University of Alberta

Asymmetric synthesis of carbocycles by intramolecular conjugate displacement and synthetic studies on sorbicillactone A

by

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DEDICATED TO

MY SUPERVISOR PROF. D. L. J. CLIVE

MY PARENTS, MY WIFE MANJU

MY FAMILY, FRIENDS AND TEACHERS

ABSTRACT

The first chapter of this thesis describes an intramolecular conjugate displacement (ICD) for the asymmetric synthesis of carbocycles using a carbon nucleophile. The precursors for ICD were synthesized by Morita-Baylis-Hillman reaction between (5*R*)-5-(*l*-menthyloxy)-2(5*H*)-furanone and aldehydes, which carry a geminal phenylthio groups in the γ or δ position. Acetylation of the resulting hydroxyl group, followed by oxidation of the phenylthio groups to phenylsulfonyl groups gave the desired ICD precursor which, on treatment with a base, underwent ring closure by intramolecular conjugate displacement. Hydrogenation, DIBAL-H reduction and desulfonylation releases an optically pure carbocycle.

The second chapter describes studies aimed at the synthesis of the bioactive marine alkaloid sorbicillactone A. During this project, much of the carbon skeleton of sorbicillactone A was assembled, and studies to finish the total synthesis are in progress. The key reactions involved in this project are radical-mediated cyclization to synthesize the bicyclic core, 1,4 addition of a phenyldimethylsilyl unit, followed by trapping of the intermediate with methyl iodide and, finally, a one pot process for ketal protection and iodolactonization. After the successful installation of nitrogen at C-3, current research is directed at the installation of a methyl group at the same C-3 position.

ACKNOWLEDGEMENTS

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LIST OF ABBREVIATIONS

Ac	acetyl
AIBN	azobisisobutyronitrile
Ar	aromatic ring
9-BBN	9-borabicyclo[3.3.1]nonane
Bn	benzyl
Boc	*tert*-butoxycarbonyl
brsm	based on recovered starting materials
Bu	*n*-butyl
Bu-*t*	*tert*-butyl
CD	circular dichroism
Cbz	benzyloxycarbonyl
COSY	correlation spectroscopy
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	dibenzylidene acetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*'-dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
de	diastereomeric excess
DEAD	diethyl azodicarboxylate
DIBAL-H	diisobutylaluminum hydride
DMAP	4-dimethylaminopyridine

DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
ee	enantiomeric excess
ESI	electrospray ionization
EWG	electron-withdrawing group
HMBC	heteronuclear multiple bond correlation
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
HSQC	heteronuclear single quantum coherence
IBX	2-iodoxybenzoic acid
IC_{50}	concentration that gives 50% inhibition of an enzyme
ICD	intramolecular conjugate displacement
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LG	leaving group
MCPBA	*m*-chloroperoxybenzoic acid
MIC	Minimum inhibitory concentration is the lowest concentration of a drug in mg/mL that inhibits the visible growth of a strain of bacteria
mp	melting point

MS	molecular sieves
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NIS	*N*-iodosuccinimide
NMO	*N*-methylmorpholine-*N*-oxide
NMP	1-methylpyrrolidin-2-one
Nu	nucleophile
ORTEP	Oak Ridge Thermal Ellipsoid Plot
PCC	pyridinium chlorochromate
Pmb	*p*-methoxybenzyl
PPTS	pyridinium *p*-toluenesulfonate
PTC	Phase transfer catalyst
pyr	pyridine
rr	regioisomer ratio
rt	room temperature
SOMO	singly occupied molecular orbital
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxy
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMM	trimethylenemethane
TMS	trimethylsilyl

TPAP	tetrapropylammonium perruthenate
Ts	*p*-toluenesulfonyl
TsOH	*p*-toluenesulfonic acid

Chapter 1

Asymmetric synthesis of carbocycles: use of intramolecular conjugate displacement

1. Introduction[a]

1.1 General

In this chapter of my thesis, I will describe a new method for making optically pure carbocycles using a process that I call intramolecular conjugate displacement (ICD). In the review section I will cover a few of the recent literature reports for the synthesis of optically pure carbocycles and will also give the background to the development of the ICD reaction. The preparation of single enantiomers is now a fundamental aspect of organic synthesis, and the asymmetric ICD process is a new contribution in this respect.

