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Studies towards the total synthesis of CP-225,917 and CP-263,114

by

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DEDICATED TO

MY WIFE PEGAH AND MY FAMILY

ABSTRACT

This thesis describes advanced model studies directed to the synthesis of CP-225,917 and CP-263,114, complex natural products that have been shown to inhibit enzymes that are involved in cholesterol biosynthesis and in the development of many cancers.

A route was devised to the functionalized pentacyclic skeleton of these natural products. The most advanced intermediate carries the essential substituents for construction of the anhydride subunit and one of the two olefinic arms that are present in both compounds. The approach used involves a Diels-Alder reaction, an unusual fragmentation of a strained [2.2.1]bicycle and the method of intramolecular conjugate displacement, which had previously been developed in this laboratory.

A number of model studies were carried out to identify a procedure for introducing the last carbon required for the anhydride subunit and, based on these studies, that carbon was introduced via the use of a [2,3]-Wittig rearrangement.

ACKNOWLEDGEMENTS

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LIST OF ABBREVIATIONS

Ac	Acetyl
AD	Asymmetric dihydroxylation
AIBN	2,2'-azobisisobutyronitrile
APT	Attached proton test
Ar	Aromatic ring
BHT	2,6-Di-*tert*-butyl-4-methylphenol
Bn	Benzyl
Boc	*tert*-butoxycarbonyl
Bop	Bis(2-oxo-3-oxazolidinyl)phosphonic
brsm	Based on recovered starting material
Bu	*n*-Butyl
t-Bu (or Bu-*t*)	*tert*-Butyl
Bz	Benzoyl
CD	Circular Dichroism
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	Dicyclohexylcarbodiimide
DHP	3,4-dihydropyran
DIBAL	Diisobutylaluminum hydride
DKP	Diketopiperazine
DMAP	4-Dimethylaminopyridine
DME	Dimethoxyethane

DMF	*N*,*N*-Dimethylformamide
DMF-DMA	Dimethylformamide dimethyl acetal
DMP	Dess-Martin periodinane
DMSO	Dimethyl sulfoxide
DP	Desired product
EDCI	*N*-Ethyl-*N*-(3-dimethylaminopropyl)carbodiimide
dr	Diastereomeric ratio
Et	Ethyl
ETP	Epidithiodioxopiperazine
Fmoc	[(9-fluorenylmethyl)oxy]carbonyl
FTIR	Fourier transform infrared spectroscopy
HSQC	Heteronuclear Single Quantum Coherence
IBX	2-Iodoxybenzoic acid
ImH	Imidazole
LDA	Lithium diisopropylamide
m-CPBA	3-Chloroperbenzoic acid
Me	Methyl
MEM	(Methoxyethoxy)methyl
mp	Melting point
MS	Molecular sieves
MW	Microwave
NaHMDS	Sodium hexamethyldisilazide
NBS	*N*-bromosuccinimide

NCS	*N*-chlorosuccinimide
NIS	*N*-iodosuccinimide
NMO	*N*-Methyl morpholine-*N*-oxide
NMR	Nuclear magnetic resonance
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
Ph	Phenyl
PMB	*para*-Methoxybenzyl
PPTS	Pyridinium *p*-toluenesulfonate
i-Pr	Isopropyl
py	Pyridine
quant.	Quantitative yield
rt	Room temperature
SM	Starting material
TBAF	Tetrabutylammonium fluoride
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
THP	Tetrahydropyranyl
TPAP	Tetrapropylammonium perruthenate
TsOH	*p*-Toluenesulfonic acid
TBS	*t*-Butyldimethylsilyl
TBDPS	*t*-Butyldiphenylsilyl
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid

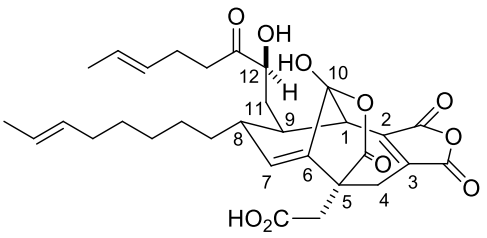
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
Ts	Toluenesulfonyl

Introduction

Based on the latest statistical data, cancer with 29.8% and heart diseases with 20.7% are the two leading causes of death in Canada[1] and hypercholesterolemia is a major risk factor in heart diseases.[2] As a result, many research groups and pharmaceutical companies are studying the development of new drugs to treat these diseases. Obviously, improvements in this area could have a huge impact on life quality and age expectancy.

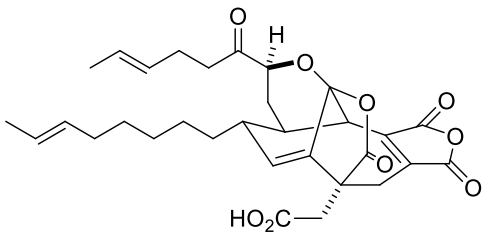
Some years ago, the Pfizer Company reported the isolation of two natural products, phomoidride A (CP-225,917) (**1**) and phomoidride B (CP-263,114) (**2**), from a fungus growing on twigs of a Juniper tree in Texas (Figure 1).[3] Both fungal metabolites have shown significant activity in inhibiting two enzymes: squalene synthase (from rat liver) with IC_{50} values of 43 μM and 160 μM, respectively for **1** and **2**, and farnesyl transferase (from rat brain) with IC_{50} values of 6 μM and 20 μM, respectively.[4]

FIGURE 1. Phomoidride family



1 Phomoidride A (CP-225,917): C-12 = *S*

3 Phomoidride C: C-12 = *R*



2 Phomoidride B (CP-263,114): C-12 = *S*

4 Phomoidride D: C-12 = *R*

Squalene synthase plays a critical role in the biosynthesis of cholesterol. The other enzyme, farnesyl transferase, is responsible for farnesylation of *ras* protein. This process happens in the early stages of cell growth. Mutations in this

enzyme have been shown to be responsible for 30% of human cancers. Upon mutation, uncontrolled growth occurs and so inhibiting *ras* farnesyl transferase should block such cell growth. Consequently, the phomoidrides are worthy of study for their potential anticancer and cholesterol-lowering activity.[5]

The unusual polycyclic system in the phomoidrides, along with the densely packed group of oxygen functionality, six chiral centers, a bridgehead double bond contained within a bicyclo[4.3.1]deca-6,7-diene carbon framework, a quaternary center held within a caged γ-lactone acetal or hemiacetal, an unusual maleic anhydride moiety, and two olefinic side chains make these compounds extremely challenging as synthetic targets.[6]

The relative stereochemistry of both compounds was assigned by Kaneko and his group by extensive NMR studies.[3] The complexity of these compounds has attracted much attention, and a great deal of synthetic work has been published in this area.[7] Four completed total syntheses and numerous model studies have been reported.

The first total synthesis (in racemic form) of CP-225,917 and CP-263,114, was published by Nicolaou's group in 1999.[8] Later, an enantioselective synthesis[9] of what turned out to be the enantiomers of the naturally occurring compounds was achieved.[10]

Compound **1** can be converted to **2** by using $MeSO_3H$[3] and the Nicolaou group found that the reverse transformation is also possible under controlled basic conditions.[8]

Shortly after Nicolaou's publication three additional syntheses of CP molecules were reported from the Danishefsky,[11] Fukuyama[12] and Shair[13] groups. The Danishefsky synthesis of **1** and **2** was in the racemic series, while Shair and Fukuyama, synthesised the optically pure isomers of **2**, Shair making (-)-**2** and Fukuyama (+)-**2**. Surprisingly, neither Shair nor Fukayama claimed the

conversion of **2** to **1** by Nicolaou's method.[14] Later, the Nicolaou group modified their original route and published the asymmetric synthesis of **1** and **2.**

Attempts at the synthesis of CP molecules have been extensively reviewed by Wood, who also dealt with model studies toward the core.[15] In the following I will summarize only the four complete syntheses.

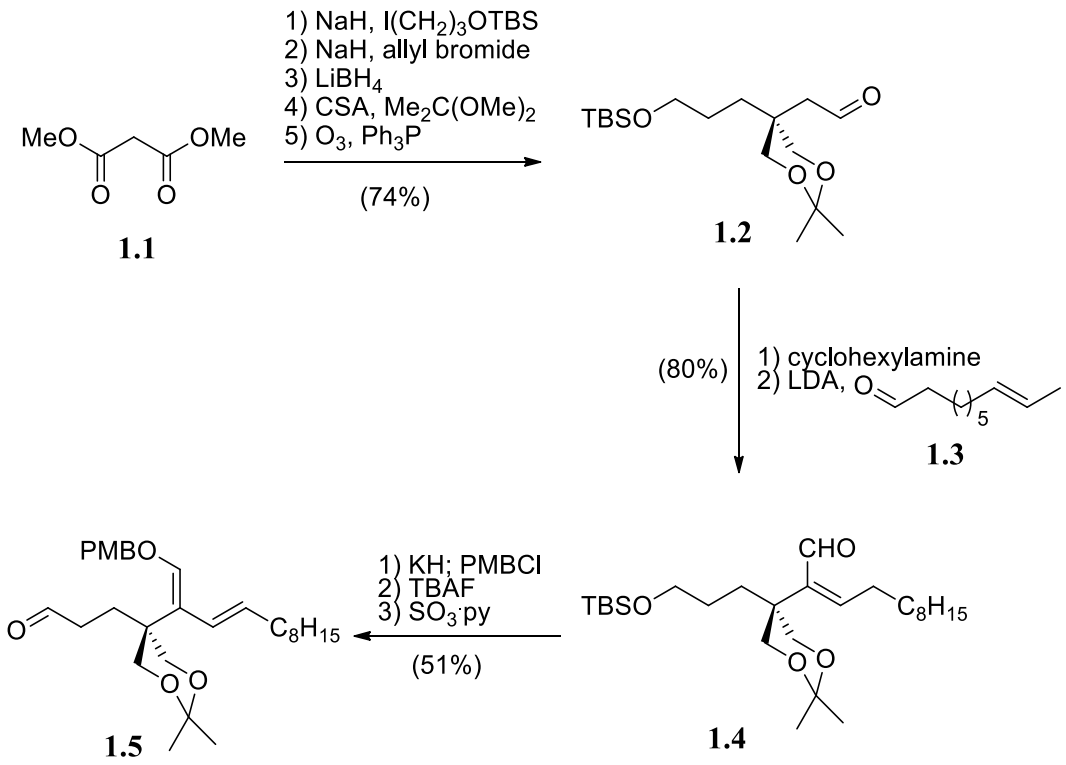
1.1 Nicolaou's asymmetric synthesis

In 1999 the first total synthesis of CP-225,917 (**1**) and CP-263,114 (**2**) was reported by Nicolaou's group in racemic form, using an intramolecular Diels-Alder reaction to build up the main carbon structure.[8,16] A year later, by modifying the same route, the first asymmetric synthesis of CP-225,917 (**1**) and CP-263,114 (**2**) was accomplished using an asymmetric Diels-Alder reaction.

In order to carry out the intramolecular Diels-Alder reaction, the diene **1.5** first prepared (Scheme 1). The synthesis of this diene was begun by double alkylation of dimethyl malonate (**1.1**) first with a saturated iodide and then with allyl bromide, and the ester groups were reduced to give a diol which was protected as an acetonide. The double bond from the allyl unit was cleaved by ozonolysis to afford aldehyde **1.2**. Imine formation, followed by reaction with aldehyde **1.3**, gave aldehyde **1.4**. At that point, reaction with KH in the presence of PMBCl, desilylation and oxidation, produced the diene **1.5** in which the stage is set to add to the dienophile piece.

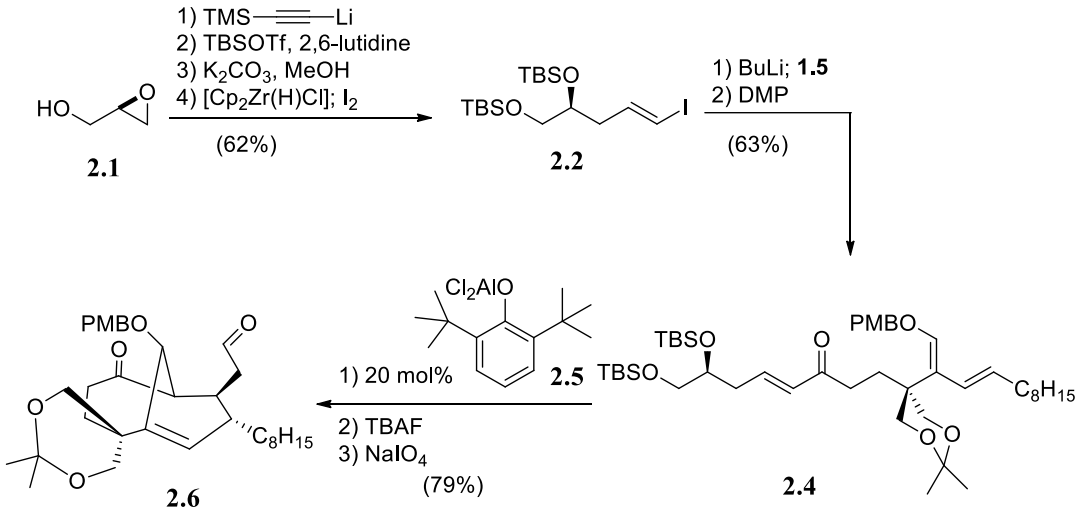
For further elaboration of the dienophile, the *R* enantiomer of glycidol (**2.1**) was used and addition of lithium trimethylsilylacetylide, followed by silylation with *t*-$BuMe_2SiOSO_2CF_3$, produced the expected acetylene. The Me_3Si group on the alkyne was removed and hydrozirconation, followed by I_2 addition gave iodide **2.2** (Scheme 2).

SCHEME 1. Construction of the Diels-Alder precursor



Transmetallation with BuLi and addition to aldehyde **1.5** gave an alcohol, and oxidation with Dess-Martin periodinane then produced the Diels-Alder precursor **2.4**. In the presence of the Lewis acid **2.5**, a smooth intramolecular Diels-Alder reaction generated the desired tricyclic product with the bridgehead double. The presence of this bridgehead double bond does not violate Bredt's rule as the bond is within a nine-membered ring. The product of the Diels-Alder reaction was a 5.7:1 mixture of a diastereomers. These were deprotected with Bu_4NF and the resulting diols were then separated. Oxidative cleavage with $NaIO_4$ produced aldehyde **2.6** in an enantiomerically enriched form.

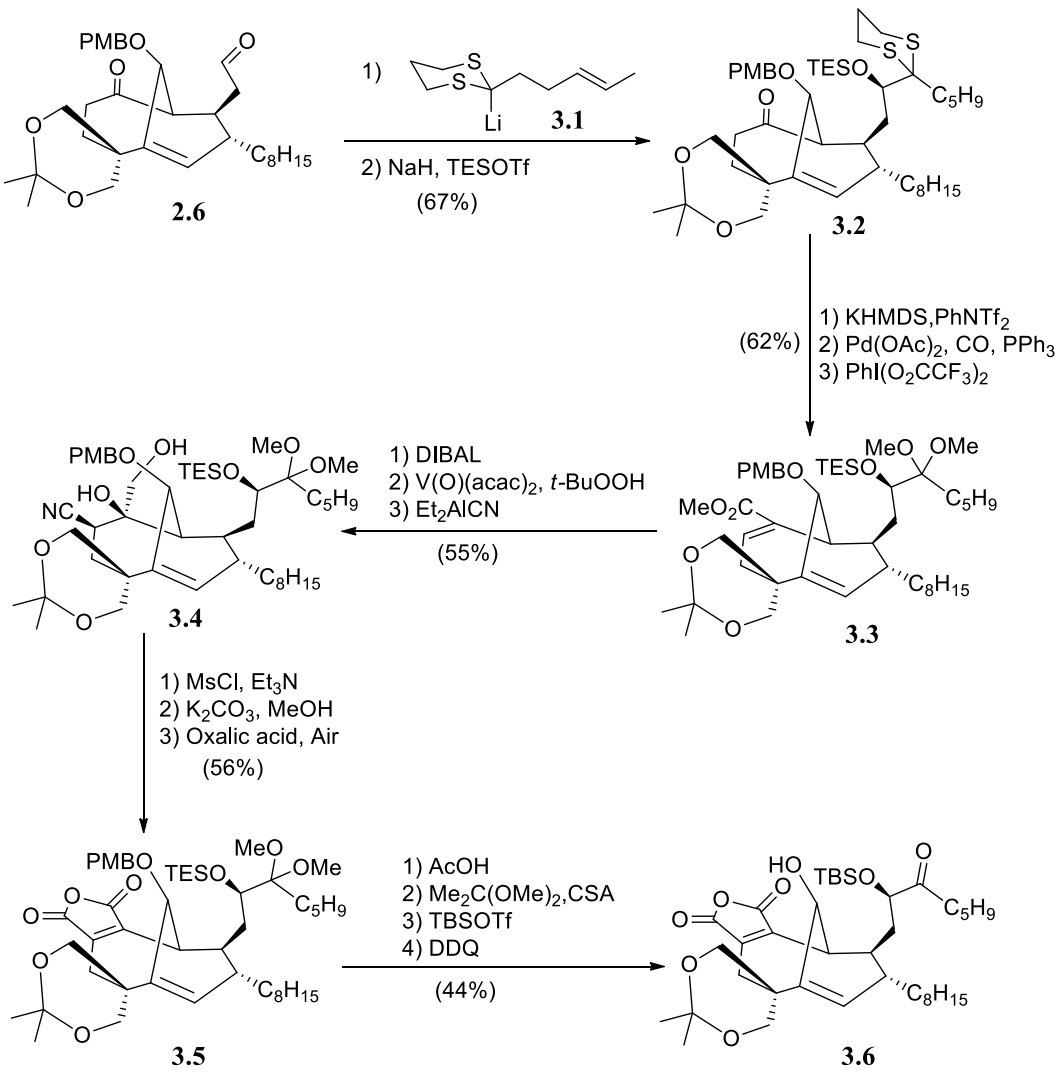
SCHEME 2. The intramolecular Diels-Alder reaction



The alkyllithium **3.1** was added to aldehyde **2.6** and the resulting hydroxyl group was protected with $Et_3SiOSO_2CF_3$. The highly functionalized ketone **3.2** was then converted into its enol triflate. Palladium-mediated methoxycarbonylation furnished an α,β-unsaturated ester and the dithiane group was replaced by a dimethyl ketal, affording **3.3** (Scheme 3).

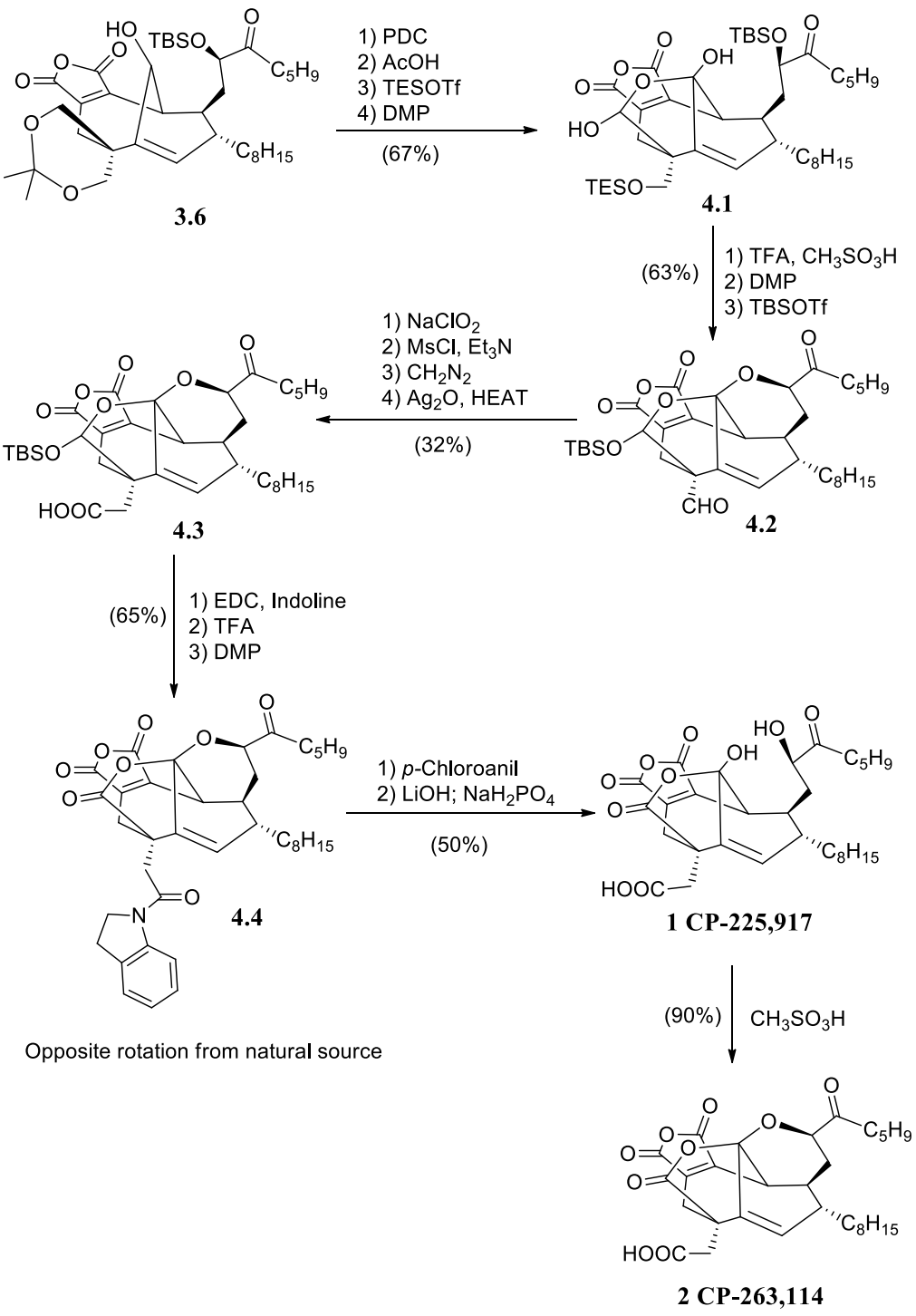
Reduction of the ester generated an allylic alcohol which was then subjected to Sharpless epoxidation, and the epoxide was opened with Et_2AlCN to give the hydroxy cyanide **3.4**. The primary hydroxyl group was mesylated and treatment with base produced an epoxide. The hydrogen α to the cyano group is acidic and β-elimination formed an unsaturated nitrile intermediate. This sequence was followed by cyclization to an imino butenolide, tautomerization to an 2-aminofuran, and autoxidation by triplet oxygen. Finally, extrusion of ammonia yielded the maleic anhydride **3.5**.[17] A series of deprotection and protection steps then resulted in alcohol **3.6**.

SCHEME 3. Construction of the anhydride unit



The bridgehead alcohol **3.6** was oxidized with PDC and the acetonide was removed to form a bis-hemiketal with the bridgehead carbonyl. The primary hydroxyl group on the lower one-carbon chain was protected by reaction with $Et_3SiOSO_2CF_3$.[9,15] In the presence of Dess-Martin periodinane and water the γ-hydroxylactol **4.1** was then formed via the open form of the lactol. Compound **4.1** was desilylated and oxidized, and the free hydroxyl was silylated to give **4.2**. The aldehyde group was oxidized to a carboxylic acid and, using the Arndt-Eistert

SCHEME 4. Completion of the total synthesis



protocol, an extra carbon was introduced to form the corresponding homologated acid. This acid was coupled with indoline, using EDC.

Having reached this very advanced stage, the *t*-BuMe_2Si group was removed in an acidic medium and oxidation with the Dess-Martin periodinane produced lactone **4.4**, which is the amide derivative of CP-263,114 (**2**). Compound **4.3** was compared with material made from the natural product and found to have the opposite optical rotation, thus establishing the absolute configuration of natural CP-263,114 as shown by **2**.

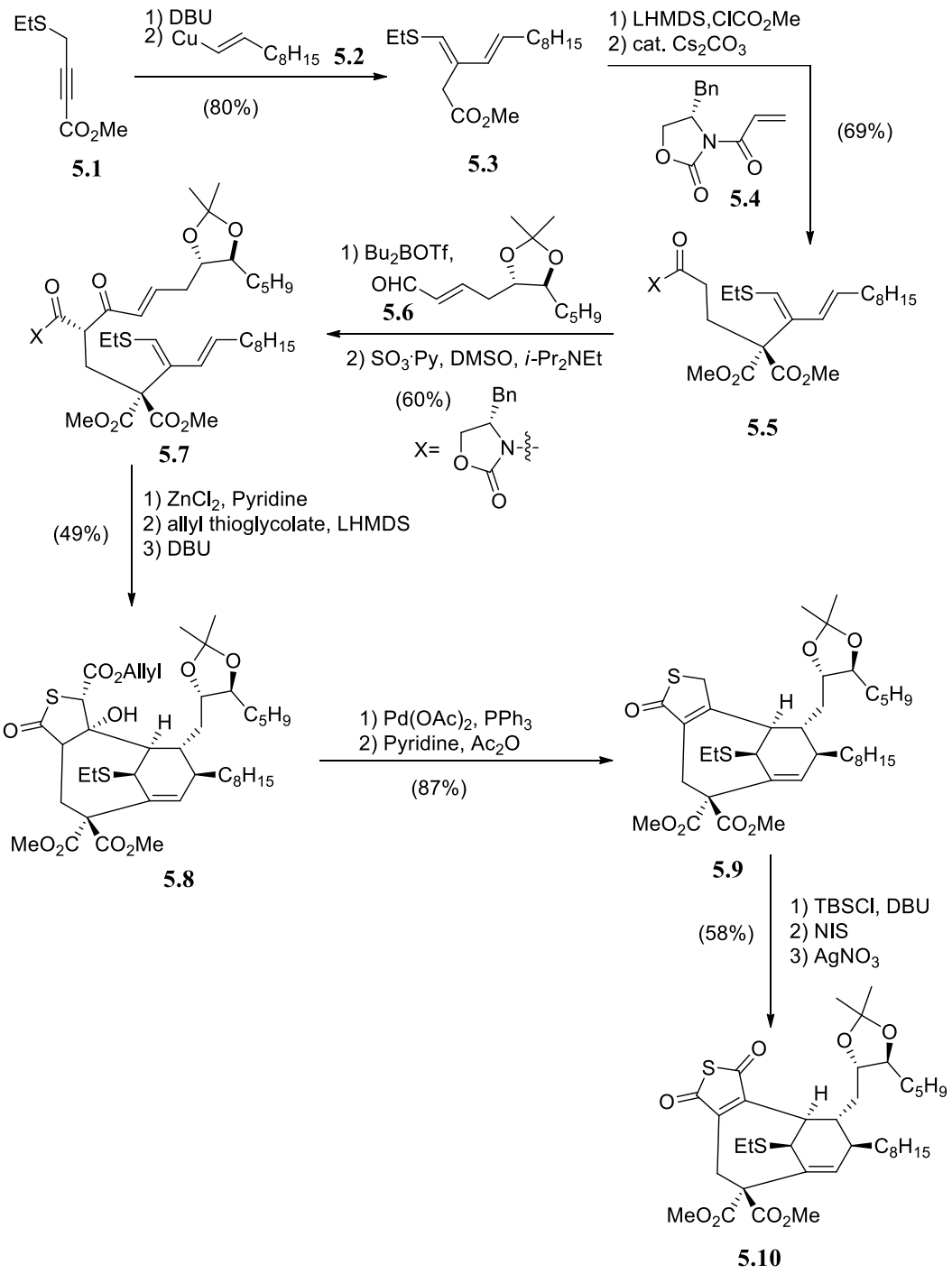
Oxidation of the indoline with *p*-chloranil, and hydrolysis of resulting amide produced a carboxylic acid along with a cascade opening of the lactone-ketal system to produce CP-225,917 (**1**). In the presence of $MeSO_3H$ it was converted into CP-263,114 (**2**) (Scheme 4).

1.2. Fukuyama's enantioselective total synthesis of CP-263,114 (2)

The Fukuyama group published the enantioselective synthesis of CP-263,114 (**2**) shortly after Nicolaou's synthesis appeared. The Japanese group also used an intramolecular Diels-Alder reaction but their product was more highly functionalized and the overall route much shorter than Nicolaou's.

The synthesis began with isomerisation of **5.1** to an allene by the action of DBU, followed by 1,4-addition of a vinyl cuprate to the allene so as to generate the diene **5.3**. A carbomethoxy group was introduced next at the position adjacent to the original ester. This step was followed by Michael addition of the Evans auxiliary derivative **5.4**. Boron-mediated diastereoselective aldol reaction of **5.5** with aldehyde **5.6,** followed by Parikh-Doering oxidation of the resulting alcohol, furnished the Diels-Alder precursor **5.7**. In the presence of $ZnCl_2$, an intramolecular Diels-Alder reaction took place. Next, the Evans chiral auxiliary

SCHEME 5. Fukuyama synthesis of core structure

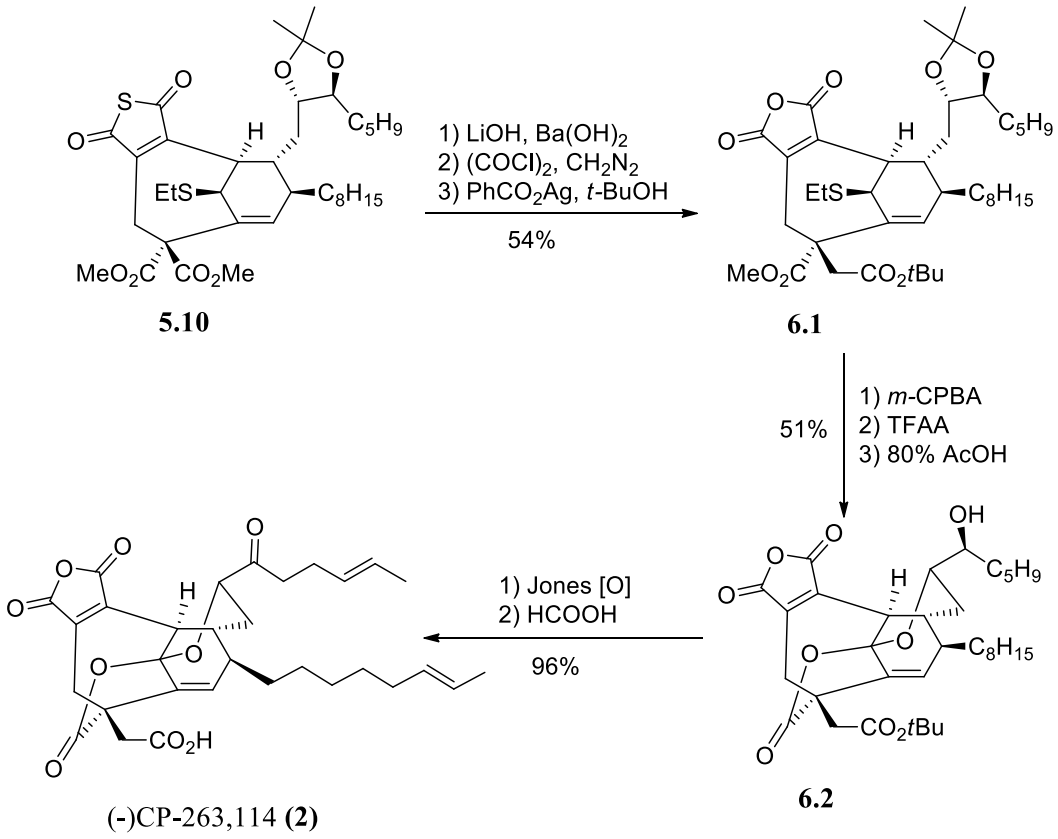


was replaced by reaction with allyl thioglycolate in the presence of base, and an intramolecular aldol reaction then furnished the highly functionalized compound **5.8.** The allyl group was removed and the angular tertiary hydroxyl was acetylated. Finally, decarboxylation gave **5.9**. This was silylated to afford a 2-silyloxythiophene, which was oxidized with NIS and treated with $AgNO_3$. These operations gave the thiomaleic anhydride **5.10** (Scheme 5).[18]

From this point, Fukuyama's group was able to finish the synthesis in a few steps. The thiomaleic anhydride was converted to a maleic anhydride along with selective hydrolysis of the less hindered methyl ester by treatment with LiOH and $Ba(OH)_2$.

With **5.10** in hand, the less hindered ester was selectively hydrolyzed and the Arndt-Eistert protocol was then applied, so as to form **6.1**. Oxidation of the sulfur in **6.1** with *m*-CPBA, followed by treatment with $(CF_3CO)_2O$ and *i*-Pr_2NEt generated a bridgehead ketone after aqueous workup. Hydrolysis of the acetonide resulted in spontaneous cyclization to afford γ-lactone-acetal **6.2** (Scheme 6). Finally, Jones oxidation of the secondary alcohol and deprotection of the *tert*-butyl ester with HCO_2H gave (-)-CP-263,114 (**2**). This enantiomer had exactly the same physical properties as the natural product, establishing the absolute configuration of the latter.

SCHEME 6. The completion of the total synthesis



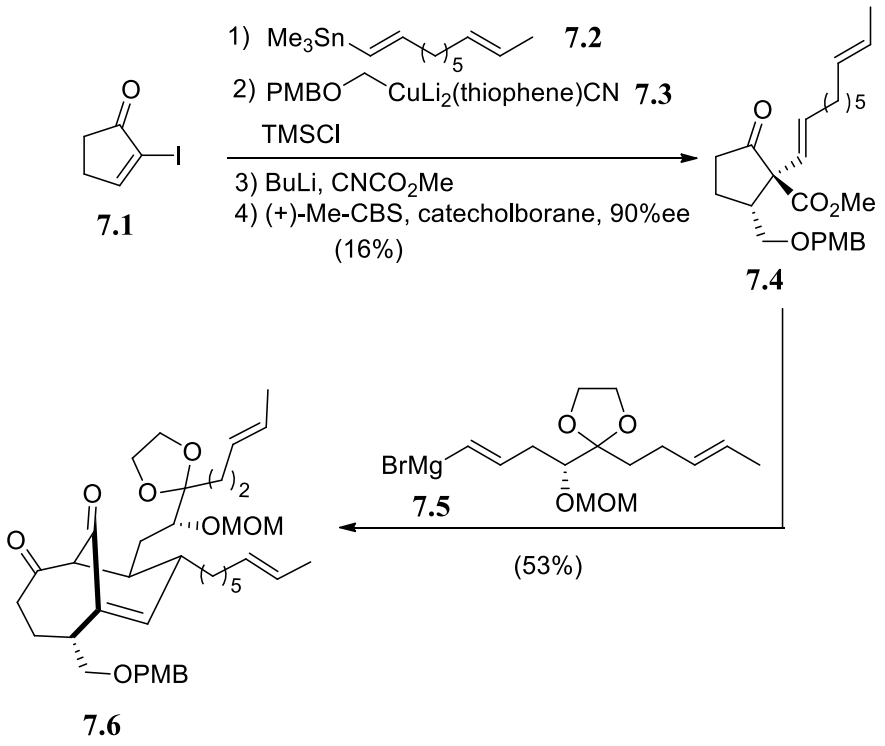
1.3. Shair's total synthesis of (+)-CP-263,114

Shair and his group published their synthesis shortly after Nicolaou. The synthesis is the shortest of the available routes, but the final product contains an impurity that could not be separated. The route benefits from an elegant three-step tandem cyclization used to build the highly functionalized core of CP-263,114 (**2**).[19]

The synthesis began with a Pd(0)-catalyzed cross-coupling between iodo-enone **7.1** and vinyl stannane **7.2**, affording a triene. Double conjugate addition of the cuprate **7.3**, followed by *C*-acylation using Mander's reagent ($NCCO_2Me$),

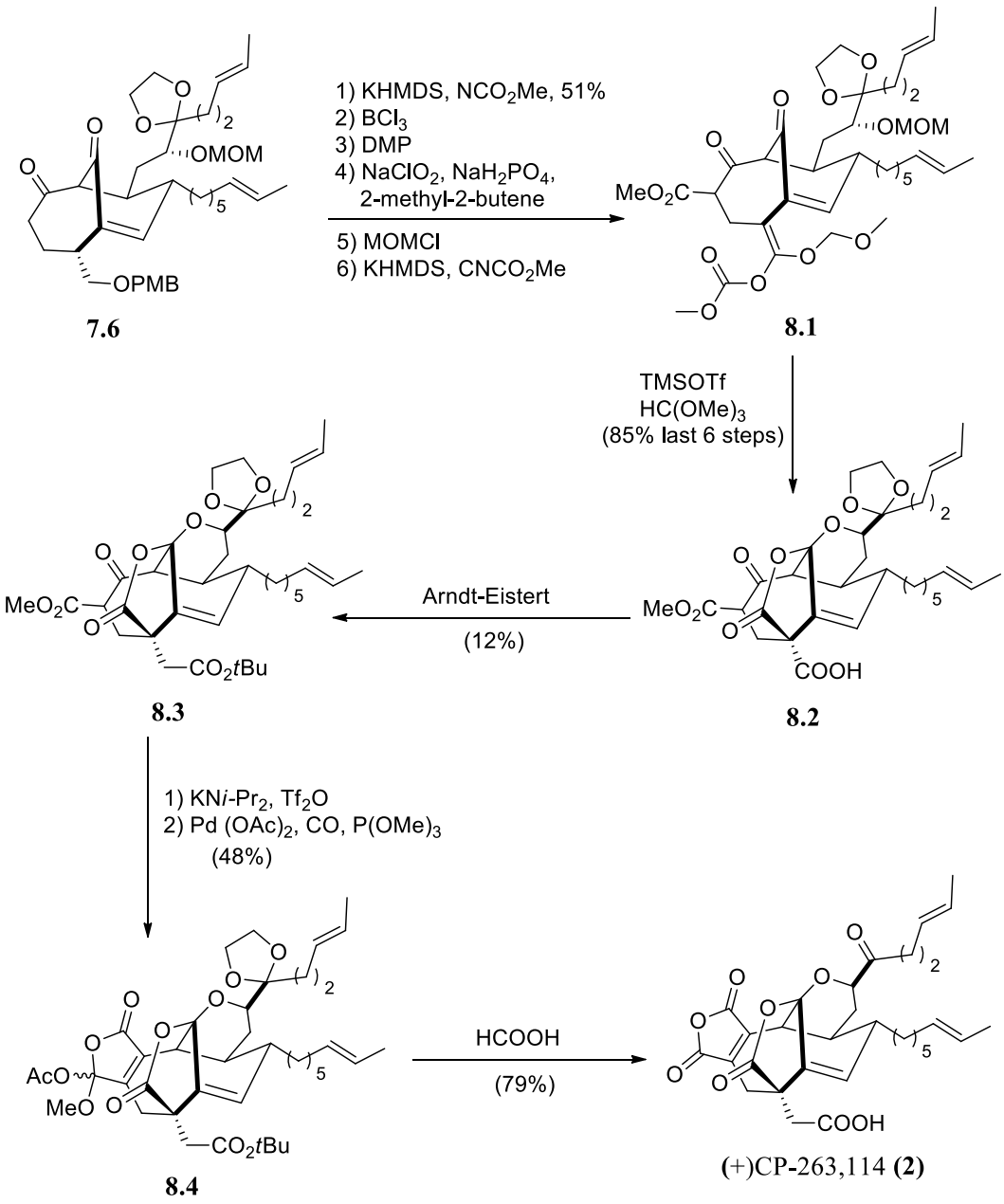
generated **7.4** as a racemate. Treatment of *rac*-**7.4** with Corey's oxazaborolidine reduction catalyst and catecholborane produced an efficient kinetic resolution that gave (+)-**7.4.** A Grignard reaction using reagent **7.5**, which was generated from glyceraldehyde, gave a bromomagnesium alkoxide that underwent anion-accelerated oxy-Cope rearrangement and spontaneous transannular Dieckmann-like cyclization to produce **7.6** (Scheme 7).

SCHEME 7. Shair synthesis of the core structure



Thermodynamic *C*-acylation with $NCCO_2Me$, followed by removal of the PMB group and oxidation of the resulting alcohol provided a carboxylic acid. The acid was then protected by reaction with MOMCl and the enol carbonate **8.1** was generated. Exposure of enol carbonate **8.1** to $Me_3SiOSO_2CF_3$ and $(MeO)_3CH$ initiated a multistep cascade Fries-like rearrangement that formed the lactone and

SCHEME 8. Completion of the synthesis



quaternary carbon and liberated the carboxylic acid **8.2**. An Arndt-Eistert homologation then gave the ester **8.3** in 12%. The low in yield was suggested to be due to the sensitivity of the product to the reaction conditions. An enol triflate was then prepared and carbonylation was accomplished by exposure to a catalyst

derived from $Pd(OAc)_2$ and $P(OMe)_3$ in the presence of CO, affording an anhydride ortho ester. This was deprotected using HCO_2H to generate (+)-CP-263,114, the enantiomer of the naturally occurring compound.

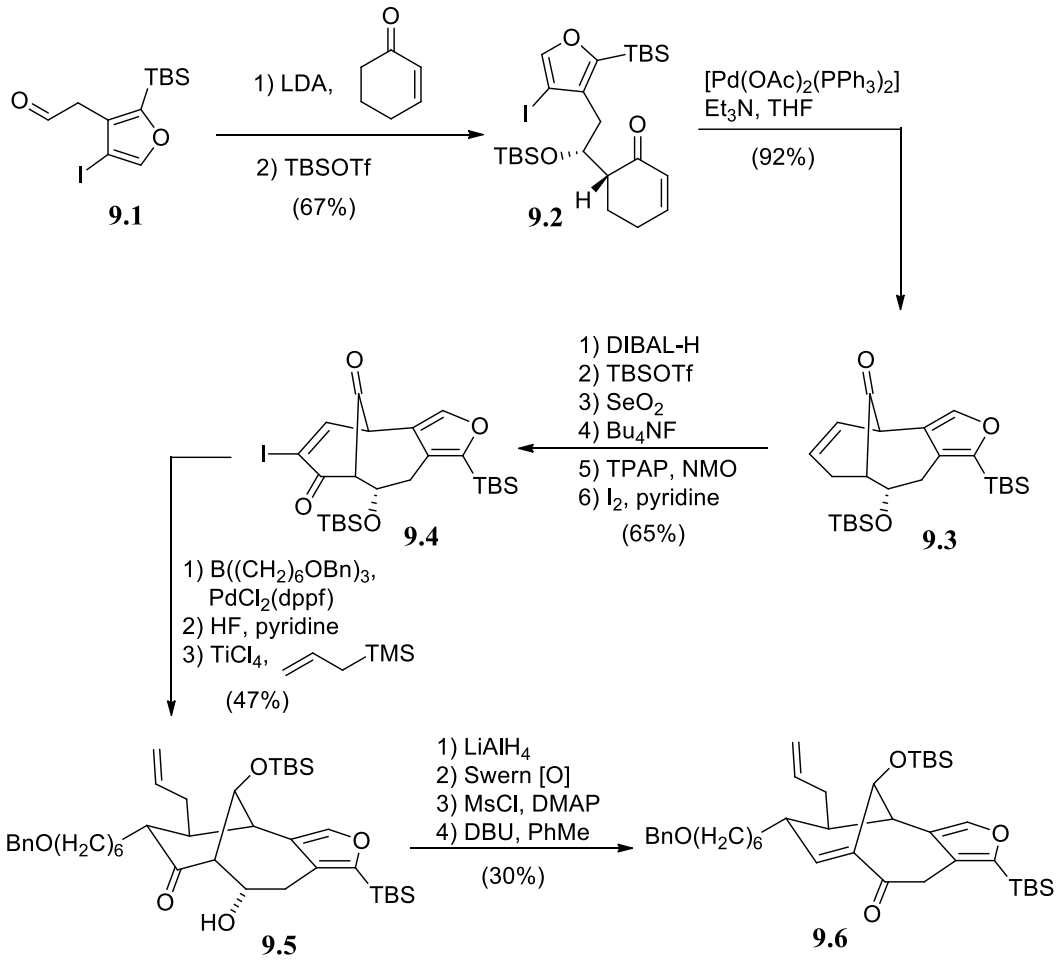
1.4. Danishefsky's total synthesis of CP-225,917 (1) and CP-263,114 (2)

The Danishefsky synthesis began with the aldol reaction between 2-cyclohexanone and **9.1**, followed by protection of the free hydroxyl group as a silyl ether, to generate **9.2**. An intramolecular Heck coupling then generates the 9-membered skeleton of the CP-molecules. The diastereoselectivity of the initial aldol reaction was 8:1. The fused furan ring serves as a masked maleic anhydride that will be revealed late in the synthesis, and the double bond in **9.3** is ideally positioned for subsequent elaboration of the bridgehead olefin. Within a few steps, a conjugated ketone was produced from **9.3**. Treatment with I_2 and pyridine gave the vinyl iodide **9.4**. From this point, a Suzuki-Miyaura cross coupling and a Sakurai allylation were carried out, and monodesilylation then released alcohol **9.5.**[11,20] This sequence provided the desired trans side chain stereochemistry found in the natural product. Then the ketone group was changed to a leaving group in three steps, and treatment of the product with DBU generated the bridgehead double bond regioselectively **9.6** (Scheme 9).

