s, 2 H), 6.65 (t, J = 2.4 Hz, 1 H), 7.19 (d, J = 2.4 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ -5.0 (q), 18.2 (s), 25.8 (q), 29.4 (t), 55.6 (q), 64.4 (t), 66.7 (t), 105.8 (d), 107.3 (d), 132.0 (s), 160.7 (s), 166.1 (s); exact mass (electrospray) m/z calcd for $C_{18}H_{30}NaO_5SSi$ 409.1475, found 409.1477.

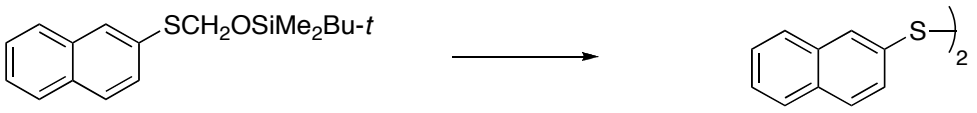
α,α-Diphenylbenzenemethanethiol (16) from 16a.



43.1a **43.1**

Bu_4NF (1.0 M in THF, 55 μL, 0.055 mmol) was added to a stirred and cooled (-78 °C) solution of **43.1a** (19.4 mg, 0.046 mmol) in dry THF (2.2 mL). Stirring at -78 °C was continued for 15 min, the cooling bath was removed and the cold mixture was quenched with saturated aqueous NH_4Cl (5 mL) as soon as the mixture became a clear solution (at ca -10 °C). The mixture was warmed to room temperature and extracted with EtOAc (3 x 5 mL), and the combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Preparative TLC of the residue (silica gel, 0.25 mm, 10 cm x 11 cm), using 2.2% EtOAc in hexane, gave **43.1** (8.6 mg, 68%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.11 (s, 1 H), 7.26–7.34 (m, 15 H).

1,2-Di-2-naphthalenyl disulfide (44.1[79]) from 43.2a.



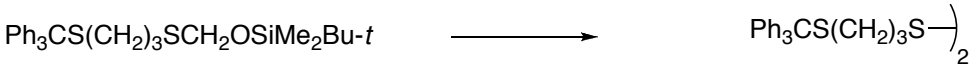
43.2a **44.1**

Bu_4NF (1.0 M in THF, 69.6 μL, 0.070 mmol) was added to a stirred solution of **43.2a** (17.6 mg, 0.058 mmol) in dry THF (1.9 mL). Stirring at room temperature was continued for 20 min and the mixture was quenched with saturated aqueous NH_4Cl (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (0.7 x 7 cm), using 2.5% EtOAc in hexane, gave 2-naphthalenethiol and its disulfide (8.3 mg, 89%) as a mixture in a molar ratio of 20:3.

I_2 (ca 16 mg, 0.06 mmol) was added to a solution of the above mixture in $CDCl_3$ (0.7 mL), which was then briefly swirled. After 30 min at room temperature the mixture was quenched with a mixture of saturated aqueous $NaHCO_3$ (3 mL) and saturated aqueous $Na_2S_2O_3$ (3 mL). The mixture was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated to give **44.1** quantitatively: mp 138–

140 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.41–7.51 (m, 4 H), 7.63 (dd, *J* = 8.6, 1.9 Hz, 2 H), 7.70–7.84 (m, 6 H), 7.95–8.03 (m, 2 H).

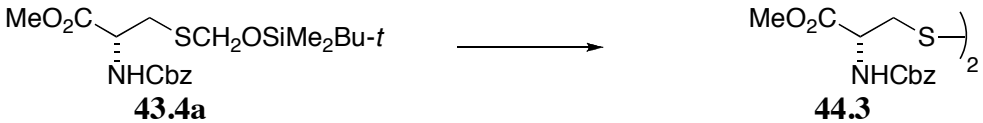
Bis[3-[(triphenylmethyl)thio]propyl] Disulfide (44.2) from 43.3a.



43.3a **44.2**

Bu_4NF (1.0 M in THF, 17.5 μL, 0.0175 mmol) was added to a stirred solution of **43.3a** (7.2 mg, 0.015 mmol) and AcOH (1.06 mg, 0.018 mmol) in THF (0.3 mL). Stirring at room temperature was continued for 40 min and Et_3N (6.65 mg, 0.066 mmol) was added, followed by a solution of I_2 (1.86 mg, 0.073 mmol) in THF (0.17 mL). Stirring at room temperature was continued for 3 min and the mixture was quenched with a mixture of saturated aqueous $NaHCO_3$ (3 mL) and saturated aqueous $Na_2S_2O_3$ (3 mL). The mixture was extracted with EtOAc (3 x 5 mL) and the combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Preparative TLC of the residue (silica gel, 0.25 mm, 7 cm x 5 cm), using 3.0% EtOAc in hexane, gave **44.2** (2.7 mg, 53%) as a viscous oil: FTIR (CH_2Cl_2, cast) 3082, 3056, 3030, 2952, 2926, 2853, 1595, 1488, 1444 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.71 (quintet, *J* = 7.2 Hz, 4 H), 2.26 (t, *J* = 7.2 Hz, 4 H), 2.56 (t, *J* = 7.2 Hz, 4 H), 7.19–7.26 (m, 6 H), 7.26–7.36 (m, 12 H), 7.37–7.50 (m, 12 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 28.0 (t), 30.6 (t), 37.8 (t), 66.7 (s), 126.7 (d), 127.9 (d), 129.6 (d), 144.9 (s); exact mass (electrospray) *m*/*z* calcd for $C_{44}H_{42}NaS_4$ 721.2062, found 721.2058.

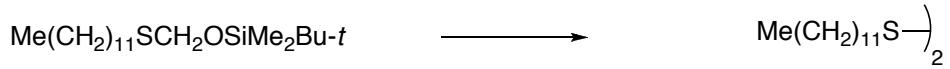
***N*,*N*'-Bis[(phenylmethoxy)carbonyl]-L-cystine 1,1'-dimethyl ester (44.3[78]) from 43.4a.**



43.4a **44.3**

A stock solution of HF·pyr (1:2:5 HF·pyr/pyr/THF by volume, 0.2 mL) was added to a solution of **43.4a** (9.7 mg, 0.023 mmol) in dry THF (0.1 mL). The solution was briefly swirled and kept at room temperature for 60 min. A solution of I_2 (20 mg, 0.079 mmol) in THF (1 mL) was added dropwise with swirling until a light brown color persisted. After 60 min the mixture was quenched with a mixture of saturated aqueous $NaHCO_3$ (3 mL) and saturated aqueous $Na_2S_2O_3$ (3 mL). The aqueous phase was extracted with EtOAc (3 x 5 mL) and the combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (0.7 x 7 cm), using 2:5 EtOAc–hexane, 3:5 EtOAc–hexane and 4:5 EtOAc–hexane, gave **44.3** (5.4 mg, 87%) a viscous oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.16 (d, *J* = 4.9 Hz, 4 H), 3.75 (s, 6 H), 4.67 (dd, *J* = 12.6, 4.9 Hz, 2 H), 5.12 (s, 4 H), 5.68 (d, *J* = 7.5 Hz, 2 H), 7.28–7.40 (m, 10 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 41.2 (t), 52.8 (q), 53.3 (d), 67.3 (t), 128.2 (d), 128.3 (d), 128.6 (d), 136.1 (s), 155.7 (s), 170.8 (s); exact mass (electrospray) *m/z* calcd for $C_{24}H_{28}N_2NaO_8S_2$ 559.1179, found 559.1175.

Dododecyl disulfide (44.4[80]) from 43.5a.