1.2 Asymmetric synthesis of carbocycles

In order to indicate the types of approach that are available for the asymmetric synthesis of optically pure carbocycles, I have selected a four examples from the recent literature to represent enantioselective and diastereoselective methods.

1.2.1 Method of MacMillan and co-workers[1]

Recently, MacMillan and co-workers reported[1] a method for the synthesis of carbocycles and heterocycles from unactivated aldehyde-olefin precursors, achieved via enantioselective SOMO-catalysis.

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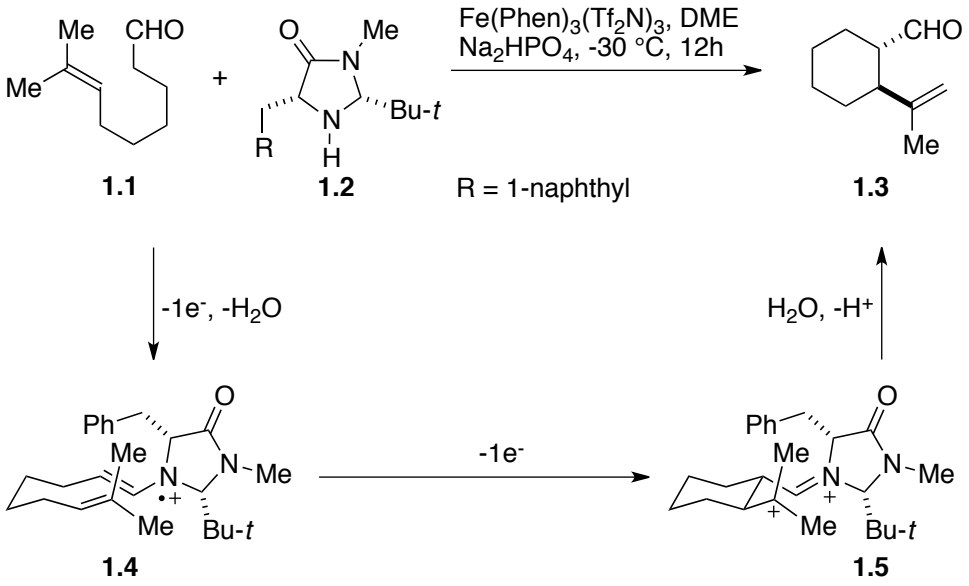
[a] A part of this chapter has been published: Sreedharan, D. T.; Clive, D. L. J. *Org. Biomol. Chem.* **2013**, *11*, 3128-3144.

Their protocol involves a carbonyl-ene cyclization via an enamine radical cation (Scheme 1).