To install the quaternary carbon, the Danishefsky group built up the cyclobutanone **10.1** by Tebbe olefination of ketone **9.6** and reaction with dichloroketene. Selective desilylation generated alcohol **10.1.** This was regioselectively sulfenylated from the less hindered face by deprotonation and reaction with diphenyl disulfide. The sulfenylation step controls the selectivity of a subsequent Baeyer-Villiger oxidation, as well as fragmentation of the resulting lactone. After the sulfenylation, the bridgehead hydroxyl group was oxidized

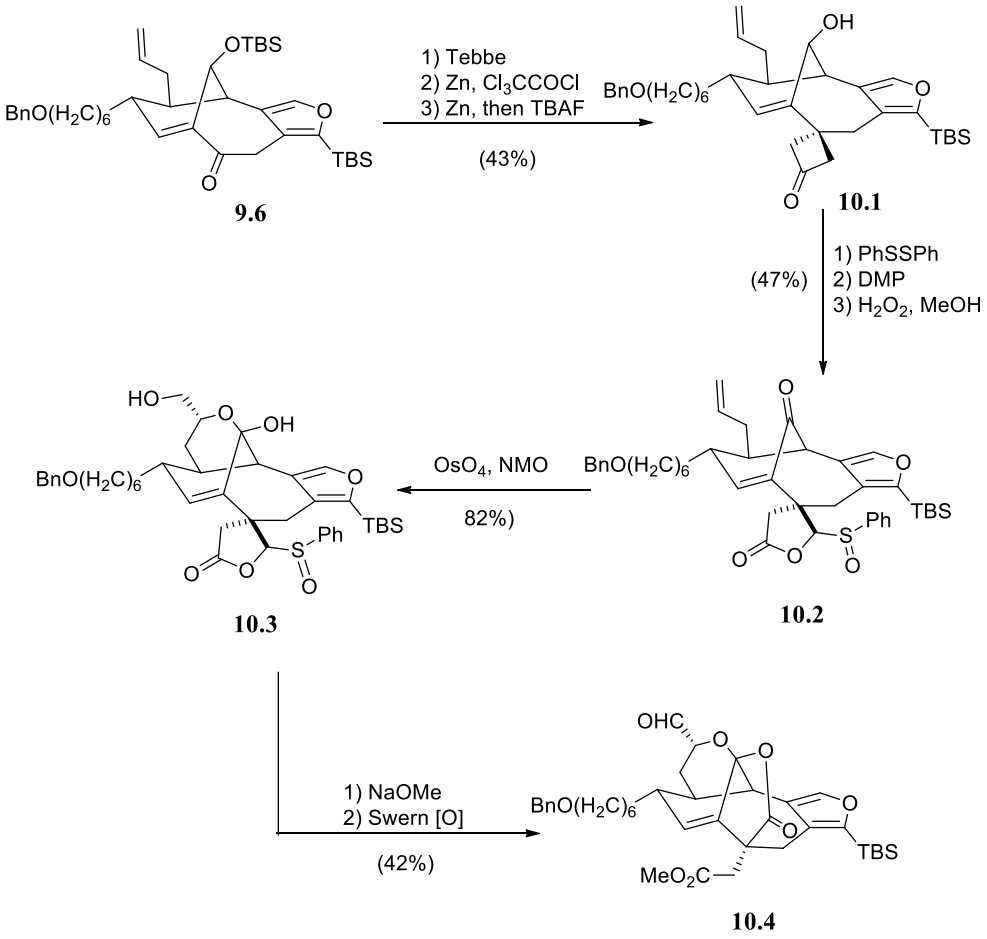
with the Dess-Martin periodinane and, by using H_2O_2, both regiospecific Baeyer-Villiger reaction and oxidation to a sulfoxide is accomplished to generate **10.2** (Scheme 10)**.**

SCHEME 9. Danishefsky route to the core of CP molecules



The pendant double bond was then dihydroxylated by OsO_4 and one of the resulting hydroxyl groups reacted with the bridgehead ketone to produce the lactol **10.3.** Upon saponification by MeONa, the lactol cage formed and, after Swern oxidation, aldehyde **10.4** was obtained**.**

SCHEME 10. Construction of the quaternary center

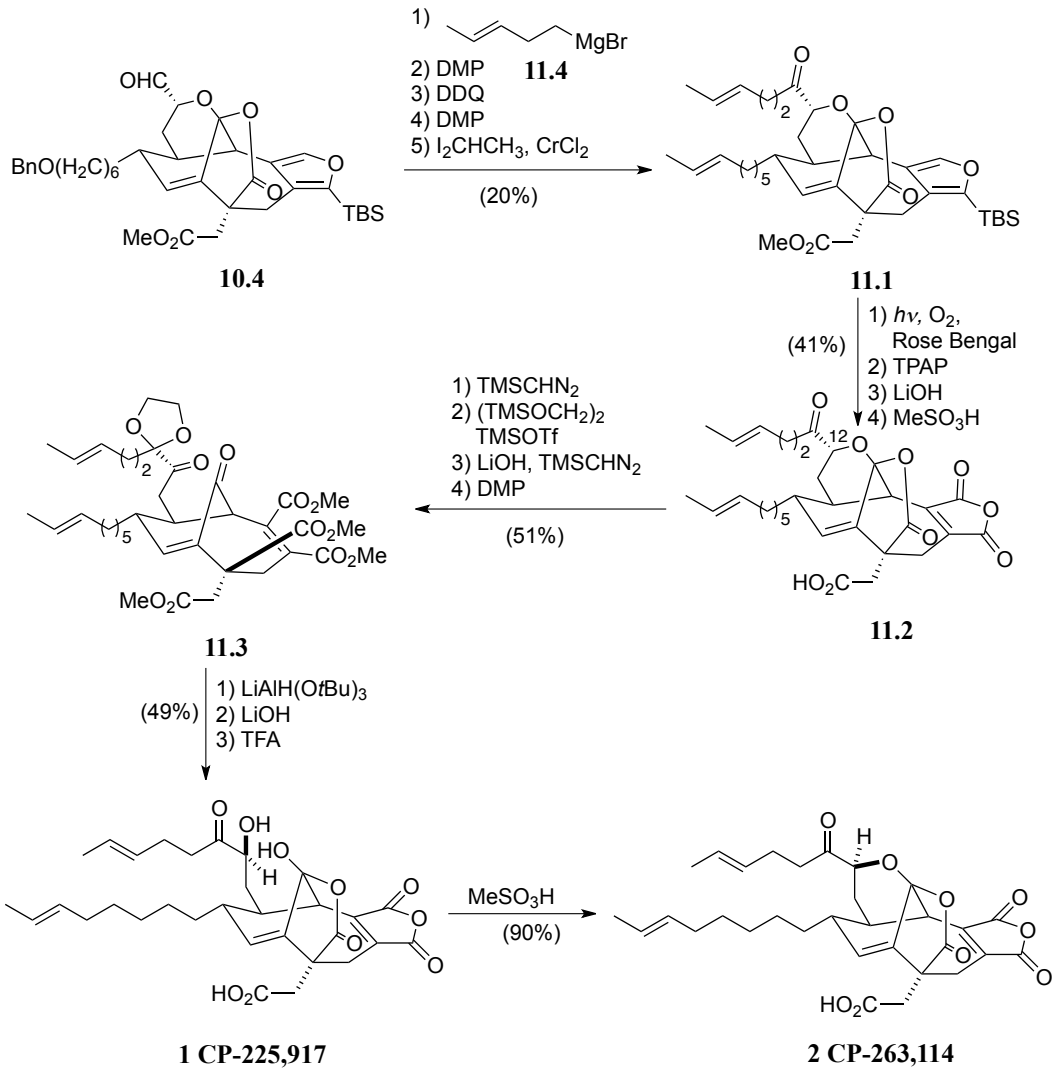


In order to attach the side chains, the Grignard reagent **11.4** was first added and the resulting alcohol was oxidized. Then the benzyl protecting group was removed to release an hydroxyl group, which was also oxidized so that the second side chain could be elaborated.

Unmasking of the anhydride unit was accomplished via the action of singlet oxygen and Ley oxidation.[21] Base hydrolysis and acidification then gave compound **11.2** (≡ **4**), which is the C-12 epimer of CP-263,114 (i.e. phomoidride D). Ultimately phomoidride D was converted to **1** in a seven-step sequence in which the lactone cage was reopened, oxidized and reduced again, and this time

CP-225,917 (**1**) was produced. Upon treatment with $MeSO_3H$, CP-263,114 (**2**) was produced.

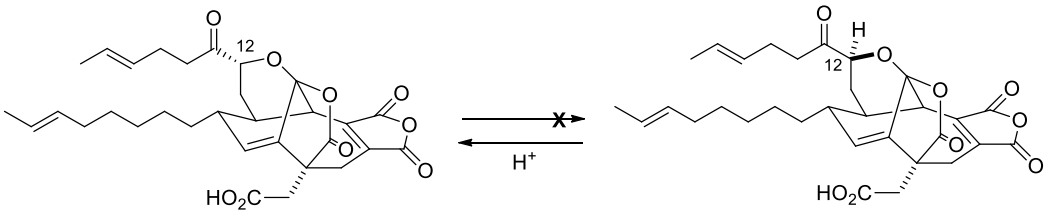
SCHEME 11. Attachment of the side chains and completion of the synthesis



During their epimerization studies, the Danishefsky group uncovered useful information regarding the stereochemical preference at C-12 (Scheme 11). Conversion of material from the 12*S* to the 12*R* configuration (**2** → **4**) occurred readily, while epimerization in the reverse direction could not be effected under

any conditions. These results suggested that compounds containing the *R* configuration at C-12 represent the thermodynamically favored epimeric series.

SCHEME 12. Epimerization of C-12



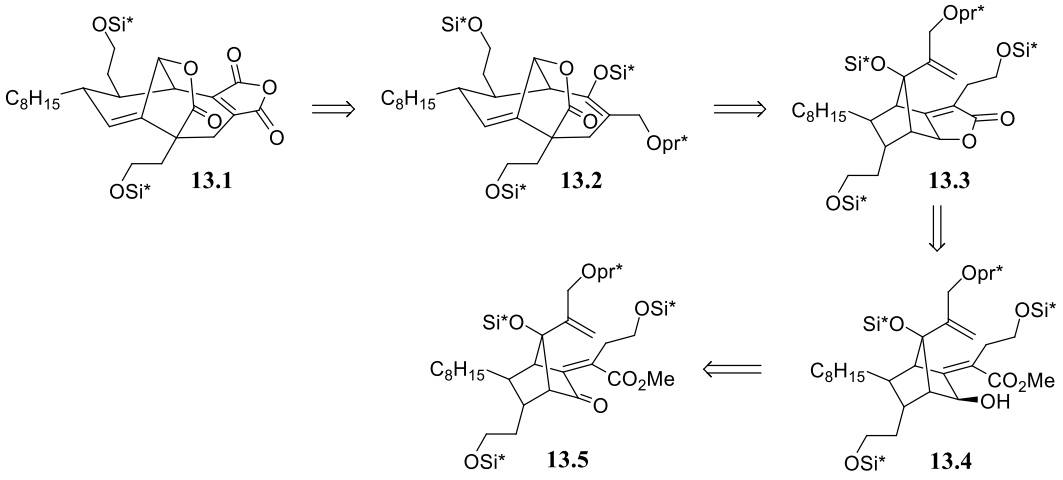
4 Phomoidride D: C-12 = *R*

2 Phomoidride B (CP-263,114): C-12 = *S*

2. Results and discussion

In prior research in this laboratory, two general approaches toward the construction of CP-225,917 (**1**) have been followed. The initial attempts were based on using Cope, oxy-Cope and anionic oxy-Cope[22] rearrangements. By using these reactions it was possible to construct the tricyclic lactone **13.2**, which could be converted to the corresponding anhydride **13.1** in a few steps (Scheme 13).

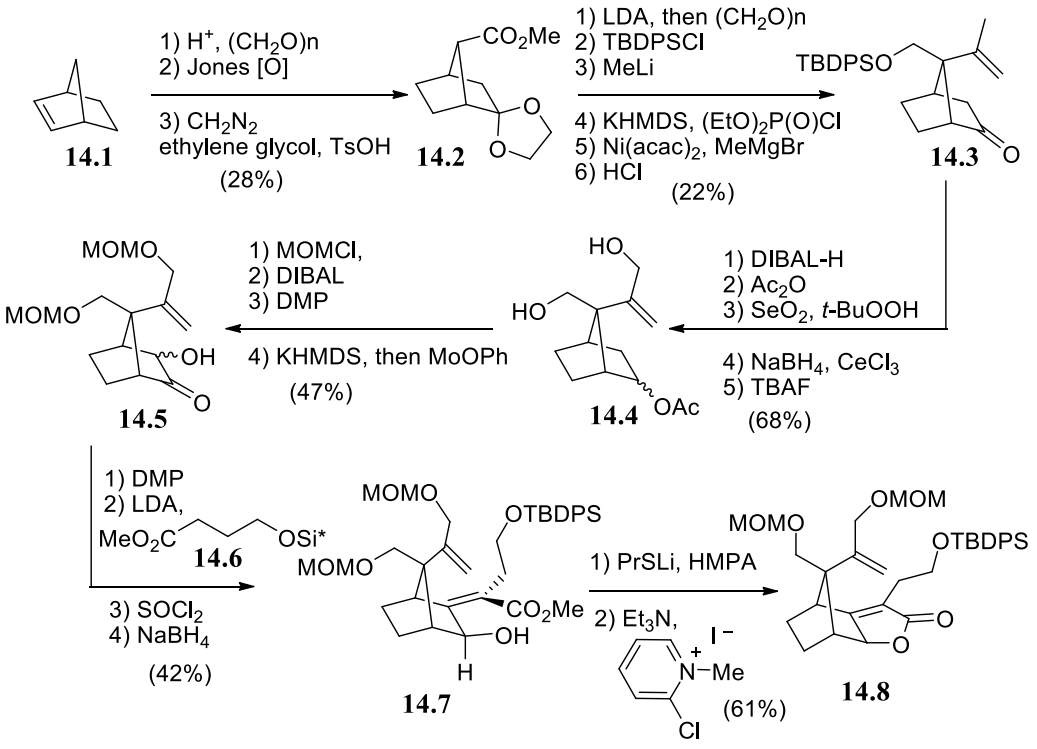
SCHEME 13. First generation approach towards the core structure



The scope of this route was examined first by synthesis of simpler structures such as **14.8** (Scheme 14). Norbornene (**14.1**) was converted in four steps into the ester acetal **14.2**. Deprotonation of the acidic hydrogen by LDA and reaction with formaldehyde introduced a hydroxymethyl group which was protected with *t*-BuPh$_2$SiCl. Conversion of the ester to a ketone, using MeLi, followed by Kumada coupling, generated the isopropenyl unit which was converted into ketone **14.3** by removing the acetal group in the presence of acid.

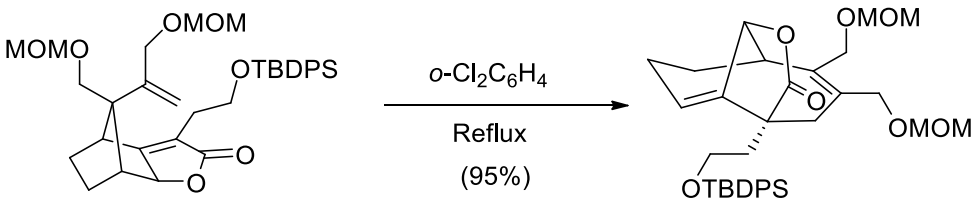
Ketone **14.3** was then reduced to a mixture of alcohols which were acetylated. Allylic oxidation, reduction and desilylation gave the diol **14.4**. This diol was protected as a bis MOM ether, and the acetyl group was removed by DIBAL-H reduction. The resulting secondary alcohol was oxidized to a ketone using DMP. α-Hydroxyketone **14.5** was then synthesized using Vedejs's protocol, and oxidation then gave a diketone. Condensation of the diketone with protected ester **14.6**, and diastereoselective reduction of the remaining ketone group gave alcohol **14.7**. This was lactonized in two steps, using Mukaiyama's reagent[23] to give **14.8**, the precursor for the Cope rearrangement.

SCHEME 14. Synthesis of Cope rearrangement precursor



Heating **14.8** in 1,2-dichlorobenzene resulted in smooth formation of the tricyclic lactone **15.1** (Scheme 15). At this stage, before making more complex models, the construction of the anhydride unit was explored (Scheme 16).

SCHEME 15. Cope Rearrangement

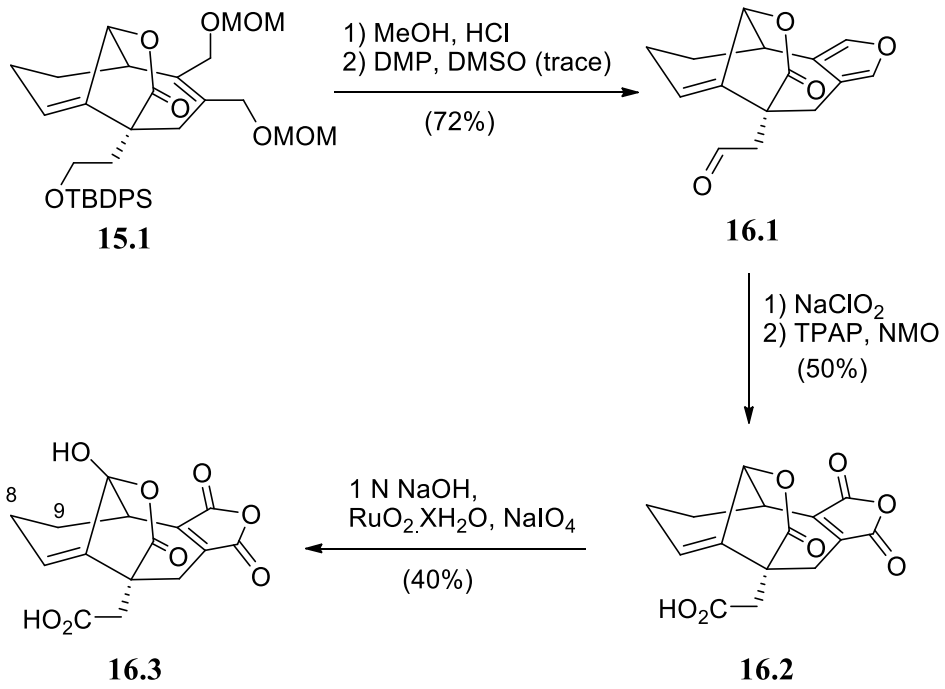


14.8 **15.1**

The MOM and *t*-BuPh$_2$Si groups were removed from **15.1** under acidic conditions and, upon oxidation with DMP, the furan **16.1** was generated, with an aldehyde group being formed at the same time. Pinnick oxidation generated a carboxylic acid and, unexpectedly, produced a mixture of isomeric hydroxybutenolides. These were oxidized to the anhydride **16.2**.

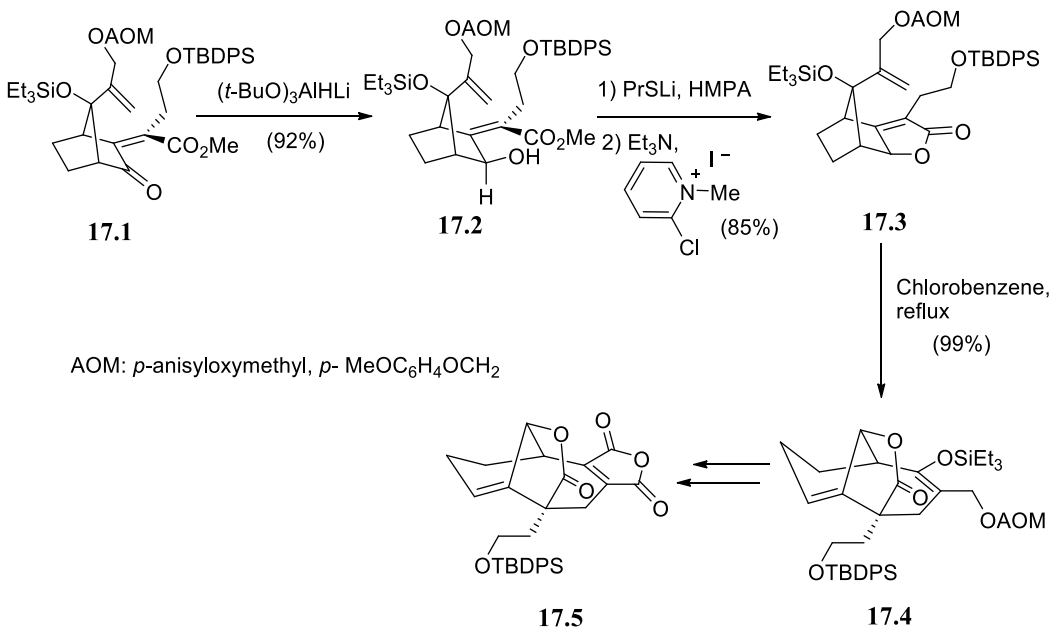
Finally, hydrolysis of the lactone, followed by oxidation and relactonization, installed the hemiacetal unit (**16.3**). Comparison of **16.3** with CP-225,917 shows that the two side chains at C-9 and C-8 need to be installed in order to reach the natural product.

SCHEME 16. Building the anhydride



In an alternative route, an oxy-Cope rearrangement was used. The ketone **17.1** was reduced stereoselectively and the resulting hydroxy ester **17.2** was demethylated with PrSLi and lactonized, using Mukaiyama's reagent. Upon heating in refluxing chlorobenzene, the tricycle **17.3** smoothly rearranged to **17.4**[24] (Scheme 17).

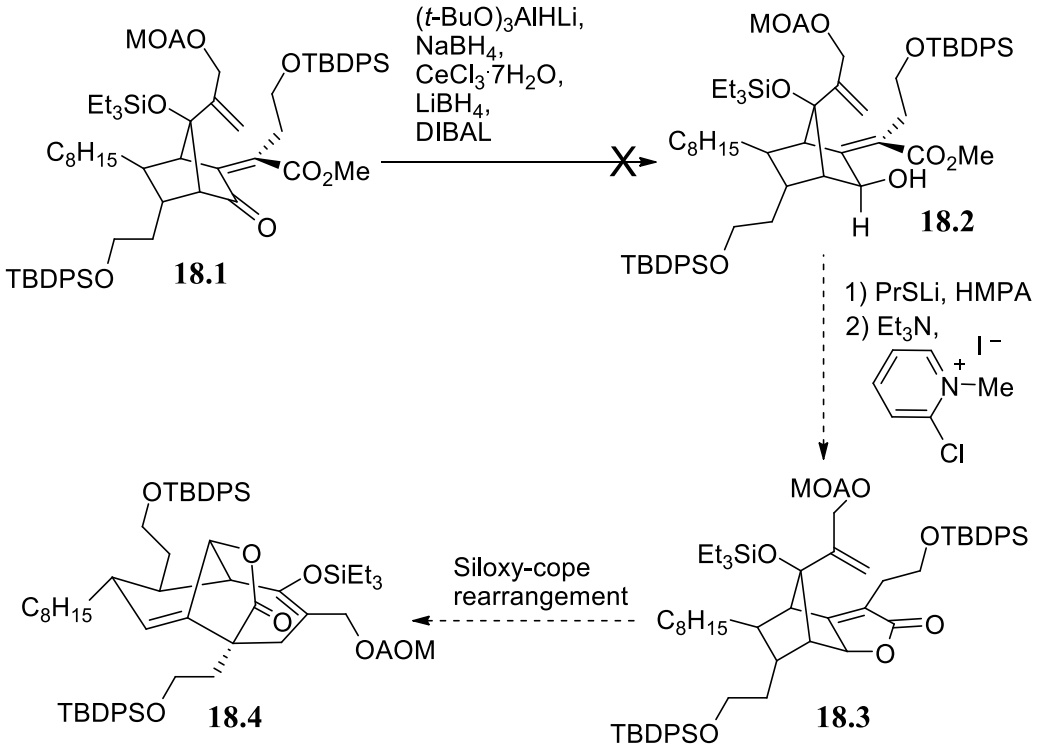
SCHEME 17. Siloxy-Cope rearrangement route



Based on the above model work, the core of the natural product was targeted and compound **18.1** was prepared. Unfortunately, all attempts to reduce the ketone carbonyl gave either a complex mixture or the ketone failed to react. Stronger reagents, such as $LiAlH_4$, reduced both the ester and ketone[25] (Scheme 18).

While all the attempts to reach the core structure of **1** were unsuccessful, new chemistry for making carbocycles was developed in this laboratory by Dr. Prabhudas and Dr. Wang and provided an alternative synthetic plan. This chemistry was a new method of ring closure categorized as an all-carbon intramolecular conjugate displacement (ICD).[26] This reaction involves intramolecular addition of a carbanion, which is stabilized by at least one electron-withdrawing group, to a Michael acceptor which has a leaving group in an allylic position. The process formally resembles a combination of Michael

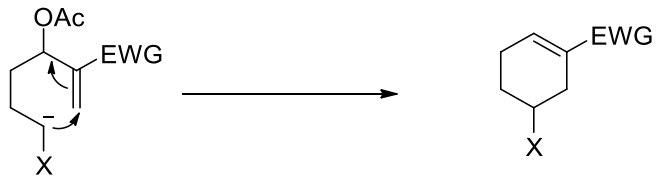
SCHEME 18. Unsuccessful attempts to make the core, using siloxy-Cope rearrangement



AOM: *p*-anisyloxymethyl, *p*- $MeOC_6H_4OCH_2$

addition and S_N2' displacement. The overall result is formation of a ring with loss of the allylic leaving group and shift of the original double bond to a new location spanning the positions of the electron-withdrawing substituent of the Michael acceptor subunit and the original allylic leaving group.

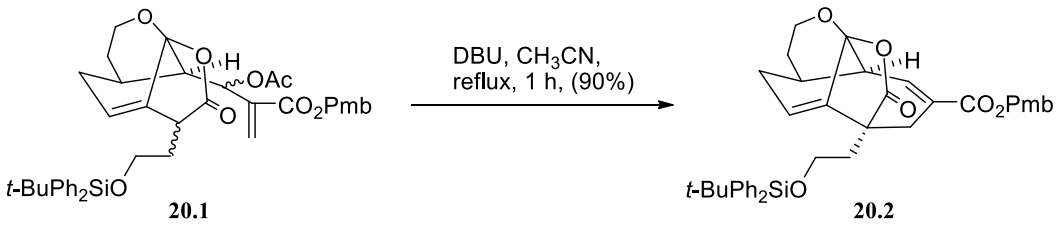
SCHEME 19. Intramolecular conjugate displacement (ICD)



19.1 **19.2**

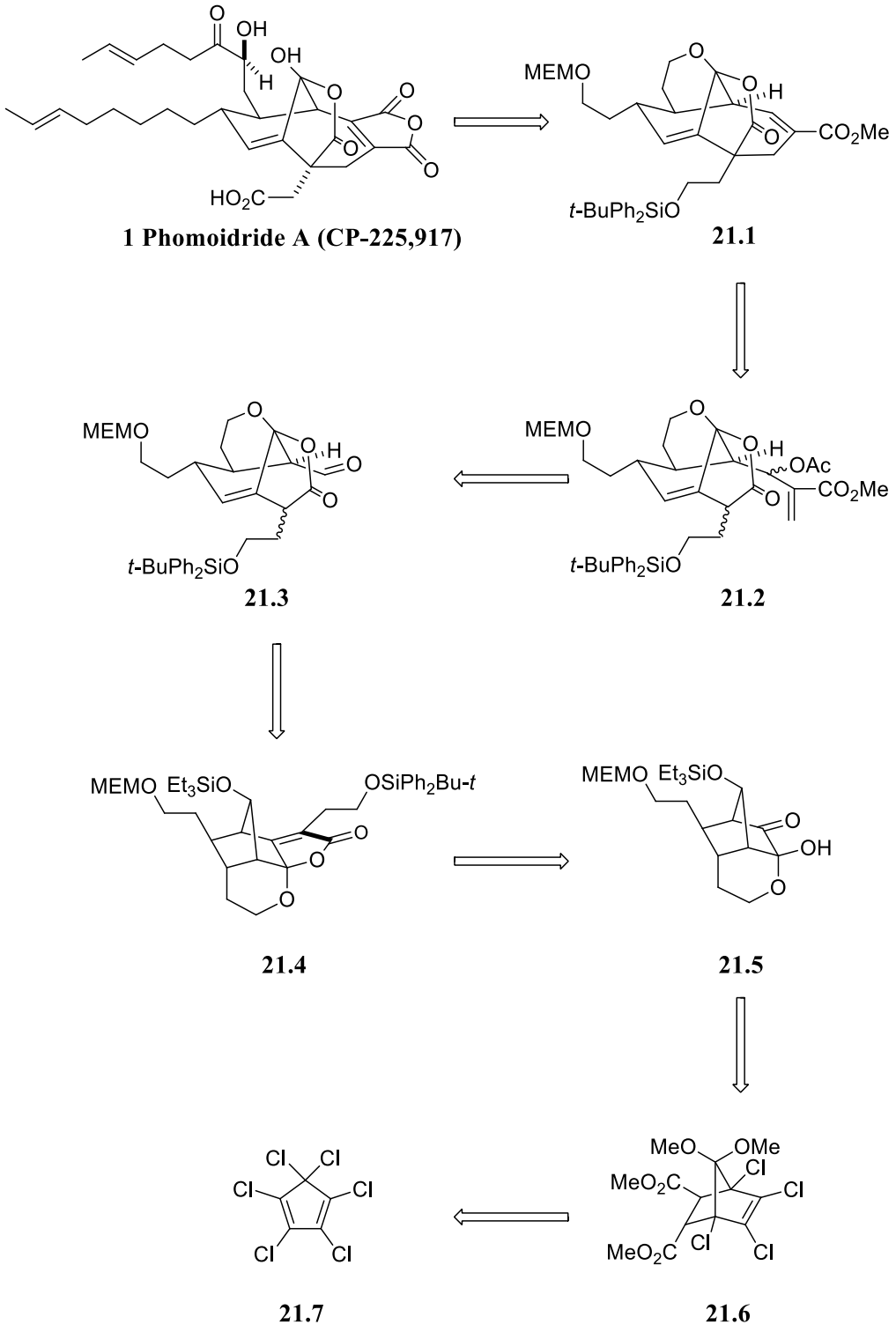
The scope of this reaction, as well as its mechanism, have been studied and this chemistry has been tried by Dr. Prabhudas on a simple structure with one side chain; the result of these experiments (Scheme 20) inspired the new route;[27] the new retrosynthesis plan is summarized in (Scheme 21).

SCHEME 20. Initial attempts toward the core using ICD



20.1 **20.2**

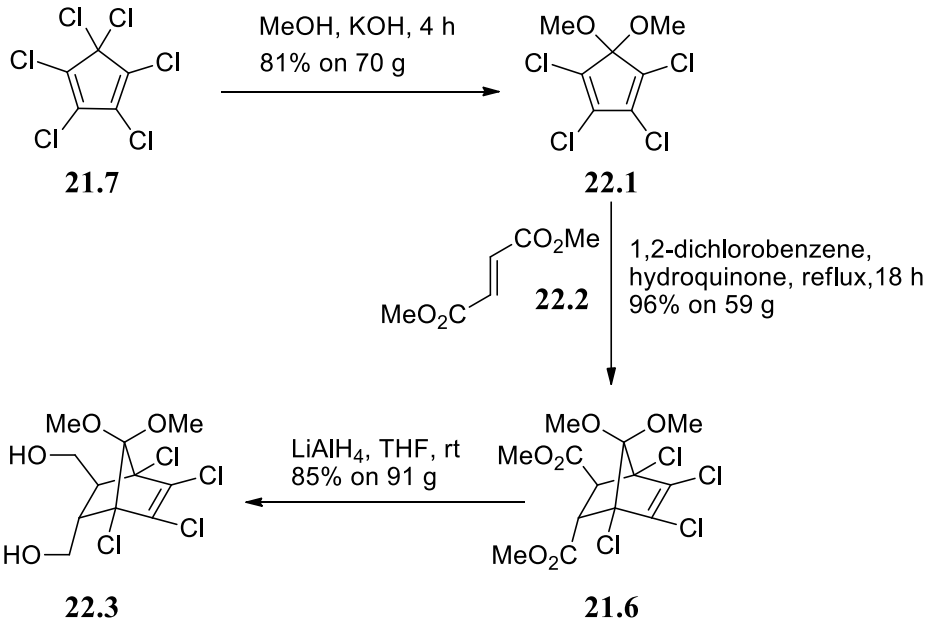
SCHEME 21. Retrosynthetic plan



The plan was to synthesis the CP-225,917 from core structure **21.1** by elaborating the side chains and making the anhydride unit. The core **21.1** is the result of an ICD reaction on Baylis-Hillman adduct **21.2** which, itself, can be synthesized from aldehyde[28] **21.3**. The aldehyde is the result of the rearrangement of butenolide **21.4**. The butenolide should be accessible from hemiacetal **21.5** by esterification, followed by intramolecular Wittig reaction. The hemiacetal, in turn, should be obtained in a few steps from diester **21.6** which is the result of a Diels-Alder reaction involving **21.7**.

As I took over the project, the first few steps had been optimized and the pattern of this path was established by Dr. Cheng and Dr. Minurazzaman who worked briefly on the project. I began my synthesis by conversion of hexachlorocyclopentadiene **21.7** to 1,2,3,4-tetrachloro-5,5-dimethoxycyclopenta-1,3-diene (**22.1**)[29] (Scheme 22).

SCHEME 22. Synthesis of **22.3**

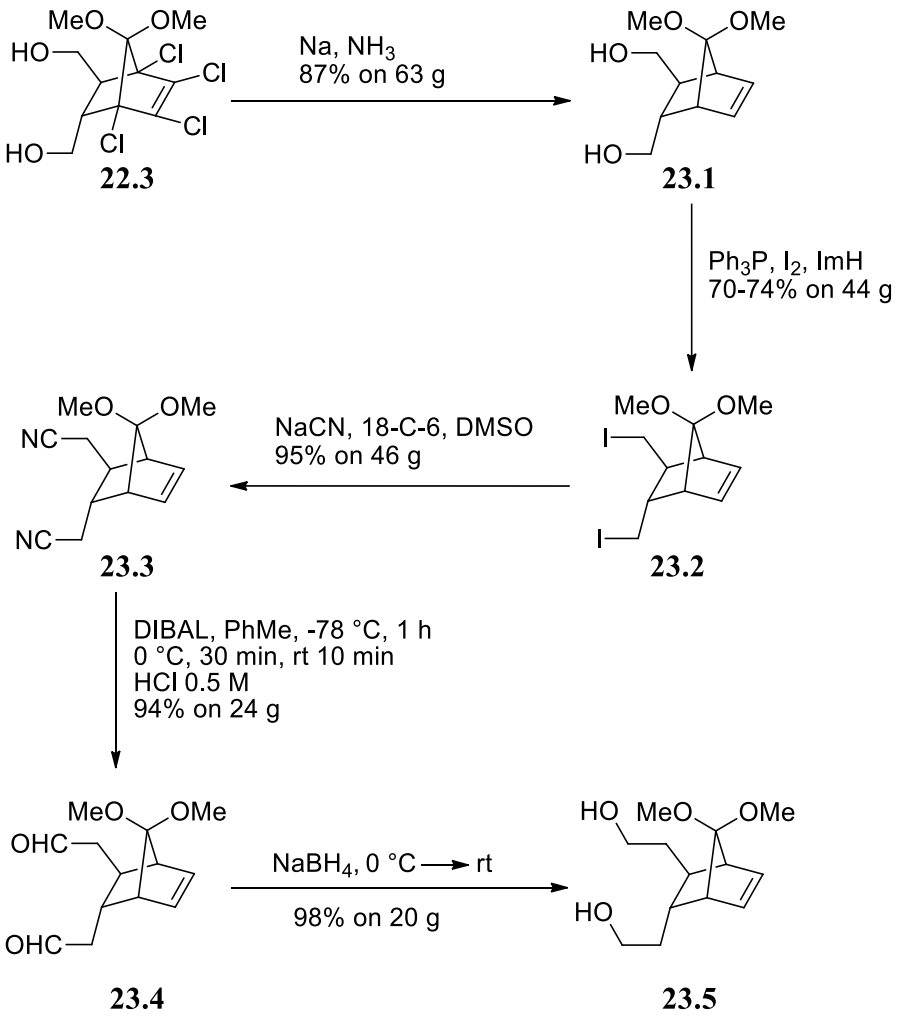


The acetal group will afford a ketone at a later stages; cyclopentadienone itself is unsuitable as it dimerizes.[30] It very quickly became apparent that very large amounts of **22.3** would be needed and so I optimized the route in order to work on a multi-gram scale. Once the diene **22.1** was prepared, the Diels-Alder reaction with dimethyl fumarate **(22.2)** in refluxing 1,2-dichlorobenzene produced the diester **21.6** in an excellent yield. The first goal was reaching hemi-acetal **21.5** and, in order to do that we needed to add an extra carbon to the side chains. To accomplish that, the diester was reduced with $LiAlH_4$ to give diol **22.3**.

Next the hydroxyl groups had to be changed to leaving groups. Dr. Chang had shown that direct conversion to mesylates was not possible, although the reasons for this are not understood. As a result, the chlorines were removed from **22.3** by treatment with sodium in liquid NH_3, to give the less hindered dehalogenated diol **23.1** smoothly. This time, the diol was converted easily to the diiodide **23.2** by an Appel-type reaction. Displacement of iodide with cyanide, using NaCN in DMSO in the presence of a catalytic amount of 18-crown-6, provided the bis cyanide **23.3**. This compound was converted efficiently to dialdehyde **23.4** by DIBAL-H reduction; further reduction with $NaBH_4$ then gave diol **23.5** (Scheme 23). This diol was obtained in an overall yield of 37% from **21.7**.

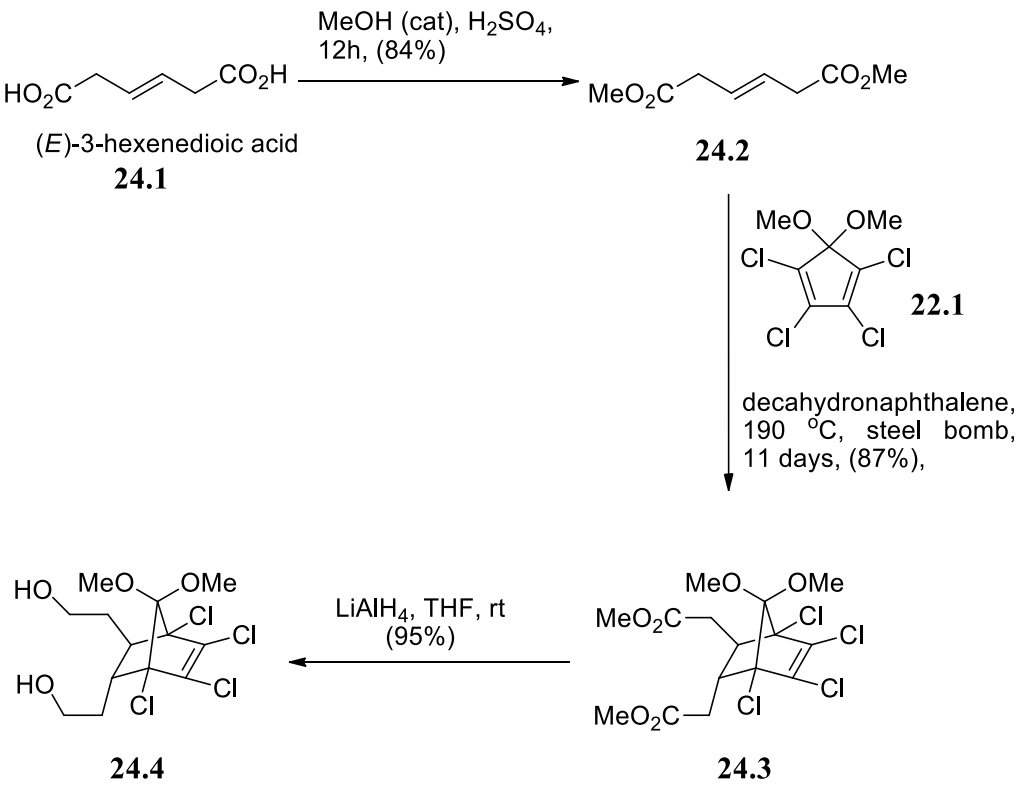
Obviously, this route takes four steps to install the extra carbons on the side chains and it is important to note that shorter routes were tried by Dr. Cheng initially. In the first of those cases, the idea was to include the carbon at the very beginning, using a suitable dienophile (Scheme 24).

SCHEME 23. Formation of **23.5**



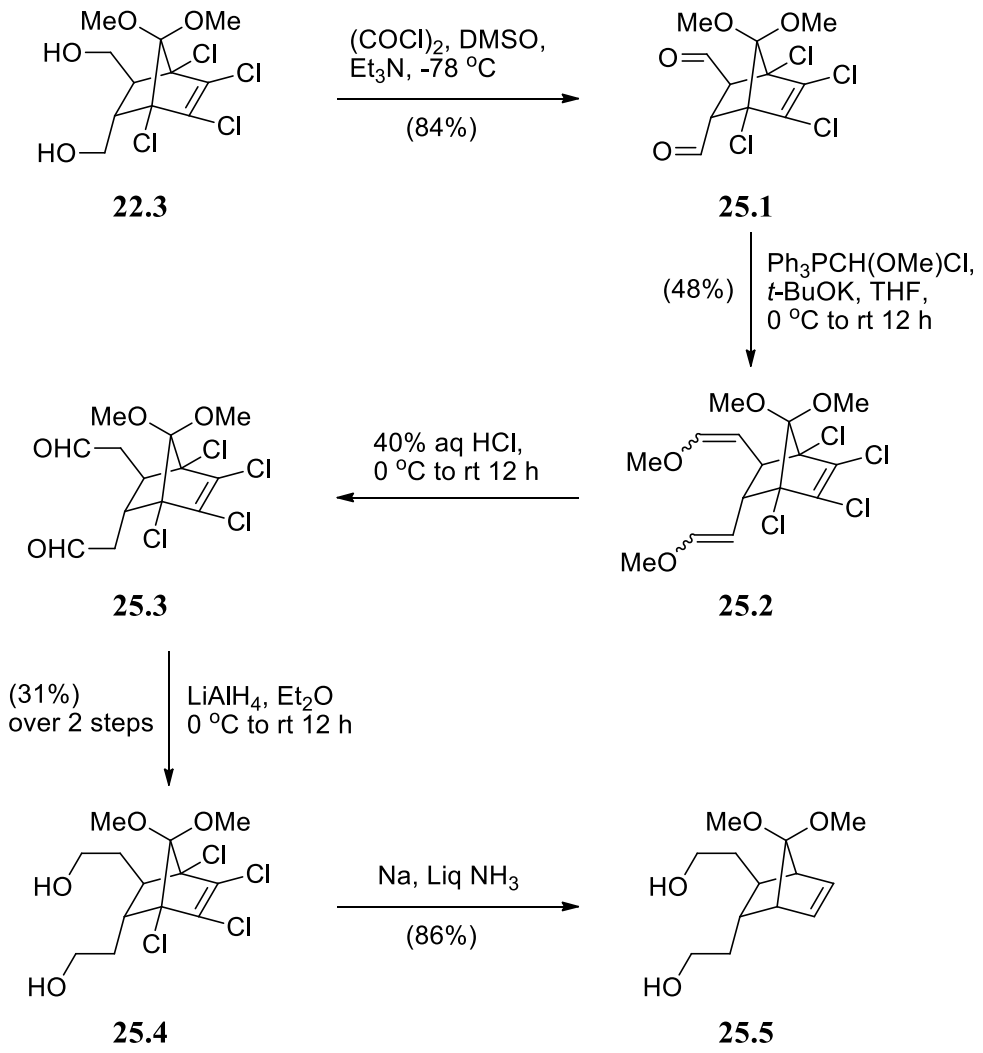
To this end, (*E*)-3-hexenedioic acid (**24.1**) was converted to diester **24.2** (Scheme 24) under Fisher-Speier[31] conditions and, using the procedure described by Leighton,[32] it was subjected to a Diels-Alder reaction with 1,2,3,4-tetrachloro-5,5-dimethoxycyclopenta-1,3-diene (**22.1**). The reaction gives a high yield but takes 11 days at 190 °C, which makes it inconvenient. Furthermore, the *E*)-3-hexenedioic acid is quite expensive and so we decided to change the pathway as in Scheme 25.

SCHEME 24. Formation of **24.4** (Dr. Minaruzzaman)



In the second case, the diol **22.3** was converted to dialdehyde **25.1** by Swern oxidation. The resulting dialdehyde, which was unstable on silica, was treated with the Wittig salt, $Ph_3PCH(OMe)Cl$ in the presence of *t*-BuOK (Scheme 25). The enol ethers **25.2** were obtained in moderate yield and converted to dialdehyde **25.3** under acidic conditions. This compound was also unstable but, upon reduction with $LiAlH_4$, it gave diol **25.4** which was dehalogenated with sodium in liquid ammonia to produce diol **25.5** in an overall yield of 7% from **21.7**.