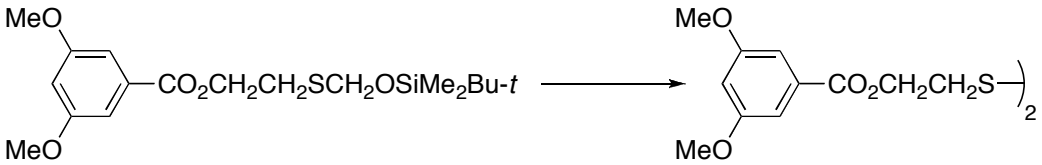


43.5a **44.4**

A stock solution of HF·pyr (1:2:5 HF·pyr/pyr/THF by volume, 0.2 mL) was added to a solution of **43.5a** (13 mg, 0.038 mmol) in dry THF (0.2 mL). The mixture was briefly swirled and kept at room temperature for 50 min. A solution of I_2 (20 mg, 0.079 mmol) in THF (1 mL) was added dropwise with swirling until a light brown color persisted. The mixture was left at room temperature overnight and quenched with a mixture of saturated aqueous $NaHCO_3$ (3 mL) and saturated aqueous $Na_2S_2O_3$ (3 mL). The aqueous phase was extracted with EtOAc (3 x 5 mL) and the combined organic extracts were washed with aqueous $NaHSO_4$ (1 M, 3 mL) and brine, dried ($MgSO_4$) and evaporated. Preparative TLC of the residue (silica gel, 0.25 mm, 10 cm x 10 cm), using hexane, gave **44.4** (6.7 mg, 89%): mp

31–32 °C; FTIR (CH_2Cl_2, cast) 2954, 2920, 2871, 2850, 1470 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.88 (t, *J* = 6.8 Hz, 6 H), 1.05–1.33 (m, 32 H), 1.34–1.43 (m, 4 H), 1.67 (quintet, *J* = 7.4 Hz, 4 H), 2.68 (t, *J* = 7.3 Hz, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.2 (q), 22.7 (t), 28.6 (t), 29.3 (t), 29.4 (t), 29.6 (t), 29.66 (t), 29.69 (t), 29.71(t), 32.0 (t), 39.3 (t); exact mass *m/z* calcd for $C_{24}H_{50}S_2$ 402.3354, found 402.3352.

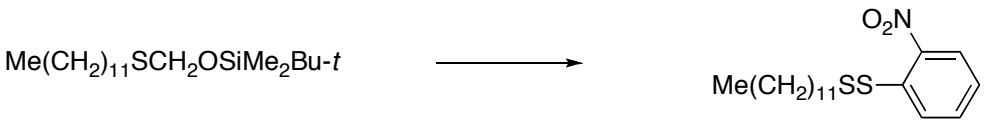
3,4-Dimethoxybenzoic acid, 1,1'-(dithiodi-2,1-ethanediyl) ester (44.5) from 43.6b.



43.6b **44.5**

A stock solution of HF·pyr (1:2:5 HF·pyr/pyr/THF by volume, 0.1 mL) was added to a solution of **43.6b** (4.3 mg, 0.011 mmol) in dry THF (0.1 mL). The mixture was briefly swirled and kept at room temperature for 6 h and a solution of I_2 (0.083 M in THF, 67 μL, 0.0056 mmol) was added. The mixture was swirled for 1 min and quenched with a mixture of saturated aqueous $NaHCO_3$ (3 mL) and saturated aqueous $Na_2S_2O_3$ (3 mL). The aqueous phase was extracted with EtOAc (3 x 5 mL) and the combined organic extracts were washed with aqueous $NaHSO_4$ (1 M, 3 mL) and brine, dried ($MgSO_4$) and evaporated. Preparative TLC of the residue (silica gel, 0.25 mm, 7 cm x 5 cm), using 3:10 EtOAc–hexane, gave **44.5** (2.4 mg, 91%) as a colorless oil: FTIR (CH_2Cl_2, cast) 3002, 2942, 2840, 1720, 1597, 1460, 1428 cm^{-1}; ^1H NMR ($CDCl_3$, 498 MHz) δ 3.08 (t, *J* = 6.6 Hz, 4 H), 3.82 (s, 12 H), 4.58 (t, *J* = 6.6 Hz, 4 H), 6.64 (t, *J* = 2.4 Hz, 2 H), 7.18 (d, *J* = 2.4 Hz, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 37.4 (t), 55.6 (q), 63.0 (t), 105.9 (d), 107.3 (d), 131.8 (s), 160.7 (s), 166.2 (s); exact mass (electrospray) *m/z* calcd for $C_{22}H_{26}NaO_8S_2$ 505.0961, found 505.0961.

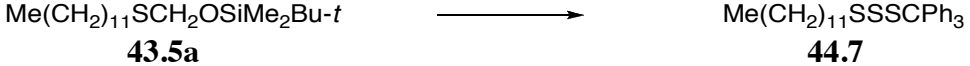
Dodecyl 2-nitrophenyl disulfide (44.6) from 43.5a.



43.5a **44.6**

2-Nitrobenzenesulfenyl chloride (16.2 mg, 0.083 mmol) was added to a stirred solution of **43.5a** (12.4 mg, 0.036 mmol) and 2,6-lutidine (15.3 mg, 0.14 mmol) in dry CH_2Cl_2 (0.8 mL). Stirring at room temperature was continued for 20 min and the mixture was quenched with water (5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic extracts were washed with aqueous $NaHSO_4$ (1 M, 3 mL) and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (0.7 x 7 cm), using 2% EtOAc in hexane and 3% EtOAc in hexane, gave **44.6** (12.2 mg, 96%): mp 41–44 °C; FTIR (CH_2Cl_2, cast) 3058, 2924, 2853, 1491, 1465, 1443 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.88 (t, *J* = 7.0 Hz, 3 H), 1.11–1.33 (m, 16 H), 1.34–1.43 (m, 2 H), 1.67 (dt, *J* = 14.9, 7.5 Hz, 2 H), 2.73 (t, *J* = 7.5 Hz, 2 H), 7.34 (ddd, *J* = 8.3, 7.1, 1.3 Hz, 1 H), 7.67 (ddd, *J* = 8.3, 7.1, 1.4 Hz, 1 H), 8.26 (dd, *J* = 8.3, 1.5 Hz, 1 H), 8.29 (dd, *J* = 8.2, 1.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.2 (q), 22.7 (t), 28.6 (t), 29.1 (t), 29.2 (t), 29.4 (t), 29.5 (t), 29.6 (t), 29.7 (t), 32.0 (t), 38.6 (t), 126.0 (d), 126.2 (d), 127.4 (d), 133.9 (d), 138.1 (s), 145.8 (s); exact mass (electrospray) *m/z* calcd for $C_{18}H_{29}NNaO_2S_2$ 378.1532, found 378.1531.

Dodecyl triphenylmethyl trisulfide (44.7) from 43.5a.