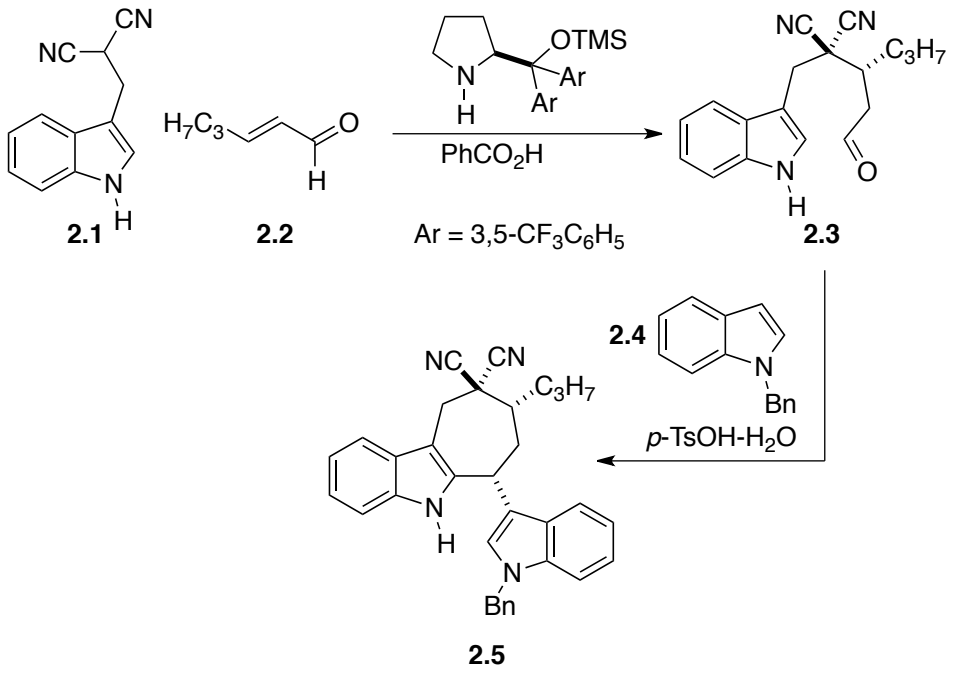


Scheme 1

The enamine radical cation adds stereoselectively from the unshielded face to the pendent olefin. MacMillan and his group have synthesized five-membered as well as six-membered heterocycles and carbocycles through this approach with *ee* 85-99% and *dr* > 20:1.[1]

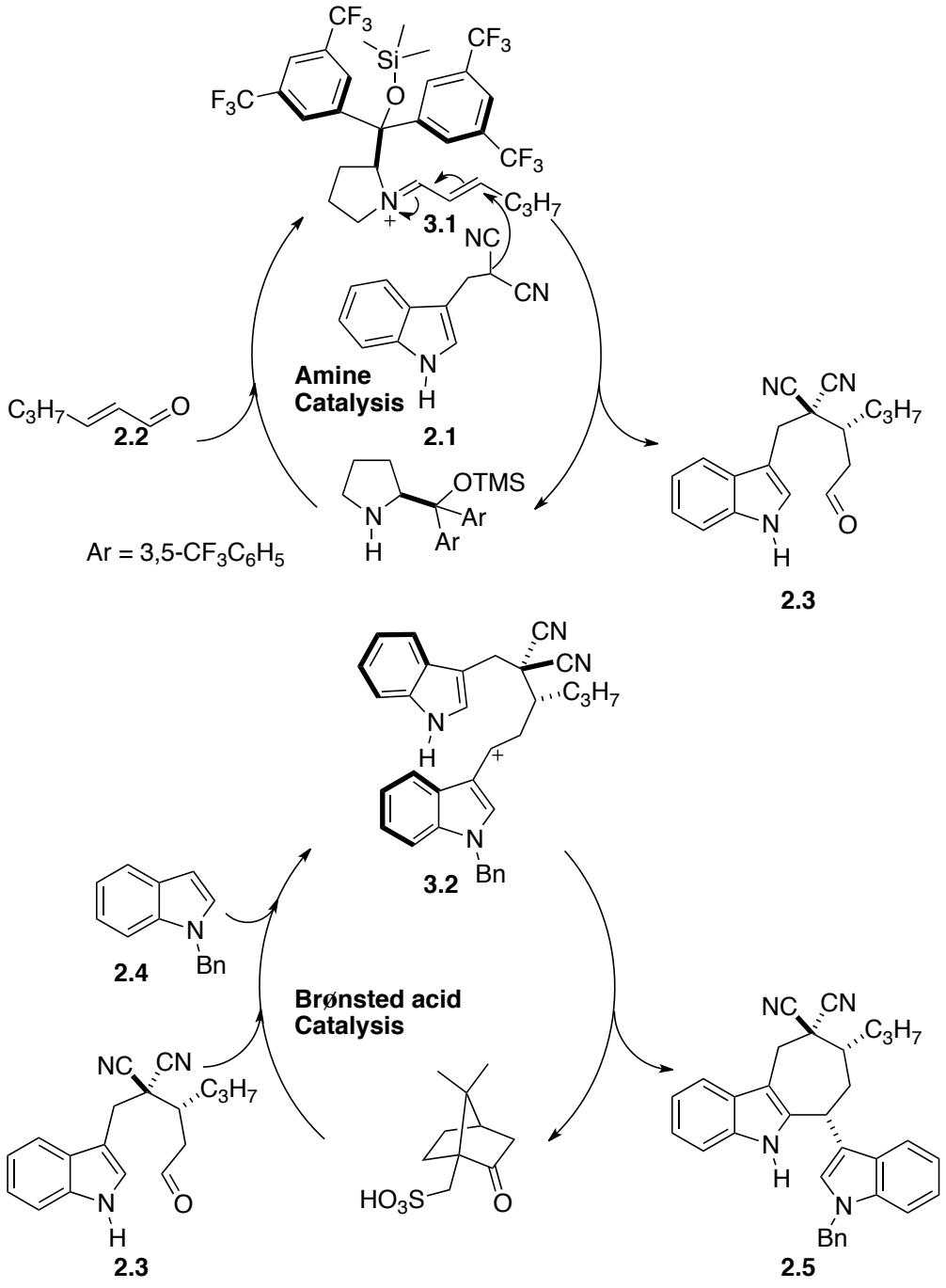
1.2.2 Method of Hong and co-workers[2]