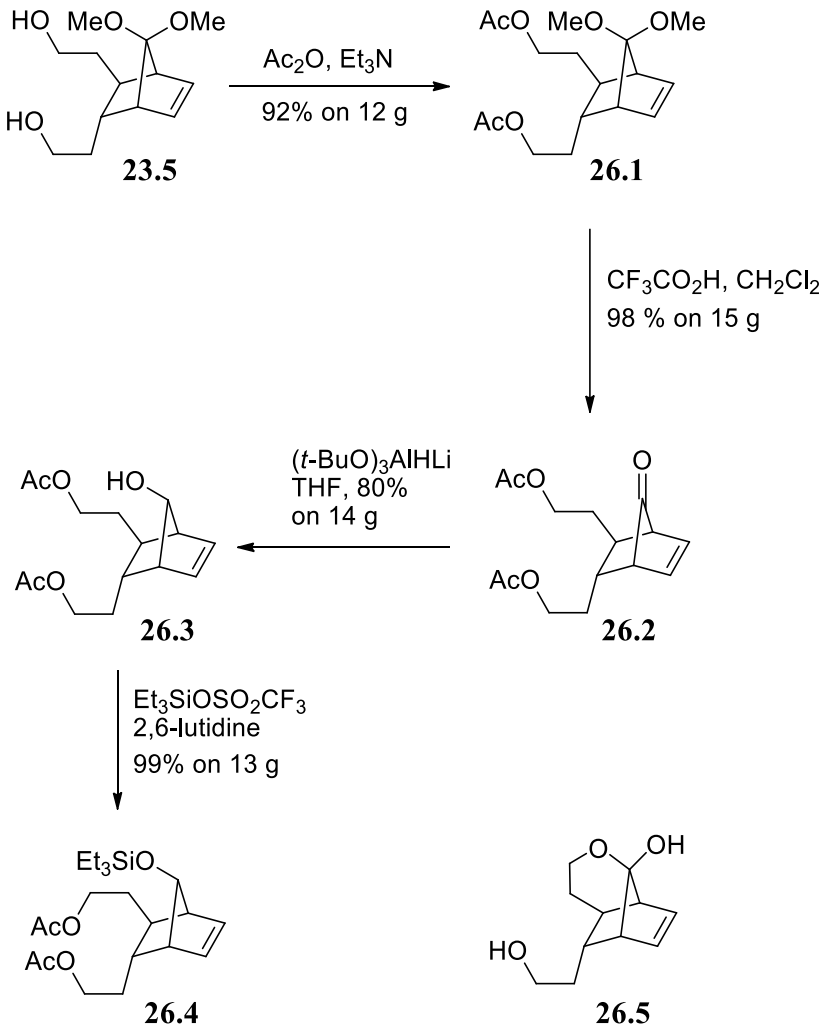
SCHEME 25. Formation of **25.5** (Dr. Minaruzzaman)



Based on the above observations, we decided to accept the longer route for its higher overall yield and use of cheap and readily available starting materials.

The hydroxyl groups of diol **23.5** were acetylated, using Ac_2O and Et_3N, to give **26.1**. The acetal group was then removed with CF_3CO_2H and the resulting ketone **26.2** was stereoselectively reduced from the less hindered side to give **26.3** as a single isomer. It is important that the acetylation step should be done prior to acetal removal; otherwise the hemiacetal **26.5** would be obtained (Scheme 26).

SCHEME 26. Formation of **26.4**

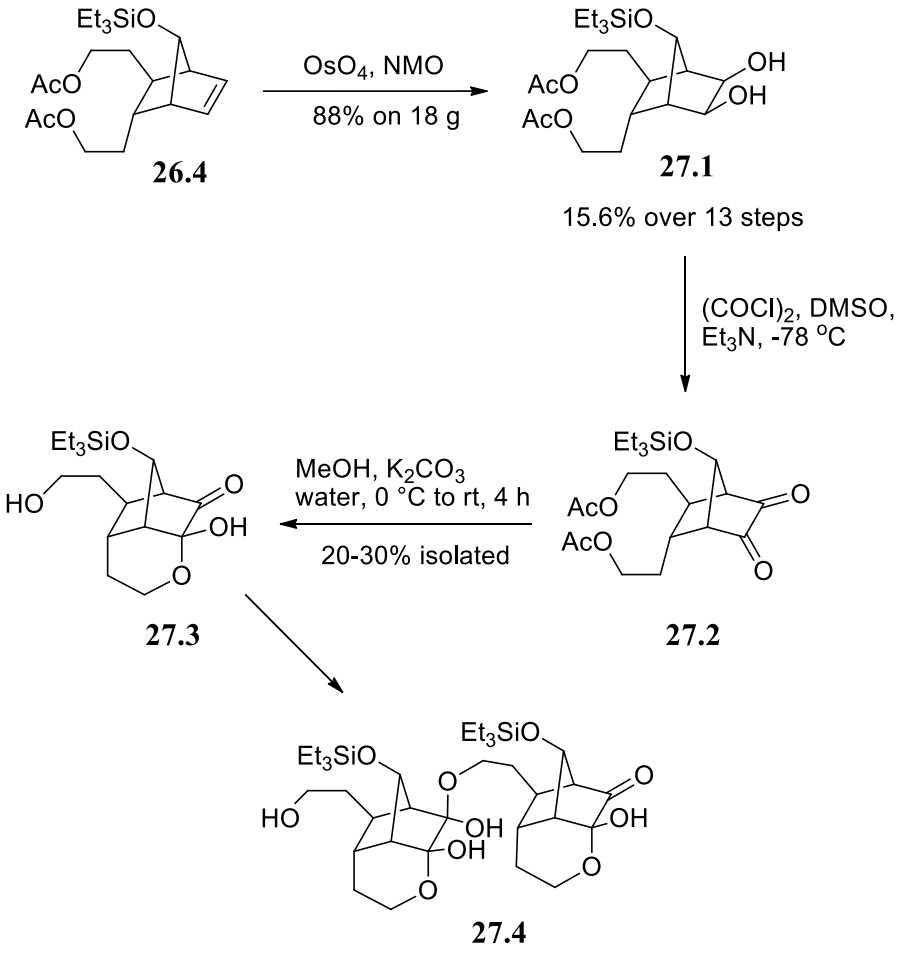


Alcohol **26.3** was smoothly protected by reaction with $Me_3SiOSO_2CF_3$ in the presence of 2,6-lutidine to give **26.4**.

At this point, **26.4** was dihydroxylated to diol **27.1** with OsO_4 and *N*-methylmorpholine *N*-oxide. The diol was oxidized by the Swern method to the unstable diketone **27.2**, which had to be taken forward promptly without purification. Removal of the acetyl groups under basic conditions allowed cyclization to occur so as to produce the hemiacetal **27.3**. The reaction proceeded

very smoothly (and was monitored by TLC) but unlike prior model studies in this laboratory, when solutions of the crude compound were concentrated a side reaction appeared to occur, as described below, and the desired product was obtained in only 20-30%.

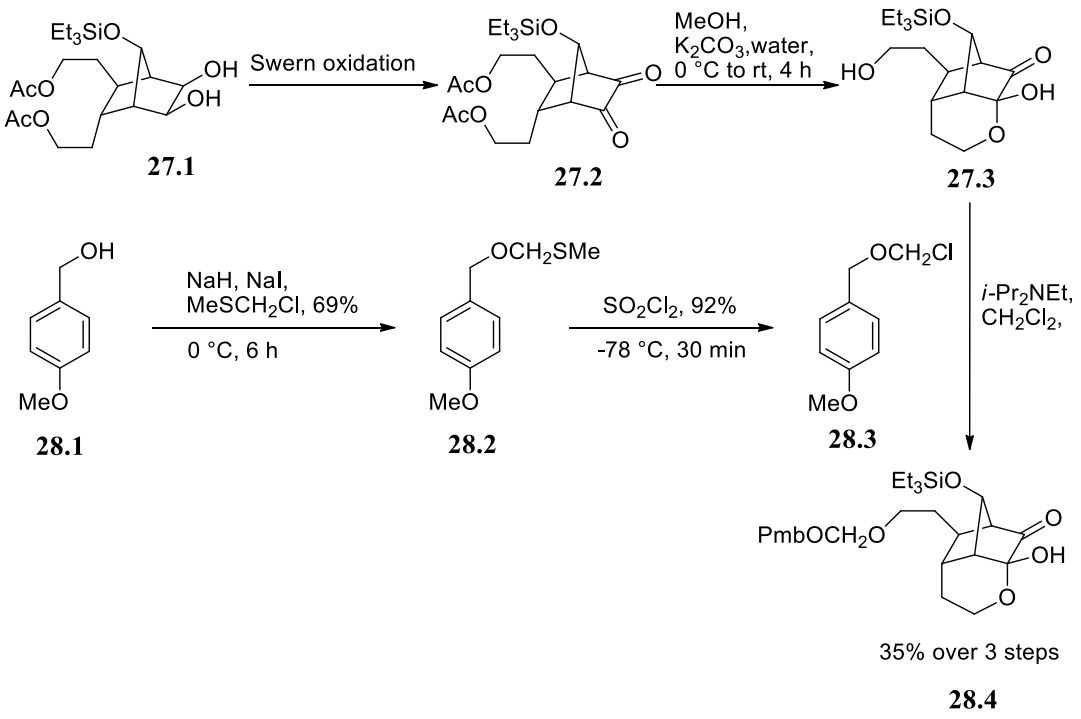
SCHEME 27. Formation of **27.3** and **27.4**



Further investigation revealed that upon concentration of solutions of crude **27.3** the major portion of the product dimerizes to **27.4**. The only way to avoid this problem was to protect the free hydroxyl of hydroxy ketone **27.3** without concentrating the crude mixture. To this end we decided to try PMBMCl

(*p*-methoxybenzyloxymethyl chloride) to install a protecting group. This reagent needs to be prepared just before use, as it is not storable[33] (Scheme 28). Treating the sodium salt of *p*-methoxybenzyl alcohol (**28.1**) with chloromethyl sulfide produced the sulfur compound **28.2** which was reacted with SO_2Cl_2 to give the required reagent **28.3**. Both the reagent and it precursor **28.2** are unstable and they were used immediately after preparation.

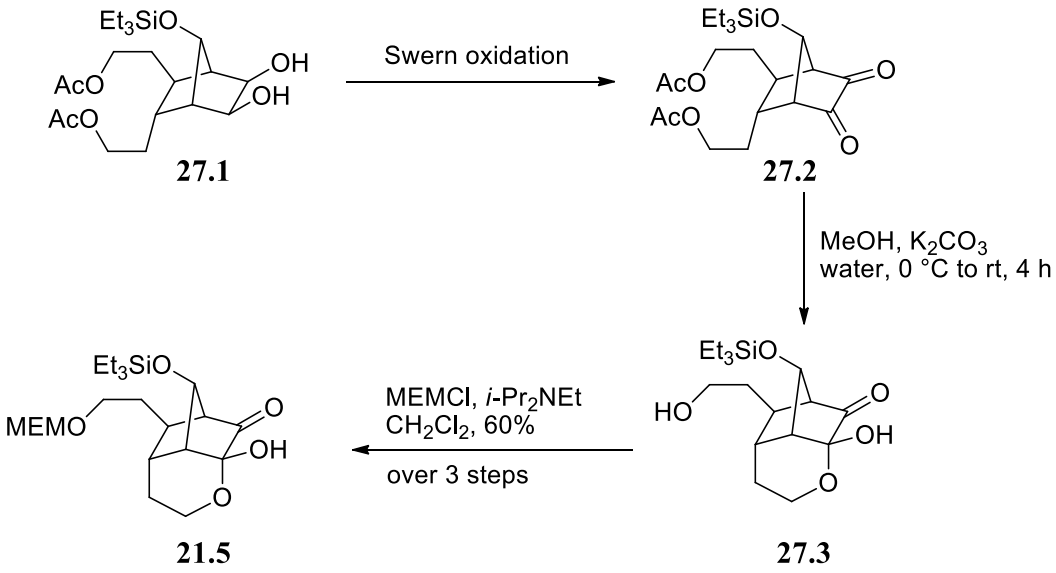
SCHEME 28. Use of the *p*-methoxybenzyloxymethyl protecting group



The preparation of **27.3** was repeated and this time the crude hemiacetal was protected without concentration; **28.4** was obtained in 35% yield over 3 steps, which represented an improvement in yield. However, having to carry out five reactions in a single day was inconvenient. Consequently, we searched for protecting groups provided by commercially available reagents. Eventually,

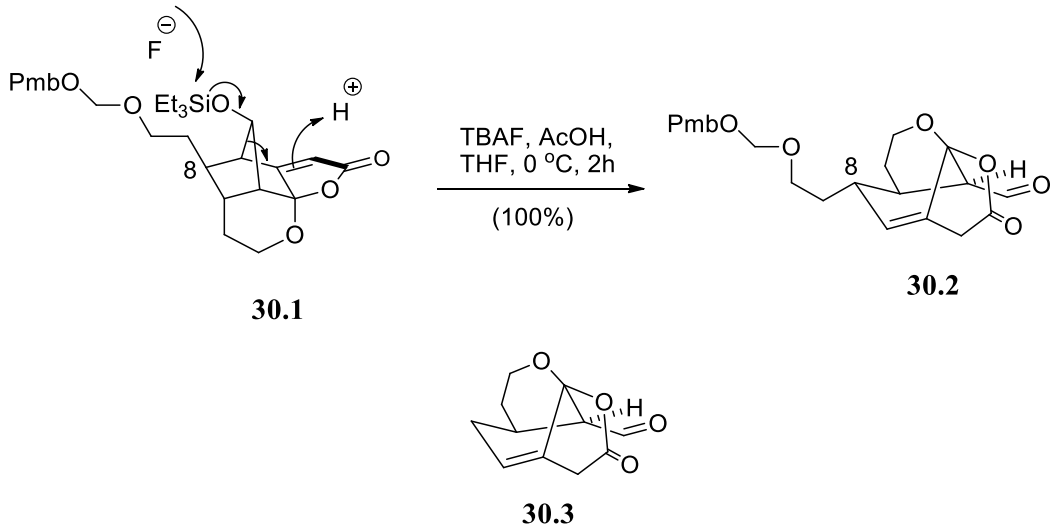
MEMCl was chosen and the whole sequence was repeated; this time the desired protected hemiacetal **21.5** was obtained as 60% yield over 3 steps (Scheme 29). This was clearly a very satisfactory result.

SCHEME 29. Preparation of **21.5**



It is noteworthy that under the proper conditions only the primary hydroxyl is protected. The next stage was to make butenolide **21.4**. Based on the model study[27] in which only a side chain on C-8 was present, the group knew that treatment of butenolide **30.1** with Bu_4NF would initiate a strain-assisted fragmentation to release aldehyde **30.2** (Scheme 30).

SCHEME 30. Fragmentation of butenolide **30.1**

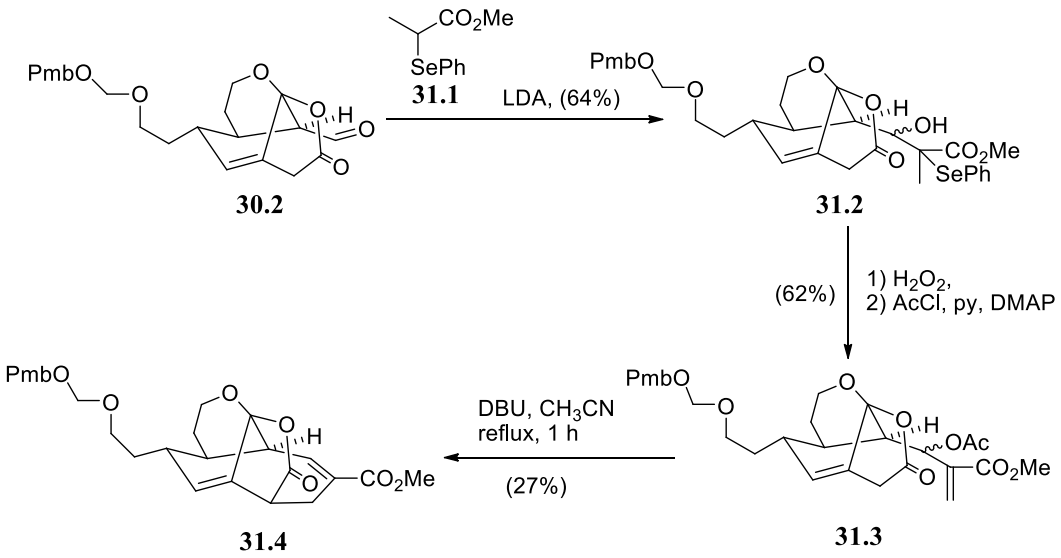


30.1 **30.2**

30.3

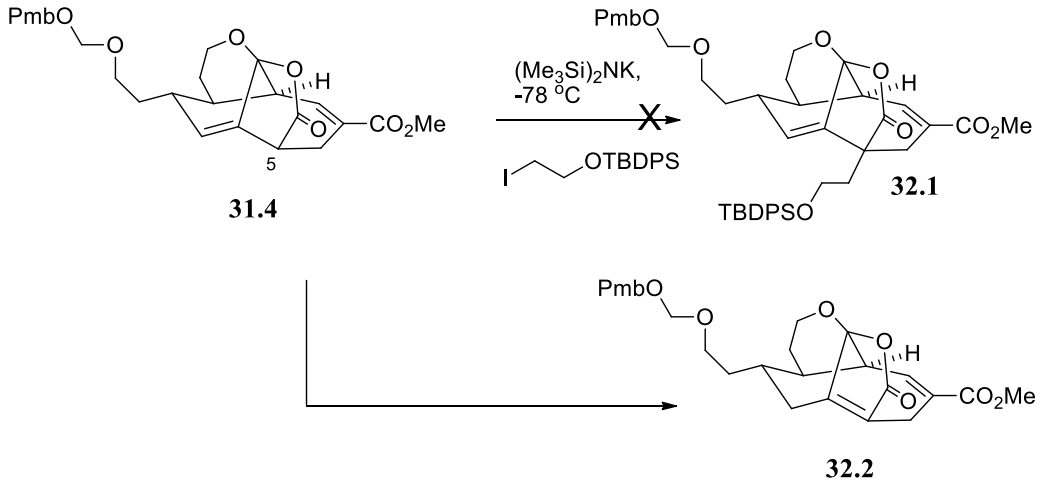
The structure of **30.2** was confirmed by extensive NMR studies as well as by comparison with NMR data of compound **30.3** which had been made by a different route in this laboratory. Our assignment was confirmed by single crystal X-ray analysis. It is important to note that in order for the ICD reaction to work, the aldehyde must point towards the inside of the structure so as to make the ring closure possible. The model study summarized in Scheme 30 was continued by Dr. Minaruzzaman, as follows. The precursor of the intramolecular conjugate displacement was prepared in three steps (Scheme 31). Addition of seleno ester **31.1** in the presence of LDA to aldehyde **30.2**, followed by oxidation, provided an allylic alcohol which was protected with AcCl to give ester **31.3** and, upon treatment with DBU, the model core structure **31.4** was produced.

SCHEME 31. Formation of model **31.4** by ICD reaction (Dr. Minaruzzaman)



Attempts to functionalize **31.4** by attaching a side chain at C-5 were not successful and resulted only in movement of the strained bridgehead double bond into conjugation (**31.4→32.2**) (Scheme 32).

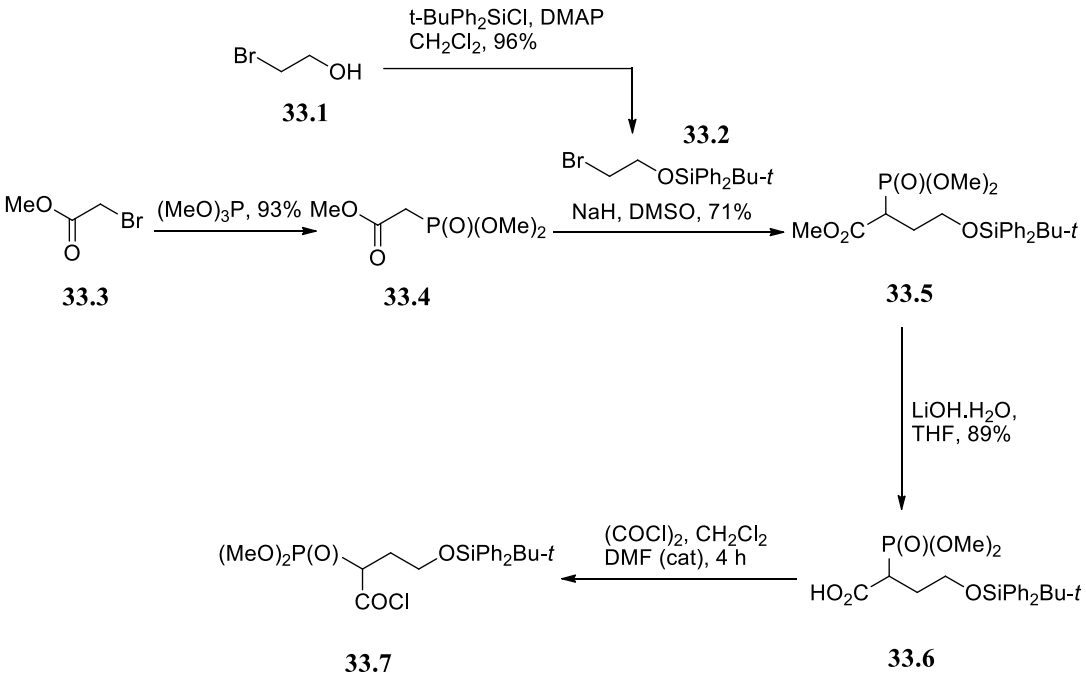
SCHEME 32. Attempted alkylation at C-5



Accordingly, we aimed to install this side chain at an early stage such as in the formation of the butenolide subunit, as described below.

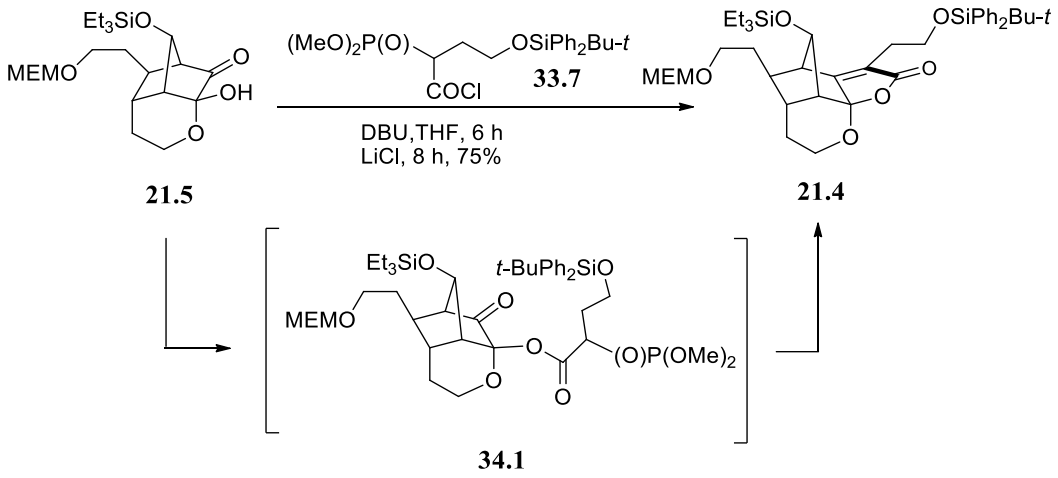
The acid **33.6** was prepared as shown in Scheme 33. Protection of bromoethanol (**33.1**) with *t*-BuPh$_2$SiCl in the presence of DMAP gave[34] **33.2** which was added to phosphonate **33.4** to give **33.5** (Scheme 21).[35]

SCHEME 33. Preparation of the side chain



The methyl ester was hydrolyzed with LiOH and the resulting crystalline carboxylic acid **33.6** was converted to acid chloride **33.7** using $(COCl)_2$ in the presence of a catalytic amount of DMF. The acid chloride **33.7** is sensitive and was prepared just before to use. Addition of the acid chloride to a solution of **21.5** in THF, followed by addition of DBU, generated the intermediate **34.1**. This was transformed in situ to butenolide **21.1** by addition of LiCl as in the Masamune-Roush protocol[36] for the Horner-Emmons-Wadsworth olefination.

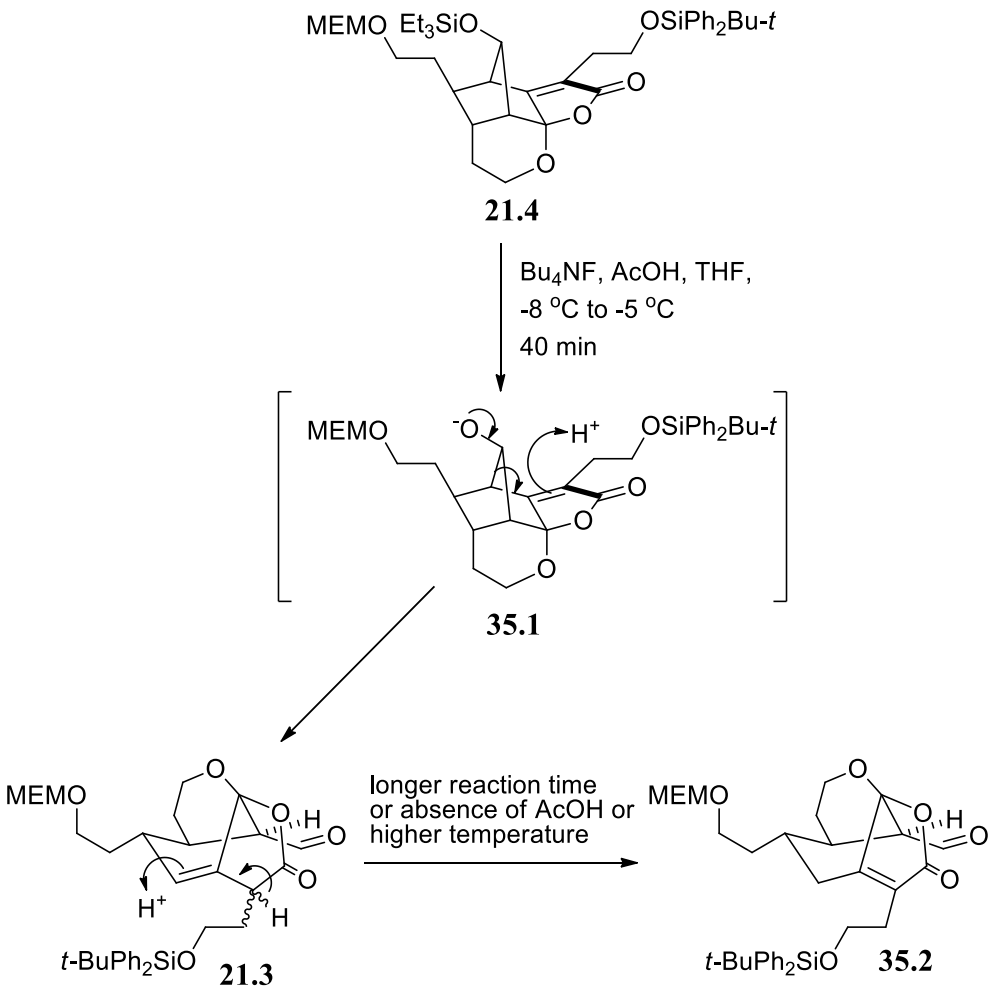
SCHEME 34. Construction of butenolide **21.4**



Once butenolide **21.4** was synthesized, the Bu_4NF-induced fragmentation was tried, but it turned out that the process is not as smooth as with the simpler analogs. Extensive optimization was required to identify the proper conditions and exact amounts of reagents. If the temperature is less than -10 °C there is no reaction, but once the temperature reaches -3 °C the bridgehead double bond isomerizes rapidly to the conjugated position. Also it is imperative to buffer the Bu_4NF with AcOH, as Bu_4NF itself is too basic and again causes rearrangement of the bridgehead double bond. Finally, I found that the reaction time is important, as immediately after rearrangement the excess of Bu_4NF causes migration of the double bond. For all these reasons, the reaction needs to be monitored frequently and must be quenched as soon as it is complete or is just short of completion (Scheme 35).

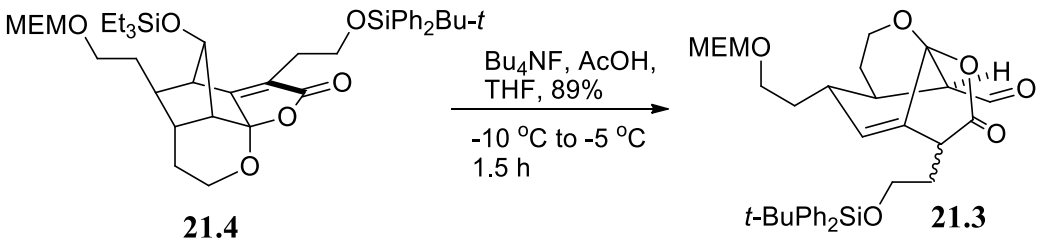
An explanation for this different behaviour might be due to the additional strain caused by the extra sidechain and also the presence of the quaternary center that will stabilize the double bond if it moves.

SCHEME 35. Mechanistic challenges for fragmentation



Eventually, by using the optimized conditions, rearrangement went smoothly and provided the aldehyde **21.3** in excellent yield and with the right stereochemistry (Scheme 36).

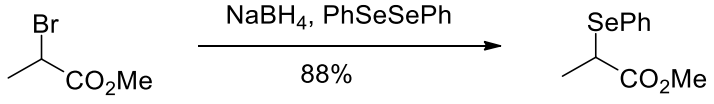
SCHEME 36. Fragmentation of **33.4**



21.4 **21.3**

The Baylis-Hillman subunit **38.2** was the next target and the selenium mediated method via **37.2** seemed a reliable route.[37] Methyl 2-(phenylseleno)propionate **37.2** was prepared by reaction of 2-bromopropionate (**37.1**) with diphenyl diselenide in the presence of $NaBH_4$ in MeOH (Scheme 37).

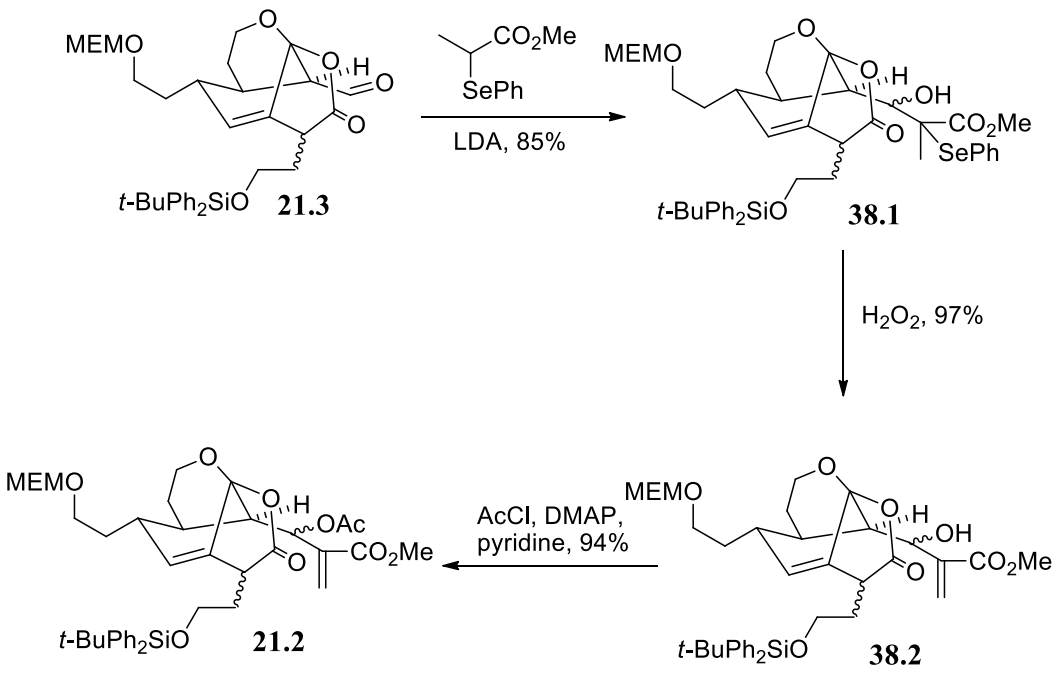
SCHEME 37. Preparation of **37.2**



37.1 **37.2**

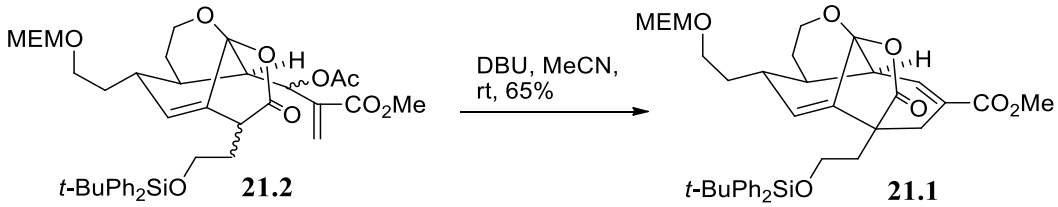
The selenoester **37.2** was then deprotonated using LDA and the resulting anion was allowed to react with aldehyde **21.3** to produce phenylseleno ester **38.1** as a mixture of isomers. These were taken forward without separation and oxidized with H_2O_2 to produce the Baylis-Hillman subunit **38.2** as an inseparable mixture of isomers. The compound is highly functionalized and quite unstable; the classical Baylis-Hillman method would not be suitable for its preparation. The allylic hydroxyl in **38.2** was then acetylated to give the ICD substrate **21.2** as an inseparable mixture of isomers (Scheme 38).

SCHEME 38. Forming the precursor of the ICD reaction



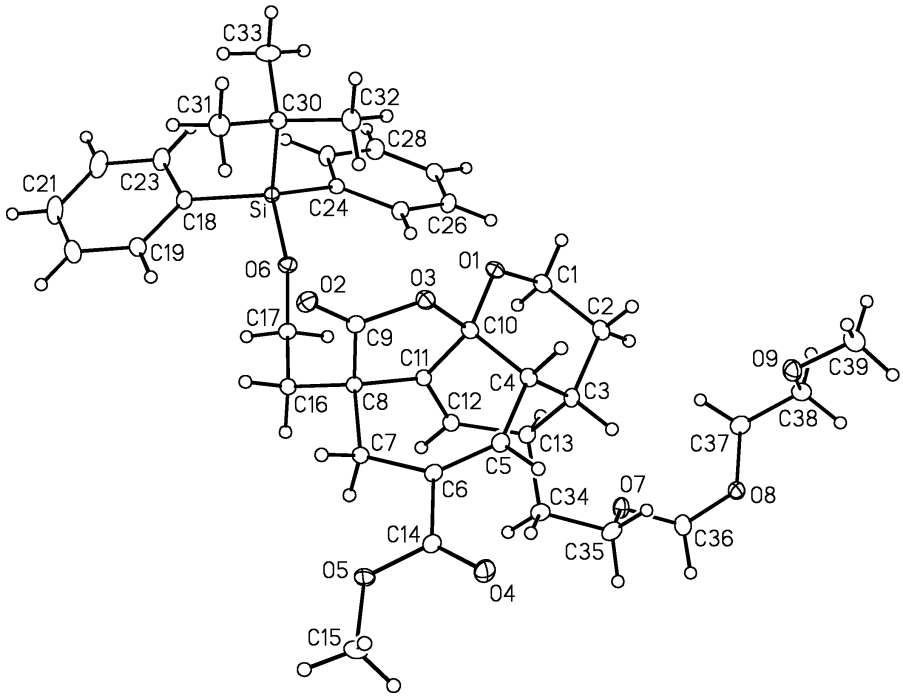
The mixture of isomers **21.2** was subjected to conditions for the ICD reaction by treatment with an excess of DBU at room temperature, and the bicyclic natural core structure **21.1** of CP molecules **1** and **2** was obtained as a single isomer (Scheme 39).

SCHEME 39. The key ICD reaction



It was possible to obtain crystals suitable for X-ray analysis and the structure of **21.1** was confirmed (Figure 2).

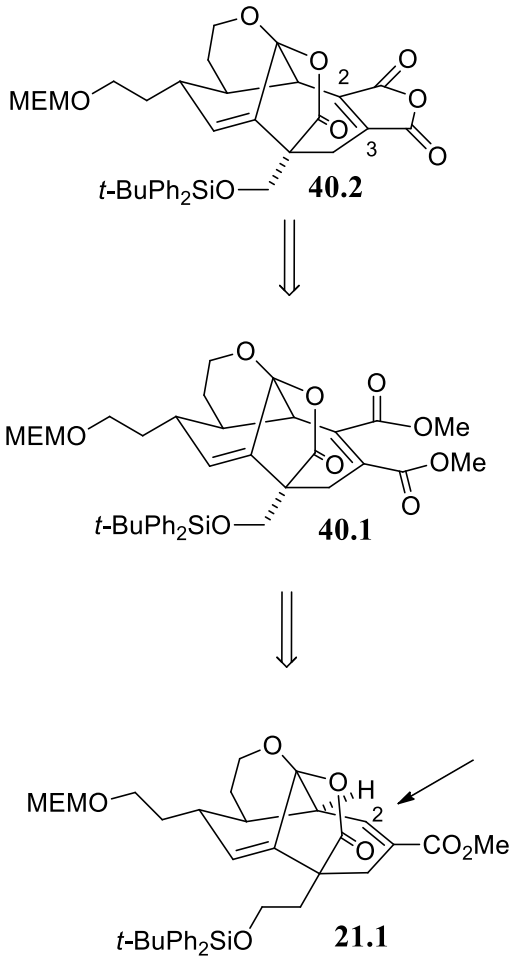
FIGURE 2. ORTEP diagram of compound **21.1**



Our next target was to construct the anhydride ring on the molecule. In order to build up the anhydride ring we needed to functionalize carbon C-2 and the most obvious way to do that was by conjugate addition (Scheme 40). Using an appropriate nucleophile it should be possible to form the diester **40.1** and from that point the anhydride core structure **40.2** should be accessible (Scheme 28).

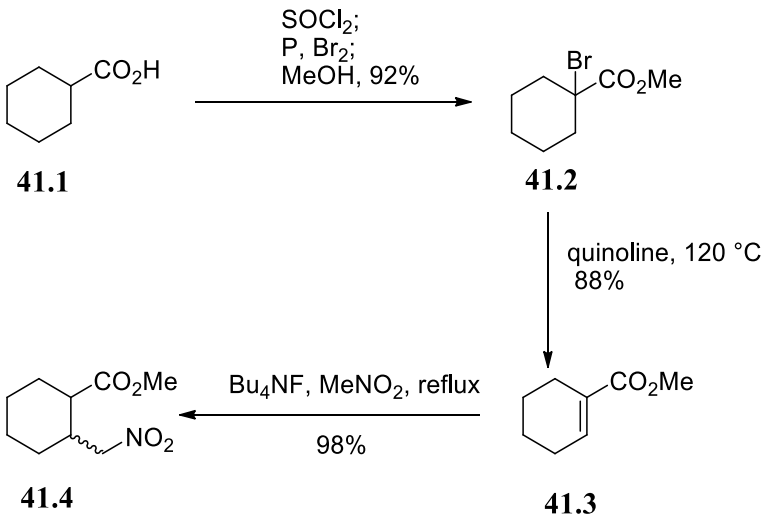
Obviously, **21.1** is an advanced and highly functionalized compound which is 22 steps away from the starting material **21.7**. Therefore, we decided to try to optimize the necessary reactions on simple models such as methyl cyclohex-1-ene-1-carboxylate (**41.3**) before applying them to the valuable sample of **21.1**.

SCHEME 40. General retrosynthetic plan to construct the anhydride portion



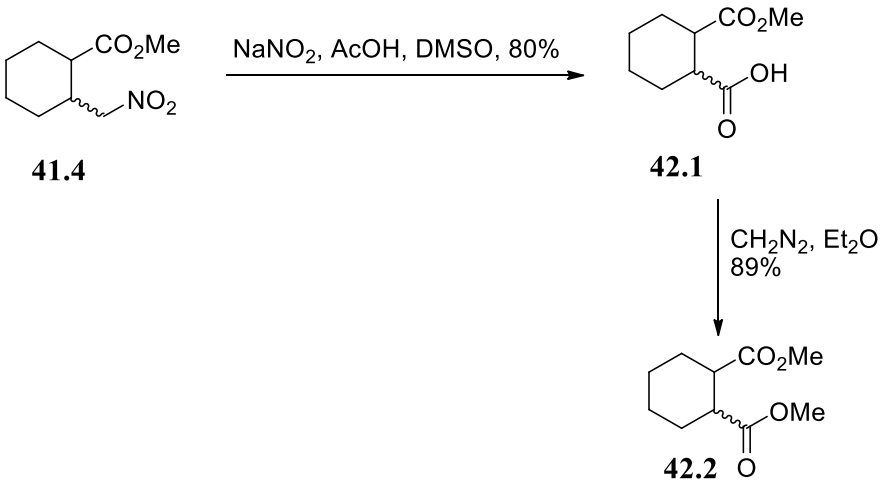
In order to test the Michael addition on a model, compound **41.3** was prepared in a standard way from cyclohexanecarboxylic acid (**41.1**) by Hell-Vollhard-Zelinsky reaction, followed by elimination of bromine under basic conditions.[38a] Compound **41.3** was then subjected to many reaction conditions that seemed appropriate for conjugate addition, and eventually we found that the best results involve using $MeNO_2$ and Bu_4NF as the base in THF. Under these conditions $MeNO_2$ adds smoothly to the model (Scheme 41).[38b]

SCHEME 41. Conjugate addition of nitromethane to **41.3**



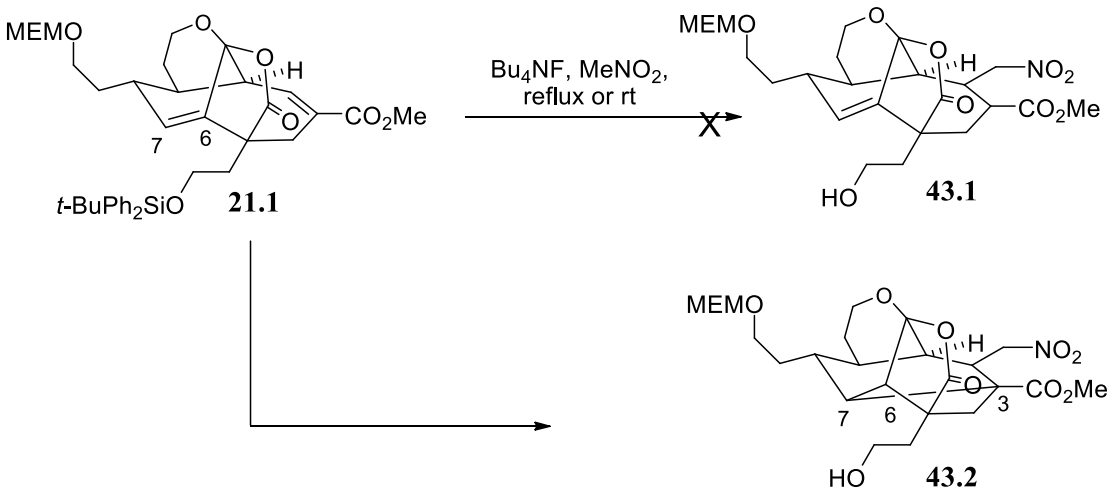
The nitro compound **41.4** can be converted to carboxylic acid **42.1** using $NaNO_2$ and AcOH in DMSO,[39] and the carboxylic acid group was then esterified to give diester **42.2**, using CH_2N_2 (Scheme 30).

SCHEME 42. Formation of diester **42.2**



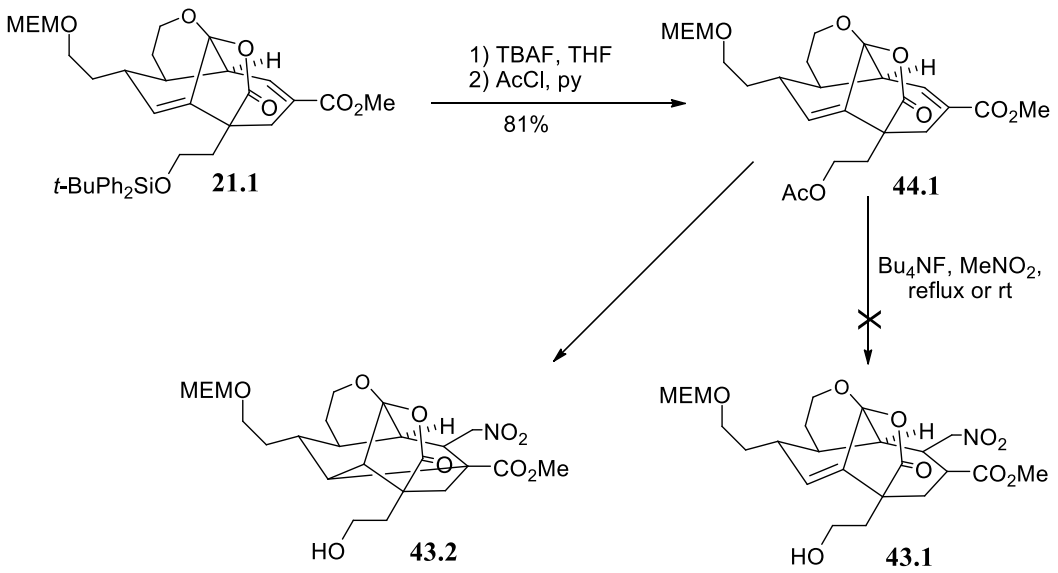
With this satisfying result, we decided to use the same conditions on **21.1** in the expectation that the use of Bu_4NF would also remove the *t*-$BuPh_2Si$ group. Of course, this could be replaced later. We found that a fast reaction occurs and the preliminary data confirmed the addition of $MeNO_2$ to the structure but we soon found that the intermediate carbanion formed α to the ester attacks the strained double bond at C-7 to give **43.2** instead of the desired product **43.1** (Scheme 43).