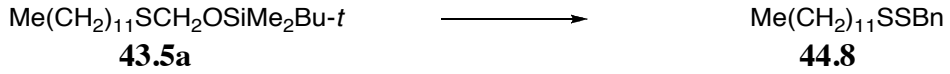


43.5a **44.7**

Ph_3CSSCl[64] (7.7 mg, 0.025 mmol) was added to a stirred solution of **43.5a** (7.8 mg, 0.023 mmol) and 2,6-lutidine (2.4 mg, 0.023 mmol) in dry CH_2Cl_2 (0.5 mL). Stirring at room temperature was continued for 1 h and the mixture was

quenched with water (5 mL) and aqueous $NaHSO_4$ (1 M, 2 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (0.7 x 7 cm), using 1% EtOAc in hexane and 1.5% EtOAc in hexane, gave **44.7** (10.6 mg, 93%) as a colorless, viscous oil: FTIR (CH_2Cl_2, cast) 3092, 2925, 2853, 1591, 1567, 1517, 1466, 1450 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.91 (t, J = 7.0 Hz, 3 H), 1.20–1.37 (m, 18 H), 1.61 (quintet, J = 7.3 Hz, 2 H), 2.64 (t, J = 7.3 Hz, 2 H), 7.20–7.43 (m, 15 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.2 (q), 22.7 (t), 28.4 (t), 29.0 (t), 29.2 (t), 29.4 (t), 29.5 (t), 29.6 (t), 29.68 (t), 29.69 (t), 32.0 (t), 39.7 (t), 73.3 (s), 127.2 (d), 127.9 (d), 130.5 (d), 143.6 (s); exact mass (electrospray) m/z calcd for $C_{31}H_{40}NaS_3$ 531.2184, found 531.2186.

Dodecyl phenylmethyl disulfide (44.8[81]) from 43.5a.



SO_2Cl_2 (41.6 mg, 0.31 mmol) was added to a stirred solution of BnSSBn (94.8 mg, 0.39 mmol) in dry CH_2Cl_2 (3 mL) and stirring at room temperature was continued for 7 h.[12]

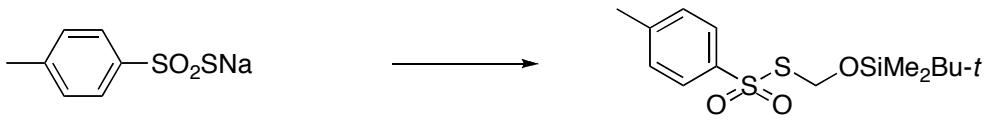
A solution of the resulting BnSCl (0.21 M, 0.21 mL, 0.44 mmol) was added to a stirred solution of **43.5a** (14 mg, 0.040 mmol) and 2,6-lutidine (8.6 mg, 0.080 mmol) in dry CH_2Cl_2 (0.5 mL). Stirring at room temperature was continued for 10 min, and mixture was diluted with CH_2Cl_2 (5 mL) and washed with aqueous $NaHSO_4$ (1 M, 5 mL). The aqueous phase was extracted with CH_2Cl_2 (5 mL), and the combined organic extracts were dried ($MgSO_4$) and evaporated. Preparative TLC of the residue (silica gel, 0.25 mm, 10 cm x 10 cm), using hexane, gave **44.8** (8.5 mg, 66%) as a colorless oil: FTIR ($CDCl_3$, cast) 3063, 2954, 2924, 2853, 1495, 1465, 1454, 1414 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.89 (t, J = 7.0 Hz, 3 H), 1.26–1.32 (m, 18 H), 1.54 (quintet, J = 7.0 Hz, 2 H),

2.40 (t, J = 7.0 Hz, 2 H), 3.89 (s, 2 H), 7.25–7.34 (m, 5 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.2 (q), 22.7 (t), 28.5 (t), 29.1 (t), 29.2 (t), 29.4 (t), 29.5 (t), 29.6 (t), 29.69 (t), 29.70 (t), 32.0 (t), 38.8 (t), 43.8 (t), 127.4 (d), 128.5 (d), 129.3 (d), 137.7 (s); exact mass m/z calcd for $C_{19}H_{32}S_2$ 324.1946, found 324.1951.

Method of analysis of amount of test substrate remaining (Table 1).

The ^{1}H NMR spectrum of the test substrate **43.5a** shows a sharp signal at 4.8 ppm (SCH_2O) and a methylene envelope at 1.2-1.44 pp (18 H). To determine the extent of decomposition of **43.5a**, the ^{1}H NMR spectrum of the crude reaction mixture was run; the 4.8 ppm signal was taken as corresponding to 2 H and the intensity of the high-field methylene envelope was measured and found to correspond on the same scale to x H. Division of 18 (the value for no decomposition) by x gives the percent of **43.5a** remaining. Dodecanethiol and its derivatives have a very high boiling point and there should be no losses on workup (we use only a water pump vacuum at room temperature). We confirmed this assumption with dodecanethiol itself and found 0.8% loss even after brief oil-pump exposure of the crude material (we used a water pump for the tests).

***S*-[[[(1,1-Dimethyl)ethyl)dimethylsilyl]oxy]methyl] 4-methylbenzene-sulfonothioic acid ester (45.2).**

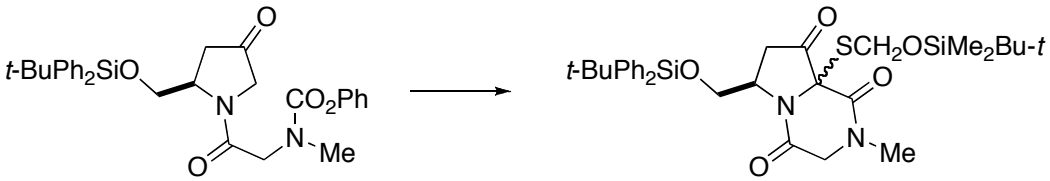


- **45.2**

$TolSO_2SNa$ (385.3 mg, 2.46 mmol) was added to a stirred solution of *t*-$BuMe_2SiOCH_2Cl$ (**42.4**) (121.7 mg, 2.46 mmol) in dry MeCN (3 mL). Stirring at room temperature was continued for 16 h, and the mixture was diluted with Et_2O (10 mL) and filtered through a pad of Celite, using Et_2O as a rinse. Evaporation of the filtrate and flash chromatography of the residue over silica gel (2.2 x 15 cm), using 1:50 EtOAc–hexane and then 1:20 EtOAc–hexane, gave **45.2** (483 mg,

59%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ -0.04 (s, 6 H); 0.75 (s, 9 H), 2.42 (2, 3 H), 5.40 (s, 2 H), 7.28–7.31 (m, 2 H), 7.81–7.86 (m, 2 H). The compound is unstable at room temperature, decomposes slowly on attempted flash chromatography (silica or alumina), but can be kept in a freezer for at least 2 months.

(6*R*)-8a-({[(*tert*-Butyldimethylsilyl)oxy]methyl}sulfanyl)-6-{[(*tert*-butyldiphenylsilyl)oxy]methyl}-2-methyloctahydropyrrolo[1,2-*a*]piperazine-1,4,8-trione (45.3a,b).



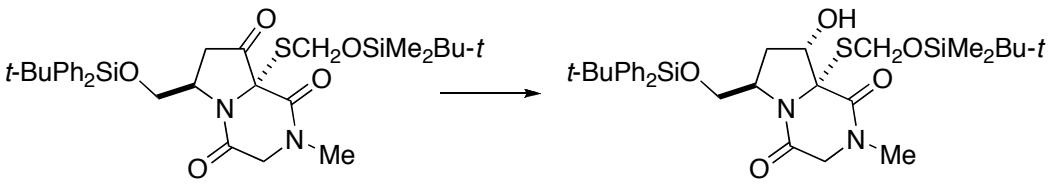
NaH (60% in mineral oil, 309.7 mg, 7.7 mmol) was added to a solution of **25.8** (1.92 g, 3.5 mmol) in dry THF (35 mL). The reaction flask was lowered into a preheated oil bath (70 °C), and the mixture was heated for 20 min, cooled to 0 °C, quenched with pH 7.0 buffer (0.2 M, 35 mL) and then with aqueous HCl (1.0 M, 7.7 mL). The aqueous phase was extracted with EtOAc (3 x 20 mL) and the combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated.