Hong and co-workers developed[2] a method for the enantioselective synthesis of cyclohepta[*b*]indoles. Their approach involves an organocatalytic Michael addition, followed by double Friedel-Crafts alkylation (Scheme 2).



Scheme 2

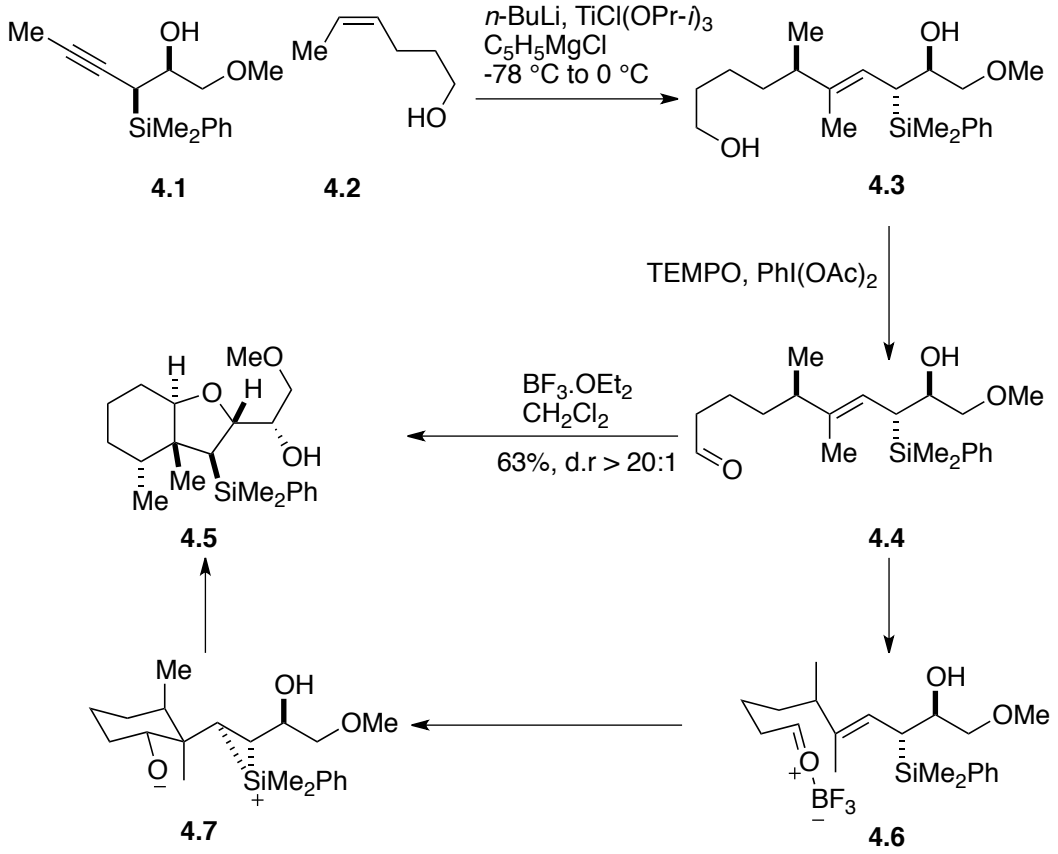
Hong's group was able to synthesize cyclohepta[*b*]indoles in yields up to 72% and stereoselectivity up to 96% *ee*. The stereochemical rationale for this reaction (Scheme 3) is initial nucleophilic attack of indole malononitrile **2.1** on the iminium derivative of the α,β-unsaturated aldehyde **3.1**, which occurs from the less hindered *Re* face to give the product **2.3**. Subsequent treatment of **2.3** with **2.4** provides the cation **3.2**. This prefers the stabilized π-π stacking and half-chair cycloheptane conformer **3.2**, to afford the cyclohepta[b]indole **2.5** as the major isomer.[2]