SCHEME 43. Reaction of nitromethane with **21.1**



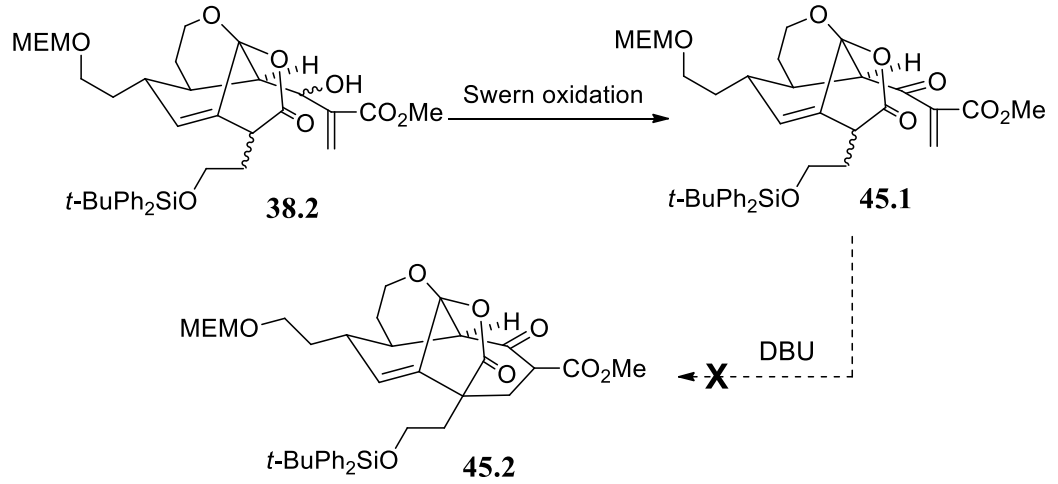
This was a very unwelcome observation, as such behaviour would prevent us from adding any nucleophile in a Michael fashion. We first thought that if we could preserve the protecting group on the C-5 chain before adding $MeNO_2$ we might find that steric factors suppressed the transannular reaction. To this end, we replaced the *t*-$BuPh_2Si$ group by an acetyl group but obtained the same result on repeating the reaction (Scheme 44). We also made a model of the product and observed that the [5.5.7] system of fused rings could be constructed without undue strain on the model.

SCHEME 44. Transannular reaction after acetylation



Next, we decided to try the possibility of functionalizing C-2 before the ICD reaction. In order to try this approach the allylic alcohol **38.2** was oxidized by the Swern method to produce **45.1**.

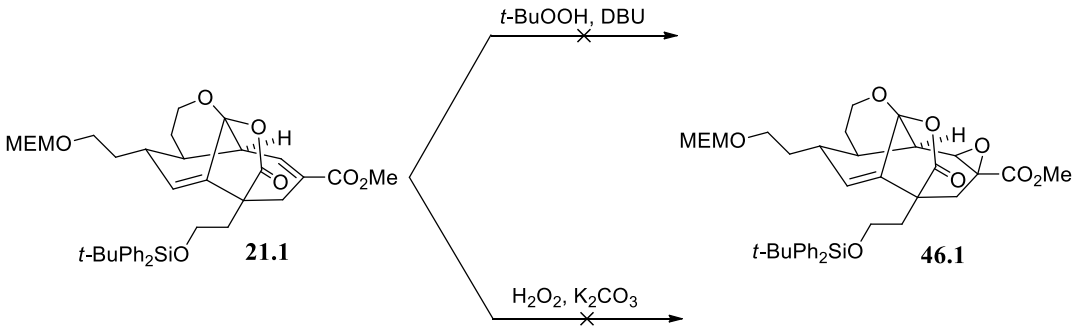
SCHEME 45. Simple Michael addition approach



The compound with its doubly activated double bond was exposed to DBU but unfortunately none of the desired product was detected (Scheme 45).

As we were unable to add nucleophiles to **21.1**, we decided to use epoxides instead, as attack of a nucleophile on an epoxide would avoid the build-up of negative charge on C-3. However, attempts at epoxidizing **21.1** directly did not give any product (Scheme 46).[40]

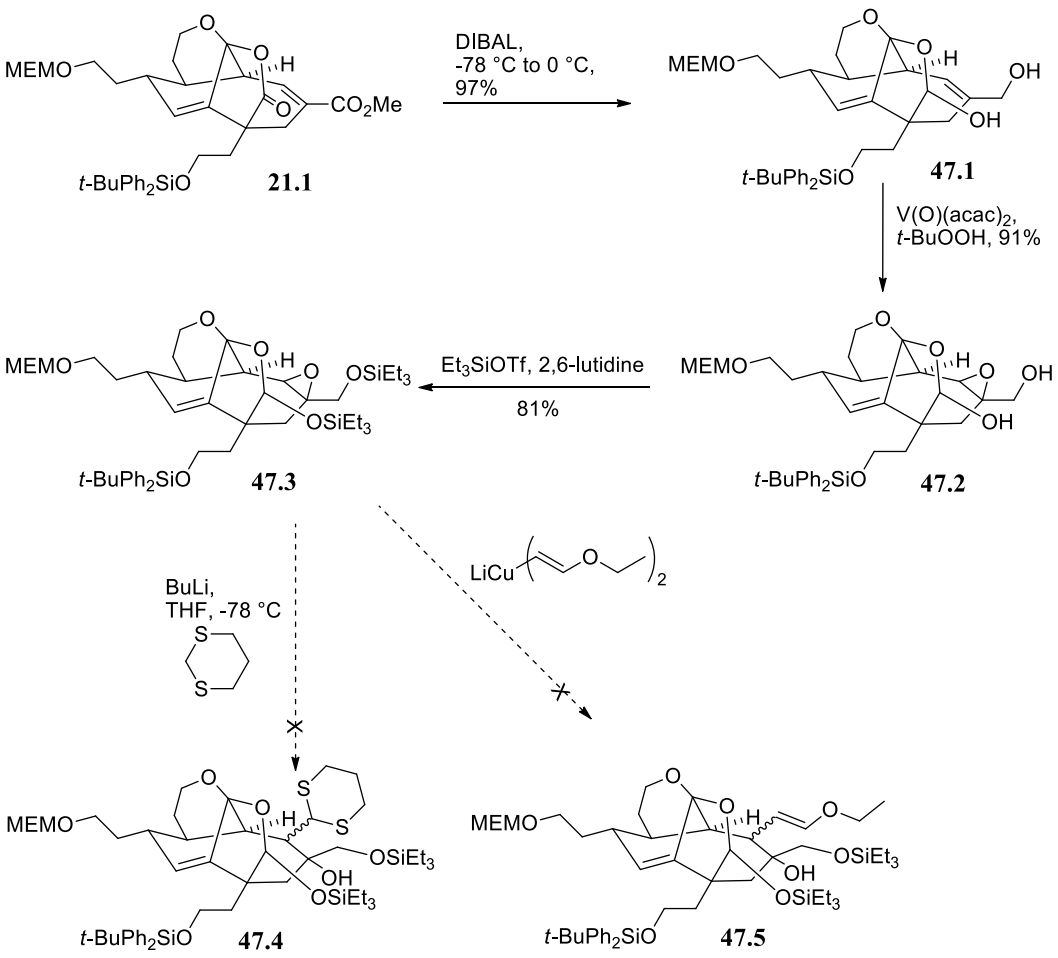
SCHEME 46. Attempts at epoxidizing **21.3**



Consequently, we reduced the ICD product **21.1** to allylic alcohol **47.1** and then used Sharpless epoxidation conditions to selectively oxidize **47.1** to epoxide **47.2** in excellent yield.[41] The free hydroxyl groups were then protected as triethylsilyl ethers **47.3** (Scheme 47).

All attempts to add nucleophiles to the resulting epoxide were unsuccessful and gave only starting material back.[42] One explanation for this lack of reactivity could be that epoxidation has occurred form the top face as that is the less hindered face of **47.1**, and the nucleophile then has to attack the epoxide from the much more hindered bottom face of molecule.

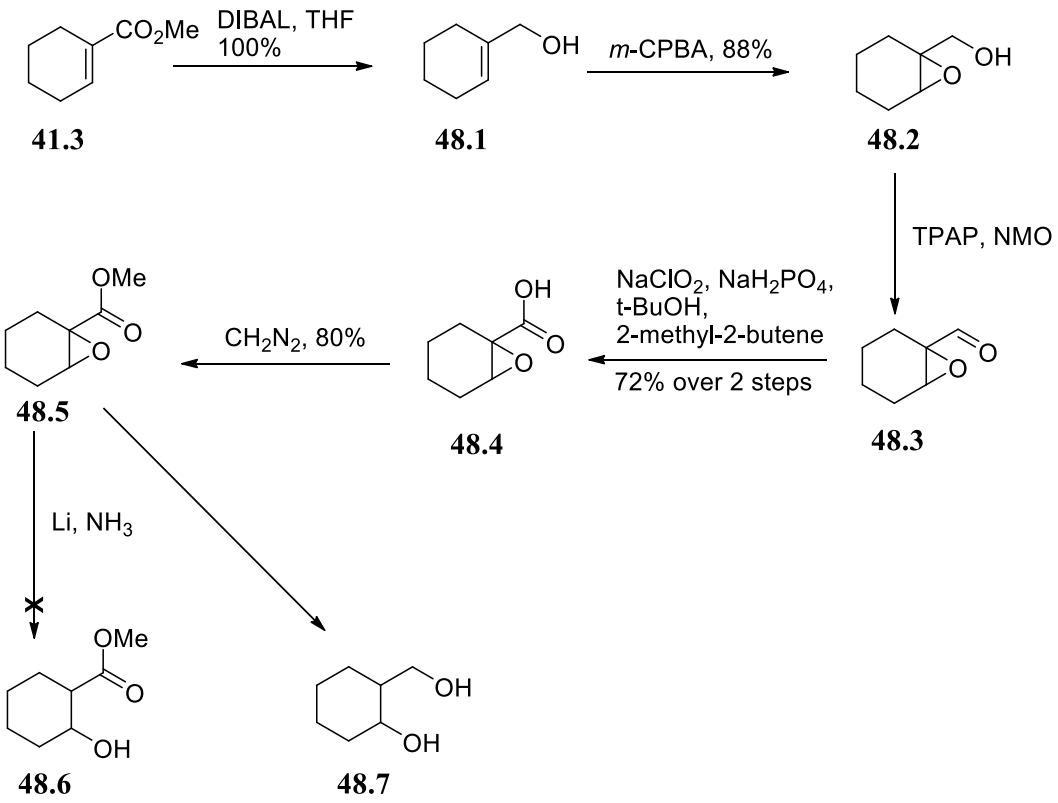
SCHEME 47. Attempted epoxide opening



Another option was to reduce the epoxide and open it so as to have a hydroxyl group on C-3. In order to examine this route, a model substrate was prepared by reducing **41.3** and epoxidizing the resulting allylic alcohol **48.1** to epoxy alcohol **48.2**. This alcohol was then oxidized to aldehyde **48.3** using TPAP and NMO. Aldehyde **48.3** was transformed to epoxy ester **48.5** in two steps by Pinnick oxidation, followed by esterification with CH_2N_2. The resulting epoxy ester was treated with Li and NH_3.[43] Under these reaction conditions the ester was also reduced and we obtained diol **48.6** instead of our desired product **48.7**.

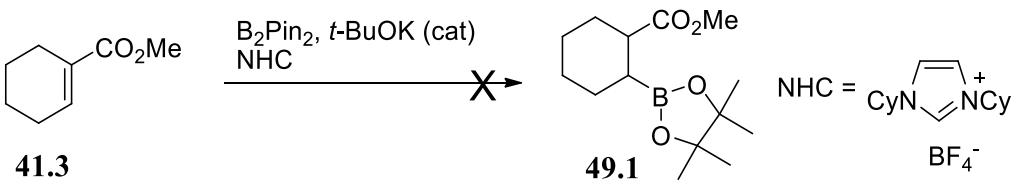
Obviously, this route was too long to pursue because reoxidation would be necessary, and we decided to abandon this approach (Scheme 48).

SCHEME 48. The epoxide reduction route



The next approach that we tried was based on the new chemistry invented by the Hoveyda group, using bis(pinacolato)diboron and an NHC catalyst to form a boron-carbon bond; the boron can then be replaced easily by an hydroxyl group (Scheme 49).[44] Unfortunately, the reaction was not successful, probably because the ester conjugated system is not as reactive as the carbonyl systems (ketones) used by the Hoveyda group.

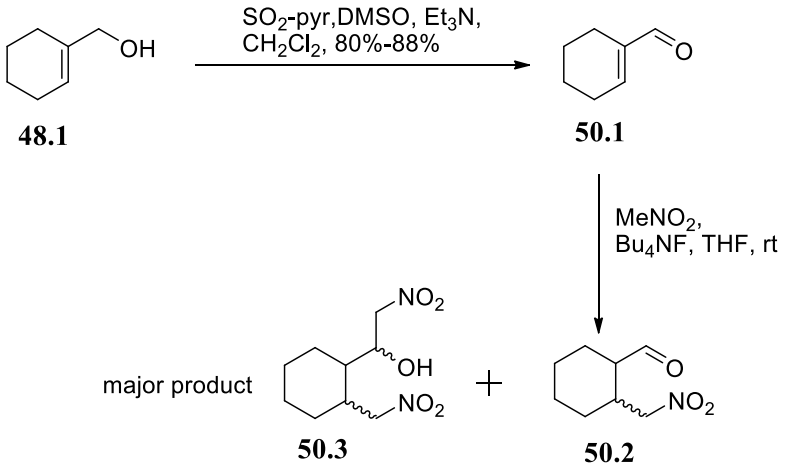
SCHEME 49. Attempted hydroboration



Our next attempt toward addition of a carbon unit was by way of using enamines. In this approach we were aiming first to convert methyl ester **41.3** to an aldehyde for two reasons. The aldehyde is the natural precursor of an enamine and formation of an aldehyde would give us an opportunity to see if it reacted differently towards $MeNO_2$ than an ester. The second reason is that charge build-up with an enamine might be sufficiently small to preclude attack on the bridgehead double bond.

The model study began by converting allylic alcohol **48.1** to aldehyde **50.1**

SCHEME 50. Nitromethane addition to unsaturated aldehyde **50.1**

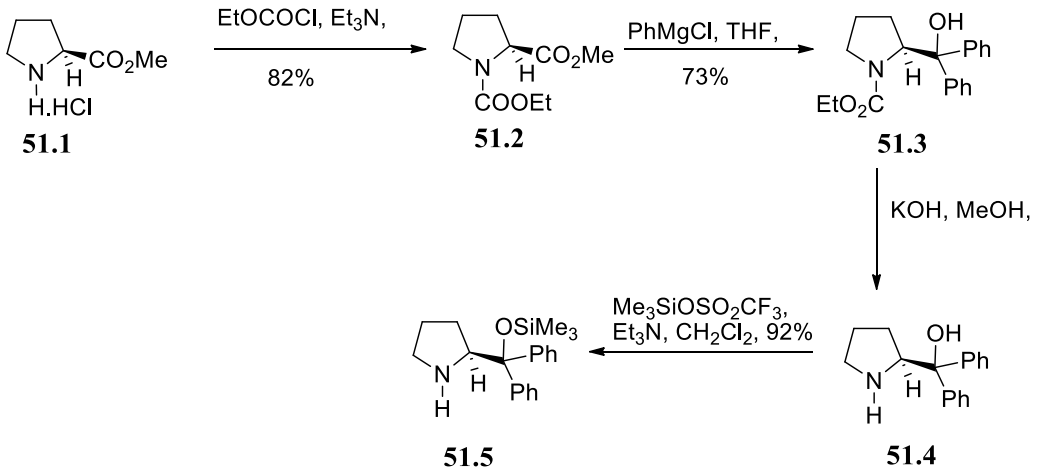


using Parikh-Doering oxidation. We then applied the optimized conditions for conjugate addition of $MeNO_2$ in the presence of Bu_4NF but the double addition product **50.3** was obtained as the major product (Scheme 50).

Therefore, we decided to use an organocatalyst to mask the aldehyde. At first, proline was tried but the nitromethane addition did not work with **50.1**. Consequently, we explored different catalysts and eventually found that (2*S*)-2-{diphenyl[(trimethylsilyl)oxy]methyl}pyrrolidine (**51.5**) was suitable.

The catalyst was prepared by conversion of proline methyl ester hydrochloride (**51.1)** to its carbamate, using EtOCOCl and Et_3N. Reaction with phenylmagnesium chloride, followed by removal of the carbamate gave the hydroxyproline **51.4**. The hydroxyl group was protected with $Me_3SiOSO_2CF_3$ to give catalyst **51.5** (Scheme 39).[45]

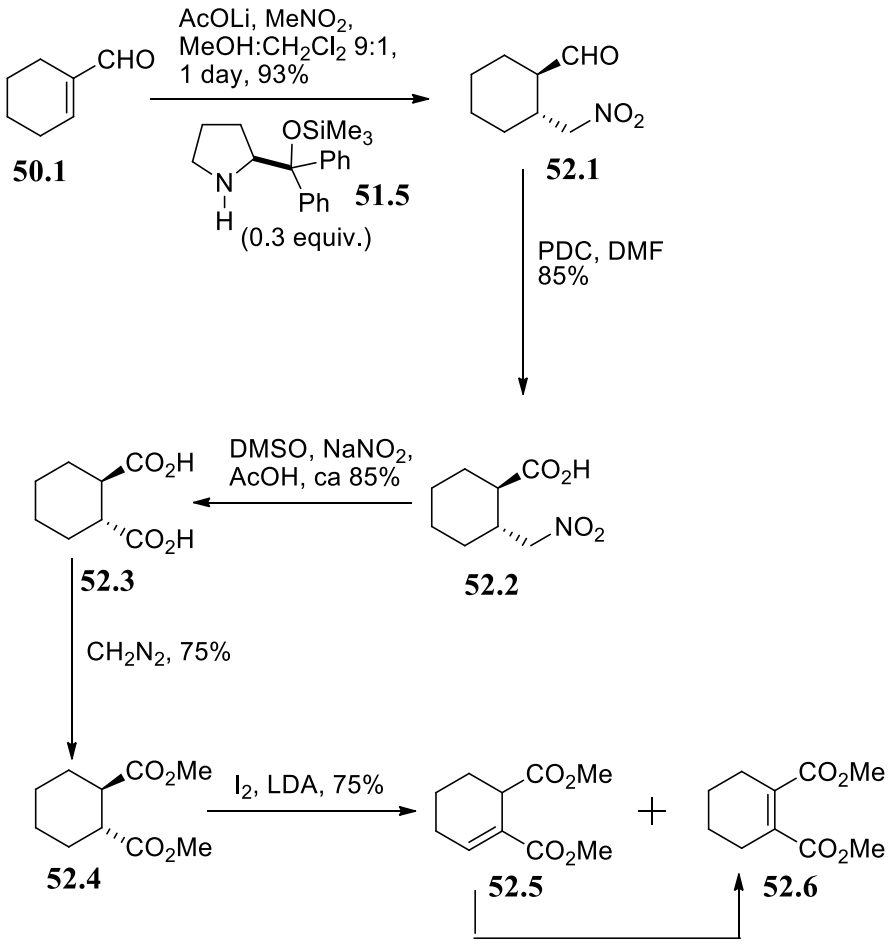
SCHEME 51. Preparation of catalyst **51.5**



Treatment of aldehyde **50.1** with $MeNO_2$ in the presence of a catalytic amount of **51.5** and LiOAc gave the desired product **52.1** as a 6:1 mixture of isomers in excellent yield.[46] The aldehyde was then oxidized with PDC in DMF

to carboxylic acid **52.2** which then gave the dicarboxylic acid **52.3** on reaction with AcOH and $NaNO_2$. Esterification with CH_2N_2 provided the diester **52.4**. Deprotonation with LDA and addition of I_2 to **52.4** gave the unsaturated diesters **52.5** and **52.6**. The latter can be isomerized easily with methanolic HCl to **52.6** (Scheme 52).[47]

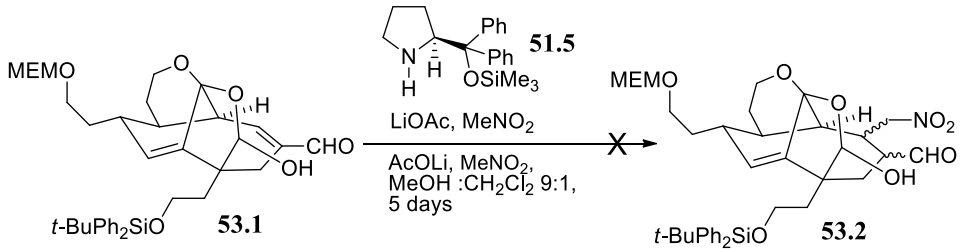
SCHEME 52. Model study on formation of unsaturated diester



With this satisfactory outcome, the allylic alcohol **47.1** was converted to the corresponding aldehyde **53.1** using Swern oxidation. However, when we tried

the optimized conditions on the aldehyde **53.1**, no product was observed even after 5 days (Scheme 53).

SCHEME 53. Attempted addition of nitromethane to **53.1**

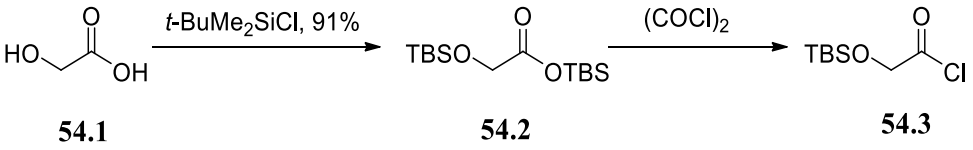


The lack of reactivity of the highly functionalized structure **21.1** was surprising. The proximity of functional groups as well as steric hindrance suggested that the best way to overcome these problems is to install the required carbon intramolecularly.

First we decided to examine the idea of nucleophilic attack on an epoxide but in an intramolecular manner, as shown in Scheme 55, so as to increase the chance of overcoming steric factors. Our approach began with glycolic acid (**54.1**). In order to attach this unit to our epoxy alcohol **48.2** we needed to make the acid chloride, but this was not straightforward. Several approaches were tried and finally glycolic acid **54.1** was converted to the doubly protected **54.2**, using an excess of *t*-BuMe$_2$SiCl and imidazole in DMF. The crude compound was purified partially and treated with $(COCl)_2$ in order to produce the acid chloride **54.3**[48] mixed with *t*-BuMe$_2$SiCl (Scheme 42).

We used this mixture, relying on the greater reactivity of the acid chloride over the silyl chloride, and we treated the epoxy alcohol **48.2** with the crude mixture. The desired reaction occurred and the addition product **55.1** was obtained as a 2:1 mixture of isomers. However, attempts to promote intramolecular nucleophilic

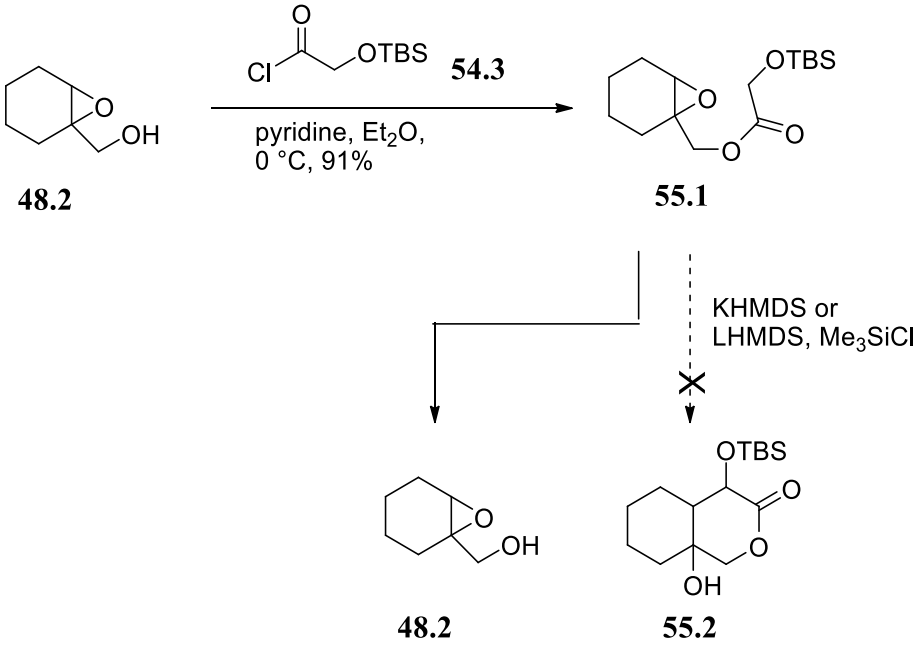
SCHEME 54. Preparation of acid chloride **54.3**



54.1 **54.2** **54.3**

attack on the epoxide did not give any of the desired product **55.2** and we isolated only the original epoxy alcohol **48.2** (Scheme 55).

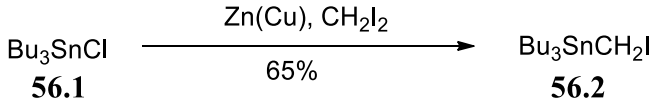
SCHEME 55. Attempted intramolecular epoxide opening



48.2 **55.1** **48.2** **55.2**

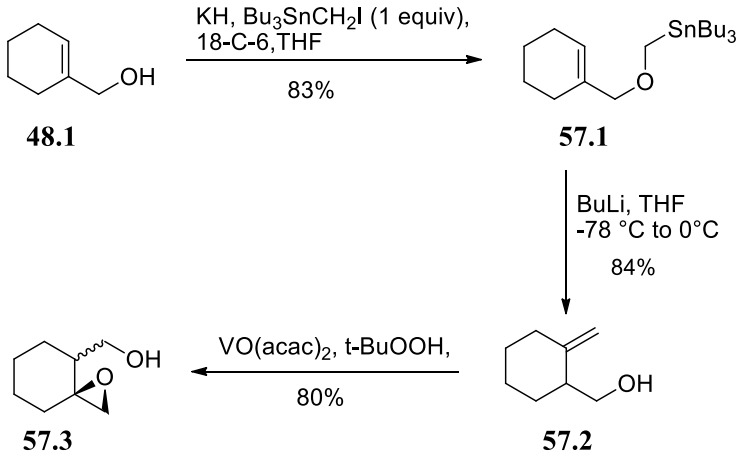
At this point we decided to use a [2,3]-Wittig rearrangement and again we optimized the conditions on a model first. The required component for the [2,3]-Wittig rearrangement, Bu_3SnCH_2I (**56.2**), was prepared by a literature procedure from Bu_3SnCl (**56.1**) using Zn-Cu couple and CH_2I_2 (Scheme 56).[49]

SCHEME 56. Preparation of **56.2**



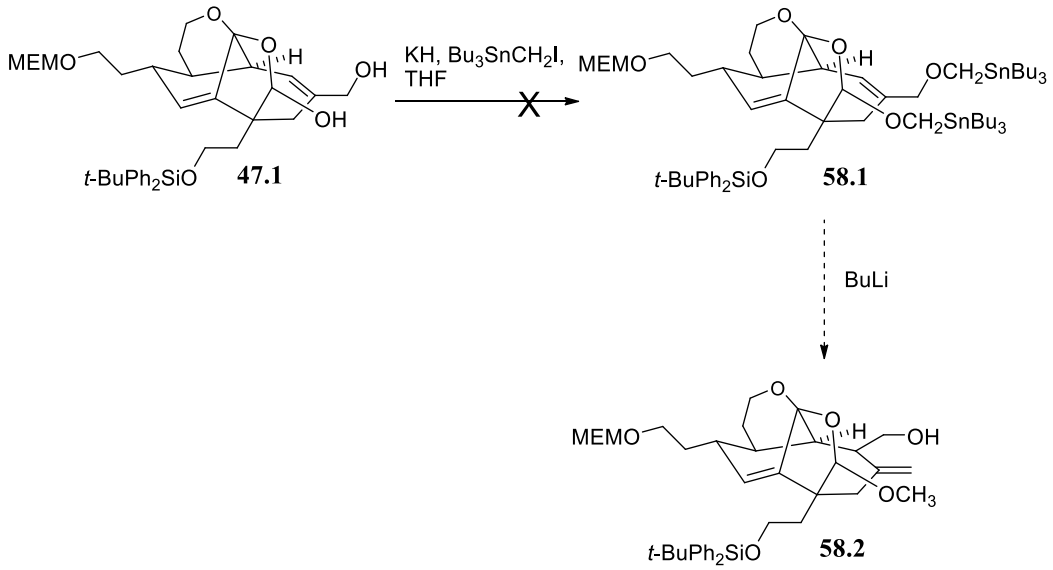
Once **56.2** had been made we found it surprisingly difficult to connect the allylic alcohol **48.1** to the tin reagent. We used a variety of bases and eventually we found that either NaH/HMPA or KH/18-crown-6 are required for the reaction to work.[50] Using the later conditions gave a slightly better yield of the [2,3]-Wittig rearrangement precursor **57.1**. We were pleased to observe that **57.1** smoothly underwent rearrangement on treatment with BuLi to give the homoallylic alcohol **57.2**. With that compound available, we also examined the possibility of epoxidation of the double bond, using the Sharpless homoallylic epoxidation method. This worked smoothly (Scheme 57) and prompted us to apply the same conditions to our advanced substrate.

SCHEME 57. [2,3]-Wittig rearrangement and epoxidation on the model **48.1**



In the case of allylic alcohol **47.1**, we first needed to protect the free lactol hydroxyl group. Our initial attempt was to attach a Bu_3SnCH_2-group to both the allylic and lactol hydroxyls; after treatment with BuLi and workup the lactol oxygen would be protected as a methyl ether, while the allylic system would have undergone rearrangement (Scheme 58). Unfortunately, experiments to test this idea led to decomposition of **47.1**, and so we decided to protect the lactol hydroxyl first.

SCHEME 58. Attempted reaction of **47.1** with **56.2**

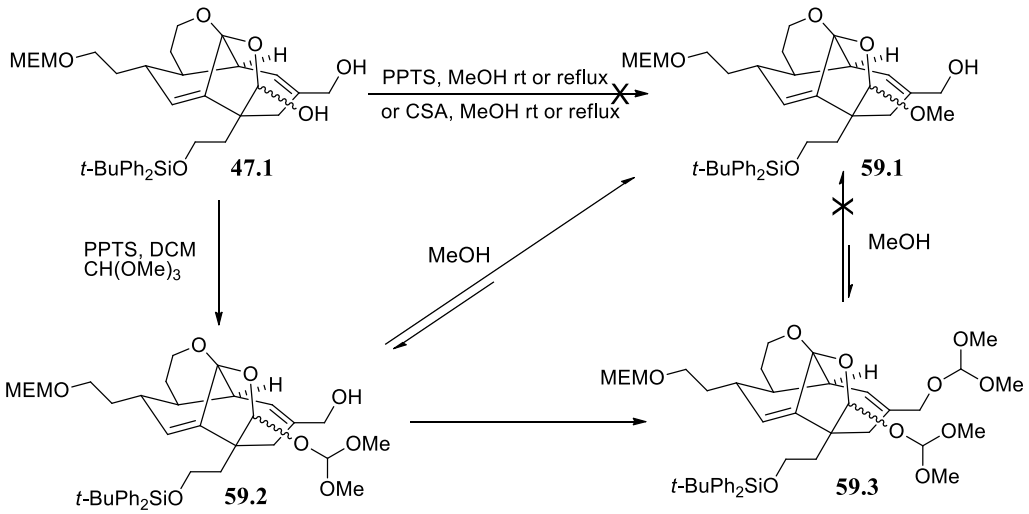


The traditional methods for protecting lactols did not work.[51] When $HC(OMe)_3$ and PPTS were used in CH_2Cl_2 with very close monitoring of the reaction by mass spectroscopy (ESI), it was possible to observe that first the lactol reacted to give **59.2** and then the allylic alcohol reacted to give **59.3** (Scheme 59).

Attempts to convert compound **59.3** to the desired product **59.1** did not work; however, by following the reaction until the starting material is fully

converted to intermediate **59.2**, and stopping the reaction by addition of methanol, the desired product **59.1** was obtained together with some starting allylic alcohol, which could be recycled. Numerous experiments were required to unravel the sequence of events, but they were eventually established and allowed us to make further progress.

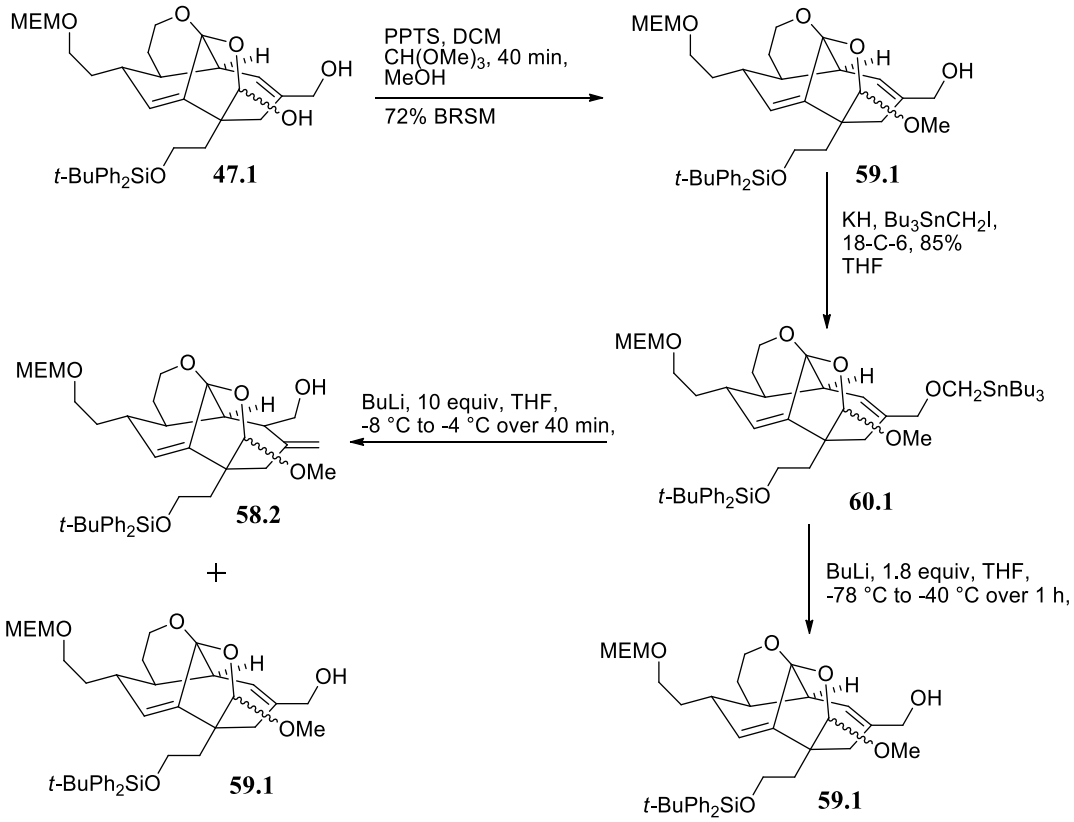
SCHEME 59. Protection of the lactol



The protected allylic alcohol **59.1** was treated with KH and 18-crown-6, followed by Bu_3SnCH_2I (**56.2**) in THF, to form the [2,3]-Wittig rearrangement precursor **60.1** (Scheme 60). This reaction is started at 0 °C and it is essential to remove the ice bath after addition of the tin reagent **56.2**. The presence of the basic KH/18-crown-6, results in loss of the *t*-$BuPh_2Si$ protecting group if the reaction time is too long. Consequently, the reaction must be monitored at intervals by TLC and quenched as soon as the starting material has reacted. The conditions for the next step were also critical, but this was not appreciated at this stage. BuLi was added to the reaction mixture at -78 °C and the mixture allowed

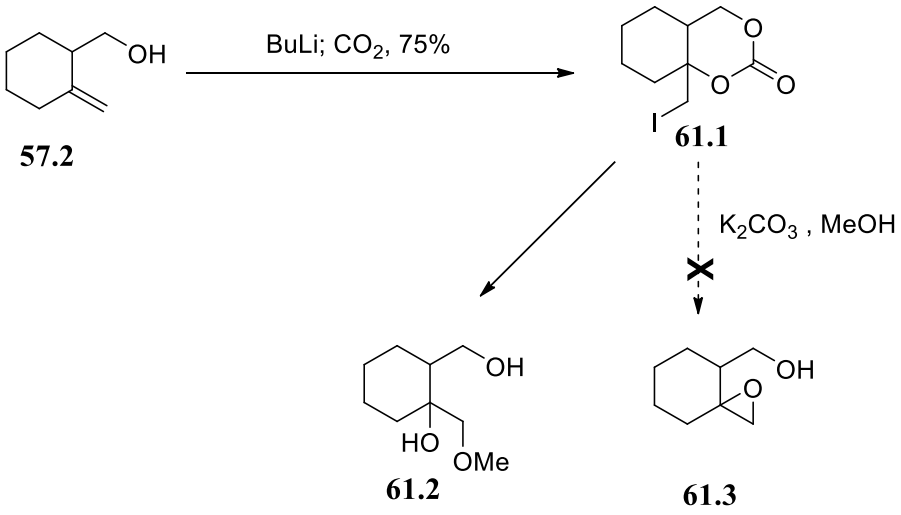
to warm up to room temperature. Surprisingly, only compound **59.1** was isolated. In subsequent runs, higher temperatures were tried and eventually I found that if the reaction is started at -8 °C and allowed to warm to -4 °C over 40 minutes (this rate of warming is important) it gives the rearranged product to the extent of 80:20 in favor of the desired alcohol **58.2** versus **59.1.** Separation of the product **58.2** from the starting material **59.1** was extremely difficult and could be done only on a milligram scale, using TLC analytical plates which were developed several times. By this means we could separate very small portions of the two alcohols and confirm their identity. Unfortunately, all our attempts at epoxidation of the rearranged alcohol **58.2** led to decomposition.

SCHEME 60. [2,3]-Wittig rearrangement of the advanced substrate



At this point we decided to use iodocyclization along the lines shown in Scheme 61, followed by ring opening under basic conditions, in order to produce an epoxy alcohol. Therefore, the rearranged model alcohol **57.2** was deprotonated with BuLi and then CO_2 was bubbled into the mixture, which was quenched with I_2 in order to obtain iodocarbonate **61.1**. When this iodocarbonate was treated with K_2CO_3 in MeOH the iodide reacted faster than the carbonate and, as a result, the diol **61.2** was obtained (Scheme 61).

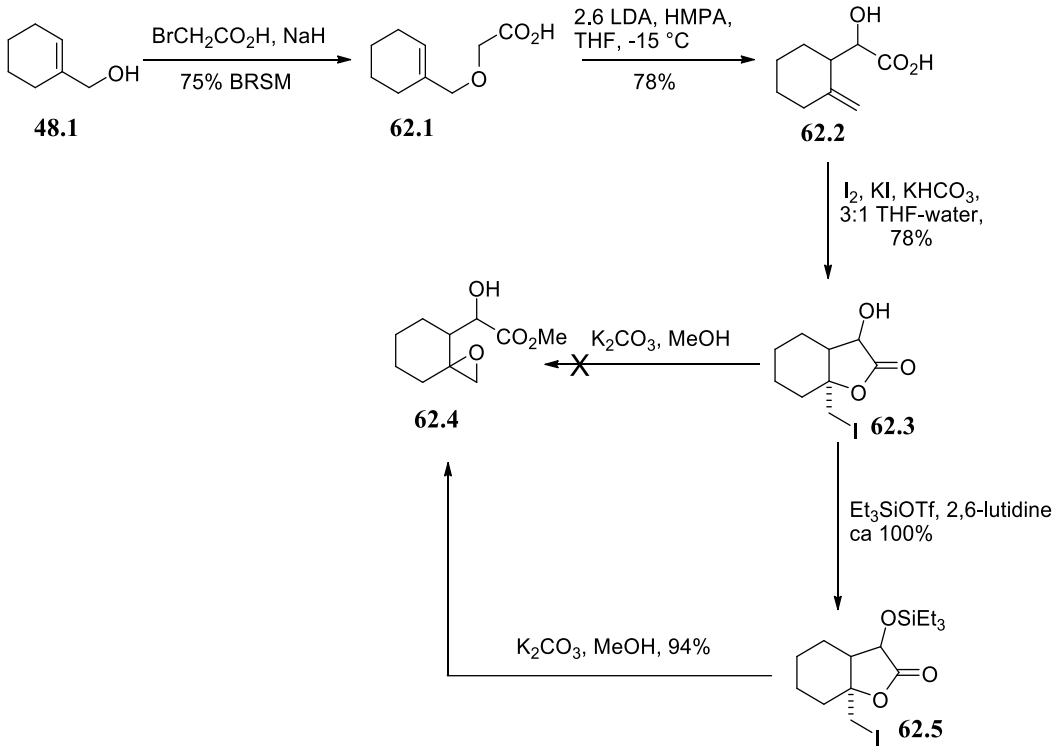
SCHEME 61. Formation and opening of iodocarbonate **61.1**



These unfruitful experiments caused us to examine modified conditions for a [2,3]-Wittig rearrangement in the hope of avoiding formation of the allylic alcohol **59.1**. We planned to modify the rearrangement in such a way that it would set the stage for a subsequent iodolactonization. A lactone is more reactive than a carbonate and this difference would allow us to access the required epoxide (Scheme 62).

To examine the iodolactonization route, the acid **62.1** was produced by reaction of allylic alcohol **48.1** in the presence of NaH with α-bromoacetic acid. This time the rearrangement was promoted by LDA and it smoothly afforded hydroxy acid **62.2** over 24 h. Addition of I_2 and $KHCO_3$ gave the iodolactonization product **62.3**. Attempts at opening the lactone and converting **62.3** to epoxy alcohol **62.4** were unsuccessful and led only to decomposition products. However, once the free hydroxyl of **62.3** was protected with $Et_3SiOSO_2CF_3$, the epoxy alcohol **62.4** was produced smoothly, the triethylsilyl protecting group being lost during the iodolactonization (Scheme 62).

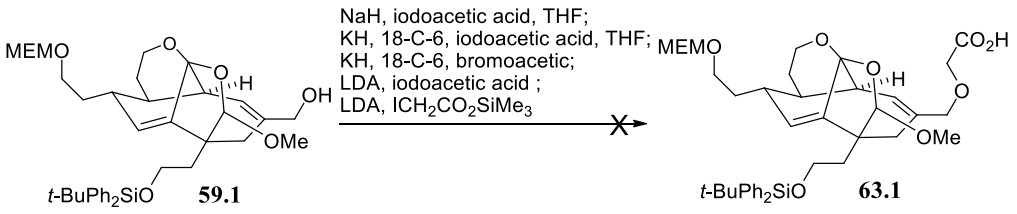
SCHEME 62. Iodolactonization studies



The next task was to apply this methodology to our most advanced model **59.1** but, surprisingly, we were unable to alkylate the allylic hydroxyl, even

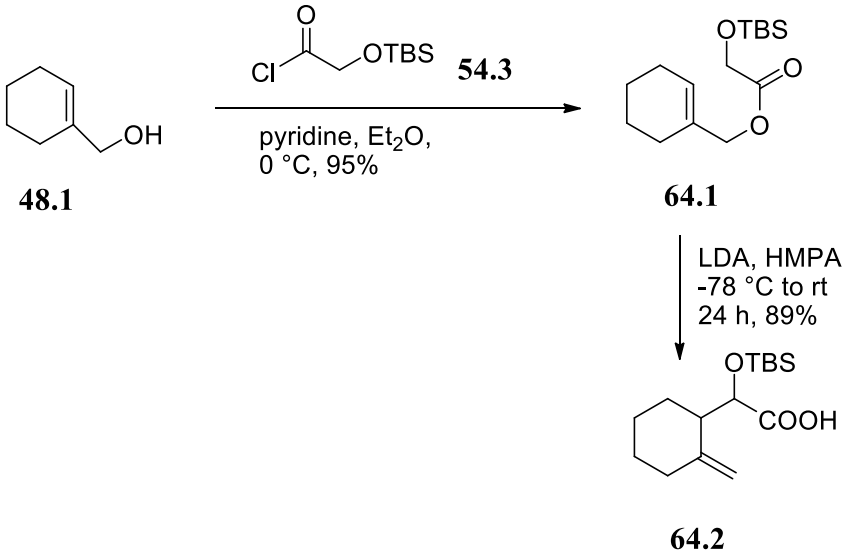
though a number of apparently suitable conditions were tried, including the use of the very reactive iodoacetic acid. Consequently, this seemingly promising route was abandoned.

SCHEME 63. Attempted alkylation of **59.1**



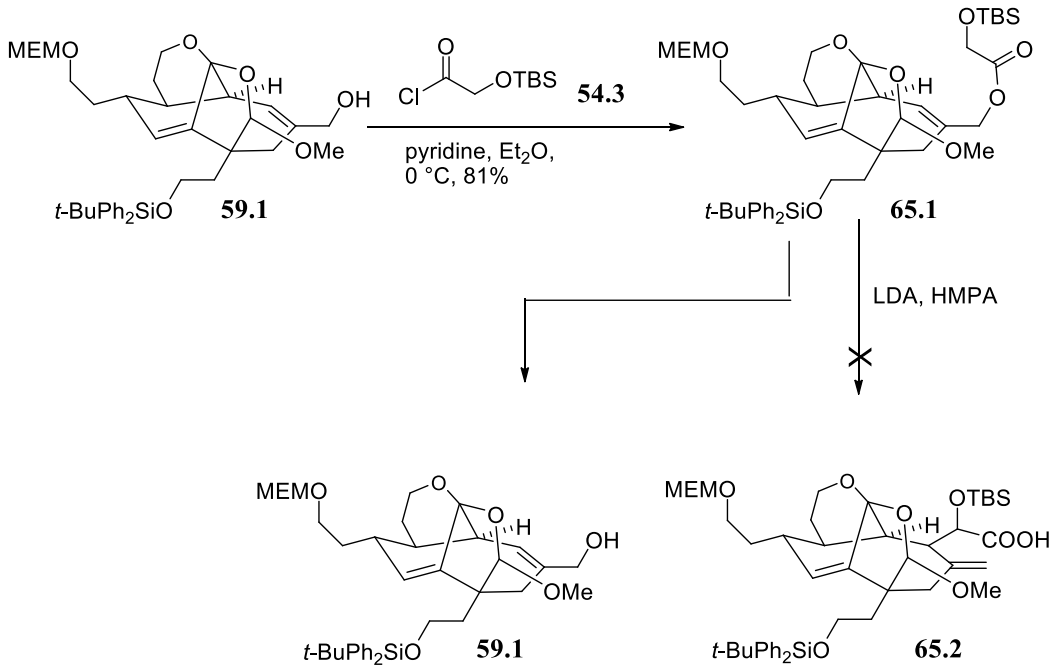
We examined next an approach based on the Ireland-Claisen rearrangement in a way that would give the same type of compound we had tried to make by [2,3]-Wittig rearrangement. Reaction of allylic alcohol **48.1** with **54.3** in the presence of pyridine gave the Ireland-Claisen rearrangement precursor **64.1**.