The resulting residue was dissolved in dry CH_2Cl_2 (35 mL) and a solution of *t*-$BuMe_2SiOCH_2SSO_2Tol$ (1.16 g, 3.5 mmol) in CH_2Cl_2 (2 mL) was added, followed by slow addition (3 min) of Et_3N (531.2 mg, 5.25 mmol). The homogeneous mixture was swirled occasionally for 10 min and filtered through a pad of silica gel (1.8 x 10 cm), using 3:2 EtOAc–hexane. Evaporation of the filtrate and flash chromatography of the residue over silica gel (3 x 15 cm), using 1:5 EtOAc–hexane, 3:10 EtOAc–hexane, 2:5 EtOAc–hexane and 3:5 EtOAc–hexane, gave **45.3a** (672.8 mg, 31%) as a foam and **45.3b** (257.0 mg 12%) as a foam.

45.3a: mp 123-126 °C; $[\alpha]_D$ = 13.16 (*c* 1.12, CH_2Cl_2); FTIR (CH_2Cl_2, cast) 3072, 3051, 2954, 2931, 2886, 2858, 1780, 1690, 1590, 1472, 1428, 1407 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.09 (s, 3 H), 0.10 (s, 3 H), 0.88 (s, 9 H), 0.97 (s, 9 H), 2.63 (dd, *J* = 18.1, 3.2 Hz, 1 H), 2.98 (s, 3 H), 3.25 (dd, *J* = 18.0, 9.7 Hz, 1 H), 3.56 (dd, *J* = 10.6, 1.7 Hz, 1 H), 3.76 (d, *J* = 17.0 Hz, 1 H), 4.30 (dd, *J* = 10.6, 3.0 Hz, 1 H), 4.35 (dquintet, *J* = 9.5, 1.5 Hz, 1 H), 4.39 (d, *J* = 17.0 Hz, 1 H), 4.96 (d, *J* = 11.4 Hz, 1 H), 5.18 (d, *J* = 11.4 Hz, 1 H), 7.35-7.39 (m, 4 H), 7.41-7.44 (m, 2 H), 7.51-7.53 (m, 2 H), 7.56-7.58 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ -5.3 (q), -5.1 (q), 18.2 (s), 19.1 (s), 25.7 (q), 26.6 (q), 33.9 (q), 36.6 (t), 53.0 (d), 53.3 (t), 62.3 (t), 62.8 (s), 65.8 (t), 127.8 (d), 127.9 (d), 129.9 (d), 130.0 (d), 132.67 (s), 132.69 (s), 135.6 (d), 135.7 (d), 161.1 (s), 165.8 (s), 196.1 (s); exact mass (electrospray) *m*/*z* calcd for $C_{32}H_{46}N_2NaO_5SSi_2$ 649.2558, found 649.2554.

45.3b: $[\alpha]_D$ = 1.79 (*c* 1.04, CH_2Cl_2); FTIR (CH_2Cl_2, cast) 3071, 3050, 2998, 2955, 2930, 2886, 2857, 1776, 1728, 1689, 1589, 1472, 1463, 1427 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.067 (s, 3 H), 0.069 (s, 3 H), 0.86 (s, 9 H), 1.06 (s, 9 H), 2.76 (dd, *J* = 19.1, 9.5 Hz, 1 H), 2.94 (dd, *J* = 19.1, 2.8 Hz, 1 H), 2.98 (s, 3 H), 3.72-3.77 (m, 2 H), 3.98 (dd, *J* = 10.0, 4.8 Hz, 1 H), 4.44 (d, *J* = 16.6 Hz, 1 H), 4.56 (dddd, *J* = 9.6, 8.1, 4.9, 3.1 Hz, 1 H), 4.93 (d, *J* = 11.7 Hz, 1 H), 5.20 (d, *J* = 11.7 Hz, 1 H), 7.37-7.45 (m, 6 H), 7.63-7.66 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -5.2 (q), 18.2 (s), 19.3 (s), 25.7 (q), 26.9 (q), 34.4 (q), 37.4 (t), 52.7 (t), 52.8 (d), 63.4 (s), 63.8 (t), 65.7 (t), 127.8 (d), 127.9 (d), 129.9 (d), 130.0 (d), 132.93 (s), 132.95 (s), 135.59 (d), 135.60 (d), 160.9 (s), 164.7 (s), 199.3 (s); exact mass (electrospray) *m*/*z* calcd for $C_{32}H_{46}N_2NaO_5SSi_2$ 649.2558, found 649.2554.

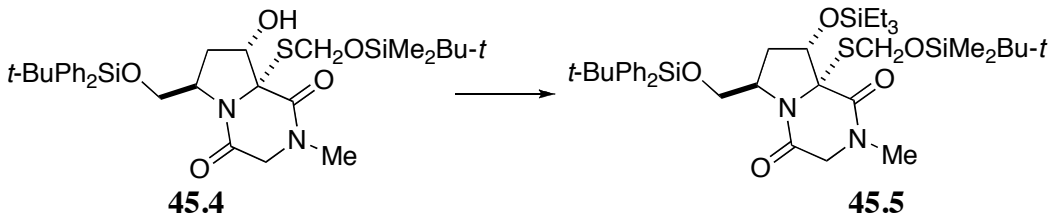
(6*R*,8*S*,8a*R*)-8a-({[(*tert*-Butyldimethylsilyl)oxy]methyl}sulfanyl)-6-{[(*tert*-butyldiphenylsilyl)oxy]methyl}-8-hydroxy-2-methyloctahydro-pyrrolo[1,2-*a*]piperazine-1,4-dione (45.4).



45.3a **45.4**

$NaBH_4$ (40.7 mg, 1.07 mmol) was added to a stirred and cooled (0 °C) solution of **45.3a** (672.8 mg, 1.07 mmol) in a mixture of THF (5 mL) and water (0.63 mL). Stirring at 0 °C was continued for 18 min and the mixture was diluted with water and extracted with EtOAc (3 times). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.8 x 15 cm), using 1:5 EtOAc–hexane and 2:5 EtOAc–hexane, gave **45.4** (633 mg, 94%) as a foam: $[\alpha]_D$ = -71.54 (*c* 0.40, CH_2Cl_2); FTIR (CH_2Cl_2, cast) 3436 (br), 3072, 3050, 2954, 2930, 2886, 2857, 1679, 1590, 1472, 1463, 1428, 1414 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.117 (s, 3 H), 0.121 (s, 3 H), 0.89 (s, 9 H), 1.02 (s, 9 H), 2.28-2.38 (m, 2 H), 2.98 (s, 3 H), 3.44 (d, *J* = 4.8 Hz, 1 H), 3.63 (dd, *J* = 10.5, 2.0 Hz, 1 H), 3.69 (d, *J* = 17.2 Hz, 1 H), 4.06 (dquintet, *J* = 9.0, 1.5 Hz, 1 H), 4.21 (dd, *J* = 10.5, 3.8 Hz, 1 H), 4.41 (d, *J* = 17.2 Hz, 1 H), 4.86-4.92 (m, 3 H), 7.35-7.44 (m, 6 H), 7.56-7.61 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ -5.2 (q), -5.0 (q), 18.2 (s), 19.2 (s), 25.7 (q), 26.8 (q), 32.5 (t), 33.4 (q), 53.4 (t), 55.7 (d), 62.4 (t), 64.5 (t), 73.70 (s), 73.71 (d), 127.7 (d), 127.8 (d), 129.8 (d), 132.8 (s), 133.1 (s), 135.5 (d), 135.6 (d), 165.0 (s), 166.3 (s); exact mass (electrospray) *m*/*z* calcd for $C_{32}H_{48}N_2NaO_5SSi_2$ 651.2715, found 651.2710.

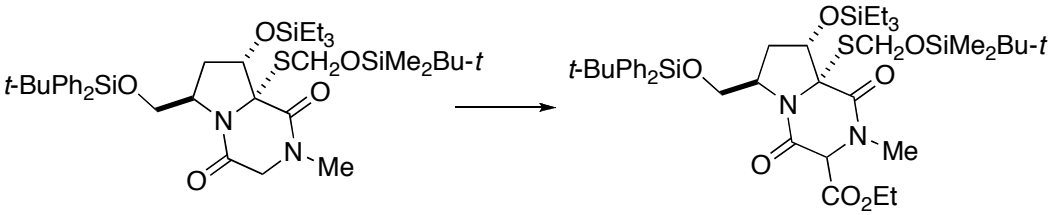
(6*R*,8*S*,8a*R*)-8a-({[(*tert*-Butyldimethylsilyl)oxy]methyl}sulfanyl)-6-{[(*tert*-butyldiphenylsilyl)oxy]methyl}-2-methyl-8-[(triethylsilyl)oxy]octahydropyrrolo[1,2-*a*]piperazine-1,4-dione (45.5).



$Et_3SiOSO_2CF_3$ (23.3 mg, 0.088 mmol) was added to a stirred and cooled (-78 °C) solution of **45.4** (46.1 mg, 0.073 mmol) and 2,6-lutidine (18.1 mg, 0.17 mmol) in CH_2Cl_2 (1 mL). Stirring at -78 °C was continued for 30 min and the mixture was quenched with water (2 mL). The cooling bath was removed and the mixture was allowed to warm to room temperature (ca 3 min). Aqueous $NaHSO_4$ (1 M, 0.5 mL) and saturated aqueous $CuSO_4$ (5 mL) were added and the aqueous phase was extracted with CH_2Cl_2 (3 times). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (0.8 x 18 cm), using 1:10 EtOAc–hexane and 1:5 EtOAc–hexane, gave **45.5** (54.4 mg, 100%) as a white solid: mp 95-97 °C; $[\alpha]_D$ = 18.12 (*c* 0.32, CH_2Cl_2); FTIR (CH_2Cl_2, cast) 3072, 3050, 2954, 2932, 2858, 1683, 1590, 1487, 1472, 1463, 1428, 1412 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.07 (s, 3 H), 0.08 (s, 3 H), 0.62-0.75 (m, 6 H), 0.88 (s, 9 H), 0.98 (t, *J* = 7.9 Hz, 9 H), 1.03 (s, 9 H), 2.17 (ddd, *J* = 12.4, 7.1, 0.9 Hz, 1 H), 2.28 (dt, *J* = 12.3, 10.1 Hz, 1 H), 2.98 (s, 3 H), 3.56 (dd, *J* = 10.3, 1.8 Hz, 1 H), 3.67 (d, *J* = 16.9 Hz, 1 H), 4.04-4.06 (m, 1 H), 4.09 (dd, *J* = 10.3, 3.7 Hz, 1 H), 4.50 (d, *J* = 17.0 Hz, 1 H), 4.85 (d, *J* = 11.4 Hz, 1 H), 4.95 (dd, *J* = 10.4, 7.1 Hz, 1 H), 5.11 (d, *J* = 11.4 Hz, 1 H), 7.34-7.44 (m, 6 H), 7.56 (dt, *J* = 6.5, 1.5 Hz, 2 H), 7.60 (dt, *J* = 6.4, 1.6 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ -5.1 (q), -4.9 (q), 4.9 (t), 6.9 (q), 18.2 (s), 19.2 (s), 25.8 (q), 26.8 (q), 33.8 (t), 34.5 (q), 53.6 (t), 55.3 (d), 62.9 (t), 65.2 (t), 72.5 (s), 73.6 (d), 127.7 (d), 129.8 (d), 129.9 (d), 132.8 (s), 133.3 (s), 135.5 (d), 135.6 (d), 165.5 (s),

166.0 (s); exact mass (electrospray) *m*/*z* calcd for $C_{38}H_{62}N_2NaO_5SSi_3$ 765.3579, found 765.3576.

Ethyl (6*R*,8*S*,8a*R*)-8a-({[(*tert*-Butyldimethylsilyl)oxy]methyl}-sulfanyl)-6-{[(*tert*-butyldiphenylsilyl)oxy]methyl}-2-methyl-1,4-dioxo-8-[(triethylsilyl)oxy]octahydropyrrolo[1,2-*a*]piperazine-3-carboxylate (45.6a,b).



45.5 **45.6a,b**

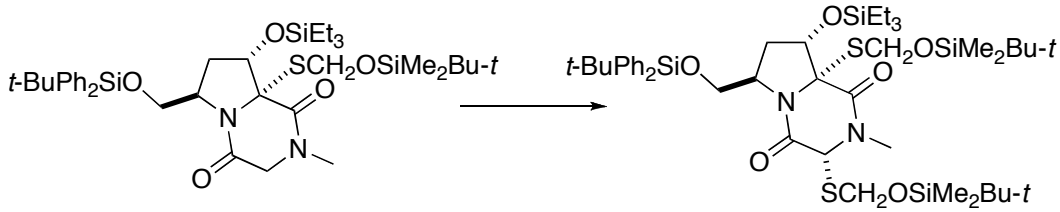
$ClCO_2Et$ (120.6 mg, 1.11 mmol) was added to a stirred and cooled (-78 °C) solution of **45.5** (41.2 mg, 0.056 mmol) in THF (2 mL), followed by LDA (0.079 M, 1.8 mL, 0.14 mmol) which was added at a fast dropwise rate. Stirring at -79 °C was continued for 5 min and the mixture was quenched with aqueous $NaHSO_4$ (1 M, 5 mL). The cooling bath was removed and the mixture was allowed to warm to room temperature (ca 5 min). The mixture was diluted with water and the aqueous phase was extracted with EtOAc (3 x 7 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (0.8 x 15 cm), using 1:20 EtOAc–hexane, 1:10 EtOAc–hexane, 3:20 EtOAc–hexane and 2:5 EtOAc–hexane, gave **45.6a** (13.7 mg, 30%) as a foam and **45.6b** (26.0 mg, 57%) as a foam.

45.6a: $[\alpha]_D$ = 33.16 (*c* 0.41, CH_2Cl_2); FTIR (CH_2Cl_2, cast) 3072, 3050, 2955, 2932, 2877, 2858, 1757, 1686, 1590, 1472, 1464, 1444, 1428, 1414 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.08 (s, 3 H), 0.09 (s, 3 H), 0.59-0.72 (m, 6 H), 0.88 (s, 9 H), 0.96 (t, *J* = 7.9 Hz, 9 H), 1.04 (s, 9 H), 1.28 (t, *J* = 7.1 Hz, 3 H), 2.14 (dd, *J* = 12.4, 7.2 Hz, 1 H), 2.23-2.29 (m, 1 H), 2.96 (s, 3 H), 3.52 (dd, *J* = 10.4, 1.6 Hz, 1 H), 4.06-4.08 (m, 1 H), 4.11-4.14 (m, 1 H), 4.25 (dq, *J* = 10.8, 7.1 Hz, 1

H), 4.38 (dq, *J* = 10.8, 7.1 Hz, 1 H), 4.83 (d, *J* = 11.6 Hz, 1 H), 4.95 (dd, *J* = 10.2, 7.1 Hz, 1 H), 5.13 (s, 1 H), 7.34-7.43 (m, 6 H), 7.58-7.62 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ -5.1 (q), -4.8 (q), 4.9 (t), 6.8 (q), 14.1 (q), 18.3 (s), 19.2 (s), 25.9 (q), 26.9 (q), 32.7 (q), 34.4 (t), 55.9 (d), 62.3 (t), 62.6 (t), 65.2 (t), 66.7 (d), 72.2 (s), 73.6 (d), 127.8 (d), 129.7 (d), 129.8 (d), 132.7 (s), 133.4 (s), 135.5 (d), 135.7 (d), 163.1 (s), 165.5 (s), 165.6 (s); exact mass (electrospray) *m*/*z* calcd for $C_{41}H_{66}N_2NaO_7SSi_3$ 837.3791, found 837.3786.