SCHEME 64. Ireland-Claisen rearrangement approach



On treatment with LDA and HMPA it rearranged smoothly to the desired carboxylic acid **64.2** (Scheme 52). We then tried this optimized sequence on **59.1** and this time the acylation worked smoothly and we obtained the Ireland-Claisen rearrangement precursor **65.1**. However, on treatment with LDA and HMPA we isolated the allylic alcohol **59.1** as the major product (Scheme 65).

SCHEME 65. Attempted Ireland-Claisen rearrangement with **59.1**

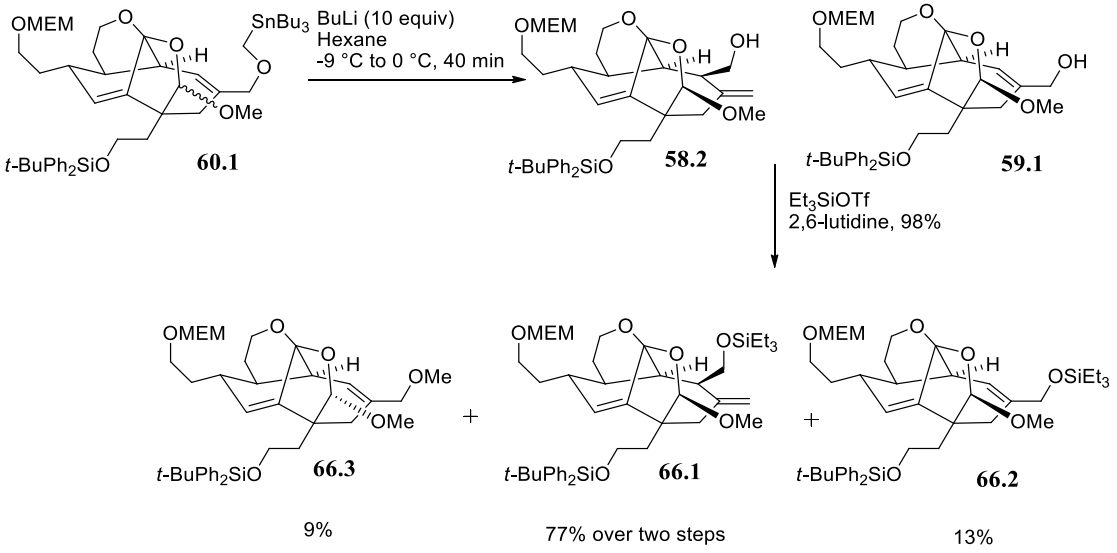


Apparently, the anion expels the allylic alcohol unit faster than the rearrangement. We tried to suppress this side reaction by using Me_3SiCl or *t*-$BuMe_2SiCl$ to capture the initial enolates; unfortunately, no rearranged product was observed in these experiments.

In the face of the above difficulties we returned to the only reaction which actually worked — the [2,3]-Wittig rearrangement from **60.1**. The major drawback to that process was the recovery of 20% of the allylic alcohol **59.1**

which was very difficult to separate from our desired product **58.2**. We decided to protect the free hydroxyl groups by reaction with $Me_3SiOSO_2CF_3$ in the hope that the resulting less polar products would have more widely differing R_f values. In the event, upon protection we were pleased to observe that the two products are easily separable and the desired rearranged triethylsiloxy-protected compound **66.1** was obtained in 77% yield over two steps from **60.1** along with 9% of the dimethoxy-protected compound **66.3** and 13% of the protected allylic alcohol **66.2**. Surprisingly, we noticed that compound **58.2** was formed as a single isomer (Scheme 66).

SCHEME 66. The successful Wittig rearrangement

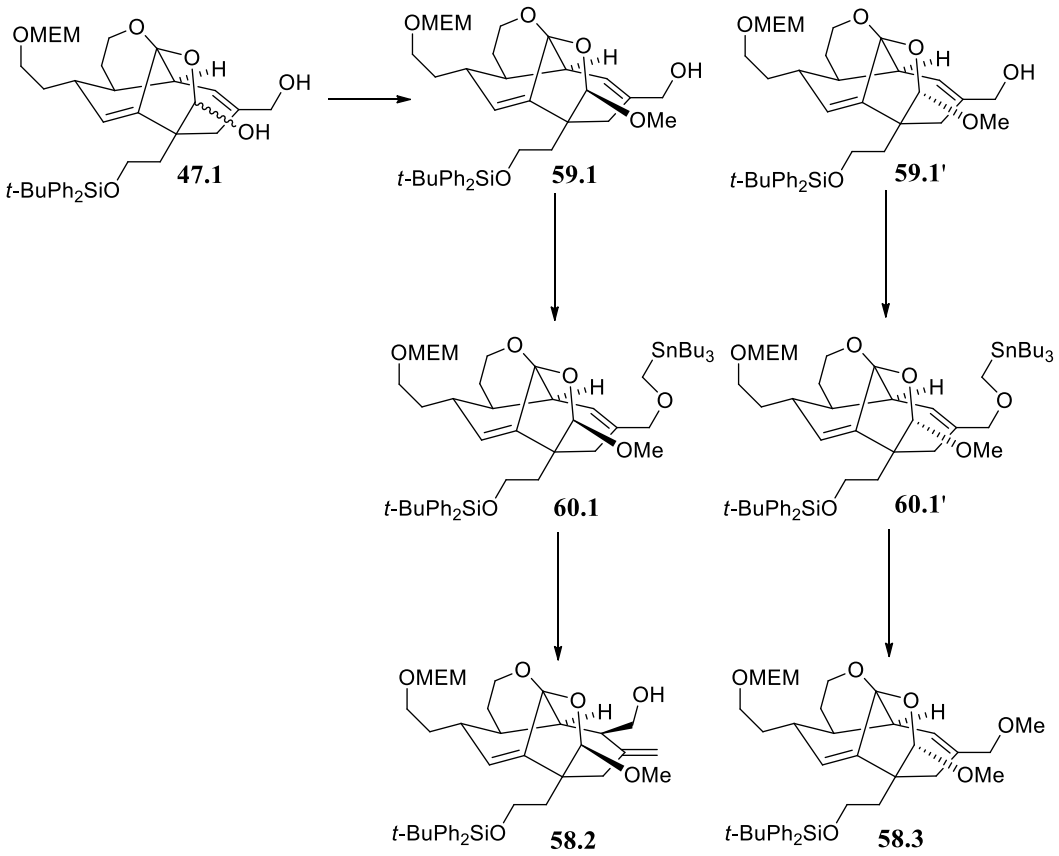


We interpret our observations on the [2,3]-Wittig rearrangement as follows (Scheme 67):

When the lactols **47.1** are converted into the acetal **59.1**, the material always contains a small proportion (ca 10%) of what we take to be the isomer **59.1'**. It is reasonable to assume that the major product has the stereochemistry

shown in **59.1** because the precursor oxonium ion would be expected to suffer attack by methanol from the less hindered face. It was not possible to determine whether an anomeric effect also plays a role in the stereochemical outcome. The mixture of **59.1** and **59.1'** is then converted into the tributylstannyl ethers **60.1** and **60.1'**, respectively. When these (still as a mixture) are subjected to the action of

SCHEME 67. Interpretation of the course of the [2,3]-Wittig rearrangement



BuLi at a moderately low temperature (-8 °C), both are converted into the corresponding carbanions. Examination of physical models suggests that the intended [2,3]-sigmatropic rearrangement can most easily occur from the top face;

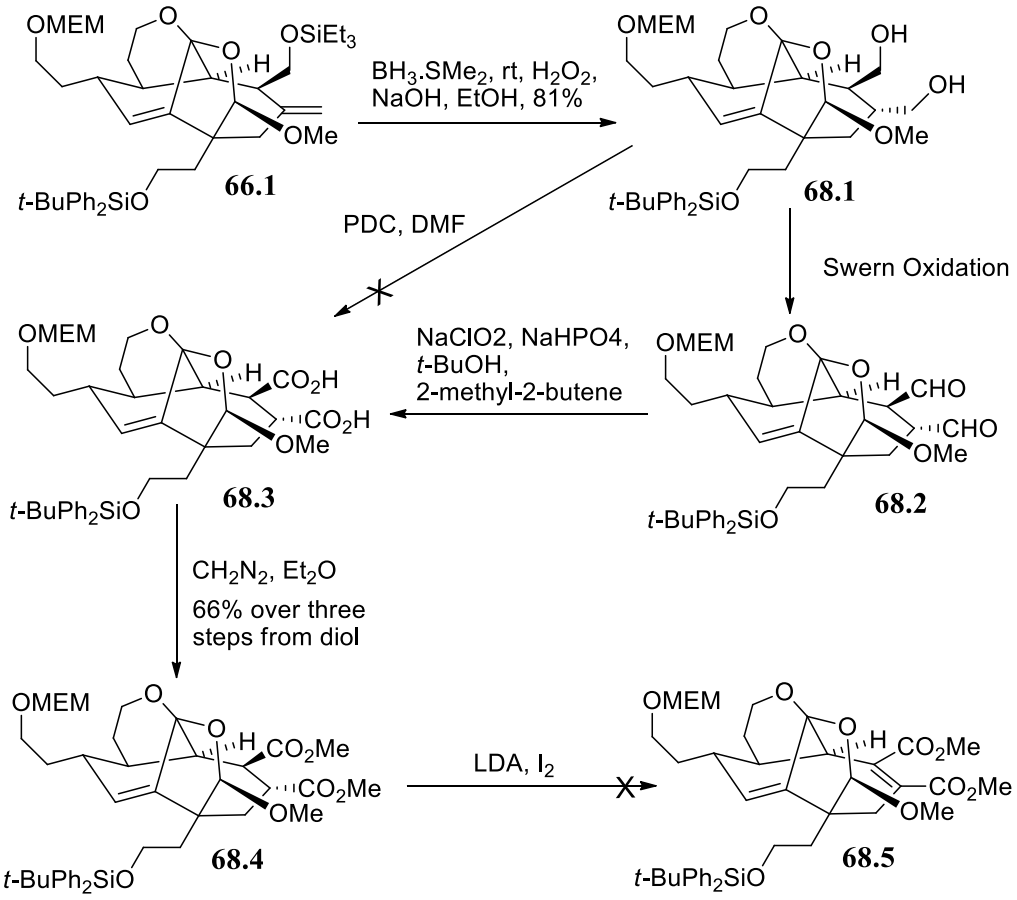
in the case of the carbanion from **60.1**, this is easily achieved, leading to the observed product **58.2**.

However, we suspect that similar rearrangement of the carbanion derived from **60.1'** is sterically hindered, as is its rearrangement from the bottom face. Consequently the carbanion derived from **60.1**' does not rearrange, or does so very slowly. On quenching the reaction mixture with aqueous NH_4Cl, the carbanion from **60.1**' affords the methyl ether **66.3**, which is always isolated in ca 10% yield.

At this point we decided to hydrate the double bond and manipulate the resulting hydroxyl group in order to build up the anhydride ring. The presence of another double bond in the structure could, of course, complicate the initial hydration, but the target double bond was exocyclic and very accessible. First we tried 9-BBN but observed no reaction. The bulkiness of 9-BBN ensured that the other double bond would not react but it seemed that it was too bulky to react with the exocyclic double bond. Therefore, we tried the more reactive $BH_3.SMe_2$ and this time reaction proceeded very smoothly, and during the basic workup the Et_3Si protecting group came off as well to provide diol **68.1** (Scheme 68).

Direct oxidation of diol **68.1** to diacid **68.3** using PDC in DMF did not work and we decided to try a two-step pathway instead. Diol **68.1** was first oxidized to the dialdehyde **68.2** using Swern oxidation. The ^1H NMR spectrum of the crude material and nominal mass (ESI) confirmed the presence of the desired compound, but we took the compound forward as we observed some decomposition upon chromatography. Pinnick oxidation of the dialdehyde gave the diacid **68.3** which was extremely polar. Esterification of crude diacid **68.3** using diazomethane provided the diester **68.4** as a single isomer in excellent yield, 66% over three steps.

SCHEME 68. Formation of advanced diester **68.4**

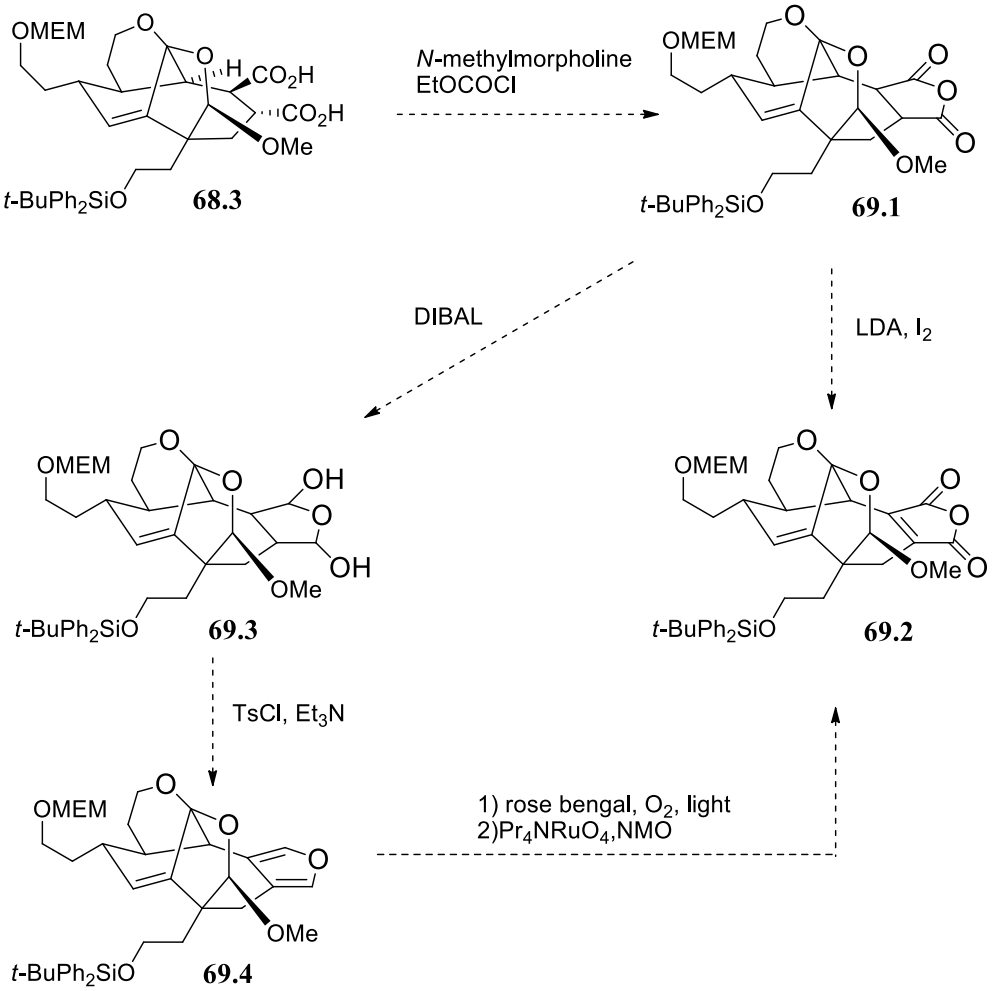


Its noteworthy that only one isomer of **68.4** is observed. Based on the above explanation for the outcome of the rearrangement leading to **58.2** and the addition of boron from the top face, we believe that diol **68.1** as well as the diacid **68.3** and diester **68.4** are trans.

Having reached diester **68.4** we needed to install the double bond and hydrolyze the ester **68.5** to form the anhydride as a fully functionalized core structure of CP-225,917 (**1**). Based on our previous model study (Scheme 52), we used LDA and I_2 in order to install the double bond but it seemed that the α-hydrogens in **68.4** are not accessible to the bulky LDA. We are currently working

on several possibilities to overcome this problem. One of them could be to make the anhydride ring from the diester (**68.3→69.1**) and then to introduce the double bond; we suspect that the relevant hydrogens are more accessible in the anhydride **69.1** than in the diester **68.4**. Alternatively, we may reduce the carbonyl groups to lactol **69.3** and convert the hydroxyls to leaving groups such as tosylate and then generate a furan, which could be converted to the desired anhydride based on our previous papers (Scheme 69).

SCHEME 69. Proposed routes to the unsaturated anhydride

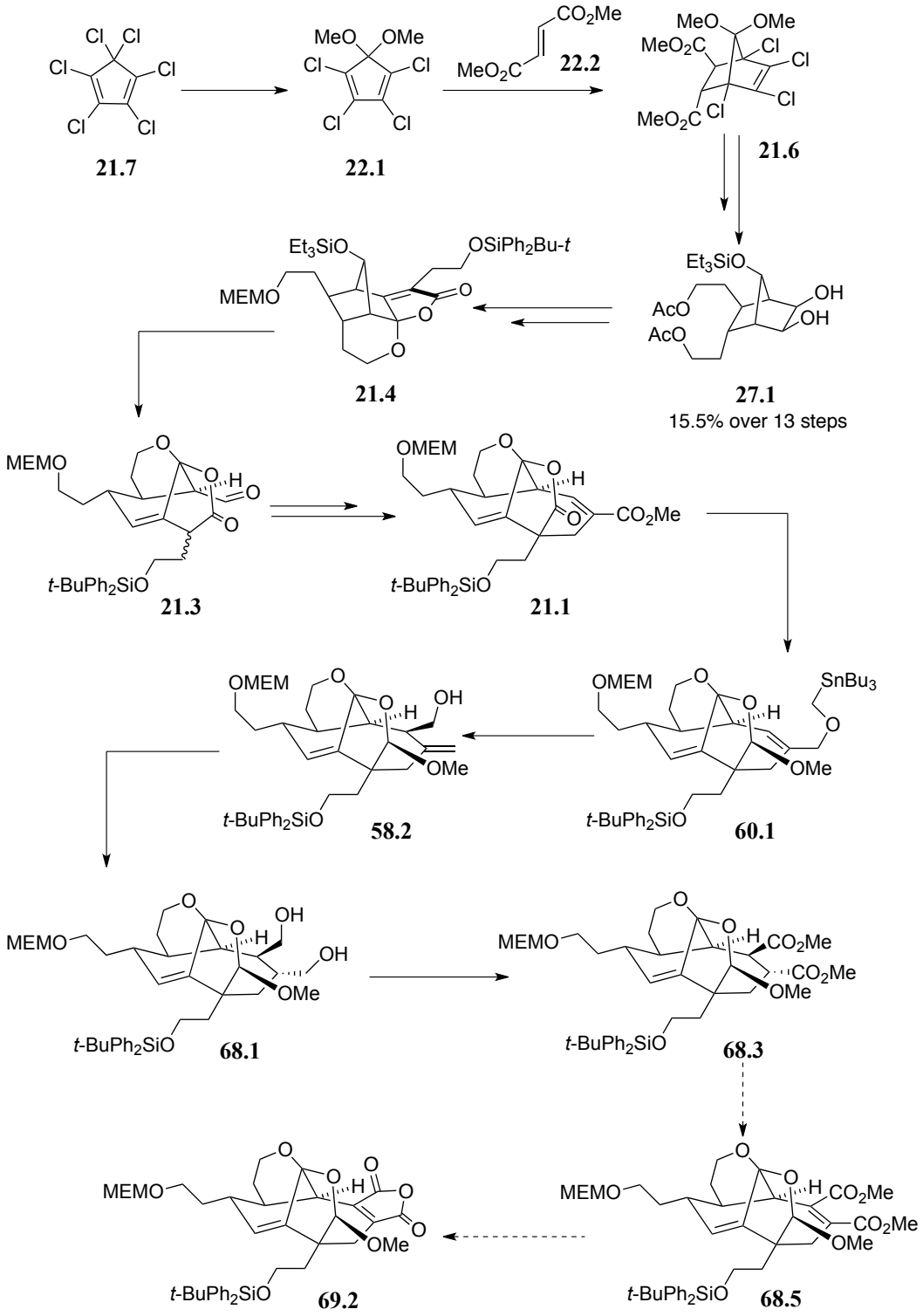


3. Conclusion

The route we have developed (Scheme 70) to the advanced intermediate **68.3** takes the synthesis to a stage where we need to introduce a double bond so as to generate the unsaturated anhydride subunit, and efforts in that direction are now underway.

Our route leads to material with truncated but protected sidechains that, in principle should be amenable to homologation so as to afford the actual CP-molecules.

The essential features of the approach are, first of all, an efficient method based on Diels-Alder cycloaddition, of constructing a substituted [2.2.1]bicycle (**27.1**). This compound is accessible in multi-gram amounts. An intramolecular Horner-Wadsworth-Emmons olefination then leads to a strained system (**21.4**) which undergoes a Grob fragmentation to afford, in a stereocontrolled manner, the key aldehyde **21.3**. This aldehyde is converted into a Baylis-Hillman acetate which undergoes a very efficient intramolecular conjugate displacement to give the desired tetracyclic core skeleton **21.1**. A [2,3]-Wittig rearrangement was then used to introduce the last carbon needed for the anhydride subunit (**21.1→60.1→58.2**).


21.7
22.1
22.2
21.6
21.4
27.1
15.5% over 13 steps
21.3
21.1
58.2
60.1
68.1
68.3
68.5
69.2

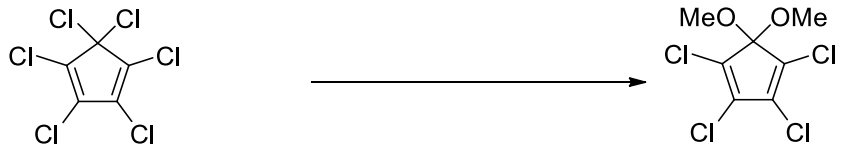
4. Experimental Section

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 from APT spectra.

1,2,3,4-Tetrachloro-5,5-dimethoxycyclopenta-1,3-diene (22.1).

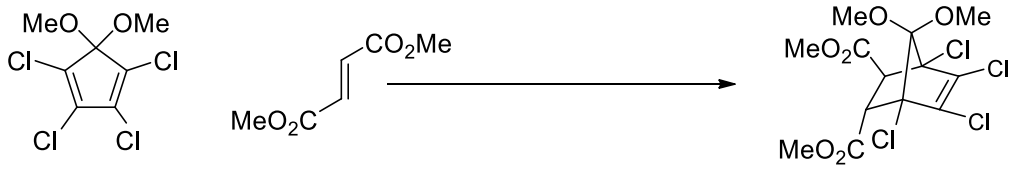


21.7 **22.1**

A solution of KOH (33 g, 0.59 mol) in MeOH (165 mL) was added dropwise from an addition funnel over 2 h to a stirred solution of **21.7** (70 g, 0.26 mol) in MeOH (220 mL) at room temperature. Stirring was continued for an additional 2.5 h and the mixture was then poured onto chopped ice (850 mL). After the ice had melted, the mixture was extracted with CH_2Cl_2 (3 x 150 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated. The residue was distilled through a vacuum-jacketed Vigreux column at 65 °C under vacuum (0.5 mm Hg) to yield **22.1** (59.3 g, 87%) as a yellow oil: FTIR ($CHCl_3$ cast) 3003, 2951, 2839, 1644, 1614, 1457, 1314, 1244, 1213, 1175, 1127, 1099, 1067 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.35 (s, 6 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 51.9 (q), 104.7 (s), 128.5 (s), 129.4 (s); exact mass (electrospray) *m*/*z* calcd for $C_7H_6Cl_4NaO_2$ (M + Na) 284.9014, found 284.9015.

A subsequent experiment starting with 70 g of **21.7** gave **22.1** in 80% yield.

(1*R*,2*S*,3*S*,4*S*)-*rel*-2,3-Dimethyl 1,4,5,6-tetrachloro-7,7-dimethoxy-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate (21.6).

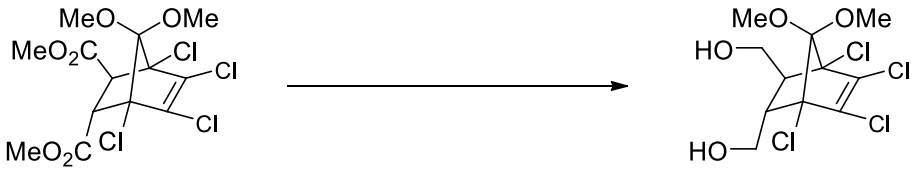


22.1 **22.2** **21.6**

A mixture of 1,1-dimethoxy-2,3,4,5-tetrachlorocyclopentadiene (**22.1**) (59.3 g, 0.22 mol), dimethyl fumarate (32.37 g, , 0.22 mol) and hydroquinone (211 mg, 1.92 mmol) in *o*-dichlorobenzene (21 mL) was refluxed (oil bath at 200 °C) for 20 h. The mixture was cooled to room temperature and applied directly to

a column of flash chromatography silica gel (10 x 23 cm) made up with 1:7 EtOAc-hexane. The column was developed with 1:7 EtOAc-hexane to give the adduct **21.6** (87.47 g, 96%) as a viscous liquid: FTIR (CH_2Cl_2 cast) 2997, 2954, 2846, 1740, 1608, 1437, 1243, 991 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.22 (d, *J* = 5.2 Hz, 1 H), 3.55 (s, 3 H), 3.57 (s, 3 H), 3.75 (s, 3 H), 3.79 (s, 3 H), 4.06 (d, *J* = 5.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 51.7 (d), 52.4 (q), 52.5 (d), 52.6 (q), 52.7 (q), 53.4 (q), 75.7 (s), 111.7 (s), 129.9 (s), 131.4 (s), 167.6 (s), 169.6 (s); exact mass (electrospray) *m*/*z* calcd for $C_{13}H_{14}Cl_4NaO_6$ (M + Na) 428.9437, found 428.9441.

(1*R*,2*S*,3*S*,4*S*)-*rel*-[1,4,5,6-Tetrachloro-3-(hydroxymethyl)-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-yl]methanol (22.3).



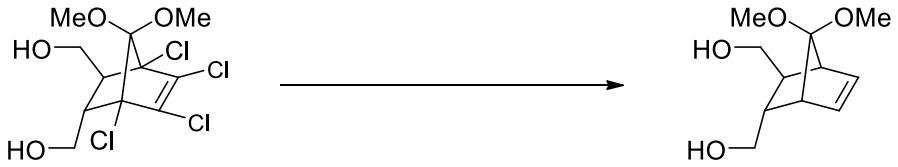
21.6 **22.3**

$LiAlH_4$ (25 g, 0.66 mol) was added in portions to a stirred solution of **21.6** (91 g, 0.22 mol) in THF (1.7 L) and the mixture was then refluxed for 12 h, cooled to room temperature and quenched by dropwise addition of water (25 mL), followed by continued stirring for 5 min. Aqueous NaOH (1 *N*, 25 mL) was added and stirring was continued for 5 min; water (75 mL) was added and stirring was continued for 15 min; finally, aqueous NaOH (1 *N*, 75 mL) was added and stirring was continued for 15 min. The mixture was filtered and evaporated. Flash chromatography of the residue over silica gel (10 x 20 cm), using 1:1 EtOAc-hexane, gave **22.3** (63 g, 82%) as a white solid: FTIR (CH_2Cl_2 cast) 3328,

2952, 2847, 1605, 1450, 1266, 1199, 1177, 1118, 1039 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.96-2.00 (m, 1 H), 2.67-2.72 (m, 1 H), 2.95 (br s, 2 H), 3.24 (t, *J* = 10.3 Hz, 1 H), 3.54 (s, 3 H), 3.58 (s, 3 H), 3.92 (t, *J* = 10.0 Hz, 1 H), 4.00 (dt, *J* = 10.5, 3.7 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 51.5 (d), 52.7 (d), 53.7 (q), 53.8 (q), 61.9 (t), 62.0 (t), 76.3 (s), 76.5 (s), 111.8 (s), 128.6 (s), 131.7 (s); exact mass (electrospray) *m*/*z* calcd for $C_{11}H_{14}Cl_4NaO_4$ (M + Na) 372.9538, found 372.9536.

A subsequent experiment starting with 91 g of **21.6** gave **22.3** in 85% yield.

(1*R*,2*R*,3*R*,4*S*)-*rel*-[3-(Hydroxymethyl)-7,7-dimethoxybicyclo[2.2.1]-hept-5-en-2-yl]methanol (23.1).



22.3 **23.1**

Liquid NH_3 (1.4 L), followed by small pieces of Na (39 g, 1.70 mol), were added to a stirred and cooled (-78 °C) solution of **22.3** (63 g, 0.18 mol) in THF (1.4 L). The resulting blue solution was stirred for 4 h at -78 °C and then the cold bath was removed. Within 3 h the solution became colorless and most of the NH_3 had evaporated. The mixture was carefully quenched by adding solid NH_4Cl (50 g) in portions, and the reaction flask was left open for 2 h to allow the remaining NH_3 to evaporate. Finally, water (500 mL) was added to the residue, which was then extracted with EtOAc (3 x 300 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the

residue over silica gel (10 x 20 cm), using 5% MeOH-EtOAc, gave **23.1** (33.9 g, 88%) as a pale yellow oil: FTIR (neat) 3355, 2938, 2832, 1457, 1286, 1119, 1081, 1061, 1028 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.34-1.39 (m, 1 H), 2.21-2.26 (m, 1 H), 2.67 (s, 1 H), 2.80 (br s, 1 H), 2.88 (s, 1 H), 2.95 (br s, 1 H), 3.10-3.18 [m, including a singlet at δ 3.14 (3 H), 4 H in all], 3.19 (s, 3 H), 3.61-3.65 (m, 1 H), 3.73-3.78 (m, 1 H), 3.85 (t, *J* = 9.3 Hz, 1 H), 6.00 (dd, *J* = 6.2, 3.3 Hz, 1 H), 6.27 (ddd, *J* = 6.2, 3.5, 0.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 43.9 (d), 47.4 (d), 47.5 (d), 47.9 (d), 49.5 (q), 51.9 (q), 64.0 (t), 65.2 (t), 119.0 (s), 130.4 (d), 135.3 (d); exact mass (electrospray) *m*/*z* calcd for $C_{11}H_{18}NaO_4$ (M + Na) 237.1097, found 237.1099.

A subsequent experiment starting with 63 g of **22.3** gave **23.1** in 87% yield.

(1*R*,4*S*,5*S*,6*S*)-*rel*-5,6-Bis(iodomethyl)-7,7-dimethoxybicyclo[2.2.1]-hept-2-ene (23.2).

23.1 **23.2**

Ph_3P (98.93 g, 0.37 mol) was added to a stirred (mechanical stirrer) solution of **23.1** (33.6, 0.16 mol) in a mixture of PhMe (820 mL) and CH_2Cl_2 (328 mL). After the Ph_3P had dissolved, imidazole (51.38 g, 0.76 mol) and I_2 (96 g, 0.37 mol) were added sequentially and stirring was continued for 15 h. The mixture was diluted with Et_2O (200 mL) and washed with aqueous $Na_2S_2O_3$ (2 x 250 mL) and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the

residue over silica gel (10 x 20 cm), using hexane to 1:5 EtOAc-hexane, gave **23.2** (44.05 g, 64%) as a light yellow oil: FTIR (neat) 3062, 2982, 2954, 2934, 2828, 1452, 1424, 1301, 1282, 1248, 1147, 1119, 1076 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.48-1.56 (m, 1 H), 2.30-2.37 (m, 1 H), 2.85 (t, *J* = 10.4 Hz, 1 H), 2.10 (br s, 1 H), 3.18 (s, 3 H), 3.19 (br s, 1 H), 3.22 (s, 3 H), 3.31 (dd, *J* = 9.5, 6.1 Hz, 1 H), 3.46 (t, *J* = 9.0 Hz, 1 H), 3.67 (dd, *J* = 9.4, 7.4 Hz, 1 H), 6.12 (dd, *J* = 6.1, 3.2 Hz, 1 H), 6.34 (ddd, *J* = 6.2, 3.6, 0.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 9.2 (t), 47.8 (d), 49.8 (d), 51.3 (d), 51.5 (d), 51.8 (q), 52.4 (q), 118.6 (s), 130.5 (d), 136.2 (d); exact mass *m*/*z* calcd for $C_{11}H_{16}I_2O_2$ 433.9240, found 433.9244.

A subsequent experiment starting with 44 g of **23.1** gave **23.2** in 70-74% yield.

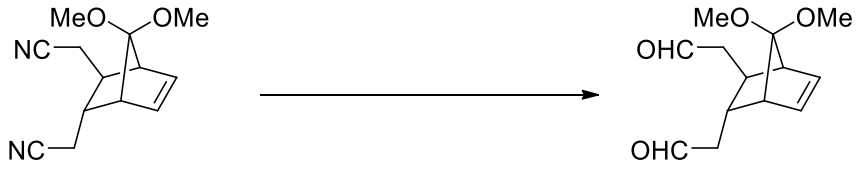
(1*R*,2*R*,3*R*,4*S*)-*rel*-2-[3-(Cyanomethyl)-7,7-dimethoxybicyclo[2.2.1]-hept-5-en-2-yl]acetonitrile (23.3).

23.2 **23.3**

NaCN (104 g, 2.11 mol), followed by a catalytic amount (2-4 crystals) of 18-crown-6, were added to a solution of **23.2** (46.1 g, 0.11 mol) in dry DMSO (600 mL) and the mixture was heated at 40 °C for 12 h, then cooled to room temperature, diluted with EtOAc (300 mL) and quenched with water (1.8 L). The aqueous layer was extracted with EtOAc (5 x 300 mL) and the combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (10 x 20 cm), using 1:1 EtOAc-

hexane, gave **23.3** (24.2 g, 95%) as a light yellow oil: FTIR (neat) 2978, 2939, 2246, 1427, 1283, 1240, 1121, 1084, 1049 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.36-1.44 (m, 1 H), 2.15-2.25 (m, 2 H), 2.30-2.40 (m, 1 H), 2.72-2.85 (m, 3 H), 3.06 (br s, 1 H), 3.15 (s, 3 H), 3.22 (s, 3 H), 6.11-6.15 (m, 1 H), 6.34-6.38 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.1 (t), 20.8 (t), 39.3 (d), 42.9 (d), 48.5 (q), 49.2 (q), 49.6 (d), 52.1 (d), 118.3 (s), 118.9 (s), 119.3 (s), 130.9 (d), 136.1 (d); exact mass (electrospray) *m*/*z* calcd for $C_{13}H_{16}NaN_2O_2$ (M + Na) 255.1104, found 255.1106.

(1*R*,2*R*,3*R*,4*S*)-*rel*-2-[7,7-Dimethoxy-3-(2-oxoethyl)bicyclo[2.2.1]hept-5-en-2-yl]acetaldehyde (23.4).



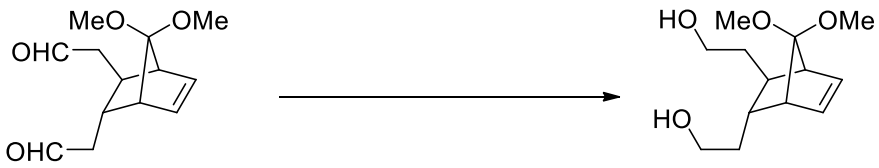
23.3 **23.4**

DIBAL-H (1 M in PhMe, 316 mL, 316 mmol) was added dropwise over 20 min to a stirred and cooled (-78 °C) solution of **23.3** (24 g, 0.10 mol) in PhMe (860 mL). Stirring at -78 °C was continued for 1 h and the cold bath was then replaced by an ice bath. Stirring was continued for 30 min, the ice bath was removed and stirring was continued for 10 min. Hydrochloric acid (0.5 N, 1.6 L) was added and the mixture was stirred for 12 h. The aqueous layer was extracted with EtOAc (3 x 200 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. The residue was passed through a pad of silica gel [6 (diameter) x 5 cm] to remove polar material, using 1:2 EtOAc-hexane, to afford **23.4** (19.94 g, 81%) as a yellow oil: FTIR (CH_2Cl_2, cast) 2938, 2831, 2724, 1721, 1121, 1081

cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.52 (dd, *J* = 7.0, 5.5 Hz, 1 H), 2.25-2.40 (m, 2 H), 2.53-2.59 (m, 2 H), 2.87-3.06 (m, 3 H), 3.12 (s, 3 H), 3.22 (s, 3 H), 6.02 (dd, *J* = 6.2, 3.3 Hz, 1 H), 6.29-6.32 (m, 1 H), 9.73 (d, *J* = 1.1 Hz, 1 H), 9.78 (d, *J* = 0.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 36.0 (d), 39.5 (d), 47.8 (t), 48.0 (t), 48.7 (q), 48.8 (q), 49.5 (d), 51.8 (d), 119.0 (s), 130.7 (d), 135.9 (d), 201.6 (d), 202.3 (d); exact mass (electrospray) *m*/*z* calcd for $C_{13}H_{18}NaO_4$ (M + Na) 261.1097, found 261.1101.

A subsequent experiment on the same scale gave a yield of 94%.

(1*R*,2*R*,3*R*,4*S*)-*rel*-2-[3-(2-Hydroxyethyl)-7,7-dimethoxybicyclo[2.2.1]-hept-5-en-2-yl]ethan-1-ol (23.5).



23.4 **23.5**

$NaBH_4$ (9.5 g, 0.261 mol) was added in portions to a stirred solution of **23.4** (20 g, 84 mmol) in MeOH (740 mL) and stirring was continued for 8 h. The mixture was evaporated and the residue was partitioned between EtOAc (150 mL) and water (80 mL). The aqueous phase was extracted with EtOAc (3 x 50 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (4.5 x 15 cm), using 10:1 EtOAc-MeOH, gave **23.5** (16.47 g, 81%), as a colorless oil: FTIR (CH_2Cl_2 cast) 3388, 2935, 2832, 1452, 1288, 1226, 1195, 1121, 1061 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.11-1.14 (m, 1 H), 1.36-1.52 (m, 2 H), 1.86-1.92 (m, 2 H), 1.94-2.01 (m, 1 H), 2.08 (br s, 2 H), 2.56 (t, *J* = 1.7 Hz, 1 H), 2.80-2.82 (m, 1 H), 3.13 (s, 3 H),

3.19 (s, 3 H), 3.58-3.72 (m, 4 H), 6.00 (apparent q, J = 3.2 Hz, 1 H), 6.24 (dq, J = 3.6, 0.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 35.9 (t), 36.8 (t), 39.4 (d), 43.4 (d), 48.3 (q), 48.7 (q), 49.6 (d), 51.6 (d), 661.7 (t), 62.3 (t), 119.1 (s), 130.4 (d), 135.7 (d); exact mass (electrospray) m/z calcd for $C_{13}H_{22}NaO_4$ (M + Na) 265.1410, found 265.1410.

A subsequent experiment on the same scale gave a yield of 98%.

(1*R*,2*R*,3*R*,4*S*)-*rel*-2-{3-[2-(Acetyloxy)ethyl]-7,7-dimethoxybicyclo-[2.2.1]hept-5-en-2-yl}ethyl acetate (26.1).

23.5 **26.1**

DMAP (734 mg, 6 mmol), Ac_2O (18.9 mL, 0.20 mol) and Et_3N (31.6 mL, 0.23 mol) were added sequentially to a stirred solution of **23.5** (12 g, 49.59 mmol) in CH_2Cl_2 (310 mL). Stirring was continued for 6 hand the organic phase was then washed with water (2 x 150 mL) and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (6 x 15 cm), using 1:1 EtOAc-hexane, gave **26.1** (14.94 g, 92%) as a colorless oil: FTIR (CH_2Cl_2 cast) 3019, 2917, 2849, 1732, 1366, 1247, 1217, 1121, 1036 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.00-1.04 (m, 1 H), 1.40-1.46 (m, 1 H), 1.51-1.58 (m, 1 H), 1.87-2.00 (m, 3 H), 2.04 (s, 3 H), 2.05 (s, 3 H), 2.57 (t, J = 1.9 Hz, 1 H), 2.84 (br s, 1 H), 3.14 (s, 3 H), 3.18 (s, 3 H), 4.00-4.11 (m, 4 H), 6.01 (dd, J = 5.8, 2.6 Hz, 1 H), 6.22-6.25 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.0 (q), 21.0 (q), 31.4 (t), 32.5 (t), 39.6 (d), 43.7 (d), 47.8 (q), 48.4 (q), 49.5 (d), 51.7 (d), 63.5 (t), 64.1 (t), 119.1 (s),

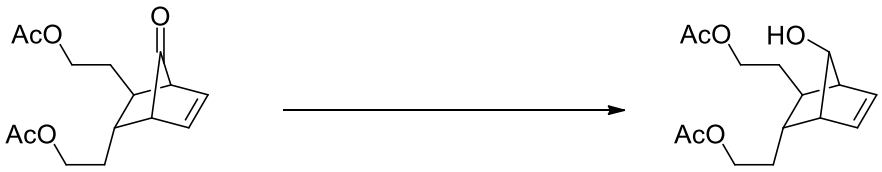
130.4 (d), 135.7 (d), 171.1 (s), 171.1 (s); exact mass (electrospray) *m*/*z* calcd for $C_{17}H_{26}NaO_6$ (M + Na) 349.1622, found 349.1620.

(1*R*,2*R*,3*R*,4*S*)-*rel*-2-{3-[2-(Acetyloxy)ethyl]-7-oxobicyclo[2.2.1]hept-5-en-2-yl}ethyl acetate (26.2).

26.1 **26.2**

CF_3CO_2H (43 mL, 579 mmol) was added to a stirred solution of **26.1** (14.94 g, 45.83 mmol) in CH_2Cl_2 (201 mL). Stirring was continued for 5 h and the solution was then evaporated. CH_2Cl_2 (200 mL) was added to the residue and the organic phase was washed twice with saturated aqueous K_2CO_3 (50 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (4.5 x 15 cm), using 40% EtOAc-hexane, gave **26.2** (12.58 g, 98%), as a yellow oil: FTIR (CH_2Cl_2 cast) 2957, 2849, 1779, 1739, 1435, 1368, 1242, 1038 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.20-1.25 (m, 1 H), 1.48-1.64 (m, 2 H), 1.68-1.82 (m, 2 H), 1.86-1.94 (m, 1 H), 2.06 (s, 6 H), 2.70 (d, *J* = 3.8 Hz, 1 H), 2.94 (t, *J* = 3.6 Hz, 1 H), 4.00-4.20 (m, 4 H), 6.44 (apparent q, *J* = 3.5 Hz, 1 H), 6.60 (dq, *J* = 3.8, 1.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.9 (q), 32.3 (t), 32.6 (t), 38.9 (d), 40.3 (d), 50.4 (d), 51.6 (d), 62.4 (t), 62.6 (t), 130.7 (d), 133.4 (d), 170.9 (s), 204.0 (s); exact mass (electrospray) *m*/*z* calcd for $C_{15}H_{20}NaO_5$ (M + Na) 303.1203, found 303.1207.

(1*R*,2*R*,3*R*,4*S*,7*R*)-*rel*-2-{3-[2-(Acetyloxy)ethyl]-7-hydroxybicyclo-[2.2.1]hept-5-en-2-yl}ethyl acetate (26.3).

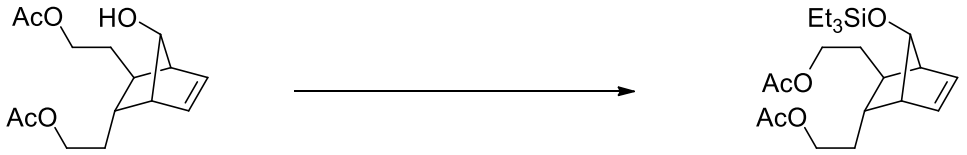


26.2 **26.3**

(*t*-BuO)$_3$AlHLi (1 M in THF, 7.6 mL, 7.6 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of keto acetate **26.2** (1.77 g, 6.3 mmol) in THF (45 mL). Stirring was continued for 2 h at -78 °C and then the cold bath was replaced by an ice bath and stirring was continued for 1 h at 0 °C. The mixture was quenched by dropwise addition of saturated aqueous Rochelle salt (7.6 mL). Et_2O (40 mL) and water (40 mL) were then added and the mixture was stirred for 3 h. The mixture was filtered through a pad of Celite (5 x 2 cm high), using Et_2O as a rinse. The aqueous phase was extracted with Et_2O [3 times; the extent of extraction from the aqueous layer was monitored by TLC (silica, 1:1 hexane-EtOAc)] and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (40 g silica, 2.8 x 15 cm), using 45% EtOAc-hexane, gave **26.3** (1.6 g, 89%) as a yellow oil: FTIR (neat) 3461, 2960, 2917, 1731, 1367, 1247, 1036 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.04-1.09 (m, 1 H), 1.46-1.56 (m, 1 H), 1.61-1.70 (m, 1 H), 2.00-2.10 (m, 9 H), 2.10-2.18 (m, 1 H), 2.42 (br s, 1 H), 2.65 (br s, 1 H), 3.77 (s, 1 H), 4.04-4.14 (m, 4 H), 5.88 (dd, *J* = 6.1, 3.2 Hz, 1 H), 6.10 (dd, *J* = 6.1, 3.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.0 (q), 31.5 (t), 32.2 (t), 39.8 (d), 42.9 (d), 49.6 (d), 50.3 (d), 63.9 (t), 64.3 (t), 84.7 (d), 131.6 (d), 136.4 (d), 170.0 (s); exact mass (electrospray) *m*/*z* calcd for $C_{15}H_{22}NaO_5$ (M + Na) 305.1359, found 305.1359.

A subsequent experiment starting with 14 g of **26.2** gave **26.3** in 89% yield.

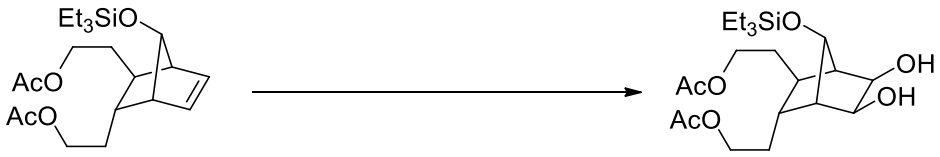
(1*R*,2*R*,3*R*,4*S*,7*R*)-*rel*-2-{3-[2-(Acetyloxy)ethyl]-7-[(triethylsilyl)oxy]-bicycle[2.2.1]hept-5-en-2-yl}ethyl acetate (26.4).



26.3 **26.4**

2,6-Lutidine (16.7 mL, 143.6 mmol), followed by $Et_3SiOSO_2CF_3$ (13.4 mL, 62.8 mmol), were added to a stirred and cooled (0 °C) solution of **26.3** (12.66 g, 44.8 mmol) in CH_2Cl_2 (500 mL). The ice bath was removed after 40 min and stirring was continued for 13 h. The mixture was quenched with saturated aqueous $NaHCO_3$ (300 mL) and the organic phase was washed with water (50 mL) and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (4 x 15 cm), using 1:5 EtOAc-hexane, gave **26.4** (17.78 g, 100%) as a pale yellow oil: FTIR (neat) 2958, 1740, 1458, 1366, 1243, 1112, 1036 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.56 (q, *J* = 7.8 Hz, 6 H), 0.94 (t, *J* = 7.9 Hz, 9 H), 1.01-1.10 (m, 1 H), 1.42-1.53 (m, 1 H), 1.60-1.70 (m, 1 H), 1.98-2.16 [m, including singlets at δ 2.04 (3 H) and 2.05 (3 H), 9 H in all], 2.33 (br s, 1 H), 2.55 (br s, 1 H), 3.62 (s, 1 H), 4.02-4.16 (m, 4 H), 5.86 (dd, *J* = 6.1, 3.3 Hz, 1 H), 6.08-6.12 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 4.6 (t), 4.6 (t), 6.7 (q), 20.9 (q), 20.9 (q), 31.3 (t), 32.1 (t), 39.7 (d), 43.1 (d), 49.9 (d), 50.8 (d), 63.8 (t), 64.3 (t), 84.7 (d), 131.3 (d), 136.1 (d), 171.0 (s), 171.1 (s); exact mass (electrospray) *m*/*z* calcd for $C_{21}H_{36}NaO_5Si$ (M + Na) 419.2224, found 419.2225.

(1*R*,2*R*,3*R*,4*S*,5*S*,6*R*,7*S*)-*rel*-2-{3-[2-(Acetyloxy)ethyl]-5,6-dihydroxy-7-[(triethylsilyl)oxy]bicyclo[2.2.1]heptan-2-yl}ethyl acetate (26.5).

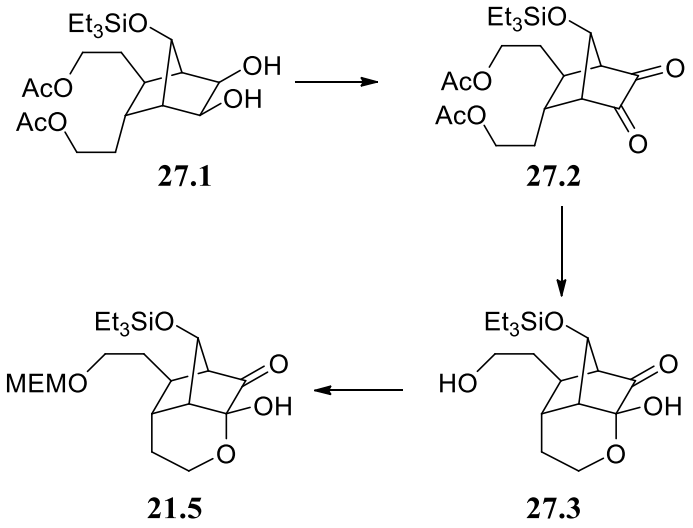


26.4 **27.1**

NMO (8.1 g, 690 mmol) was added to a stirred solution of **26.4** (18.1 g, 44.9 mmol) in a mixture of acetone (362 mL) and water (90 mL). A freshly-made solution of OsO_4 (23 mg, 0.09 mmol) in *i*-PrOH (2.26 mL) was added dropwise and stirring was continued in the dark for 9 h (reaction was left overnight, but we did not establish if it is complete sooner). Solid $Na_2S_2O_3$ (5.88 g, 37 mmol) was tipped in and stirring was continued for 30 min. The mixture was diluted with water (100 mL), saturated with NaCl and extracted with EtOAc (4 x 50 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 15 cm), using EtOAc, gave **27.1** (17.3 g, 88%) as a colorless oil: FTIR ($CHCl_3$ cast) 3420, 2956, 2914, 2877, 1740, 1242, 1117, 1036 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.60 (q, *J* = 8.0 Hz, 6 H), 0.96 (t, *J* = 8.2 Hz, 9 H), 1.56-1.67 (m, 1 H), 1.71-1.88 (m, 3 H), 1.92-2.01 (m, 2 H), 2.03-2.12 [m, including singlets at δ 2.05 (3 H) and δ 2.06 (3 H), 8 H in all], 3.60 (d, *J* = 7.0 Hz, 1 H), 3.98 (d, *J* = 6.7 Hz, 1 H), 4.04-4.16 (m, 4 H), 4.43 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 4.5 (t), 6.7 (q), 20.8 (q), 20.9 (q), 28.9 (t), 34.0 (t), 38.4 (d), 42.3 (d), 51.4 (d), 51.5 (d), 63.5 (t), 63.6 (t), 67.2 (d), 72.3 (d), 76.6 (d), 171.2 (s), 171.2 (s); exact mass (electrospray) *m*/*z* calcd for $C_{21}H_{38}NaO_7Si$ (M + Na) 453.2279, found 453.2276.

A subsequent experiment starting with 8 g of **26.4** gave **27.1** in 97% yield.

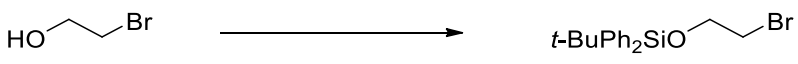
2-[(1*R*,2*R*,3*R*,4*S*,7*R*)-*rel*-3-[2-(Acetyloxy)ethyl]-5,6-dioxo-7-[(triethylsilyl)oxy]bicyclo[2.2.1]heptan-2-yl]ethyl acetate (27.2); (1*S*,3*R*,7*R*,8*R*,9*R*,10*R*)-*rel*-3-Hydroxy-10-(2-hydroxyethyl)-9-[(triethylsilyl)oxy]-4-oxatricyclo-[5.2.1.0^{3,8}]decan-2-one (27.3); (1*S*,3*R*,7*R*,8*R*,9*R*,10*R*)-*rel*-3-Hydroxy-10-{2-[(2-methoxyethoxy)methoxy]ethyl}-9-[(triethylsilyl)oxy]-4-oxatricylco[5.2.1.0^{3,8}]-decan-2-one (21.5).



Dry DMSO (0.64 mL, 9.01 mmol) was added to a stirred and cooled (-78 °C) solution of $(COCl)_2$ (0.52 mL, 6.05 mmol) in dry CH_2Cl_2 (8.5 mL). After 30 min a solution of **27.1** (500 mg, 1.16 mmol) in CH_2Cl_2 (8.5 mL) was added dropwise over 15 min, and stirring was continued at -78 °C for 1.5 h. Dry Et_3N (1.6 mL, 11.82 mmol) was then added dropwise over 15 min and stirring was continued at -78 °C for 1.5 h. The cold bath was removed, stirring was continued for 30 min, and the mixture was then poured into water (150 mL) and extracted with CH_2Cl_2 (2 x 25 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to give crude **27.2** as a yellow oil, which was kept under oil pump vacuum for 35 min.

A solution of aqueous K_2CO_3 (1.2 M, 1.5 mL, 1.8 mmol) was added dropwise over ca 15 min to a stirred and cooled (0 °C) solution of the above crude oil in MeOH (15 mL). The ice bath was removed, stirring was continued for 4 h and the mixture was partitioned between water and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 and the combined organic extracts (containing **27.3**) were dried ($MgSO_4$) and concentrated to a volume of 13 mL (using a premarked flask). The solution was stirred and *i*-Pr_2NEt (0.8 mL, 4.59 mmol) was injected dropwise, followed by MEMCl (0.334 mL, 2.92 mmol). The large excess of the base is to ensure that the mixture does not become acidic. Stirring was continued overnight, and the mixture was diluted with water and extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (12 g, 1.5 x 15 cm), using 40% EtOAc-hexane, gave pure **21.5** (335 mg, 67% over three steps) as a yellow oil: FTIR (neat film) 3335, 2955, 2877, 1762, 1458, 1414, 1293, 1240, 1152, 1115, 1091 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.63 (q, *J* = 7.8 Hz, 6 H), 0.97 (t, *J* = 7.8 Hz, 9 H), 1.56 (d, *J* = 11.7 Hz, 1 H), 1.82-1.96 (m, 2 H), 2.04-2.14 (m, 2 H), 2.19-2.22 (m, 1 H), 2.48-2.53 (m, 1 H), 2.58 (s, 1 H), 3.10 (s, 1 H), 3.4 (s, 3 H), 3.52-3.62 (m, 6 H), 3.65-3.72 (m, 2 H), 3.91 (dd, *J* = 12.5, 5.1 Hz, 1 H), 4.48 (s, 1 H), 4.69 (s, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 4.6 (t), 6.7 (q), 25.3 (t), 35.5 (t), 36.3 (d), 37.7 (d), 50.7 (d), 59.0 (d), 59.2 (q), 61.2 (t), 65.9 (t), 66.8 (t), 71.8 (t), 74.4 (d), 95.4 (t), 97.2 (s), 212.1 (s); exact mass (electrospray) *m*/*z* calcd for $C_{21}H_{38}NaO_7Si$ (M + Na) 453.2279, found 453.2277.

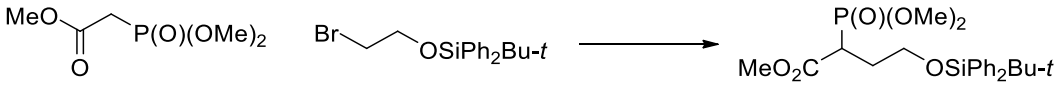
(2-Bromoethoxy)(*tert*-butyl)diphenylsilane (33.2).



33.1 **33.2**

t-$BuPh_2SiCl$ (6.1 mL, 23.5 mmol), followed by DMAP (0.546 g, 4.46 mmol), and finally Et_3N (3.9 mL, 24.2 mmol) were added to a stirred solution of 2-bromoethanol (**33.1**) (1.57 mL, 22 mmol) in CH_2Cl_2 (70 mL). Stirring at room temperature was continued for 24 h and then water (20 mL) was added to the mixture. The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL), and the combined organic extracts were washed once with water, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (4 x 15 cm), using 2.5% EtOAc-hexane, gave **33.2** (7.87 g, 98%) as a colorless oil: FTIR (film) 3080, 3020, 2970, 2940, 2895, 2870, 1475, 1465, 1430, 1190, 1120, 1030, 830, 705 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ1.13 (s, 9 H), 3.46 (t, *J* = 6.5 Hz. 2 H), 3.97 (t, *J* = 6.5 Hz, 2 H), 7.75-7.70 (m, 4 H), 7.50-7.35 (m, 6 H).

Methyl 4-[(*tert*-butyldiphenylsilyl)oxy]-2-(dimethoxyphosphoryl)-butanoate (33.5).

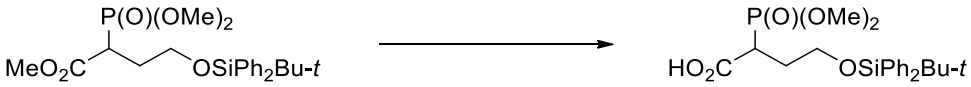


33.4 **33.2** **33.5**

Trimethyl phosphonoacetate **33.4** (0.8 mL, 4.96 mmol) was added dropwise over 30 min to a stirred suspension of NaH (60% suspension in mineral oil, 0.24 g, 5.94 mmol) in DMSO (9.35 mL) at room temperature. After 70 min, **33.2** (600 mg, 1.65 mmol) in DMSO (2.6 mL) was added. Stirring was continued for 8 h and then water (60 mL) was added. 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 column chromatography of the residue over silica gel (3 x 15 cm), using EtOAc, gave phosphonate **33.5** (3.20 g, 71%) as a

clear oil: FTIR ($CHCl_3$, cast) 3072, 3049, 2955, 2857, 1739, 1463, 1429, 1261, 1190, 1160, 1112, 1054, 1031 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.04 (s, 9 H), 2.09-2.14 (m, 1 H), 2.21-2.25 (m, 1 H), 3.39 (ddd, *J* = 23.5, 11.0, 3.5 Hz, 1 H), 3.59-3.64 (m, 1 H), 3.70-3.75 [m, including a singlet at δ 3.72 (3 H), 4 H in all], 3.79 (d, *J* = 11.0 Hz, 3 H), 3.80 (d, *J* = 11.0 Hz, 3 H), 7.36-7.45 (m, 6 H), 7.61-7.65 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) (the symbol d before the *J* value refers to multiplicity due to coupling with ^{31}P; the symbols s, d, t, q after the *J* value refer to zero, one, two, or three attached hydrogens, respectively) δ 19.2 (s), 26.8 (q), 29.7 (d, *J* = 4.5 Hz, t), 41.4 (d, *J* = 131.3 Hz, d), 52.5 (q), 53.3 (d, *J* = 6.6 Hz, q), 53.4 (d, *J* = 6.5 Hz, q), 61.6 (d, *J* = 15.6 Hz, t), 127.7 (d), 129.7 (d), 133.3 (s), 133.4 (s), 135.50 (d), 135.51 (d), 169.4 (d, *J* = 4.9 Hz, s); exact mass (electrospray) *m*/*z* calcd for $C_{23}H_{33}NaO_6PSi$ (M + Na) 487.1676, found 487.1680.

4-[(*tert*-Butyldiphenylsilyl)oxy]-2-(dimethoxyphosphoryl)butanoic acid (33.6).

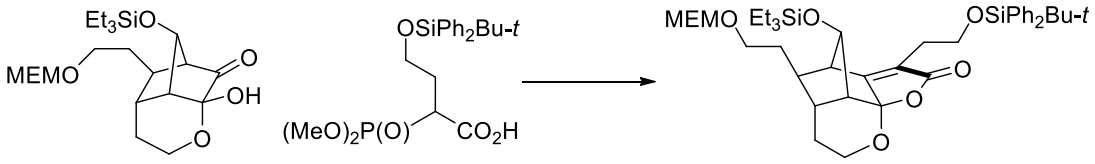


33.5 **33.6**

A solution of $LiOH.H_2O$ (18 mg, 0.43 mmol) in water (0.35 mL) was added to a stirred solution of **33.5** (100 mg, 0.22 mmol) in THF (0.77 mL). Stirring was continued for 5 h and the reaction mixture was quenched with 10% hydrochloric acid (0.5 mL) to *p*H = 3. The mixture was diluted with brine (5 mL) and solid NaCl was added to saturate the aqueous phase. The mixture was extracted with EtOAc (3 x 10 mL) and the combined organic extracts were dried (Na_2SO_4) and evaporated. The residue was recrystallized from CH_2Cl_2-hexane to

give **33.6** (88 mg, 89%) as a white solid: mp 93-94 °C; FTIR ($CHCl_3$, cast) 3072, 3049, 3012, 2999, 2957, 2933, 2890, 2858, 1727, 1609, 1463, 1428, 1389, 1220, 1188, 1112, 1059, 1035 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.04 (s, 9 H), 2.0-2.11 (m, 1 H), 2.19-2.29 (m, 1 H), 3.43 (ddd, *J* = 23.6, 10.4, 3.2 Hz, 1 H), 3.65-3.77 (m, 2 H), 3.80 (d, *J* = 10.8 Hz, 3 H), 3.84 (d, *J* = 11.2 Hz, 3 H), 7.36-7.43 (m, 6 H), 7.64-7.67 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) (the symbol d before the *J* value refers to multiplicity due to coupling with ^{31}P; the symbols s, d, t, q after the *J* value refer to zero, one, two, or three attached hydrogens, respectively) δ 19.2 (s), 26.8 (q), 29.7 (d, *J* = 4.9 Hz, t), 41.6 (d, *J* = 130.8 Hz, d), 53.4 (d, *J* = 6.8 Hz, q), 54.0 (d, *J* = 6.8 Hz, q), 61.4 (d, *J* = 15.0 Hz, t), 127.7 (d), 129.7 (d), 133.3 (s), 133.4 (s), 135.50 (d), 135.52 (d), 170.4 (s); exact mass (electrospray) *m*/*z* calcd for $C_{22}H_{31}NaO_6PSi$ (M + Na) 473.1520, found 473.1520.

(1*R*,6*S*,10*R*,11*R*,12*R*,13*R*)-*rel*-3-{2-[(*tert*-Butyldiphenylsilyl)oxy]ethyl}-13-{2-[(2-methoxyethoxy)methoxy]ethyl}-12-[(triethylsilyl)oxy]-5,7-dioxa-tetracyclo[8.2.1.$0^{2,6}$.$0^{6,11}$]tridec-2-en-4-one (21.4).



21.5 **33.6** **21.4**

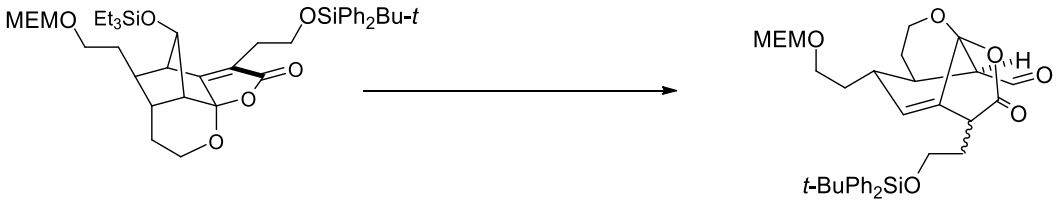
In the first part of this experiment, **33.6** was converted into the acid chloride as follows:

$(COCl)_2$ (0.21 mL, 2.44 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **33.6** (363 mg, 0.81 mmol) in CH_2Cl_2 (3.2 mL). Dry DMF (2 drops from a 19 gauge syringe needle) was added. After 15 min, the ice bath was

removed and stirring was continued for 4 h. The solvent was evaporated under water pump vacuum with protection from moisture, Ar being admitted to the flask, and residual $(COCl)_2$ was then removed under oil pump vacuum (45 min).

All of the above acid chloride in THF (4.3 mL, including the rinse) was added at a fast dropwise rate to a stirred and cooled (-78 °C) solution of **21.5** (216 mg, 0.502 mmol) in THF (2.1 mL), followed by neat DBU (0.38 mL, 2.54 mmol), which was added at a slow dropwise rate (over ca 2 min). The dry-ice bath was removed after the DBU addition, and stirring was continued for 6 h. LiCl (kept overnight in an oven at 160 °C and then cooled, 55 mg, 1.29 mmol) (material from a new bottle, without drying is also satisfactory) was tipped in and stirring was continued overnight. The reaction mixture was passed through a pad of flash chromatography silica gel (2 x 1.5 cm high) covered by $MgSO_4$ (0.5 cm thick), using 1:1 EtOAc-hexane (100 mL) as a rinse. Evaporation of the eluate and flash chromatography of the residue over silica gel (5 g, 1 x 15 cm high), using 20% EtOAc-hexane, gave **21.4** (277 mg, 75%) as a yellow oil: FTIR ($CDCl_3$ cast) 2954, 2932, 2876, 1769, 1686, 1472, 1428, 1389, 1362, 1243, 1211, 1180, 1112, 1089, 1045 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.58 (q, J = 8.1 Hz, 6 H), 0.90 (t, J = 8.1 Hz, 9 H), 1.05 (s, 9 H), 1.78-2.0 (m, 4 H), 2.1 (q, 1 H), 2.4-2.56 (m, 2 H), 2.58 (d, J = 4.0 Hz, 1 H), 2.61-2.70 (m, 1 H), 2.84 (s, 1 H), 3.39 (s, 3 H), 3.50-3.60 (m, 4 H), 3.65-3.69 (m, 2 H), 3.70-3.85 (m, 4 H), 3.95-4.01 (m, 1 H), 4.68 (s, 2 H), 7.35-7.45 (m, 6 H), 7.65-7.69 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 4.5 (t), 6.7 (q), 19.14 (s) 25.1 (t), 26.8 (q), 27.8 (d), 34.8 (t), 36.5 (t), 41.7 (d), 46.7 (d), 53.1 (d), 59.0 (q), 61.7 (t), 62.0 (t), 66.2 (t), 66.8 (t), 71.8 (t), 81.9 (d), 95.4 (t), 107.0 (s), 121.1 (s), 127.7 (d), 129.66 (d), 129.67 (d), 133.47 (s), 133.54 (s), 135.5 (s), 166.1 (s), 172.9 (s); exact mass (electrospray) m/z calcd for $C_{41}H_{60}NaO_8Si_2$ (M + Na) 759.3710, found 759.3712.

(1*S*,7*R*,8*R*,12*R*)-*rel*-4-{2-[(*tert*-Butyldiphenylsilyl)oxy]ethyl}-7-{2-[(2-methoxyethoxy)methoxy]ethyl}-3-oxo-2,11-dioxatricyclo[6.3.1.$0^{1,5}$]dodec-5-ene-12-carbaldehyde (21.3).



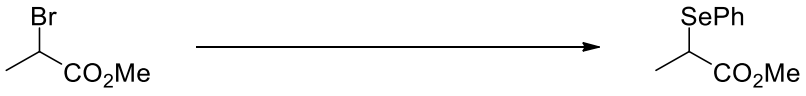
21.4 **21.3**

AcOH (18 μL, 0.31 mmol) and then Bu_4NF (1 M in THF, 0.2 mL, 0.2 mmol) were added dropwise to a stirred and cooled (-9 °C; obtained by using an immersion cooler probe in a cooling bath) solution of **21.4** (133 mg, 0.181 mmol) in THF (11 mL). Stirring at -9 °C to -8 °C was continued for 45 min and samples were examined by TLC (silica, 1:1 EtOAc-hexane) at 5-min intervals. In some runs the reaction was over in 30 min. As soon as the spot for **21.4** was faint (a better yield is obtained if the reaction is stopped just before absolute completion) the mixture was quenched with saturated aqueous NH_4Cl (6 mL). Stirring at -10 °C was continued for 10 min and the cold bath was then removed and stirring was continued for 10 min. The mixture was diluted with water and extracted with EtOAc. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (5 g, 1 x 15 cm), using 45% EtOAc-hexane, gave **21.3** (50 mg of each isomer, 100 mg in total, 89%) as a colorless oil which was a 1:1 mixture of two isomers. The less polar isomer had: FTIR (microscope) 3071, 3049, 3014, 2931, 2879, 2859, 1793, 1734, 1472, 1448, 1428, 1389, 1362, 1251, 1199, 1167, 1111, 1064, 1044 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.08 (s, 9 H), 1.45-1.62 (m, 3 H), 1.72-1.85 (m, 1 H), 1.87-2.11 (m, 1

H), 2.16-2.36 (m, 2 H), 2.84 (s, 2 H), 3.39 (s, 3 H), 3.42-3.78 (m, 9 H), 3.80-3.94 (m, 2 H), 4.70 (s, 2 H), 5.94 (d, *J* = 3.0 Hz, 1 H), 7.35-7.49 (m, 6 H), 7.62-7.72 (m, 4 H), 9.63 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.2 (s), 26.9 (q), 33.6 (t), 34.4 (t), 34.98 (t), 35.05 (d), 37.5 (d), 39.5 (d), 53.5 (d), 59.1 (q), 60.3.(t), 62.3 (t), 65.5 (t), 67.0 (t), 71.8 (t), 95.5 (t), 101.6 (s), 127.8 (d), 129.8 (d), 131.4 (s), 132.9 (d), 133.25 (s), 133.59 (s), 135.6 (d), 175.8 (s), 199.5 (s); exact mass (electrospray) *m*/*z* calcd for $C_{35}H_{46}NaO_8Si$ (M + Na) 645.2854, found 645.2857.

The more polar isomer isomer had: FTIR (microscope) 3071, 3049, 2931, 2883, 2859, 1787, 1737, 1472, 1446, 1428, 1389, 1362, 1256, 1188, 1170, 1110, 1043 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.06 (s, 9 H), 1.45-1.62 (m, 4 H), 1.89-2.16 (m, 3 H), 2.20-2.32 (m, 1 H), 2.80-2.91 (m, 2 H), 3.39 (s, 3 H), 3.42-3.70 (m, 7 H), 3.70-4.04 (m, 4 H), 4.69 (s, 2 H), 5.92 (d, *J* = 2.8 Hz, 1 H), 7.35-7.49 (m, 6 H), 7.64-7.72 (m, 4 H), 9.53 (d, *J* = 1.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.2 (s), 26.9 (q), 31.3 (t), 33.6 (t), 34.5 (t), 35.1 (d), 37.2 (d), 39.5 (d), 53.5 (d), 59.1 (q), 60.7.(t), 62.7 (t), 65.4 (t), 67.0 (t), 71.8 (t), 95.5 (t), 101.7 (s), 127.8 (d), 129.7 (d), 130.3 (d), 132.1 (d), 133.33 (s), 133.53 (s), 135.5 (d), 135.7 (d), 175.2 (s), 199.5 (d); exact mass (electrospray) *m*/*z* calcd for $C_{35}H_{46}NaO_8Si$ (M + Na) 645.2854, found 645.2853.

Methyl 2-(phenylselanyl)propanoate (37.2).



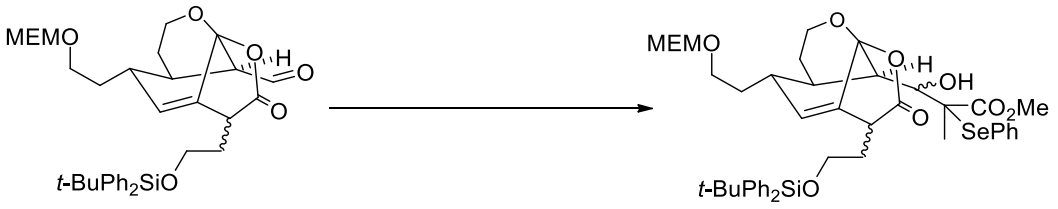
37.1 **37.2**

$NaBH_4$ (2.4 g, 63.4 mmol) was added in several portions to a stirred and cooled (0 °C) solution of PhSeSePh (4.0 g, 12.8 mmol) in MeOH (75 mL). After

the addition, a solution of **37.1** (4.01 g, 24.0 mmol) in MeOH (30 mL) was added dropwise. Stirring was continued for 2 h, the ice bath was removed and stirring was continued for 2.5 h. The solution was quenched with water (30 mL) and diluted with Et_2O (30 mL). The aqueous phase was extracted with Et_2O (3 x 15 mL), and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (4.5 x 21 cm), using 1:10 EtOAc-hexane, gave **37.2** (4.74 g, 81%) as a yellow oil: FTIR ($CHCl_3$, cast) 3072, 3058, 2991, 2950, 2928, 1730, 1579, 1477, 1450, 1438, 1376, 1333, 1258, 1213, 1148, 1062, 1022 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.55 (d, J = 7.1 Hz, 3 H), 3.65 (s, 3 H), 3.78 (q, J = 7.2 Hz, 1 H), 7.26-7.38 (m, 3 H), 7.58-7.62 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.6 (q), 37.1 (q), 52.0 (d), 127.6 (s), 128.5 (d), 128.9 (d), 135.7 (d), 173.7 (s); exact mass (electrospray) m/z calcd for $C_{10}H_{12}NaO_2{}^{80}Se$ (M + Na) 266.9895, found 266.9896.

A subsequent experiment gave **37.2** in 88% yield.

Methyl 3-[(1*S*,7*R*,8*R*,12*R*)-*rel*-(4-{2-[(*tert*-Butyldiphenylsilyl)oxy]-ethyl}-7-{2-[(2-methoxyethoxy)methoxy]ethyl}-3-oxo-2,11-dioxatricyclo-[6.3.1.0^{1,5}]dodec-5-en-12-yl)]-3-hydroxy-2-methyl-2-(phenylselanyl)-propanoate (38.1).

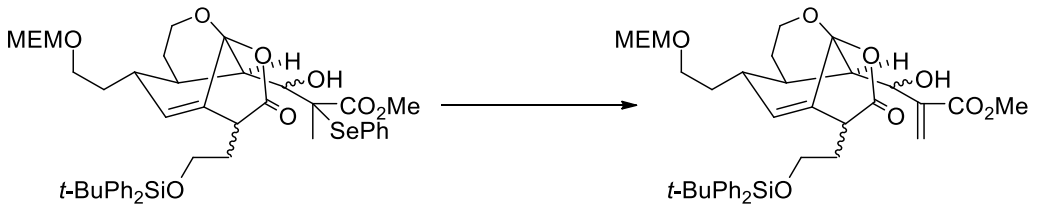


21.3 **38.1**

BuLi (2.5 M in hexane, 0.17 mL, 0.42 mmol) was injected dropwise into a stirred and cooled (-78 °C) solution of *i*-Pr_2NH (0.15 mL, 1.05 mmol) in THF (3.1 mL). Stirring was continued for 50 min and a solution of methyl 2-(phenylseleno)propionate (**37.2**) (124 mg, 0.47 mmol) in THF (3.1 mL) was injected dropwise over 5 min. Note that it is important to weigh the phenylseleno compound and keep it under oil pump vacuum (with protection from light) for 4 h before checking the weight and dissolving the substance in dry THF; the yield in this reaction is exceptionally sensitive to traces of moisture. Stirring was continued at -78 °C for 1 h (with protection from light). A solution of **21.3** (87 mg, 0.14 mmol) in THF (6.2 mL) was added dropwise over ca 3 min. Stirring was continued at -78 °C for 5 h (with protection from light) and the mixture was quenched with saturated aqueous NH_4Cl. Vigorous stirring was continued for 10 min and the cold bath was then removed and the mixture was diluted with water. Stirring was continued for 10 min and the mixture was extracted with EtOAc. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (5 g, 1 x 15 cm), using 2:1 hexane-EtOAc, gave **38.1** (90 mg, 75%) as a light yellow oil, which was an inseparable mixture of isomers: exact mass (electrospray) *m*/*z* calcd for $C_{45}H_{58}NaO_{10}{}^{80}SeSi$ (M + Na) 889.2857, found 889.2862.

A subsequent experiment starting with 250 mg of **21.3** gave **38.1** in 85% yield.

Methyl 2-[(1*S*,7*R*,8*R*,12*R*)-*rel*-[(4-{2-[(*tert*-Butyldiphenylsilyl)oxy]-ethyl}-7-{2-[(2-methoxyethoxy)methoxy]ethyl}-3-oxo-2,11-dioxa-3-oxotri-cyclo[6.3.1.$0^{1,5}$]dodec-5-en-12-yl)](hydroxy)methyl]prop-2-enoate (38.2).



38.1 **38.2**

H_2O_2 (30%, 0.32 mL, 3.7 mmol) was added to a stirred and cooled (0 °C) solution of **38.1** (57 mg, 0.066 mmol) in a mixture of THF (3.8 mL) and water (0.38 mL). Stirring at 0 °C was continued for 1 h and the mixture was quenched by dropwise addition of saturated aqueous $Na_2S_2O_3$ (12 mL), diluted with water and extracted with EtOAc. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.6 g, 0.5 x 15 cm), using 1:1 hexane-EtOAc, gave **38.2** (40 mg, 86%) as a colorless oil which was an inseparable mixture of isomers: FTIR (microscope) 3464, 3071, 3048, 2930, 2878, 2858, 1791, 1717, 1629, 1472, 1441, 1428, 1362, 1261, 1197, 1160, 1112, 1041 cm^{-1}; exact mass (electrospray) *m*/*z* calcd for $C_{39}H_{52}NaO_{10}Si$ (M + Na) 731.3222, found 731.3223.

A subsequent experiment starting with 450 mg of **38.1** gave **38.2** in 97% yield.

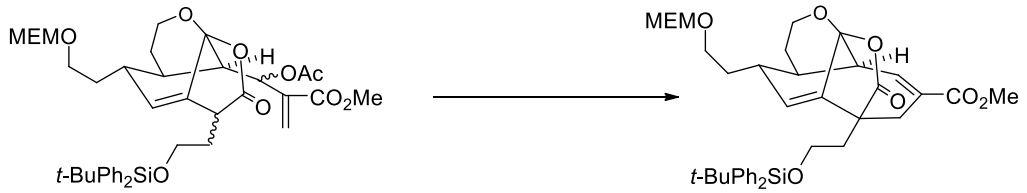
Methyl 2-[(1*S*,7*R*,8*R*,12*R*)-*rel*-[(Acetyloxy)(4-{2-[(*tert*-butyldiphenyl-silyl)oxy]ethyl}-7-{2-[(2-methoxyethoxy)methoxy]ethyl}-3-oxo-2,11-dioxatri-cyclo[6.3.1.$0^{1,5}$]dodec-5-en-12-yl)]methyl]prop-2-enoate (21.2).

38.2 **21.2**

DMAP (3.6 mg, 0.017 mmol), pyridine (100 μL, 1.27 mmol) and AcCl (36 μL, 0.59 mmol) were added sequentially to a stirred and cooled (0 °C) solution of **38.2** (60 mg, 0.085 mmol) in CH_2Cl_2 (3.6 mL). Stirring at 0 °C was continued for 2 h and then the mixture was diluted with water. Dilute hydrochloric acid (10%, 0.5 mL) was added and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 g, 1 x 15 cm), using 1:1 EtOAc-hexane, gave **21.2** (55 mg, 87%) as a colorless oil which was an inseparable mixture of isomers: FTIR (cast film) 3071, 3048, 2932, 2877, 2859, 1791, 1794, 1742, 1722, 1632, 1472, 1441, 1429, 1366, 1298, 1277, 1236, 1196, 1154, 1112, 1064, 1023; exact mass (electrospray) *m*/*z* calcd for $C_{41}H_{54}NaO_{11}Si$ (M + Na) 773.3328, found 773.3321.

A subsequent experiment starting with 209 mg of **38.1** gave **21.2** in 94% yield.

Methyl (1*S*,5*R*,6*R*,9*S*,13*R*)-*rel*-9-{2-[(*tert*-Butyldiphenylsilyl)oxy]-ethyl}-6-{2-[(2-methoxyethoxy)methoxy]ethyl}-15-oxo-2,14-dioxatetracyclo-[7.4.2.0^{1,8}.0^{5,13}]pentadeca-7,11-diene-11-carboxylate (21.1).

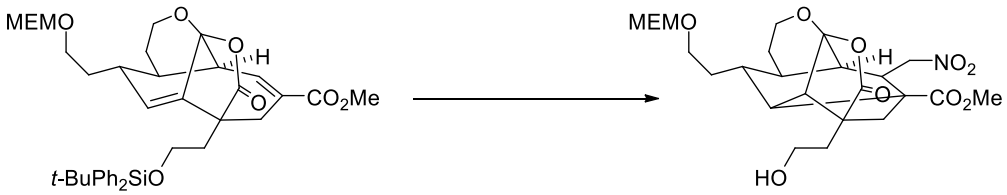


21.2 **21.1**

DBU (73 μL, 0.47 mmol) was added to a stirred solution of **21.2** (55 mg, 0.073 mmol) in MeCN (7.3 mL) at room temperature. Stirring was continued for 50 min and the solution was then passed through a pad of flash chromatography silica gel (2.5 x 2.5 cm) to remove DBU, which causes decomposition of the product on concentrating the solution, using 50% EtOAc-hexane as a rinse. Evaporation of the solvent and flash chromatography of the residue over silica gel (1.5 g silica, 6 mm x 15 cm), using 1:1 EtOAc-hexane, gave **21.1** (33 mg, 65%) as an oil which slowly partially crystallized on storage at -78 °C for several days: FTIR (cast film) 3071, 3048, 2930, 2881, 2858, 1788, 1713, 1615, 1472, 1428, 1388, 1363, 1332, 1303, 1250, 1158, 1113, 1064, 1048; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.04 (s, 9 H), 1.41-1.54 (m, 2 H), 1.60-1.66 (m, 1 H), 1.85-1.94 (m, 1 H), 1.96-2.04 (m, 1 H), 2.31-2.39 (m, 2 H), 2.41-2.54 (m, 2 H), 2.85-2.94 (m, 1 H), 2.96 (s, 1 H), 3.38 (s, 3 H), 3.52-3.56 (m, 2 H), 3.56-3.62 (m, 2 H), 3.64-3.72 (m, 6 H), 3.78-3.88 (m, 2 H), 3.96 (dd, J = 10.4, 5.2 Hz, 1 H), 4.70 (s, 2 H), 5.52 (s, 1 H), 6.75-6.8 (m, 1 H), 7.35-7.45 (m, 6 H), 7.62-7.72 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.0 (s), 26.6 (q), 33.3 (t), 34.4 (t), 36.2 (t), 36.4 (d), 37.8 (d), 47.1 (d), 49.1 (s), 49.9 (t), 52.3 (q), 59.1 (q), 60.4.(t), 61.3 (t), 65.5 (t), 67.0 (t), 71.8 (t), 95.5 (t), 103.8 (s), 127.59 (d), 127.62 (d), 128.8 (s), 129.54 (d) 129.57 (d), 130.7 (d), 133.4 (s), 133.6 (s), 135.66 (d), 135.69 (d), 136.5 (s), 138.5 (d), 168.0 (s), 176.1 (s); exact mass (electrospray) m/z calcd for $C_{39}H_{50}NaO_9Si$ (M + Na) 713.3116, found 713.3111.

A sample for X-ray analysis was crystallized from EtOAc-hexane.

Methyl (1*R*,5*S*,6*S*,7*R*,8R,9*R*,11*S*,13*S*)-*rel*-9-(2-hydroxyethyl)-6-{2-[(2-methoxyethoxy)methoxy]ethyl}-12-(nitromethyl)-15-oxo-2,14-dioxapenta-cyclo[7.4.2.$0^{1,8}$.$0^{5,13}$.$0^{7,11}$]pentadecane-11-carboxylate (43.2).

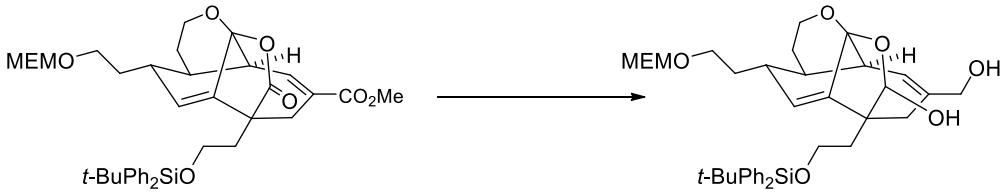


21.1 **43.2**

$MeNO_2$ (24 μL, 0.43 mmol) and Bu_4NF (1 M in THF, 33 μL, 0.033 mmol) were added to a stirred solution of **21.1** (10 mg, 0.0145 mmol) in THF (0.15 mL) and stirring was continued for 6 h, by which time the starting material was consumed completely (TLC control, silica, 1:1 hexane-EtOAc). The reaction mixture was evaporated and flash chromatography of the residue over silica gel (Pasteur pipette 4 cm), using 2:98 MeOH-EtOAc, gave **43.2** (6 mg, 85%) as a colorless liquid: FTIR (cast film) 3467, 2925, 2886, 1779, 1727, 1556, 1458, 1435, 1384, 1307, 1239, 1189, 1158, 1114, 1100, 1060; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.02 (s, 1 H), 1.32-1.54 (m, 2 H), 1.60-1.72 (m, 1 H), 1.85-2.02 (m, 5 H), 2.08-2.18 (m, 2 H), 2.32 (d, *J* = 14.8, 1 H), 2.84-2.91 (m, 2 H), 3.17 (dd, *J* = 9.7, 4.8, 1 H), 3.40 (s, 3 H), 3.46-3.72 (m, 6 H), 3.74 (s, 3 H), 3.80-3.90 (m, 3 H), 3.98 (dd, *J* = 12.9, 5.4 Hz, 1 H), 4.37 (dd, *J* = 12.8, 9.9 Hz, 1 H), 4.49 (dd, *J* = 12.8, 4.8 Hz, 1 H), 4.69 (s, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 30.8 (t), 31.8 (d), 35.5 (t), 37.1 (t), 38.5 (d), 38.6 (d), 39.8 (d), 45.9 (t), 47.8 (d), 49.9 (s), 51.4 (s), 52.3 (d), 53.0 (q), 59.1 (q), 59.2.(t), 60.7 (t), 65.0 (t), 67.1 (t), 71.8 (t), 76.3 (t), 95.6 (t),

106.9 (s), 174.9 (s), 177.8 (s); exact mass (electrospray) *m*/*z* calcd for $C_{24}H_{35}NNaO_{11}$ (M + Na) 536.2102, found 536.2100.

(1*S*,5*R*,6*R*,9*S*,13*R*)-*rel*-9-{2-[(*tert*-Butyldiphenylsilyl)oxy]ethyl}-11-(hydroxymethyl)-6-{2-[(2-methoxyethoxy)methoxy]ethyl}-2,14-dioxatetracyclo[7.4.2.0^{1,8}.0^{5,13}]pentadeca-7,11-dien-15-ol (47.1).

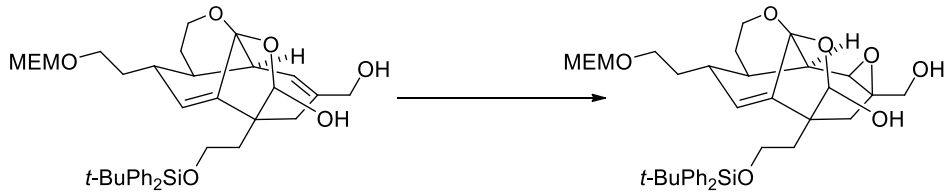


21.1 **47.1**

DIBAL-H (1 M in PhMe, 0.9 mL, 0.9 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of **21.1** (32 mg, 0.05 mmol) in THF (2 mL). Stirring at -78 °C was continued for 3.5 h, and the cold bath was replaced by an ice bath. After 5 min, the mixture was quenched with $Na_2SO_4.10H_2O$. The ice bath was removed, Et_2O (2 mL) was added and stirring was continued for 40 min. The mixture was filtered through a fritted funnel. Evaporation of the filtrate and flash chromatography (Pasteur pipette, 7 cm) of the residue, using EtOAc, gave **47.1** (30 mg, 97%) as a colorless oil which was a 3:1 mixture of two isomers: FTIR (cast film) 3421, 3071, 3048, 2930, 2877, 2858, 1472, 1428, 1389, 1363, 1281, 1246, 1199, 1039, 1008 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) (major isomer signals) δ 1.04 (s, 9 H), 1.49-1.64 (m, 4 H), 1.80-2.03 (m, 3 H), 2.10-2.42 (m, 4 H), 2.54 (s, 1 H), 3.33 (d, *J* = 4.0 Hz, 1 H), 3.39 (s, 3 H), 3.52-3.60 (m, 4 H), 3.64-3.71 (m, 2 H), 3.74-3.90 (m, 6 H),4.70 (s, 2 H), 5.19 (s, 1 H),5.27 (d, *J* = 4.0 Hz, 1 H), 5.54 (s, 1 H), 6.75-6.8 (m, 1 H), 7.35-7.45 (m, 6 H), 7.62-7.72 (m, 4 H); ^{13}C

NMR ($CDCl_3$, 100 MHz) (major isomer signals) δ 19.0 (s), 26.8 (q), 33.8 (t), 34.2 (t), 36.3 (t), 37.1 (d), 37.6 (d), 45.8 (s), 46.1 (d), 53.8 (t), 59.0 (q), 60.7.(t), 61.1 (t), 66.1 (t), 66.9 (t), 70.8 (t), 71.8 (t), 95.5 (t), 103.4 (d), 104.3 (s), 124.0 (d), 127.7 (d), 127.9 (d), 129.72 (d), 129.75 (d), 133.26 (s),133.35 (s), 135.59 (d), 135.61 (d), 137.9 (s), 140.4 (s); exact mass (electrospray) *m*/*z* calcd for $C_{38}H_{52}NaO_8Si$ (M + Na) 687.3324, found 687.3321.

(1*S*,5*R*,6*R*,9*R*,14*R*)-*rel*-9-{2-[(*tert*-Butyldimethylsilyl)oxy]ethyl}-11-(hydroxymethyl)-6-{2-[(2-methoxyethoxy)methoxy]ethyl}-2,12,15-trioxa-pentacyclo[7.5.2.$0^{1,8}$.$0^{5,14}$.$0^{11,13}$]hexadec-7-en-16-ol (47.2).