45.6b: $[\alpha]_D$ = 17.87 (*c* 0.62, CH_2Cl_2); FTIR (CH_2Cl_2, cast) 3072, 2955, 2932, 2878, 2858, 1749, 1687 1472, 1464, 1445, 1427, 1414 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.08 (s, 3 H), 0.09 (s, 3 H), 0.60-0.74 (m, 6 H), 0.98 (t, *J* = 8.0 Hz, 9 H), 1.01 (s, 9 H), 1.32 (t, *J* = 7.1 Hz, 3 H), 2.12 (dd, *J* = 12.3, 7.0 Hz, 1 H), 2.37-2.44 (m, 1 H), 3.16 (s, 3 H), 3.52 (dd, *J* = 10.5, 1.7 Hz, 1 H), 4.09 (d, *J* = 8.8 Hz, 1 H), 4.19-4.25 (m, *J* = 5.8 Hz, 2 H), 4.32 (dq, *J* = 10.7, 7.1 Hz, 1 H), 4.43 (s, 1 H), 4.91-4.95 (m, 2 H), 4.99 (d, *J* = 9.3 Hz, 1 H), 7.35-7.44 (m, 6 H), 7.50-7.60 (m, *J* = 1.3 Hz, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ -5.33 (q), -5.26 (q), 4.9 (t), 6.9 (q), 14.0 (q), 18.2 (s), 19.2 (s), 25.8 (q), 26.7 (q), 34.4 (t), 35.0 (q), 56.0 (d), 62.57 (t), 62.61 (t), 65.6 (t), 66.9 (d), 71.6 (s), 74.1 (d), 127.78 (d), 127.80 (d), 129.8 (d), 129.9 (d), 132.6 (s), 133.3 (s), 135.5 (d), 135.7 (d), 161.9 (s), 165.5 (s), 165.8 (s); exact mass (electrospray) *m*/*z* calcd for $C_{41}H_{66}N_2NaO_7SSi_3$ 837.3791, found 837.3786.

(3*R*,6*R*,8*S*,8a*R*)-3,8a-Bis({[(*tert*-butyldimethylsilyl)oxy]methyl}-sulfanyl)-6-{[(*tert*-butyldiphenylsilyl)oxy]methyl}-2-methyl-8-[(triethylsilyl)oxy]octahydropyrrolo[1,2-*a*]piperazine-1,4-dione (45.8).



45.5 **45.8**

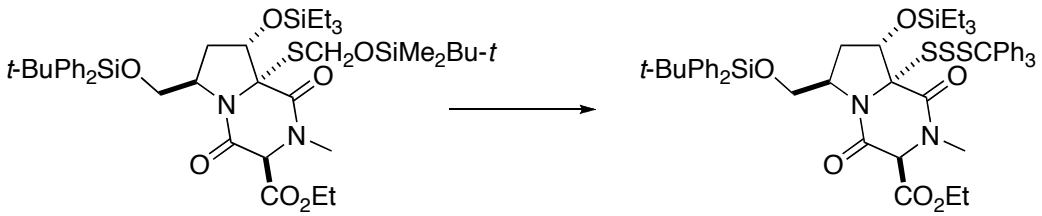
n-BuLi (2.4 M, 0.3 mL, 0.72 mmol) was added dropwise to a stirred and cooled (-78°C) solution of *i*-Pr_2NH (80.1 mg, 0.79 mmol) in THF (8.7 mL). Stirring at -78°C was continued for 30 min.

The above fresh LDA solution (0.079 M, 0.64 mL, 0.051 mmol) was added dropwise over a few seconds to a stirred and cooled (-78 °C) solution of **45.5** (34 mg, 0.046 mmol) in THF (1 mL). Stirring at -78 °C was continued for 1 min and a solution of $TolSO_2SCH_2OSiMe_2Bu$-*t* (15.3 mg, 0.046 mmol) in THF (0.5 mL) was added dropwise over a few seconds. Stirring at -78 °C was continued for 5 min and the mixture was quenched with aqueous $NaHSO_4$ (1 M, 2 mL). The cooling bath was removed, and the mixture was diluted with water (8 mL) and allowed to warm to room temperature. The mixture was extracted with EtOAc (3 x 6 mL), and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (0.8 x 10 cm), using 1:20 Et_2O–pentane, 2:25 Et_2O–pentane, and then 3:25 Et_2O–pentane, gave crude product (33.8 mg, 80%) as a foam.

LDA in THF (0.079 M, 1.9 mL, 0.15 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of the above compound (33.8 mg, 0.037 mmol) in THF (2.8 mL). Stirring at -78 °C was continued for 2 min, and the mixture was quenched with a mixture of aqueous HCl (1 M, 0.3 mL) and THF (1 mL) in one shot. The cooling bath was removed and the mixture was allowed to warm to room temperature. The mixture was diluted with water (10 mL) and extracted with EtOAc (2 x 10 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (0.8 x 10 cm), using 3:25 Et_2O–pentane, gave **45.8** (31 mg, 92%) as a foam: $[\alpha]_D$ = -28.57 (*c* 0.66, CH_2Cl_2); FTIR (CH_2Cl_2, cast) 3072, 2955, 2931, 2880, 2858, 1680, 1590, 1472, 1463, 1428, 1418 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.09 (s, 3 H), 0.10 (s, 3 H), 0.16 (s, 6 H), 0.60-0.73 (m, 6 H), 0.88 (s, 9 H), 0.95 (s, 9 H), 0.98 (t, *J* = 7.9 Hz, 9 H), 1.02 (s, 9 H), 2.11-2.14 (m, 1 H), 2.39 (dt, *J* = 12.3, 10.3 Hz, 1 H), 3.05 (s, 3 H), 3.56 (dd, *J* = 10.4, 1.8 Hz, 1 H), 4.07-4.09 (m, 1 H), 4.18 (dd, *J* = 10.4, 3.6 Hz, 1 H), 4.74 (d, *J* = 11.0 Hz, 1 H), 4.84 (s, 1 H), 4.88-4.93 (m, 2 H), 5.14 (d, *J* = 10.8 Hz, 1 H),

5.22 (d, *J* = 11.0 Hz, 1 H), 7.34-7.44 (m, 6 H), 7.55-7.60 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ -5.4 (q), -5.3 (q), -5.0 (q), -4.9 (q), 4.9 (t), 6.9 (q), 18.3 (s), 18.4 (s), 19.2 (s), 25.8 (q), 25.9 (q), 26.8 (q), 31.5 (q), 34.2 (t), 55.9 (d), 62.8 (t), 64.5 (d), 65.8 (t), 67.3 (t), 71.1 (s), 73.9 (d), 127.8 (d), 129.8 (d), 129.9 (d), 132.8 (s), 133.4 (s), 135.5 (d), 135.7 (d), 165.9 (s), 166.6 (s); exact mass (electrospray) *m/z* calcd for $C_{45}H_{78}N_2NaO_6S_2Si_4$ 941.4271, found 941.4271.

Ethyl (3*R*,6*R*,8*S*,8a*R*)-6-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-2-methyl-1,4-dioxo-8-[(triethylsilyl)oxy]-8a-{[(triphenylmethyl)sulfanyl]-disulfanyl}octahydropyrrolo[1,2-*a*]piperazine-3-carboxylate (45.7).

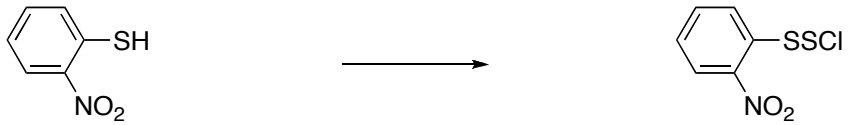


45.6a **45.7**

Ph_3CSSCl[64] (9.3 mg, 0.049 mmol) was added to a stirred solution of **45.6a** (8.0 mg, 0.0098 mmol) and 2,6-lutidine (6.3 mg, 0.059 mmol) in CH_2Cl_2 (0.5 mL). Stirring at room temperature was continued for 30 min, and more Ph_3CSSCl (12.0 mg, 0.063 mmol) and 2,6-lutidine (9.3 mg, 0.087 mmol) were added. Stirring was continued for another 30 min and mixture was quenched with aqueous $NaHSO_4$ (1 M, 4 mL) and water (5 mL). The aqueous phase was extracted with EtOAc (3 x 6 mL) and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$) and evaporated. Preparative TLC of the residue (silica gel, 0.25 mm, 10 x 10 cm), using 1:10 EtOAc–hexane, gave **45.7** (8.4 mg, 88%) as an oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.55-0.71 (m, 6 H), 0.96 (t, *J* = 7.9 Hz, 9 H), 1.06 (s, 9 H), 1.24 (t, *J* = 7.1 Hz, 3 H), 2.11-2.14 (m, 2 H), 2.92 (s, 3 H), 3.57 (dd, *J* = 10.6, 2.0 Hz, 1 H), 4.10-4.19 (m, 2 H), 4.27-4.35 (m, 2 H), 4.85 (t, *J* = 8.5 Hz, 1 H), 5.15 (s, 1 H), 7.25-7.43 (m,

21 H), 7.60-7.63 (m, 4 H); exact mass (electrospray) *m/z* calcd for $C_{53}H_{64}N_2NaO_6S_3Si_2$ 999.3357, found 999.3361.

1-(Chlorodisulfanyl)-2-nitrobenzene (48.2).[72]



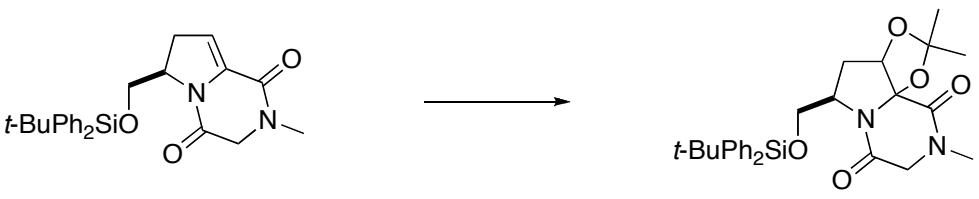
48.1 **48.2**

Distillation of SCl_2: PCl_3 (5 drops from a pipette) was added to SCl_2 (10 mL), and SCl_2 was distilled at 1 atm pressure with protection from moisture (drying tube packed with Drierite). The bp was 58-60 °C and the freshly distilled SCl_2 was used immediately for the reaction.

A solution of **48.1** (0.74 g, 4.8 mmol) in dry Et_2O (17 mL) was added to a stirred and cooled (-78 °C) solution of SCl_2 (2.46 g, 23.9 mmol) in dry Et_2O (17 mL) over 1 h. The cooling bath was removed and the mixture was allowed to warm to room temperature (over ca 30 min). The solvent and excess of SCl_2 was evaporated (protection from moisture). The resulting yellow solid was dissolved in dry Et_2O (8 mL) and the solution was evaporated again; this process (addition of Et_2O and evaporation with protection from moisture) was repeated 3 times. The residual solid was further dried under oil pump for ca 3 min, and the flask was filled with N_2; this process of evacuation and filling with N_2 was repeated 3 times. The resulting solid was dissolved in dry Et_2O (ca 8 mL) and the mixture was filtered through a pad of cotton wool in a pipette to remove some particulate matter. The round bottom flask containing the filtrate was sealed with a septum (Parafilm being used to wrap around the septum), put into a Drierite bottle containing some Drierite and stored in the freezer (ca -20 °C) overnight. Yellow crystals precipitated out during this time. The flask was placed in a cold bath at -20 °C and slowly cooled (over ca 30 min) from -20 °C to -78 °C by slowly adding more dry ice into the dry ice-acetone cooling bath. The supernatant was removed, using a needle and syringe. The residual solid was washed with dry Et_2O (2 mL)

at -78 °C [Et_2O at room temperature was added to the flask which was in the cold bath (-78 °C)], and the supernatant solution was again removed. The solid was quickly dried under oil pump vacuum, the flask was sealed with a septum (Parafilm), filled with N_2 and stored in the freezer in a Drierite bottle: mp 61-64 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.53 (ddd, *J* = 8.2, 7.3, 1.3 Hz, 1 H), 7.85 (ddd, *J* = 8.2, 7.3, 1.4 Hz, 1 H), 8.30-8.32 (m, 1 H), 8.33 (ddd, *J* = 8.2, 1.3, 0.3 Hz, 1 H).

(7*R*)-7-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-3,3,11-trimethyl-2,4-dioxa-8,11-diazatricyclo[6.4.0.0^{1,5}]dodecane-9,12-dione (50.1a,b).



36.2 **50.1a,b**

NMO (204.1 mg, 1.74 mmol) and OsO_4 (4% aqueous solution, 85 μL, 0.013 mmol) were added to a stirred solution of **36.2** (580 mg, 1.34 mmol) in a mixture of acetone (8 mL) and water (2.7 mL). Stirring at room temperature was continued for 18.5 h and the mixture was quenched with saturated aqueous $NaHCO_3$ (8 mL) and saturated aqueous $Na_2S_2O_3$ (4 mL), which were added sequentially. The mixture was diluted with water and extracted with CH_2Cl_2 (3 times). The combined organic extracts were washed with aqueous $NaHSO_4$, and the aqueous phase was extracted with CH_2Cl_2 (twice). The combined organic extracts were dried ($MgSO_4$) and evaporated.

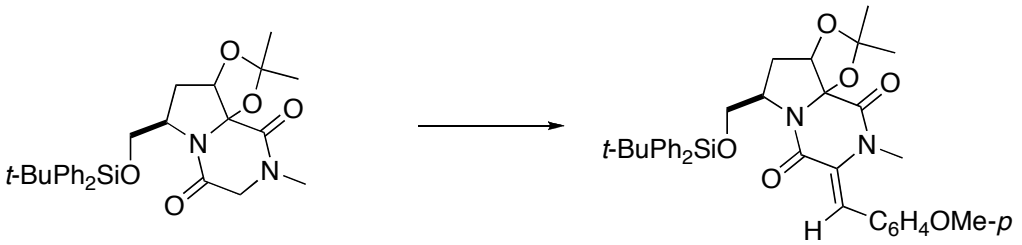
The resulting crude product was dissolved in 2,2-dimethoxypropane (12 mL) and PPTS (33.7 mg, 0.13 mmol) was added. The mixture was refluxed for 18 h, cooled to room temperature, diluted with water and extracted with EtOAc (3 times). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.7 x 15 cm), using 1:5

EtOAc–hexane, 2:5 EtOAc–hexane and 4:5 EtOAc–hexane, gave **50.1a** (264 mg, 38.8%) as a solid and **50.1b** (297 mg, 43.6%) as an oil.