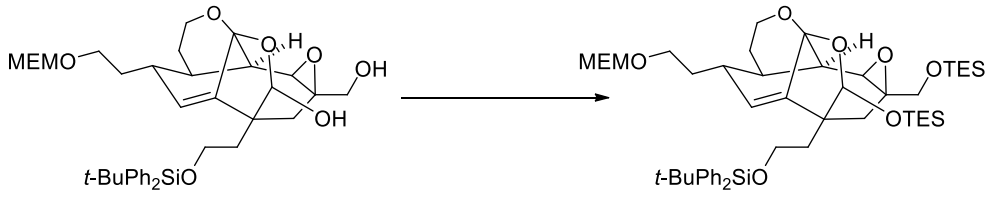


47.1 **47.2**

A stock solution of $VO(acac)_2$ (25 mg) in PhH (1 mL) was prepared and an aliquot of this solution (0.1 mL, 0.009 mmol) was added to a stirred solution of **47.1** (31 mg, 0.047 mmol) in PhH (2.5 mL). The mixture turned green after the addition. *t*-BuOOH (5.5 M in decane, 20 μL, 0.11 mmol) was added dropwise to the stirred mixture; the color changed immediately to burgundy. TLC (silica, EtOAc) showed that the staring material had been consumed after 30 min. The mixture was then diluted with EtOAc (2.5 mL) and quenched with saturated aqueous Na_2SO_3 (2.5 mL). The mixture was stirred for 1 h until the organic phase was clear. The organic phase was then washed with water (2.5 mL) and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica

gel (Pasteur pipette, size, 7 cm), using 5:95 MeOH-EtOAc, gave **47.2** (28 mg, 91%) as a colorless oil which was mixture of two inseparable isomers (1.6:1 based on NMR): FTIR (cast film) 3444, 3071, 3048, 2931, 2883, 2858, 2247, 1472, 1428, 1389, 1363, 1281, 1247, 1197, 1169, 1112, 1089, 1041, 1008; ^{1}H NMR ($CDCl_3$, 400 MHz) (major isomer signals) δ 1.06 (s, 9 H), 1.44-1.64 (m, 4 H), 1.78-2.03 (m, 3 H), 2.14-2.36 (m, 3 H), 2.59 (s, 1 H), 2.86 (d, *J* = 1.2 Hz, 1 H), 3.12 (d, *J* = 5.4 Hz, 1 H), 3.34 (d, *J* = 5.4 Hz, 1 H), 3.39 (s, 3 H), 3.52-3.59 (m, 2 H), 3.59-3.76 (m, 5 H), 3.76-3.90 (m, 3 H), 4.72 (s, 2 H), 5.11 (d, *J* = 4.8 Hz, 1 H), 5.53 (s, 1 H), 7.35-7.52 (m, 6 H), 7.62-7.72 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100 MHz) (major isomer signals) δ 19.0 (s), 26.8 (q), 33.9 (t), 34.8 (t), 36.6 (t), 37.3 (d), 37.4 (d), 42.1 (s), 42.3 (d), 54.1 (t), 59.0 (q), 60.55.(t), 60.60 (t), 61.48 (d), 65.0 (t), 65.7 (t), 65.9 (t), 67.0 (t), 71.8 (t), 95.6 (t), 102.9 (d), 104.0 (s), 127.70 (d), 127.74 (d), 127.8 (d), 129.8 (d), 133.17 (s), 133.24 (s), 135.58 (d), 135.60 (d), 141.5 (s); exact mass (electrospray) *m*/*z* calcd for $C_{38}H_{52}NaO_9Si$ (M + Na) 703.3273, found 703.3268.

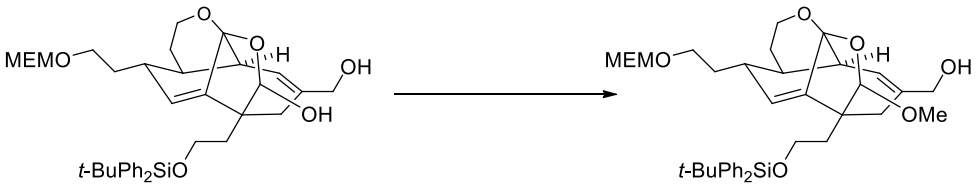
[(1*S*,5*R*,6*R*,9*R*,14*R*)-*rel*-(9-{2-[(*tert*-Butyldiphenylsilyl)oxy]ethyl}-6-{2-[(2-methoxyethoxy)methoxy]ethyl}-16-[(triethylsilyl)oxy]-2,12,15-trioxa-pentacyclo[7.5.2.0^{1,8}.0^{5,14}.01^{1,13}]hexadec-7-en-11-yl)methoxy]triethylsilane (47.3).



47.2 **47.3**

2,6-Lutidine (20 μL, 0.165 mmol) followed by $Et_3SiOSO_2CF_3$ (35 μL, 0.165 mmol) were added to a stirred and cooled (0 °C) solution of **47.2** (28 mg, 0.041 mmol) in CH_2Cl_2 (1.5 mL). After 40 min the ice bath was removed and stirring was continued for 2.5 h. The mixture was quenched with saturated aqueous $NaHCO_3$ (0.1 mL), diluted with water and extracted with CH_2Cl_2 (3 x 4 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (Pasteur pipette, 7 cm), using 3:7 EtOAc-hexane, gave **47.3** (30 mg, 81%) as a colorless oil which was a mixture of two inseparable isomers (6:1 based on NMR): FTIR (cast film) 3071, 3049, 2934, 2954, 2876, 1461, 1428, 1414, 1241, 1199, 1111, 1092, 1019 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) (major isomer signals) δ 0.46-0.68 (m, 12 H), 0.82-098 (m, 18 H), 1.06 (s, 9 H), 1.44-1.54 (m, 1 H), 1.54-1.81 (m, 3 H), 1.82-2.04 (m, 3 H), 2.1 (d, *J* = 15.4 Hz, 1 H), 2.14-2.26 (m, 2 H), 2.51 (s, 1 H), 2.57 (d, *J* = 1.3 Hz, 1 H), 3.08 (d, *J* = 10.4 Hz, 1 H), 3.41 (s, 3 H), 3.49 (d, *J* = 10.4 Hz, 1 H), 3.52-3.59 (m, 2 H), 3.59-3.70 (m, 5 H), 3.70-3.88 (m, 3 H), 4.73 (s, 2 H), 4.96 (s, 1 H), 5.44 (s, 1 H), 7.35-7.52 (m, 6 H), 7.62-7.72 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100 MHz) (major isomer signals) δ 4.3 (t), 4.8 (t), 6.7 (q), 6.8 (q), 19.1 (s), 26.9 (q), 34.2 (t), 36.1 (t), 36.3 (t), 37.37 (d), 37.40 (d), 42.2 (s), 43.0 (d), 54.5 (t), 59.1 (q), 60.0.(t), 60.9 (t), 64.0 (d), 65.1 (t), 65.9 (t), 66.9 (t), 69.7 (t), 71.8 (t), 95.6 (t), 102.9 (d), 104.0 (s), 127.0 (d), 127.61 (d), 127.62 (d), 129.5 (d), 133.8 (s), 133.9 (s), 135.5 (d), 135.6 (d), 142.1 (s); exact mass (electrospray) *m*/*z* calcd for $C_{50}H_{80}NaO_9Si_3$ (M + Na) 931.5002, found 931.5006.

(1*S*,5*R*,6*R*,9*S*,13*R*)-*rel*-9-{2-[(*tert*-Butyldiphenylsilyl)oxy]ethyl}-15-methoxy-6-{2-[(2-methoxyethoxy)methoxy]ethyl}-2,14-dioxatetracyclo-[7.4.2.$0^{1,8}$.$0^{5,13}$]pentadeca-7,11-dien-11-yl)methanol (59.1).

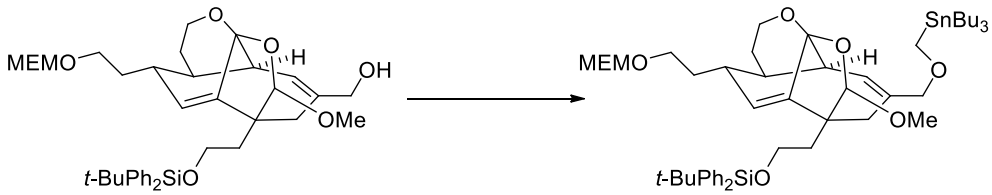


47.1 **59.1**

Pyridinium *p*-toluenesulfonate (4.6 mg, 0.3 equiv, 0.019 mmol), followed by $HC(OMe)_3$ (60 μL, 0.62 mmol, 9 equiv) were added sequentially to a stirred solution of **47.1** (41 mg, 0.062 mmol) in CH_2Cl_2 (5 mL). Stirring at room temperature was continued for 40 min, a mass spectral sample being analyzed after 30 min. The mass spectrum showed peaks at *m*/*z* 761 (M + 23) [C(15) OH attached to $CH(OMe)_2$] and disappearance of the **47.1** signal at *m*/*z* 687. Dry MeOH (3 mL) was added and stirring was continued for 5 h. The mass spectrum showed the presence of **47.1** and **59.1**. The mixture was quenched by addition of solid K_2CO_3 and the mixture was stirred for 5 min. The mixture was filtered through Celite (packed in a Pasteur pipette, 2 cm) and evaporated. The crude product was purified by TLC (20 x 20 cm, 0.25 mm thick analytical plate, EtOAc) to afford a 10:1 mixture of two isomers of the **59.1** [17 mg, 72% corrected for recovered **47.1** (21 mg)]: FTIR (cast film of the isomer mixture) 3450, 3071, 3048, 2930, 2875, 1725, 1670, 1589, 1472, 1428, 1388, 1364, 1281, 1243, 1199, 1112, 1041 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) (major isomer signals only) δ 1.08 (s, 9 H), 1.42-1.64 (m, 4 H), 1.80-2.03 (m, 4 H), 2.14-2.27 (m, 2 H), 2.3-2.42 (m, 1 H), 2.52 (s, 1 H), 2.71 (d, *J* = 17.4 Hz, 1 H), 3.41 (s, 3 H), 3.43 (s, 3 H), 3.52-3.62 (m, 4 H), 3.66-3.91 (m, 8 H), 4.73 (s, 2 H), 5.14 (s, 1 H), 5.31 (br s, 1 H), 5.42 (s, 1 H), 7.35-7.45 (m, 6 H), 7.62-7.72 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) (major isomer signals only) δ 19.1 (s), 26.9 (q), 33.9 (t), 35.2 (t), 36.3 (t), 36.9 (d), 37.5 (d), 41.7 (s), 46.0 (d), 51.1 (t), 58.1 (q), 59.1 (q), 60.5.(t), 61.0 (t), 66.1 (t), 66.9 (t), 70.7 (t), 71.8 (t), 95.6 (t), 101.6 (d), 108.1 (s), 123.6 (d), 127.3

(d), 127.7 (d), 129.65 (d), 129.67 (d), 133.72 (s), 133.73 (s), 135.60 (d), 135.64 (d), 138.5 (s), 140.3 (s); exact mass (electrospray) *m*/*z* calcd for $C_{39}H_{54}NaO_8Si$ (M + Na) 701.348, found 701.3483.

(1*S*,5*R*,6*R*,9*S*,13*R*)-*rel-tert*-Butyl[2-(15-methoxy-6-{2-[(2-methoxy-ethoxy)methoxy]ethyl}-11-{[(tributylstannyl)methoxy]methyl}-2,14-dioxa-tetracyclo[7.4.2.0^{1,8}.0^{5,13}]pentadeca-7,11-dien-9-yl)ethoxy]diphenylsilane (60.1).

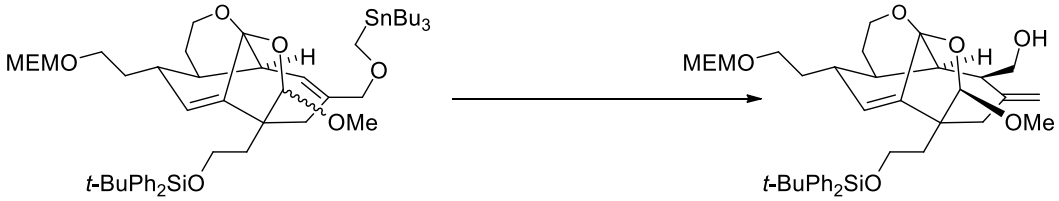


59.1 **60.1**

KH (35% w/w in oil, 48 mg, 0.42 mmol) was added to a stirred and cooled (0 °C) solution of **59.1** (70 mg, 0.103 mmol) in dry THF (1.4 mL). 18-Crown-6 (one crystal) was added, followed Bu_3SnCH_2I[49] (56 mg, 0.12 mmol), using THF as a rinse (0.5 mL). The ice bath was removed after the addition and, after 35 min, all **59.1** and stannane had been consumed (TLC, EtOAc). The mixture was quenched with water and extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (Pasteur pipette, 7 cm), using 1:1 EtOAc-hexane, gave **60.1** (86 mg, 85%) as a yellow oil which was a 10:1 mixture of two isomers: FTIR (cast film on the isomer mixture) 3071, 3048, 2955, 2928, 2871, 2856, 1735, 1589, 1464, 1428, 1388, 1363, 1339, 1242, 1213, 1180, 1113, 1091, 1052 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) (major isomer signals only) δ 0.8-0.94 (m, 12 H), 1.05 (s, 9

H), 1.2-1.34 (m, 9 H) 1.42-1.58 (m, 9 H), 1.80-1.98 (m, 2 H), 2.0-2.12 (m, 1 H), 2.16-2.28 (m, 2 H), 2.47 (s, 1 H), 2.62 (d, *J* = 17.6 Hz, 1 H), 3.38 (s, 6 H), 3.46-3.62 (m, 7 H), 3.62-3.68 (m, 4 H), 3.69-3.88 (m, 4 H), 4.70 (s, 2 H), 5.10 (s, 1 H), 5.21 (d, *J* = 4.6 Hz, 1 H), 5.37 (s, 1 H), 7.35-7.45 (m, 6 H), 7.62-7.72 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) (major isomer signals only) δ 8.9 (t), 13.7 (q), 19.1 (s), 26.9 (q), 27.3 (t), 29.2 (t), 33.9 (t), 35.3 (t), 36.3 (t), 36.8 (d), 37.2 (d), 41.9 (s), 46.1 (d), 51.0 (t), 57.9 (q), 59.1 (q), 60.6 (t), 60.7 (t), 61.0 (t), 65.9 (t), 66.9 (t), 71.8 (t), 83.6 (t), 95.5 (t), 101.6 (d), 107.9 (s), 124.8 (d), 127.2 (d), 127.7 (d), 129.6 (d), 133.8 (s), 135.6 (d), 136.4 (s), 140.2 (s); exact mass (electrospray) *m*/*z* calcd for $C_{52}H_{82}NaO_8Si^{120}Sn$ (M + Na) 1005.4693, found 1005.4699.

(1*S*,5*R*,6*R*,9*S*,12*R*,13*R*)-*rel*-(9-{2-[(*tert*-Butyldiphenylsilyl)oxy]ethyl}-15-methoxy-6-{2-[(2-methoxyethoxy)methoxy]ethyl}-11-methylidene-2,14-dioxatetracyclo[7.4.2.0^{1,8}.0^{5,13}]pentadec-7-en-12-yl)methanol (58.2).

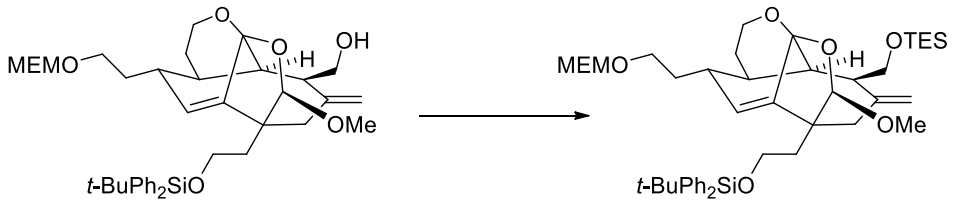


60.1 **58.2**

A solution of **60.1** (74 mg, 0.075 mmol) in dry, but not degassed, hexane (9.9 mL) was cooled to -9 °C (dry ice added to acetone to maintain -9 °C; double walled silvered Dewar) and BuLi (2.5 M in hexane, 0.30 mL, 10 equiv) was then added dropwise over a few seconds (ca 10 sec). The reaction mixture was allowed to warm to -3 °C over 40 min (the double cold bath was left to warm spontaneously without further addition of dry ice). The mixture was quenched

with saturated aqueous NH_4Cl (ca 4.5 mL), diluted with EtOAc and extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. The residue was subjected to preparative TLC (silica plate, 10 x 10 cm, 0.25 mm thick) using EtOAc. Both bands were extracted together with 10% MeOH in EtOAc and the solution was evaporated and the products (i.e. **58.2** and **59.1**) were taken forward. In earlier runs, the two compounds were separated using a TLC analytical plate with EtOAc as eluent to obtain samples for characterization. In later preparative experiments the crude material was used directly in the next step. Compound **58.2** had: FTIR (cast film) 3465, 3071, 2929, 2857, 1732, 1632, 1471, 1428, 1390, 1362, 1112, 1039; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.08 (s, 9 H), 1.72-1.90 (m, 5 H), 1.98-2.14 (m, 2 H), 2.2-2.32 (m, 2 H), 2.87 (d, *J* = 12.5 Hz, 1 H), 3.40 (s, 3 H), 3.42 (s, 3 H), 3.55-3.62 (m, 2 H), 3.62-3.74 (m, 5 H), 3.74-3.92 (m, 5 H), 4.75 (s, 2 H), 4.85 (s, 1 H), 4.93 (s, 1 H), 5.14 (s, 1 H), 5.43 (s, 1 H), 7.35-7.45 (m, 6 H), 7.62-7.72 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.1 (s), 26.9 (q), 33.8 (t), 34.0 (t), 37.5 (t), 37.76 (d), 37.84 (d), 45.0 (d), 49.4 (d), 49.7 (s), 51.8 (t), 57.6 (q), 59.1 (q), 60.3.(t), 60.4 (t), 62.4 (t), 66.1 (t), 67.0 (t), 71.8 (t), 95.6 (s), 102.1 (t), 108.8 (d), 113.3 (t), 126.8 (d), 127.7 (d), 129.64 (d), 129.66 (d), 133.8 (s), 135.62 (d), 135.64 (d), 142.4 (s), 146.3 (s); exact mass (electrospray) *m*/*z* calcd for $C_{40}H_{56}NaO_8Si$ (M + Na) 715.3637, found 715.3628.

{[(1*S*,5*R*,6*R*,9*S*,12*R*,13*R*,15*R*)-*rel*-9-{2-[*(tert*-butyldimethylsilyl)oxy]-ethyl}-15-methoxy-6-{2-[(2-methoxyethoxy)methoxy]ethyl}-11-methylidene-2,14-dioxatetracyclo[7.4.2.0^{1,8}.0^{5,13}]pentadec-7-en-12-yl]methoxy}triethyl-silane (66.1).



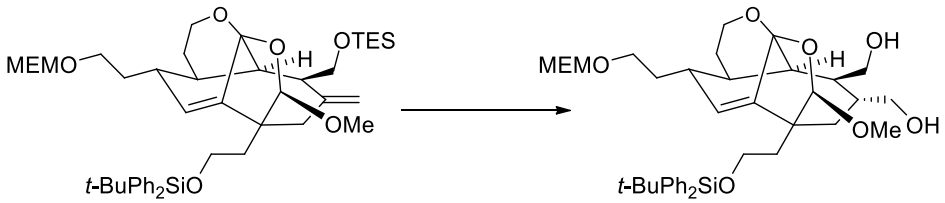
58.2 **66.1**

2,6-Lutidine (28 μL, 0.24 mmol, 4 equiv), followed by $Et_3SiOSO_2CF_3$ (26 μL, 0.12 mmol, 2 equiv) were added at room temperature to a stirred solution of a mixture of the two alcohols (i.e. **58.2** and **59.1**) in CH_2Cl_2 (9 mL). Stirring was continued for 3 h and the mixture was then quenched with water and extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated. Preparative TLC over silica gel (5 x 10 x cm, 0.25 mm thick), using 4:1 hexane-EtOAc, gave **66.1** as a single isomer (36 mg, 77% over two steps) and **66.2** (11 mg, 21%). Compound **66.1** had: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.62 (q, *J* = 10.0 Hz, 6 H), 0.97 (t, *J* = 10.0 Hz, 9 H), 1.08 (s, 9 H), 1.42-1.74 (m, 3 H), 1.78-1.90 (m, 5 H), 2.0-2.12 (m, 1 H), 2.25 (t, *J* = 7.5 Hz, 1 H), 2.35-2.42 (m, 1 H), 2.53 (s, 1 H), 2.77 (d, *J* = 12.5 Hz, 1 H), 3.40 (s, 3 H), 3.43 (s, 3 H), 3.55-3.62 (m, 2 H), 3.62-3.68 (m, 3 H), 3.69-3.75 (m 2 H), 3.75-3.88 (m, 4 H), 4.65 (s, 1 H), 4.74 (s, 1 H), 4.76 (s, 2 H), 5.13 (s, 1 H), 5.43 (s, 1 H), 7.35-7.45 (m, 6 H), 7.62-7.72 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 4.3 (t), 6.8 (q), 19.1 (s), 26.9 (q), 33.9 (t), 34.0 (t), 37.55 (d) (two carbons), 37.60 (t), 47.0 (d), 47.5 (d), 50.33 (s), 51.7 (t), 57.6 (q), 59.1 (q), 60.39.(t), 60.44 (t), 66.11 (t), 66.14 (t), 66.9 (t), 71.8 (t), 95.6 (s), 102.6 (t), 108.8 (d), 113.4 (t), 127.0 (d), 127.69 (d), 127.72 (d), 129.61 (d), 129.64 (d), 133.8 (s), 135.63 (d), 135.65 (d), 142.6 (s), 147.1 (s); exact mass (electrospray) *m*/*z* calcd for $C_{46}H_{70}NaO_8Si_2$ (M + Na) 829.4501, found 829.4486.

Compound **66.2** had: exact mass (electrospray) *m*/*z* calcd for $C_{45}H_{68}NaO_8Si_2$ (M + Na) 815.4345, found 815.4331.

When the experiment was done without prior removal of **66.3**, the yield of **66.2** was 13%.

[(1*S*,5*R*,6*R*,9*S*,11*R*,12*S*,13*R*,15*R*)-*rel*-9-{2-[(*tert*-Butyldimethylsilyl)-oxy]ethyl}-11-(hydroxymethyl)-15-methoxy-6-{2-[(2-methoxyethoxy)-methoxy]ethyl}-2,14-dioxatetracyclo[7.4.2.0^{1,8}.0^{5,13}]pentadec-7-en-12-yl]methanol (68.1).



66.1 **68.1**

$BH_3.SMe_2$ (10 M solution in THF, 1.5 μL, 0.015 mmol) was added to a stirred solution of **66.1** (10 mg, 0.012 mmol) in THF (1 mL) at room temperature. The mixture was stirred for 1 h and was then quenched by sequential addition of EtOH (10 μL), aqueous NaOH (2 *N*, 20 μL) and H_2O_2 (30%, 20 μL, 0.23 mmol). The mixture was stirred for an additional 20 min and then diluted with water and extracted with EtOAc (3 x 3 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Preparative TLC (silica plate, 5 x 7 cm, 0.25 mm thick), using 5% MeOH-EtOAc, gave **68.1** (7 mg, 78%) as a colorless oil: FTIR (cast film) 3348, 3071, 3049, 2928, 2857, 1735, 1653, 1589, 1544, 1471, 1451, 1428, 1390, 1363, 1243, 1218, 1157, 1112, 1045 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.08 (s, 9 H), 1.42-1.74 (m, 3 H), 1.78-1.90 (m, 5 H), 2.0-2.12 (m, 2 H),

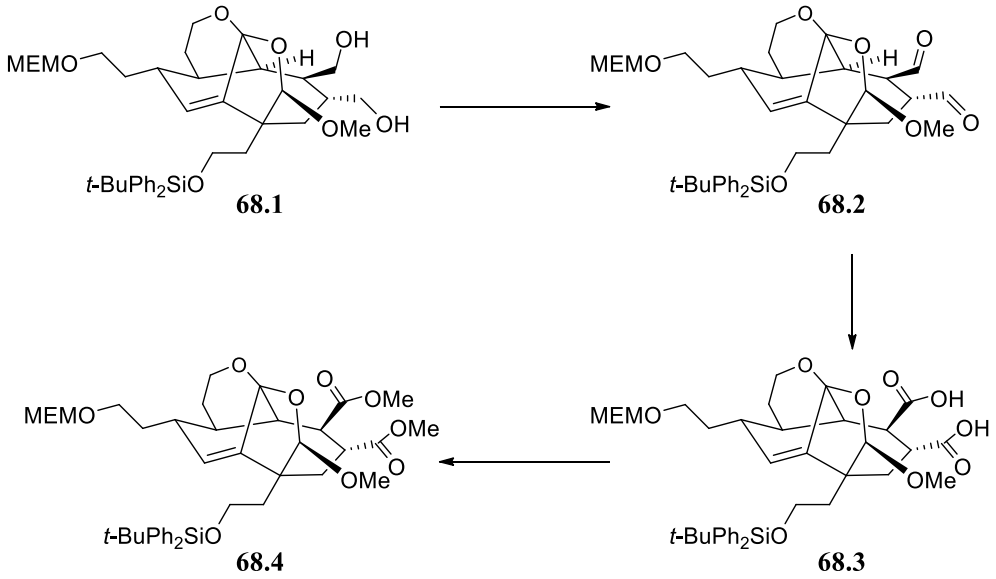
2.19 (br s, 1 H), 2.25 (d, J = 10.8 Hz, 2 H), 3.42 (s, 3 H), 3.45 (s, 3 H), 3.52 (s, 1 H), 3.55-3.62 (m, 2 H), 3.62-3.69 (m, 4 H), 3.69-3.75 (m 5 H), 3.75-3.88 (m 2 H), 3.9 (br s, 2 H), 4.75 (s, 2 H), 5.10 (s, 1 H), 5.33 (s, 1 H), 7.35-7.45 (m, 6 H), 7.62-7.72 (m, 4 H); exact mass (electrospray) m/z calcd for $C_{40}H_{58}NaO_9Si$ (M + Na) 733.3742, found 733.3733.

In a subsequent experiment starting with 12 mg of **66.1**, the yield of **68.1** was 81%.

(1*S*,5*R*,6*R*,9*S*,11*R*,12*S*,13*R*,15*R*)-*rel*-9-{2-[(*tert*-Butyldimethylsilyl)oxy]-ethyl}-15-methoxy-6-{2-[(2-methoxyethoxy)methoxy]ethyl}-2,14-dioxatetra-cyclo[7.4.2.0^{1,8}.0^{5,13}]pentadec-7-ene-11,12-dicarbaldehyde (68.2);

(1*S*,5*R*,6*R*,9*S*,11*R*,12*R*,13*R*,15*R*)-*rel*-9-{2-[(*tert*Butyldimethylsilyl)oxy]-ethyl}-15-methoxy-6-{2-[(2-methoxyethoxy)methoxy]ethyl}-2,14-dioxatetra-cyclo[7.4.2.0^{1,8}.0^{5,13}]pentadec-7-ene-11,12-dicarboxylic acid (68.3);

11,12-Dimethyl (1*S*,5*R*,6*R*,9*S*,11*R*,12*R*,13*R*,15*R*)-*rel*-9-{2-[(*tert*-Butyl-dimethylsilyl)oxy]ethyl}-15-methoxy-6-{2-[(2-methoxyethoxy)methoxy]-ethyl}-2,14-dioxatetracyclo[7.4.2.0^{1,8}.0^{5,13}]pentadec-7-ene-11,12-dicarboxylate (68.4).



(1*S*,5*R*,6*R*,9*S*,11*R*,12*S*,13*R*,15*R*)-*rel*-9-{2-[(*tert*-Butyldimethylsilyl)oxy]-ethyl}-15-methoxy-6-{2-[(2-methoxyethoxy)methoxy]ethyl}-2,14-dioxatetra-cyclo[7.4.2.0^{1,8}.0^{5,13}]pentadec-7-ene-11,12-dicarbaldehyde (68.2).

Dry DMSO (6 μL, 0.08 mmol) was added to a stirred and cooled (-78 °C) solution of $(COCl)_2$ (5 μL, 0.06 mmol) in dry CH_2Cl_2 (0.5 mL). After 30 min a solution of **66.1** (7 mg, 0.01 mmol) in CH_2Cl_2 (0.6 mL) was added dropwise, and stirring was continued at -78 °C for 1 h. Dry Et_3N (18 μL, 0.12 mmol) was then added dropwise and the cold bath was removed and stirring was continued for 30 min. The mixture was then poured into water (3 mL) in a separatory funnel and extracted with CH_2Cl_2 (2 x 2.5 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to give **68.2** which showed a nominal mass of 729.3 in its mass spectrum (electrospray) and two aldehyde hydrogen signals at δ 9.48 and 9.76 ppm in its ^{1}H NMR spectrum. This crude material was taken forward as it was not stable to chromatography.

(1*S*,5*R*,6*R*,9*S*,11*R*,12*R*,13*R*,15*R*)-*rel*-9-{2-[(*tert*-Butyldimethylsilyl)-oxy]ethyl}-15-methoxy-6-{2-[(2-methoxyethoxy)methoxy]ethyl}-2,14-dioxa-tetracyclo[7.4.2.0^{1,8}.0^{5,13}]pentadec-7-ene-11,12-dicarboxylic acid (68.3).

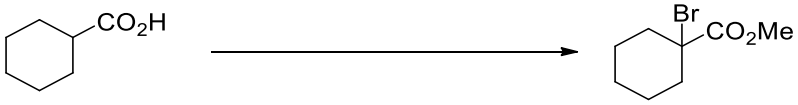
An aliquot (50 μL, 0.04 mmol $NaClO_2$) from a stock solution made up of $NaClO_2$ (1.0 g, 8.8 mmol) and $NaHPO_4$ (1 g) in water (10 mL) was added to a stirred solution of crude **68.2** (7 mg, 0.01 mmol) in *t*-BuOH (0.65 mL) and 2-methyl-2-butene (0.15 mL) (protection from light) at room temperature. The mixture was stirred overnight by which time TLC (silica, EtOAc) showed the consumption of **68.2**. The reaction mixture was diluted with water and acidified to *p*H = 2-3 (*p*H paper), and the aqueous phase was saturated with salt and extracted with EtOAc (5 x 4 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to give **68.3**: exact mass (electrospray) *m*/*z* calcd for $C_{40}H_{53}O_{11}Si$ (M - H) 737.3363, found 737.3363.

11,12-Dimethyl (1*S*,5*R*,6*R*,9*S*,11*R*,12*R*,13*R*,15*R*)-*rel*-9-{2-[(*tert*-Butyl-dimethylsilyl)oxy]ethyl}-15-methoxy-6-{2-[(2-methoxyethoxy)methoxy]-ethyl}-2,14-dioxatetra-cyclo[7.4.2.0^{1,8}.0^{5,13}]pentadec-7-ene-11,12-dicarboxylate (68.4).

CH_2N_2 was bubbled into a solution of crude **68.3** in Et_2O (2 mL) at 0 °C until the solution turned yellow (fumehood). The ice bath was then removed and the reaction mixture left open to allow the excess of CH_2N_2 to evaporate. Water was added and the aqueous phase was extracted with EtOAc (3 x 4 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated and the residue was purified by preparative TLC on a silica plate (2.5 x 7 cm, 0.25 mm thick), using 2:1 EtOAc-hexane, to give **68.4** (5 mg, 66% over three steps): ^{1}H NMR

($CDCl_3$, 500 MHz) δ 1.08 (s, 9 H), 1.48-1.54 (m, 1 H), 1.60-1.84 (m, 4 H), 1.95-2.06 (m, 2 H), 2.12 (dd, *J* = 7.9, 3.1 Hz, 1 H), 2.20-2.32 (m, 1 H), 2.34-2.42 (m, 1 H), 2.85-290 (m, 1 H), 3.37 (s, 3 H), 3.42 (s, 3 H), 3.45-3.52 (m, 1 H), 3.55-3.62 (m, 2 H), 3.62-3.68 (m including a singlet for MeO, 5 H in all), 3.69 (s, 3 H), 3.70-3.82 (m 5 H), 3.82-3.92 (m 2 H), 4.75 (s, 2 H), 5.03 (s, 1 H), 5.37 (s, 1 H), 7.39-7.49 (m, 6 H), 7.65-7.78 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.1 (s), 26.9 (q), 33.2 (t), 33.7 (t), 37.16 (d), 37.19 (d), 38.1 (t), 39.1 (d), 40.0 (t), 45.6 (d), 46.9 (d), 51.3 (t), 51.4 (q), 52.1 (q), 57.4 (q), 59.1 (q), 60.1.(t), 60.5 (t), 65.9 (t), 67.0 (t), 71.8 (t), 95.6 (s), 101.7 (t), 107.5 (d), 125.0 (d), 127.67 (d), 127.68 (d), 127.72 (d), 129.64 (d), 129.66 (d), 133.7 (s), 133.8 (s), 142.0 (s), 172.4 (s), 173.7 (s); exact mass (electrospray) *m*/*z* calcd for $C_{42}H_{58}NaO_{11}Si$ (M + Na) 789.3641, found 7789.3625.

Methyl 1-bromocyclohexane-1-carboxylate (41.2).[38a]

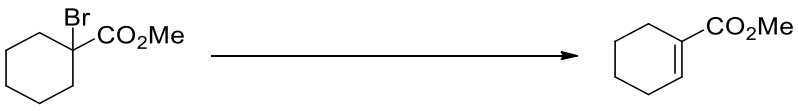


41.1 **41.2**

$SOCl_2$ (6.83 mL, 93.6 mmol) was added dropwise from an addition funnel to stirred cyclohexanecarboxylic acid (10 g, 78.02 mmol) contained in a three-necked 100 mL, round-bottomed flask equipped with a condenser closed with a drying tube (Drierite). The mixture was heated at 85 °C for 2 h and then cooled to room temperature. Red phosphorus (120 mg, 4 mmol) was added and the mixture was warmed to 85 °C and bromine (4.8 mL, 93.6 mmol) was added through the addition funnel over 20 min. The mixture was stirred at 85 °C for 4 h and then cooled to 0 °C. Dry MeOH (15.8 mL, 390 mmol) was added dropwise over 20

min. After the addition the mixture was heated to reflux for 30 min and then cooled to room temperature. The mixture was poured into ice-water (35 mL) and extracted with Et_2O (4 x 30 mL). The combined organic extracts were washed with aqueous $Na_2S_2O_3$ (1 M, 40 mL), saturated aqueous $NaHCO_3$ (40 mL) and brine (40 mL), dried ($MgSO_4$) and evaporated to give crude **41.2** (15.35 g, 91%) which was used without further purification.

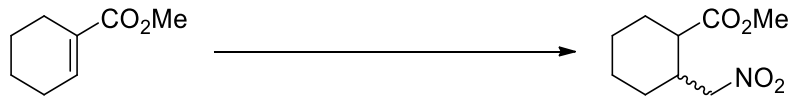
Methyl cyclohex-1-ene-1-carboxylate (41.3).[38b]



41.2 **41.3**

Quinoline (13.13 mL, 111.1 mmol) was added to crude **41.2** (15.348 g, 69 mmol) at room temperature. The mixture was then refluxed at 120 °C overnight and cooled to room temperature. Hydrochloric acid (6 M, 78 mL) was added and the mixture was extracted with Et_2O (4 x 20 mL). The combined organic extracts were washed with hydrochloric acid (3 M, 20 mL), saturated aqueous $NaHCO_3$ (20 mL) and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (6 x 15 cm), using 4:1 hexane-EtOAc, gave **41.3** (8.56 g, 88 %) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.58-1.67 (m, 4 H), 2.15-2.28 (m, 4 H), 3.73 (s, 3 H), 6.94-7.02 (m, 1 H).

Methyl 2-(nitromethyl)cyclohexane-1-carboxylate (41.4).

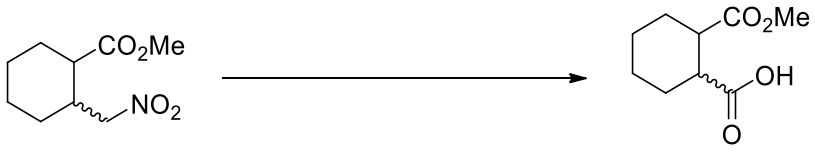


41.3 **41.4**

$MeNO_2$ (2.48 mL, 45.8 mmol) and Bu_4NF (1 M in THF, 690 μL, 0.069 mmol) were added to a stirred solution of methyl 1-cyclohexenecarboxylate (**41.3**) (320 mg, 2.29 mmol) in THF (15 mL) and the mixture was refluxed for 22 h. At this time TLC analysis (silica, 6:1 hexane-EtOAc) indicated that the starting material was completely consumed, and the mixture was then evaporated. Flash chromatography of the residue over silica gel (1.5 x 15 cm), using 6:1 hexane-EtOAc, gave two partially separable stereoisomers (2:1) of **41.4** (414 mg, 90%) as a colorless liquid. Only one of the isomers could be separated completely and had: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.3-1.59 (m, 4 H), 1.60-1.74 (m, 3 H), 1.84-1.96 (m, 1 H), 2.48-2.62 (m, 1 H), 2.2.68-2.78 (m, 1 H), 3.66 (s, 3 H), 4.47 (ddd, *J* = 12.44, 7.98, 1.9 Hz, 1 H), 4.54 (ddd, *J* = 12.52, 6.59, 2.34 Hz, 1 H).

A subsequent experiment starting with 1 g of **41.3** gave **41.4** in 98% yield.

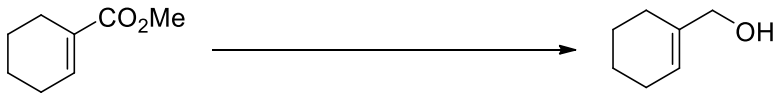
2-(Methoxycarbonyl)cyclohexane-1-carboxylic acid (42.1).



41.4 **42.1**

AcOH (212 μL, 3.71 mmol) was added to a stirred solution of **41.4** (isomer mixture) (74.5 mg, 0.371 mmol) and $NaNO_2$ (0.077 g, 1.11 mmol) in dry DMSO (1.5 mL). The reaction mixture was stirred at 40 °C for 8 h and then diluted with water (30 mL), acidified with hydrochloric acid (3 *N*) to below *p*H 2. The resulting mixture was extracted with Et_2O (5 x 30 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 1:1 hexane-EtOAc, gave **42.1** (56 mg, 81%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.36-1.64 (m, 4 H), 1.72-1.88 (m, 2 H), 1.96-2.10 (m, 2 H), 2.80-2.92 (m, 2 H), 3.79 (s, 3 H), 10.2-10.8 (br s, 1 H).

Cyclohex-1-en-1-ylmethanol (48.1).

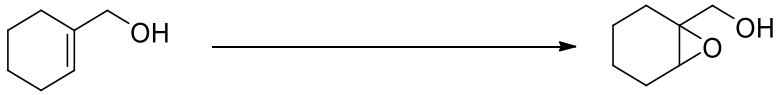


41.3 **48.1**

DIBAL-H (1 M solution in PhMe, 21.4 mL, 21.4 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of **41.3** (1 g, 7.14 mmol) in THF (30 mL). The mixture was stirred at -78 °C for 1 h, the cooling bath was replaced by an ice bath and stirring was continued for 30 min. The mixture was quenched by addition of $Na_2SO_4.10H_2O$ (10 g). The mixture was diluted with Et_2O (30 mL), stirred for 3 h, filtered and evaporated. Flash chromatography of the residue over silica gel (2.5 x 15), using 1:1 hexane-EtOAc, gave **48.1** (770 mg, 96%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.54-1.62 (m, 2 H), 1.62-1.70 (m, 2 H), 1.98-2.08 (m, 4 H), 3.99 (s, 2 H), 5.71-5.77 (m, 1 H); ^{13}C NMR

($CDCl_3$, 125 MHz) δ 22.4 (t), 22.5 (t), 24.9 (t), 25.6 (t), 67.7 (t), 123.0 (d), 137.6 (s).

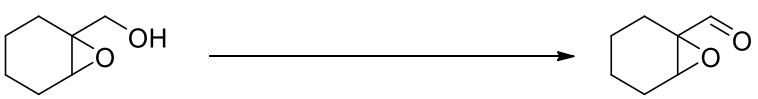
7-Oxabicyclo[4.1.0]heptan-1-ylmethanol (48.2).[52]



48.1 **48.2**

m-CPBA (75%w/w, 2.64 g, 12.63 mmol) was added to a stirred solution of **48.1** (800 mg, 7.14 mmol) in CH_2Cl_2 (77 mL) at room temperature. Stirring was continued for 16 h and the mixture was diluted with water (40 mL) and extracted with EtOAc (3 x 30 mL). The combined organic extracts were washed with aqueous NaOH (1 M, 2 x 20 mL), and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 1:1 EtOAc-hexane, gave **48.2** (804 mg, 88%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.16-1.3 (m, 2 H), 1.32-1.50 (m, 2 H), 1.58-1.71 (m, 1 H), 1.71-1.85 (m, 2 H), 1.85-1.96 (m, 1 H), 3.18 (d, *J* = 6.0 Hz, 1 H), 3.52 (d, *J* = 12.0 Hz, 1 H), 3.63 (d, *J* = 12.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.2 (t), 19.4 (t), 24.0 (t), 24.8 (t), 55.5 (d), 59.9 (s), 64.3 (t).

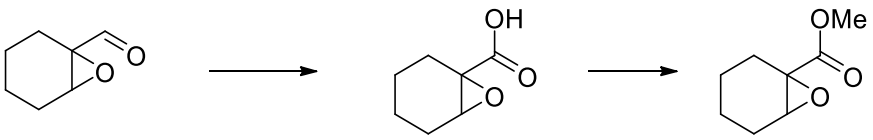
7-Oxabicyclo[4.1.0]heptane-1-carbaldehyde (48.3).[53]



48.2 **48.3**

Pr_4NRuO_4 (48 mg, 0.12 mmol) was added to a mixture of **48.2** (354 mg, 2.53 mmol), NMO (472 mg, 4 mmol) and powdered molecular sieves (4Å, 1 g) in dry MeCN (11.8 mL) at room temperature. The mixture was stirred for 30 min and passed through a pad of silica gel (3 x 3 cm), using 1:1 EtOAc-hexane as a rinse. Evaporation of the filtrate gave the crude epoxy aldehyde **48.3** which was used without further purification: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.16-1.3 (m, 1 H), 1.32-1.61 (m, 3 H), 1.62-1.76 (m, 1 H), 1.78-1.92 (m, 1 H), 2.08-2.22 (m, 1 H), 2.4-2.54 (m, 1 H), 3.42 (d, J = 6.0 Hz, 1 H), 8.86 (s, 1 H).

7-Oxabicyclo[4.1.0]heptane-1-carboxylic acid (48.4);[54] **Methyl 7-oxabicyclo[4.1.0]heptane-1-carboxylate (48.5).**[55]

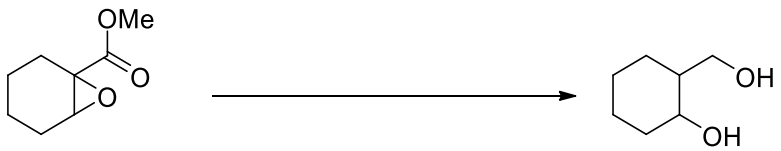


48.3 **48.4** **48.5**

An aliquot (11.7 mL, 12 mmol $NaClO_2$) from a stock solution made up of $NaClO_2$ (1.096 g, 8.8 mmol) and $NaHPO_4$ (926 mg) in water (11.7 mL) was added to a stirred solution of crude **48.3** (170 mg, 1.35 mmol) in *t*-BuOH (6.4 mL) and 2-methyl-2-butene (6.4 mL) (protection from light) at room temperature. The mixture was stirred overnight by which time TLC (silica, 1:1 hexane-EtOAc) showed consumption of **48.3**. The reaction mixture was diluted with water and acidified to *p*H 2-3 (*p*H paper). The aqueous phase was saturated with NaCl and extracted with EtOAc (5 x 4 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to give **48.4** (138 mg, 72 %) which was used without any further purification. CH_2N_2 was bubbled into a cooled (0 °C) solution of

crude **48.4** in Et_2O (5 mL) until the solution turned yellow (fumehood). The ice bath was then removed and the reaction mixture was left open to allow the excess of CH_2N_2 to evaporate. Water was added and the aqueous phase was extracted with EtOAc (3 x 4 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 15), using 1:1 hexane-EtOAc, gave **48.5** (136 mg, 80%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.24-1.42 (m, 2 H), 1.42-1.54 (m, 2 H), 1.84-2.41 (m, 3 H), 2.38-2.48 (m, 1 H), 3.89 (d, *J* = 6.0 Hz, 1 H), 3.75 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ18.9 (t), 19.2 (t), 23.8 (t), 24.0 (t), 52.4 (d), 57.9 (q), 72.1 (s), 171.7 (s).

2-(Hydroxymethyl)cyclohexan-1-ol (48.7).[43]

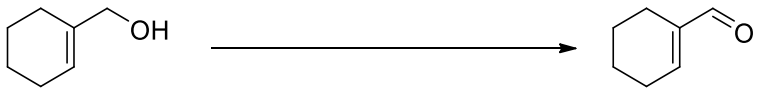


48.5 **48.7**

Liquid NH_3 (21 mL, dried over Na at -78 °C) was condensed into a premarked flask containing Li (10 mg, 3.33 mmol) and fitted with a cold finger condenser packed with dry ice. A solution of **48.5** (50 mg, 0.32 mmol) in THF (2.8 mL) was added very quickly to the resulting blue solution and, after 1 min, the mixture was quenched by addition of NH_4Cl. The cooling bath was removed to allow the excess of NH_3 to evaporate. The mixture was then diluted with water (5 mL) and extracted with Et_2O (3 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (Pasteur pipette, 8 cm), using EtOAc, gave **48.7** (35 mg, 75%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.18-138 (m, 3 H), 1.38-1.54 (m, 2 H), 1.44-1.70 (m, 3 H),

1.70-1.84 (m, 1 H), 2.4-2.7 (br s, 1 H), 2.92-3.3 (br s, 1 H), 3.61-3.69 (m, 1 H), 3.71-3.76 (m, 1 H), 4.02-4.06 (m, 1 H); exact mass (electrospray) *m*/*z* calcd for $C_7H_{14}NaO_2$ (M + Na) 153.0886, found 153.0887.

Cyclohex-1-ene-1-carbaldehyde (50.1).

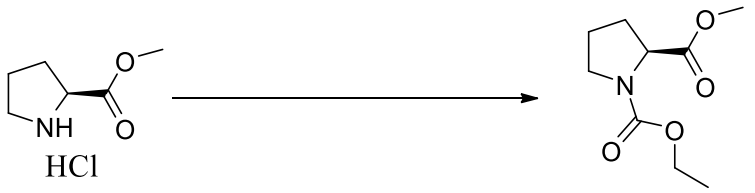


48.1 **50.1**

Et_3N (0.36 mL, 4.6 mmol) and SO_3.py (575 mg, 3.66 mmol) were added to a stirred solution of **48.1** (100 mg, 0.92 mmol) in a mixture of CH_2Cl_2 (8 mL) and DMSO (4 mL) at room temperature. Stirring was continued for 1 h and the mixture was quenched with water (100 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (0.5 x 15 cm), using 4:1 hexane-EtOAc, gave **50.1** (76 mg, 77%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.54-1.72 (m, 4 H), 2.07-2.22 (m, 2 H), 2.22-2.44 (m, 2 H), 6.75-6.81 (m, 1 H), 9.35 (s, 1 H).

A subsequent experiment starting with 661 mg of **48.1** gave **50.1** in 88% yield.

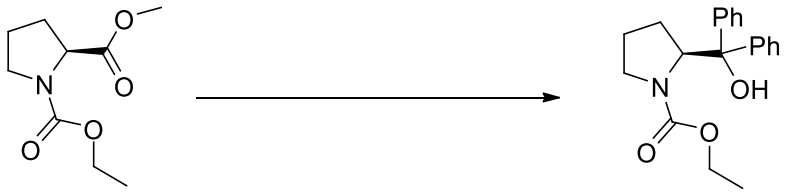
1-Ethyl 2-methyl (2*S*)-pyrrolidine-1,2-dicarboxylate (51.2).[45]



51.1 **51.2**

Et_3N (0.17 mL, 1.2 mmol), followed by EtOCOCl (0.14 mL, 1.45 mmol), were added to a stirred and cooled (0 °C) solution of **51.1** (200 mg, 1.2 mmol) in CH_2Cl_2 (3 mL). The ice bath was removed after the addition and stirring was continued for 40 min. The mixture was quenched with water (5 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (0.5 x 15 cm), using 4:1 hexane-EtOAc, gave **51.2** (200 mg, 82%) as a colorless oil (two rotamers): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.10-1.35 (m, 3 H), 1.75-2.05 (m, 3 H), 2.05-2.32 (m, 1 H), 3.33-3.63 (m, 2 H), 3.64 (s, 3 H), 4.02-4.31 (m, 2 H), 4.37 and 4.42 (two dd, J = 7.2, 4.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) (mixture of rotamers) δ 14.6 (q), 23.5 (24.3) (t), 29.9 (30.9) (t), 46.3 (46.7) (t), 52.0 (52.1) (q), 58.8 (59.0) (d), 61.1 (61.2) (t), 154.5 (155.0) (s), 173.2 (173.3) (s).

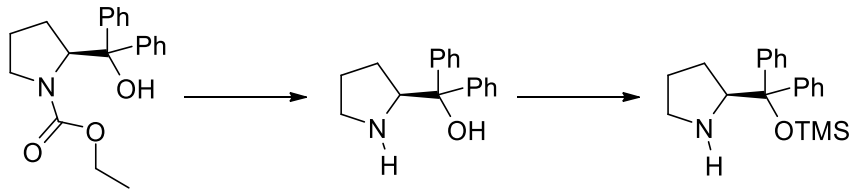
Ethyl (2*S*)-2-(hydroxydiphenylmethyl)pyrrolidine-1-carboxylate (51.3).[45]



51.2 **51.3**

PhMgCl (2 M in THF, 2 mL, 4 mmol) was added dropwise over 15 min to a stirred and cooled (0 °C) solution of **51.2** (200 mg, 1 mmol) in THF (2 mL). Stirring at 0 °C was continued for 5 h and the mixture was then quenched with saturated aqueous NH_4Cl (1 mL), diluted with water and extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 4:1 hexane-EtOAc, gave **51.3** (237 mg, 73%) as an oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.71-0.92 (br s, 1 H), 1.22 (t, *J* = 10.9 Hz, 3 H), 1.42-1.58 (m, 1 H), 1.91-2.02 (m, 1 H), 2.07-2.18 (m, 1 H), 2.89-3.06 (m, 1 H), 3.43 (q, *J* = 9.2 Hz, 1 H), 4.12 (q, *J* = 10.9 Hz, 1 H), 4.94 (dd, *J* = 11.5, 4.6 Hz, 1 H), 7.21-7.45 (m, 10 H).

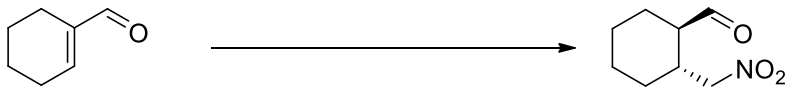
(2*S*)-Diphenyl(pyrrolidin-2-yl)methanol (51.4) and (2*S*)-2-{Diphenyl-[(trimethylsilyl)oxy]methyl}pyrrolidine (51.5).[45]



51.3 **51.4** **51.5**

KOH (300 mg, 5.37 mmol) was added to a solution of **51.3** (160 mg, 0.49 mmol) in MeOH (2 mL) and the mixture was refluxed for 4 h, cooled to room temperature and evaporated. The residue was diluted with water and extracted with EtOAc (4 x 5 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated to give crude **51.4** which was recrystallized from hexane. The resulting crystals (130 mg, 0.49 mmol) were dissolved in CH_2Cl_2 (4 mL) and cooled to 0 °C, and $Me_3SiOSO_2CF_3$ (0.13 mL, 0.73 mmol) was added dropwise. The ice bath was left in place but not recharged and stirring was continued for 8 h. The mixture was quenched with water (5 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (0.5 x 15 cm), using 4:1 hexane-EtOAc, gave **51.5** (167 mg, 92% over two steps) as a dark yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ -0.1 (s, 9 H), 1.40-1.61 (m, 1 H), 1.82-2.15 (m, 2 H), 2.25-2.42 (m, 1 H), 2.61-2.82 (m, 1 H), 3.1-3.33 (m, 1 H), 4.72-4.88 (dd, *J* = 10.0, 6.7 Hz, 1 H), 7.21-7.5 (m, 10 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 1.6 (q), 24.1 (t), 27.0 (t), 47.0 (t), 67.3 (d), 81.7 (s), 128.18 (t), 128.23 (t), 128.5 (t), 128.56 (t), 128.60 (t), 128.7 (t), 140.9 (s), 141.8 (s); exact mass (electrospray) *m*/*z* calcd for $C_{20}H_{28}NaOSi$ (M + Na) 326.1935, found 326.1941.

(1*R*,2*R*)-*rel*-2-(Nitromethyl)cyclohexane-1-carbaldehyde (52.1).[56]



50.1 **52.1**

$MeNO_2$ (50 μL, 0.9 mmol) followed by (2*S*)-2-{diphenyl-[(trimethylsilyl)oxy]methyl}pyrrolidine **(51.5)** (30 mg, 30% mmol) and AcOLi

(11 mg, 0.03 mmol) were added to a solution of **50.1** (33 mg, 0.3 mmol) in 9:1 CH_2Cl_2-MeOH (0.8 mL) at room temperature. Stirring was continued for 24 h and the mixture was diluted with water and extracted with CH_2Cl_2 (4 x 3 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (Pasteur pipette, 7 cm), using hexane-EtOAc, gave **52.1** (48 mg, 94%) which was a 6:1 mixture of diastereoisomers in favour of the *trans* compound: FTIR (cast film on the mixture) 2935, 2859, 1722, 1647, 1551, 1526, 1449, 1382, 1352, 1238; ^{1}H NMR ($CDCl_3$, 500 MHz) (major isomer signals) δ 1.15-1.42 (m, 4 H), 1.72-1.80 (m, 1 H), 1.81-1.92 (m, 2 H), 2.06-2.12 (m, 1 H), 2.24-2.34 (m, 1 H), 2.38-2.48 (m, 1 H), 4.35 (dd, *J* = 11.9, 7.7 Hz, 1 H), 4.53 (dd, *J* = 11.9, 4.4 Hz, 1 H), 9.61 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) (major isomer signals) δ 24.5 (t), 24.8 (t), 25.9 (t),28.5 (t), 35.1 (d), 51.4 (d), 78.9 (t), 202.3 (d).

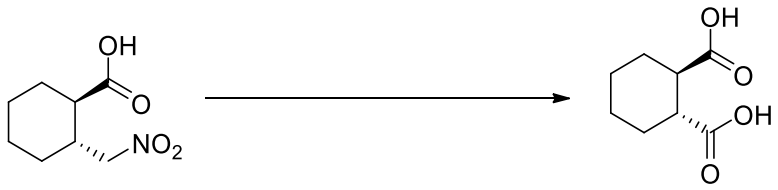
(1*R*,2*R*)-*rel*-2-(Nitromethyl)cyclohexane-1-carboxylic acid (52.2).[56]

52.1 **52.2**

PDC (34 mg, 0.09 mmol) was added to a stirred solution of **52.1** (10 mg, 0.06 mmol) in DMF (0.3 mL) at room temperature. Stirring was continued overnight and the mixture was diluted with water (2 mL) and extracted with EtOAc (4 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Preparative TLC (silica gel, 5 x 5 cm x 0.25 mm thick) of the residue, using EtOAc, gave **52.2** (9 mg, 85%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ

1.15-1.42 (m, 3 H), 1.46-1.62 (m, 1 H), 1.72-1.92 (m, 3 H), 2.06-2.15 (m, 1 H), 2.78 (dt, *J* = 12.0, 3.8 Hz, 1 H), 2.34-2.48 (m, 1 H), 4.35 (dd, *J* = 11.5, 7.5 Hz, 1 H), 4.53 (dd, *J* = 11.3, 3.8 Hz, 1 H), 9.61 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.7 (t), 24.9 (t), 28.8 (t), 29.8 (t), 37.3 (d), 45.5 (d), 79.5 (t), 179.7 (s); exact mass (electrospray) *m*/*z* calcd for $C_8H_{12}NO_4$ (M - H) 186.0772, found 186.0776.

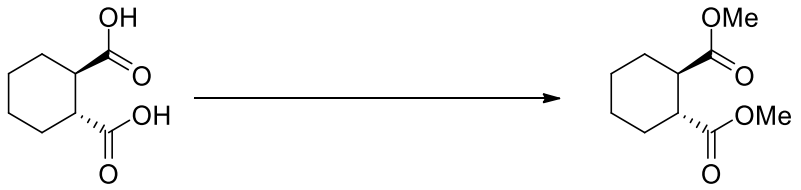
(1*R*,2*R*)-*rel*-Cyclohexane-1,2-dicarboxylic acid (52.3).



52.2 **52.3**

$NaNO_2$ (22 mg, 0.32 mmol) and AcOH (63 μL, 1.1 mmol) were added to a stirred solution of **52.2** (20 mg, 0.11 mmol) in dry DMSO (0.44 mL) and the mixture was heated at 40 °C for 8 h, cooled, quenched with water (10 mL) and extracted with Et_2O (5 x 8 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. The residue had low resolution (electrospray) *m*/*z* 171.1 for $C_8H_{11}O_4$ (M - H) (**52.3**) and the crude material was taken forward for esterification without any further purification.

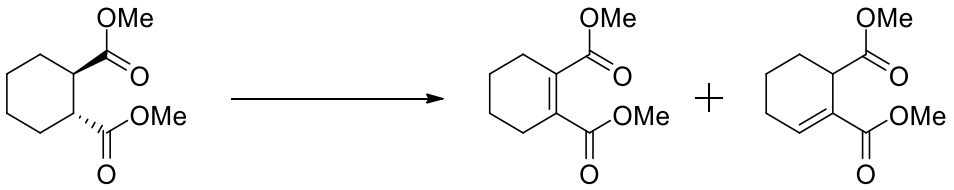
1,2-Dimethyl (1*R*,2*R*)-*rel*-cyclohexane-1,2-dicarboxylate (52.4).



52.3 **52.4**

CH_2N_2 was bubbled into a cooled (0 °C) solution of crude **52.3** (130 mg, 0.75 mmol) in Et_2O (5 mL) until the solution turned yellow (fumehood). The ice bath was then removed and the reaction mixture was left open to allow the excess of CH_2N_2 to evaporate. Water was added and the aqueous phase was extracted with EtOAc (3 x 4 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 15), using 1:1 hexane-EtOAc, gave **52.4** (151 mg, 75%) as a yellow oil: FTIR 2940, 2861, 1737, 1553, 1436, 1323, 1254, 1195, 1171, 1115, 1043, 1009; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.24-1.42 (m, 6 H), 1.72-1.86 (m, 2 H), 2.55-2.65 (m, 2 H), 2.66 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.1 (t), 28.9 (t), 44.8 (q), 51.7 (d), 175.5 (s); exact mass (electrospray) *m*/*z* calcd for $C_{10}H_{16}NaO_4$ (M + Na) 223.0941, found 223.0943.

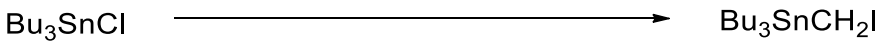
1,2-Dimethyl cyclohex-1-ene-1,2-dicarboxylate (52.6) and 1,2-Dimethyl cyclohex-2-ene-1,2-dicarboxylate (52.5).



52.4 **52.6** **52.5**

BuLi (2.5 M in THF, 0.26 mL, 0.62 mmol) was added to a stirred and cooled (-78 °C) solution of *i*-Pr_2NH (92 μL, 0.66 mmol) in THF (1.6 mL). After 40 min, a solution of **52.4** (50 mg, 0.25 mmol) in THF (4 mL) was added over 4 min and the mixture was stirred for 10 min at -78 °C. A solution of I_2 (507.8 mg, 0.5 mmol) in THF (1.5 mL) was then added dropwise at -78 °C, and after the addition the mixture was quenched with saturated aqueous NH_4Cl and extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (Pasteur pipette, 7 cm), using 4:1 hexane-EtOAc, gave a 3:2 mixture (75% yield) of **52.6** and **52.5**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ (major isomer signals) 1.42-1.64 (m, 4 H), 2.21-2.37 (m, 4 H), 3.75 (s, 6 H); ^{13}C NMR ($CDCl_3$, 100 MHz) (major isomer signals) δ 21.2 (t), 26.2 (t), 52.1 (q), 135.3 (s), 169.0 (s).

Tributyl(iodomethyl)stannane (56.2).[49]

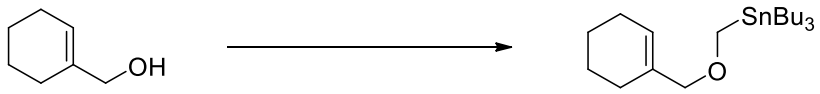


56.1 **56.2**

$Cu(OAc)_2.H_2O$ (126 mg, 0.63 mmol) was heated in AcOH (3.7 mL) to 100 °C and zinc dust (2.2 g, 33 mmol) was added to the stirred mixture. After 2 min the solvent was decanted and fresh AcOH (3.7 mL) was added and decanted

again. The solid was then washed three times with Et_2O (10 mL) (no attempt was made to first cool the mixture) and the solvent was decanted. The residue was dried for 40 min at 120 °C under oilpump vacuum, and eventually the flask was filled with N_2. THF (18 mL) then was added to the solid, followed by dropwise addition over 11 h of a solution of CH_2I_2 (9.2 g, 34.3 mmol) in THF (5.5 mL) (with protection from light). The mixture was stirred for 12 h after the addition. Bu_3SnCl (4.6 mL, 16.96 mmol) was then added dropwise and the mixture was stirred for 24 h. The mixture was diluted with Et_2O (20 mL) and washed with brine, and the organic extract was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 15 cm), using 12:1 hexane-EtOAc, gave **56.2** (4.73 g, 65%) as a colorless oil which was stored with protection from light: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.90 (t, J = 10.0 Hz, 9 H), 0.95-1.00 (m, 6 H), 1.26-1.37 (m, 6 H), 1.45-1.58 (m, 6 H), 1.94 (s, 2 H).

Tributyl[(cyclohex-1-en-1-ylmethoxy)methyl]stannane (57.1).

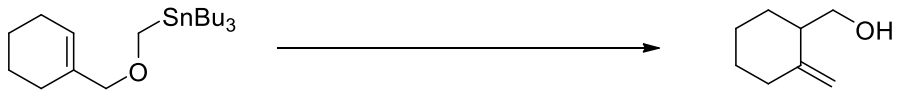


48.1 **57.1**

KH (160 mg (35%), 1.4 mmol), followed by Bu_3SnCH_2I (203 mg, 0.47 mmol), were added to a stirred and cooled (0 °C) solution of **48.1** (53 mg, 0.47 mmol) and a catalytic amount of 18-crown-6 (1 crystal) in THF (7 mL). The ice bath was removed after the addition and stirring was continued for 40 min at which time TLC (silica, 10:1 hexane-EtOAc) showed the consumption of **48.1**. The mixture was quenched with water and extracted with Et_2O (3 x 7 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash

chromatography of the residue over silica gel (1 x 15 cm), using 10:1 hexane-EtOAc, gave **57.1** (164 mg, 84%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.84-0.99 (m, 15 H), 1.24-1.37 (m, 6 H), 1.45-1.54 (m, 6 H), 1.55-1.66 (m, 4 H), 1.92-1.98 (m, 2 H), 1.99-2.08 (m, 2 H), 3.65 (s, 2 H), 3.71 (s, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 9.0 (t), 13.7 (q), 22.5 (t), 22.6 (t), 25.0 (t), 25 8 (t), 27.3 (t), 29.1 (t), 60.7 (t), 79.9 (t), 124.4 (d), 135.2 (s).

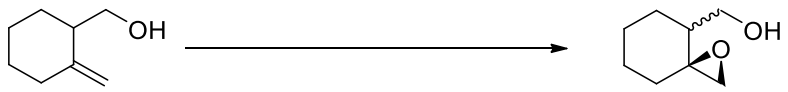
(2-Methylidenecyclohexyl)methanol (57.2).



57.1 **57.2**

BuLi (2.5 M solution in hexane, 1.5 mL, 0.39 mmol) was added to a stirred and cooled (-78 °C) solution of **57.1** (160 mg, 0.385 mmol) in hexane (50 mL). The cold bath was not recharged and was allowed to rise to 0 °C over a few h (the precise time has no effect on the outcome, but quenching must be at or below 0 °C). The mixture was quenched with water and extracted with EtOAc (3 x 15 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (Pasteur pipette, 7 cm), using 1:1 hexane-EtOAc, gave **57.2** (40 mg, 84%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.84-0.99 (m, 15 H), 1.32-1.41 (m, 1 H), 1.42-1.54 (m, 2 H), 1.55-1.66 (m, 2 H), 1.75 (ddd, *J* = 12.7, 8.4, 4.2 Hz, 1 H), 2.03-2.10 (m, 1 H), 2.15-2.21 (m, 1 H), 2.23-2.31 (m, 1 H), 3.57 (dd, *J* = 10.5, 6.0 Hz, 1 H), 3.77 (dd, *J* = 10.5, 7.9 Hz, 1 H), 4.64 (s, 1 H), 4.76 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.0 (t), 28.3 (t), 30.2 (t), 34.4 (t), 456 (d), 64.0 (t), 107.3 (t), 149.7 (s).

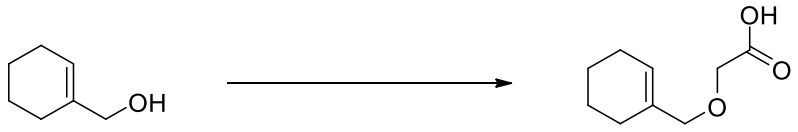
(3*R*,4*R*)-*rel*-1-Oxaspiro[2.5]octan-4-ylmethanol (57.3).



57.2 **57.3**

$VO(acac)_2$ (6 mg, 0.02 mmol) was added to a stirred solution of **57.2** (15 mg, 0.12 mmol) in PhH (6 mL). *t*-BuOOH (5.5 M in decane, 47 μL, 0.29 mmol) was added to the mixture and the color changed immediately to burgundy. Stirring was continued for 1 h and the mixture was quenched with saturated aqueous Na_2SO_3 (2 mL) and stirring was continued until the color was discharged (ca 1 h). The resulting mixture was diluted with water and extracted with EtOAc (3 x 6 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Purification of the residue by preparative TLC (silica plate, 10 x 5 cm, 0.25 mm thick), using 1:1 hexane-EtOAc, gave **57.3** (23 mg, 80%) as a colorless oil. The major isomer had: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.32-1.48 (m, 3 H), 1.62-1.91 (m, 5 H), 2.03-2.10 (m, 1 H), 2.59 (d, *J* = 4.0 Hz, 1 H m, 1 H), 2.6-2.7 (br s, 1 H), 3.05 (dd, *J* = 4.0, 2.0 Hz, 1 H), 3.34-3.42 (m, 1 H), 3.42-3.51 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.5 (t), 25.4 (t), 28.2 (t), 34.8 (t), 424 (d), 63.2 (t), 64.3 (t).

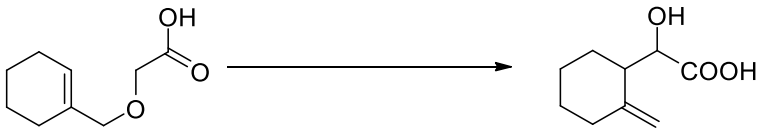
2-(Cyclohex-1-en-1-ylmethoxy)acetic acid (62.1).



48.1 **62.1**

A solution of **48.1** (169 mg, 1.5 mmol) in THF (1.7 mL) was added dropwise to a stirred and cooled (0 °C) suspension of NaH (60% in oil, 169 mg, 4.2 mmol) in THF (1.7 mL). The ice bath was removed after the addition and stirring was continued for 1 h. The mixture was then recooled to 0 °C and a solution of $BrCH_2CO_2H$ (209 mg, 1.5 mmol) in THF (1.7 mL) was added dropwise. The ice bath was removed after the addition and stirring was continued overnight. The mixture was quenched with water, acidified with 10% hydrochloric acid to *p*H 1 (*p*H paper) and extracted with EtOAc (4 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 10 cm), using EtOAc, gave **62.1** [114 mg, 75%, corrected for recovered starting material (22 mg)] as a colorless oil: FTIR (cast film) 2500-3500, 3051, 2999, 2927, 2856, 2658, 1730, 1448, 1436, 1339, 1310, 1240, 1179, 1161, 1137, 1127, 1107 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.51-162 (m, 2 H), 1.62-1.68 (m, 2 H), 1.95-2.10 (m, 4 H), 3.95 (s, 2 H), 4.06 (s, 2 H), 5.69-5.75 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.2 (t), 22.4 (t), 25.0 (t), 25.8 (t), 66.0 (t), 127.2 (d), 133.5 (s), 174.9 (s); exact mass (electrospray) *m*/*z* calcd for $C_9H_{13}O_3$ (M - H) 169.087, found 169.0872.

2-Hydroxy-2-(2-methylidenecyclohexyl)acetic acid (62.2).

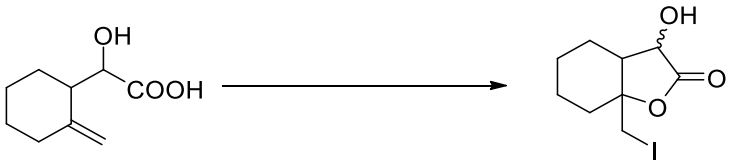


62.1 **62.2**

BuLi (2.4 M solution in THF, 4.57 mL, 10.98 mmol) was added to a stirred and cooled (0 °C) solution of *i*-Pr_2NH (1.70 mL, 11.9 mmol) and HMPA

(1.91 mL, 11 mmol) in THF (60 mL). After 7 min, the mixture was cooled to -20 °C and a solution of **62.1** (933 mg, 5.49 mmol) in THF (10 mL) was added dropwise. Stirring at -15 °C was continued for 24 h and the mixture was quenched with water and acidified with 10% hydrochloric acid to *p*H 1. The mixture was extracted with EtOAc (4 x 10 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 10 cm), using 1:1 hexane-EtOAc, gave **62.2** (727 mg, 78%) as a colorless oil (which was 4:1 mixture of isomers): FTIR (cast film) 2500-3500, 3073, 2932, 2858, 1722, 1648, 1447, 1340, 1207, 1159, 1132, 1088, 1066 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) (major isomer signals) δ 1.51-162 (m, 2 H), 1.62-1.75 (m, 3 H), 1.81-1.88 (m, 1 H), 2.14-2.24 (m, 2 H), 2.48-2.55 (m, 1 H), 4.34 (d, J = 7.6 Hz, 1 H), 4.81 (s, 1 H), 4.91 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) (major isomer signals) δ 23.1 (t), 27.7 (t), 29.7 (t), 33.8 (t), 47.1 (d), 71.2 (d), 110.8 (t), 147.3 (s), 176.5 (s); exact mass (electrospray) *m/z* calcd for $C_9H_{13}O_3$ (M - H) 169.087, found 169.0872.

3-Hydroxy-7a-(iodomethyl)octahydro-1-benzofuran-2-one (62.3).

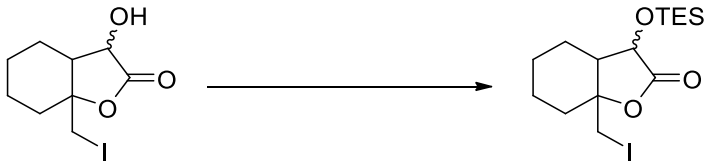


62.2 **62.3**

$KHCO_3$ (448 mg, 4.50 mmol), KI (744 mg, 4.50 mmol) and I_2 (1.143 g, 4.50 mmol) were added sequentially to a stirred solution of **62.2** (381 mg, 2.25 mmol) in a mixture of THF (8.5 mL) and water (2.9 mL) at room temperature. The mixture was stirred at room temperature for 40 min and then quenched with

saturated aqueous $Na_2S_2O_3$ (4 mL). Stirring was continued until the iodine colour was discharged. EtOAc (10 mL) was then added and the mixture was washed with brine and the organic extract was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 15 cm), using 1:1 hexane-EtOAc, gave **62.3** (519 mg, 78%) as a yellow oil: FTIR (cast film) 3423, 2938, 2861, 1775, 1447, 1369, 1332, 1268, 1214, 1176, 1139, 1118, 1093, 1047 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.12-1.26 (m, 2 H), 1.32-1.45 (m, 1 H), 1.57-1.66 (m, 1 H), 1.66-1.79 (m, 1 H), 1.80-1.93 (m, 2 H), 2.13 (dtd, *J* = 14.9, 3.9, 1.9 Hz, 1 H), 2.75- 2.90 (m, 2 H), 3.33 (d, *J* = 10.0 Hz, 1 H) 3.37 (d, *J* = 14.9 Hz, 1 H), 4.76 (dd, *J* = 7.1, 3.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ12.5 (t), 20.6 (t), 22.1 (t), 22.4 (t), 33.0 (t), 41.8 (d), 71.4 (d), 82.5 (s), 177.0 (s); exact mass (electrospray) *m*/*z* calcd for $C_9H_{13}INaO_3$ (M + Na) 318.9802, found 318.9800.

7a-(Iodomethyl)-3-[(triethylsilyl)oxy]octahydro-1-benzofuran-2-one (62.5).

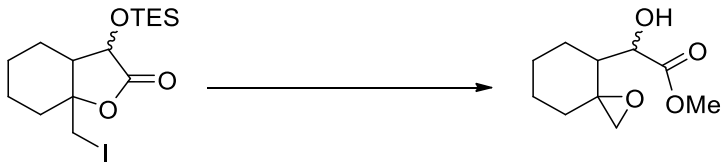


62.3 **62.5**

2,6-Lutidine (0.65 mL, 5.56 mmol), followed by $Et_3SiOSO_2CF_3$ (0.49 mL, 2.42 mmol) were added to a solution of **62.3** (358 mg, 1.21 mmol) in CH_2Cl_2 (18 mL) at room temperature. The mixture was stirred for 1.5 h, quenched with water and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 4:1 hexane-EtOAc, gave **62.5** (495 mg, 100%) as an oil:

FTIR (cast film): 2952, 2876, 1790, 1458, 1413, 1240, 1225, 1164, 1142, 1122, 1003 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.68 (q, *J* = 10.0 Hz, 6 H), 0.98 (t, *J* = 10.0 Hz, 9.0 H), 1.17-1.26 (m, 1 H), 1.32-1.42 (m, 1 H), 1.42-1.66 (m, 2 H), 1.66-1.79 (m, 2 H), 1.91 (ddd, *J* = 14.7, 10.9, 4.9 Hz, 1 H), 2.55 (dt, *J* = 14.7, 10.1 Hz, 1 H), 2.64 (dt, *J* = 9.3, 6.6 Hz, 1 H), 3.36 (s, 2 H), 4.63 (d, *J* = 6.8, Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 4.7 (t), 6.7 (q), 13.1 (t), 20.9 (t), 22.2 (t), 22.7 (t), 33.2 (t), 42.8 (d), 72.0 (d), 81.4 (s), 175.0 (s); exact mass (electrospray) *m*/*z* calcd for $C_{15}H_{27}INaO_3Si$ (M + Na) 433.0666, found 433.0662.

Methyl 2-hydroxy-2-{1-oxaspiro[2.5]octan-4-yl}acetate (62.4).

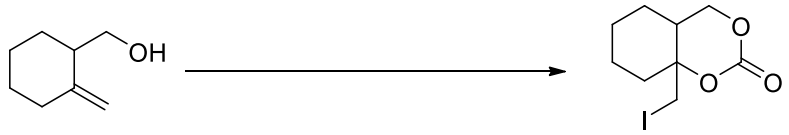


62.5 **62.4**

MeONa (58 mg, 1.08 mmol) was added to a solution of **62.5** (75 mg, 0.18 mmol) in MeOH (3 mL) at room temperature and the mixture was stirred for 5 h, diluted with water and extracted with EtOAc (4 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (Pasteur pipette, 7 cm), using 4:1 hexane-EtOAc, gave **62.4** (54 mg, 94%) as a colorless oil which was a 1:2.86 inseparable mixture of two isomers: FTIR (cast film) 3457, 2938, 2861, 1742, 1486, 1444, 1259, 1214, 1129, 1107, 1070, 1014 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) (major isomer signals) δ 1.38-1.92 (m, 8 H), 2.01- 2.08 (m, 1 H), 2.58 (d, *J* = 4.0 Hz, 1 H), 2.95 (d, *J* = 4.0 Hz, 1 H), 3.51 (br s, 1 H), 3.77 (s, 3 H), 4.18 (d, *J* = 6.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) (major isomer signals) δ 23.6 (t), 24.2 (t), 28.6 (t), 33.3 (t),

43.2 (d), 52.2 (q), 53.5 (t), 60.8 (s) 73.1 (d), 174.5 (s); exact mass (electrospray) *m*/*z* calcd for $C_{10}H_{16}NaO_4$ (M + Na) 223.0941, found 223.0937.

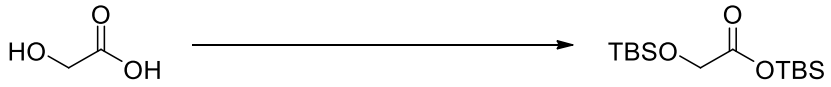
8a-(Iodomethyl)octahydro-1,3-benzodioxin-2-one (61.1).



57.2 **61.1**

BuLi (2 M in hexane, 0.25 mL, 0.52 mmol) was added to a stirred and cooled (0 °C) solution of **57.2** (56 mg, 0.5 mmol) in THF (5 mL). After 15 min, dry CO_2 (dried by passage through a tube packed with Drierite) was bubbled into the solution for 2 h. A solution of I_2 (279 mg, 1.1 mmol) in THF (1 mL) was then added dropwise and stirring was continued for 2 h. The mixture was quenched with saturated aqueous $Na_2S_2O_3$ and extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 4:1 hexane-EtOAc, gave **61.1** (99 mg, 75%) as a colorless oil: FTIR (cast film) 2936, 2863, 1801, 1746, 1486, 1448, 1432, 1402, 1221, 1192, 1144, 1115, 1027 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) (major isomer signals) δ 1.32-1.44 (m, 1 H), 1.54-1.68 (m, 3 H), 1.68-1.78 (m, 2 H), 1.90 (dtd, *J* = 13.5, 4.4, 1.0 Hz, 1 H), 1.95-2.06 (m, 1 H), 1.90 (dtd, *J* = 11.2, 4.4, 2.8 Hz, 1 H), 3.47 (AB q, *J* = 10 Hz, $\Delta\nu_{AB}$ = 16.6 Hz, 2 H), 4.10-4.18 (m, 1 H), 4.53 (dd, *J* = 11.5, 4.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) (major isomer signals) δ 10.9 (t), 21.2 (t), 23.5 (t), 25.3 (t), 32.9 (d), 34.0 (t), 69.6 (t) 81.7 (s), 148.0 (s); exact mass (electrospray) *m*/*z* calcd for $C_9H_{13}INaO_3$ (M + Na) 318.9802, found 318.9799.

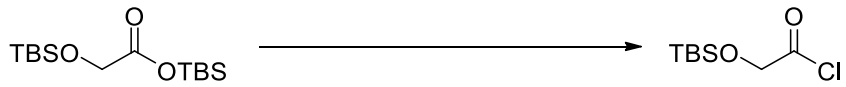
***tert*-Butyldimethylsilyl 2-[(*tert*-butyldimethylsilyl)oxy]acetate (54.2).**



54.1 **54.2**

Imidazole (12.6 g, 185 mmol) followed by *t*-$BuMe_2SiCl$ (13.4 g, 89 mmol) were added to a stirred solution of **54.1** (2.8 g, 36.4 mmol) in dry DMF (24 mL) at room temperature. Stirring was continued for 15 and the mixture was diluted with water (100 mL) and extracted with Et_2O (3 x 40 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated and the residue was left under oil pump until it turned to a solid (if the material is kept overnight under oil pump vacuum, there is significant loss of product). The resulting solid contained a 2:1 mixture of *t*-$BuMe_2SiCl$ and **54.2** which was taken forward to the next step without any further purification. Compound **54.2** (10.1 g, 91%) had: ^1H NMR ($CDCl_3$, 400 MHz) (ignoring the signals due to residual *t*-$BuMe_2SiCl$) δ 0.11 (s, 6 H), 0.29 (s, 6 H), 0.92 (s, 9 H), 0.94 (s, 9 H), 4.19 (s, 2 H).

2-[(*tert*-Butyldimethylsilyl)oxy]acetyl chloride (54.3).

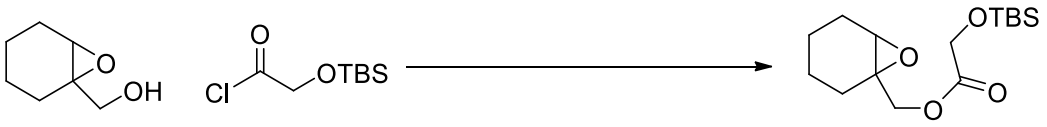


54.2 **54.3**

$(COCl)_2$ (0.36 mL, 0.4 mmol), followed by dry DMF (1 drop) were added to a stirred and cooled (0 °C) solution of **54.2** (1 g, 3.29 mmol) in CH_2Cl_2 (3.2 mL). The ice bath was removed after 15 min and stirring was continued for 4 h . The solvent and excess of $(COCl)_2$ were removed under vacuum and the resulting

oil which was mixture of 2:1 mixture of *t*-BuMe$_2$SiCl and **54.3** was used without any further purification in the next step as the acid chloride reacts much faster than the *t*-BuMe$_2$SiCl. Compound **54.3** had: ^{1}H NMR (CDCl$_3$, 500 MHz) (ignoring the signals due to residual *t*-BuMe$_2$SiCl) δ 0.16 (s, 6 H), 0.96 (s, 9 H), 4.58 (s, 2 H); ^{13}C NMR (CDCl$_3$, 125 MHz) δ -5.53 (q), 18.23 (s), 25.5 (q), 69.9 (t), 229.6 (s).

7-Oxabicyclo[4.1.0]heptan-1-ylmethyl 2-[(*tert*-butyldimethylsilyl)oxy]-acetate (55.1).

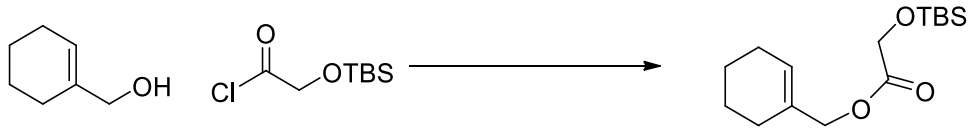


48.2 **54.3** **55.1**

Pyridine (0.6 mL, 7.8 mmol), followed by a solution of crude **54.3** (817 mg, from the 2:1 mixture of *t*-BuMe$_2$SiCl and **54.3**, 1.56 mmol of **54.3**) in Et$_2$O (5 mL), were added to a stirred and cooled (0 °C) solution of **48.2** (100 mg, 0.78 mmol) in Et$_2$O (5 mL). Stirring at 0 °C was continued for 2 h, by which time all starting material had reacted (TLC, silica, 1:1 hexane-EtOAc). The mixture was quenched with water and extracted with EtOAc (3 x 8 mL). The combined organic extracts were dried (MgSO$_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 4:1 hexane-EtOAc, gave **55.1** (255 mg, 91%) as a colorless oil: FTIR (cast film) 2936, 2858, 1766, 1739, 1472, 1463, 1390, 1254, 1188, 1145 cm^{-1}; ^{1}H NMR (CDCl$_3$, 500 MHz) δ 0.13 (s, 6 H), 0.94 (s, 9 H), 1.21-1.36 (m, 2 H), 1.40-1.54 (m, 2 H), 1.76-1.90 (m, 2 H), 1.90-2.06 (m, 2 H), 3.13 (d, *J* = 3.5 Hz, 1 H), 4.03 (d, *J* = 11.7 Hz, 1 H), 4.27 (d, *J* =

11.7 Hz, 1 H), 4.30 (s, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ -5.5 (q), 18.4 (s), 19.4 (t), 19.6 (t), 24.3 (t), 25.4 (t), 25.8 (q), 56.7 (d), 57.5 (s), 61.6 (t), 68.3 (t), 171.5 (s); exact mass (electrospray) *m*/*z* calcd for $C_{15}H_{28}NaO_4Si$ (M + Na) 323.1649, found 323.1644.

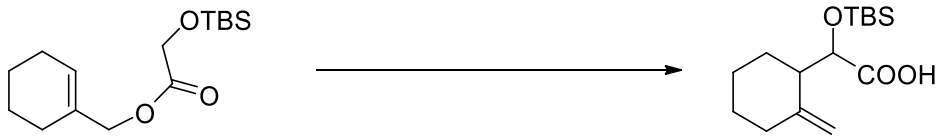
Cyclohex-1-en-1-ylmethyl 2-[(*tert*-butyldimethylsilyl)oxy]acetate (64.1).



48.1 **54.3** **64.1**

Pyridine (1.37 mL, 17.8 mmol), followed by a solution of **54.3** (955 mg from 1:1 mixture of *t*-$BuMe_2SiCl$ and **54.3**, 2.67 mmol of **54.3**) in Et_2O (11 mL), were added to a stirred and cooled (0 °C) solution of **48.1** (200 mg, 1.78 mmol) in Et_2O (11 mL). Stirring at 0 °C was continued for 2 h, by which time all starting material had reacted (TLC, silica, 1:1 hexane-EtOAc) and the mixture was quenched with water and extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 4:1 hexane-EtOAc, gave **64.1** (480 mg, 95%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.13 (s, 6 H), 0.95 (s, 9 H), 1.56-1.64 (m, 2 H), 1.64-1.72 (m, 2 H), 1.75 (d, *J* = 10.5 Hz, 1 H), 1.98-2.11 (m, 4 H), 4.28 (s, 2 H), 4.53 (s, 2 H), 5.74-5.78 (m, 1 H).

2-[(*tert*-Butyldimethylsilyl)oxy]-2-(2-methylidenecyclohexyl)acetic acid (64.2).

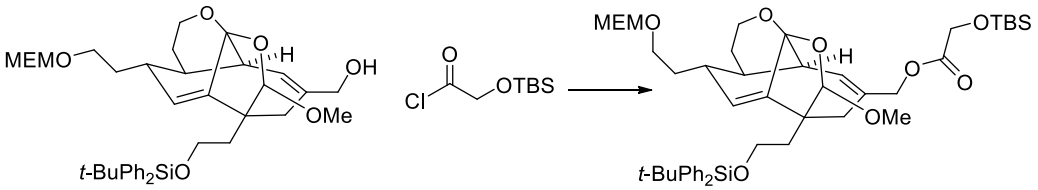


64.1 **64.2**

BuLi (2.5 M in THF, 0.27 mL, 0.67 mmol) was added to a stirred and cooled (0 °C) solution of *i*-Pr_2NH (0.1 mL, 0.72 mmol) and HMPA (1 mL, 0.72 mmol) in THF (3 mL). After 7 min, the mixture was cooled to -78 °C and a solution of **64.1** (120 mg, 0.42 mmol) in THF (0.7 mL) was added dropwise, followed by a mixture of *t*-$BuMe_2SiCl$ (73 μL, 0.59 mmol) and Et_3N (40 μL) that had been stirred for 5 min in THF (1 mL). After 5 min the ice bath was removed and stirring was continued for 24 h. The mixture was quenched with water and acidified with 10% hydrochloric acid to *p*H 1. The mixture then was extracted with EtOAc (4 x 10 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 10 cm), using 1:1 hexane-EtOAc, gave **64.2** (107 mg, 89%) as a colorless oil (which was a 4.4:1 mixture of isomers): FTIR (cast film) 2500-3500, 3073, 2931, 2858, 1722, 1648, 1472, 1463, 1449, 1362, 1257, 1214, 1186, 1120, 1037, 1006 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) (major isomer signals) δ 0.1 (s, 6 H), 0.92 (s, 9 H), 1.51-162 (m, 3 H), 1.62-1.75 (m, 2 H), 1.81-1.95 (m, 1 H), 2.07-2.24 (m, 2 H), 2.48-2.55 (m, 1 H), 4.37 (d, *J* = 8.5 Hz, 1 H), 4.68 (s, 1 H), 4.72 (s, 1 H), 8.2-9.8 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) (major isomer signals) δ -5.59 (q), 17.76 (s), 21.7 (t), 25.3 (q), 27.2 (t), 27.5 (t), 33.1 (t), 47.5 (d), 72.7 (d), 109.3 (t),

147.3 (s), 177.3 (s); exact mass (electrospray) *m*/*z* calcd for $C_{15}H_{27}O_3Si$ (M - H) 283.1735, found 283.1735.

(1*S*,5*R*,6*R*,9*S*,13*R*)-*rel*-9-{2-[(*tert*-Butyldimethylsilyl)oxy]ethyl}-15-methoxy-6-{2-[(2-methoxyethoxy)methoxy]ethyl}-2,14-dioxatetracyclo-[7.4.2.0^{1,8}.0^{5,13}]pentadeca-7,11-dien-11-yl]methyl 2-[(*tert*-butyldimethylsilyl)-oxy]acetate (65.1).



59.1 **54.3** **65.1**

Pyridine (0.11 mL, 0.147 mmol), followed by a solution of **54.3** (79 mg from the 1:1 mixture of *t*-BuMe$_2$SiCl and **54.3**, 0.22 mmol) in Et_2O (1 mL), were added to a stirred and cooled (0 °C) solution of **59.1** (100 mg, 0.147 mmol) in Et_2O (1 mL). Stirring at 0 °C was continued for 2 h, by which time all starting material had reacted (TLC, silica, EtOAc). The mixture was quenched with water and extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 1:1 hexane-EtOAc, gave **65.1** (101 mg, 81%) as a colorless oil: FTIR (cast film) 2930, 2882, 2857, 1759, 1731, 1472, 1589, 1472, 1428, 1389, 1362, 1252, 1141, 1112, 1042 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) (major isomer signals only) δ1.08 (s, 9 H), 1.42-1.64 (m, 4 H), 1.80-2.03 (m, 4 H), 2.14-2.27 (m, 2 H), 2.3-2.42 (m, 1 H), 2.52 (s, 1 H), 2.71 (d, *J* = 17.4 Hz, 1 H), 3.41 (s, 3 H), 3.43 (s, 3 H), 3.52-3.62 (m, 4 H), 3.66-3.91 (m, 8 H), 4.73 (s, 2 H), 5.14 (s, 1 H),

5.31 (br s, 1 H), 5.42 (s, 1 H), 7.35-7.45 (m, 6 H), 7.62-7.72 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ -5.4 (q), 18.4 (s), 19.1 (s), 25.8 (q), 26.9 (q), 33.8 (t), 35.1 (t), 36.1 (t), 36.7 (d), 37.2 (d), 42.0 (t), 46.0 (d), 51.1 (t), 58.1 (q), 59.1 (q), 60.5 (t), 61.0 (t), 61.7 (t), 65.8 (t), 66.9 (t), 71.8 (t), 72.5 (t), 95.5 (t), 101.2 (d), 107.7 (s), 127.6 (d), 127.66 (d), 127.68 (d), 127.9 (d), 129.64 (d), 129.65 (d), 133.5 (s), 133.6 (s), 135.5 (d), 135.59 (d), 135.6, 139.8 (s), 171.4 (s); exact mass (electrospray) *m*/*z* calcd for $C_{47}H_{70}NaO_{10}Si_2$ (M + Na) 873.4400, found 873.4386.

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