50.1a: mp 145-148 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.00 (s, 9 H), 1.42 (s, 3 H), 1.46 (s, 3 H), 2.14-2.16 (m, 2 H), 3.00 (s, 3 H), 3.67 (d, *J* = 17.1 Hz, 1 H), 3.85 (dd, *J* = 10.5, 2.2 Hz, 1 H), 4.17 (tdd, *J* = 7.7, 5.0, 2.5 Hz, 1 H), 4.30 (d, *J* = 17.1 Hz, 1 H), 4.39 (dd, *J* = 10.4, 4.7 Hz, 1 H), 5.29 (t, *J* = 3.0 Hz, 1 H), 7.35-7.39 (m, 4 H), 7.40-7.44 (m, 2 H), 7.58-7.62 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.3 (s), 25.8 (q), 26.8 (q), 27.2 (q), 33.2 (t), 33.6 (q), 53.4 (t), 59.6 (d), 61.0 (t), 80.2 (d), 96.8 (s), 113.4 (s), 127.7 (d), 127.8 (d), 129.79 (d), 129.82 (d), 133.1 (s), 133.3 (s), 135.6 (d), 135.7 (d), 164.1 (s), 166.3 (s); exact mass (electrospray) *m/z* calcd for $C_{28}H_{36}N_2NaO_5Si$ 531.2286, found 531.2288.

50.1b: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.07 (s, 9 H), 1.23 (s, 3 H), 1.40 (s, 3 H), 2.00-2.06 (m, 1 H), 2.53 (d, *J* = 14.7 Hz, 1 H), 3.01 (s, 3 H), 3.65 (d, *J* = 16.4 Hz, 1 H), 3.81 (dd, *J* = 10.5, 9.1 Hz, 1 H), 4.02 (dd, *J* = 9.1, 4.8 Hz, 1 H), 4.28 (d, *J* = 16.4 Hz, 1 H), 4.46 (ddd, *J* = 10.5, 8.3, 4.9 Hz, 1 H), 5.35 (d, *J* = 5.4 Hz, 1 H), 7.35-7.44 (m, 6 H), 7.67-7.69 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.3 (s), 25.2 (q), 26.8 (q), 26.9 (q), 30.4 (t), 34.1 (q), 53.0 (t), 60.6 (d), 63.1 (t), 83.2 (d), 96.4 (s), 114.0 (s), 127.7 (d), 127.8 (d), 129.68 (d), 129.73 (d), 133.36 (s), 133.42 (s), 135.6 (d), 135.7 (d), 164.1 (s), 165.2 (s); exact mass (electrospray) *m/z* calcd for $C_{28}H_{36}N_2NaO_5Si$ 531.2286, found 531.2288.

(7*R*,10*Z*)-7-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-10-[(4-methoxyphenyl)methylidene]-3,3,11-trimethyl-2,4-dioxa-8,11-diazatricyclo[6.4.0.0^{1,5}]dodecane-9,12-dione (50.3).



50.1b **50.3**

n-BuLi (2.4 M, 0.5 mL, 1.2 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of *i*-Pr_2NH (133.6 mg, 1.32 mmol) in dry THF (10 mL). Stirring at -78 °C was continued for 30 min to generate a stock solution of LDA.

Fresh LDA (0.114 M, 3.4 mL, 0.38 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of **50.1b** (177.0 mg, 0.35 mmol) in THF (10 mL). Stirring at -78 °C was continued for 20 min and a solution of anisaldehyde (52.1 mg, 0.38 mmol) in THF (1 mL) was added dropwise. Stirring at -78 °C was continued for 25 min and the mixture was quenched with saturated aqueous NH_4Cl (4 mL). The cooling bath was removed and the mixture was allowed to warm to room temperature over ca 10 min. The mixture was diluted with water and extracted with EtOAc (3 times). The combined organic extracts were dried ($MgSO_4$) and evaporated, and the residue was dried under oil pump for ca 2 h.

The above residue was dissolved in CH_2Cl_2 (8 mL) and Et_3N (211.3 mg, 2.09 mmol), DMAP (4.3 mg, 0.035 mmol) and Ac_2O (106.6 mg, 1.04 mmol) were added sequentially. The mixture was stirred at room temperature for 4 h, diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$. The aqueous phase was extracted with CH_2Cl_2 (twice). The combined organic extracts were washed with aqueous $NaHSO_4$ (1 M), and the aqueous phase was extracted with CH_2Cl_2 (twice). The combined organic extracts were dried ($MgSO_4$ and one scoop of K_2CO_3) and evaporated. The residue was dissolved in dry THF (10 mL), and DBU (106.0 mg, 0.70 mmol) was added. The mixture was refluxed for 18 h and cooled to room temperature. The mixture was poured into aqueous $NaHSO_4$ (1 M, 15 mL) and the aqueous phase was extracted with EtOAc (3 times). The combined organic extracts were washed with saturated aqueous $NaHCO_3$, and the aqueous phase was extracted with EtOAc (twice). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.8 x 15 cm), using 1:5 EtOAc–hexane and 3:10 EtOAc–hexane, gave **50.3** (158.6 mg, 73% over 3 steps) as a foam: FTIR (CH_2Cl_2, cast) 3072, 2997, 2957, 2933, 2892, 2858, 1689, 1632, 1607, 1574, 1511, 1472, 1463, 1407, 1428 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.08 (s, 9 H), 1.23 (s, 3 H), 1.42 (s, 3 H), 2.08 (ddd, J = 14.4, 8.0, 6.1 Hz, 1 H), 2.58 (d, J = 14.7

Hz, 1 H), 2.92 (s, 3 H), 3.82-3.86 (m, 4 H), 4.14 (dd, *J* = 9.0, 4.8 Hz, 1 H), 4.51 (ddd, *J* = 10.7, 8.2, 4.9 Hz, 1 H), 5.42 (d, *J* = 5.5 Hz, 1 H), 6.88-6.91 (m, 2 H), 7.00 (s, 1 H), 7.25 (d, *J* = 8.5 Hz, 3 H), 7.35-7.42 (m, 6 H), 7.70 (dt, *J* = 7.5, 1.4 Hz, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.3 (s), 25.2 (q), 26.7 (q), 26.9 (q), 30.6 (t), 34.6 (q), 55.4 (q), 60.8 (d), 63.0 (t), 83.0 (d), 96.3 (s), 113.9 (s), 114.0 (d), 123.1 (d), 125.6 (s), 127.7 (d), 127.8 (d), 129.66 (d), 129.71 (d), 131.1 (s), 131.3 (d), 133.45 (s), 133.52 (d), 135.6 (d), 135.7 (d), 160.0 (s), 162.8 (s), 164.4 (s); exact mass (electrospray) *m/z* calcd for $C_{36}H_{42}N_2NaO_6Si$ 649.2704, found 649.2703.

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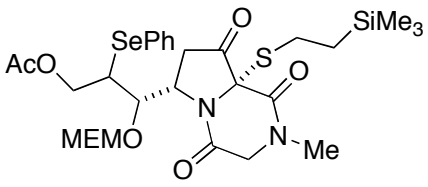
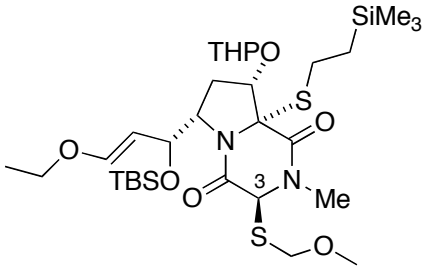


removal of the $CH_2CH_2SiMe_3$ was tried on this compound by Dr. Peng



attempted functionalization of C3 using a base, followed by RCOCl or RCHO failed in Dr. Peng's previous research

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