CF3
Si
CF3
F3C
O
CF3
N
+
3.1
C3H7
NC
CN
N
H
Amine
Catalysis
2.1
C3H7
O
2.2
OTMS
N
H
Ar
Ar
Ar = 3,5-CF3C6H5
NC
CN
C3H7
N
H
O
2.3
CN
CN
C3H7
N
H
+
N
Bn
3.2
N
Bn
2.4
Brønsted acid
Catalysis
NC
CN
C3H7
N
H
O
2.3
HO3S
O
NC
CN
C3H7
N
H
N
Bn
2.5

Scheme 3

1.2.3 Method of Panek and co-workers[3]

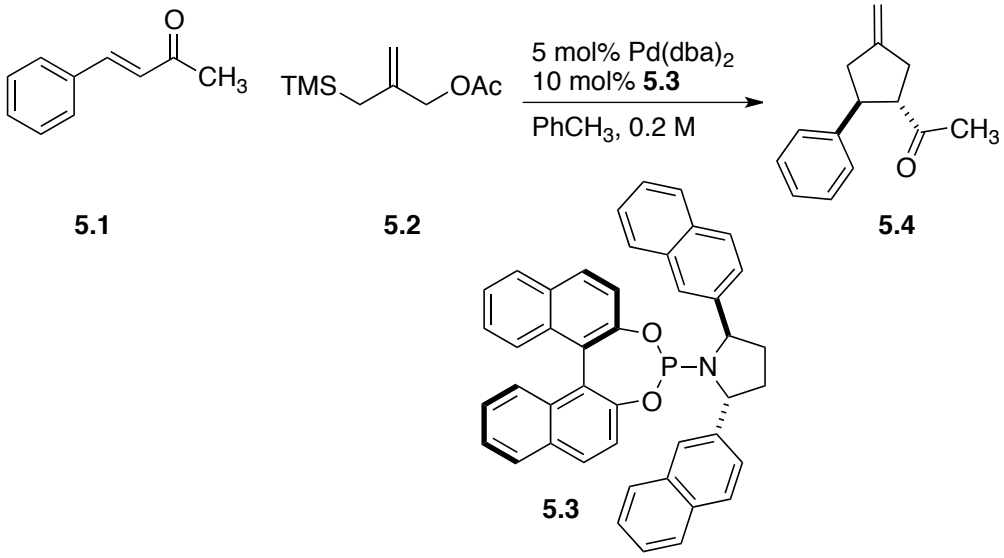
Panek and co-workers reported[3] an organosilane-directed alkyne-alkene reductive coupling, followed by intramolecular allylation, [3+2] annulation or Sakurai-like homodimerization, to synthesize a range of carbocyclic ring systems. One representative example from their work is shown in Scheme 4. The diastereoselectivity of the [3+2] annulation reaction (see **4.6→4.7→4.5**) is attributed to the stereocontrolling effect of the chiral center carrying the silyl group.



Scheme 4

1.2.4 Method of Trost and co-workers[4]

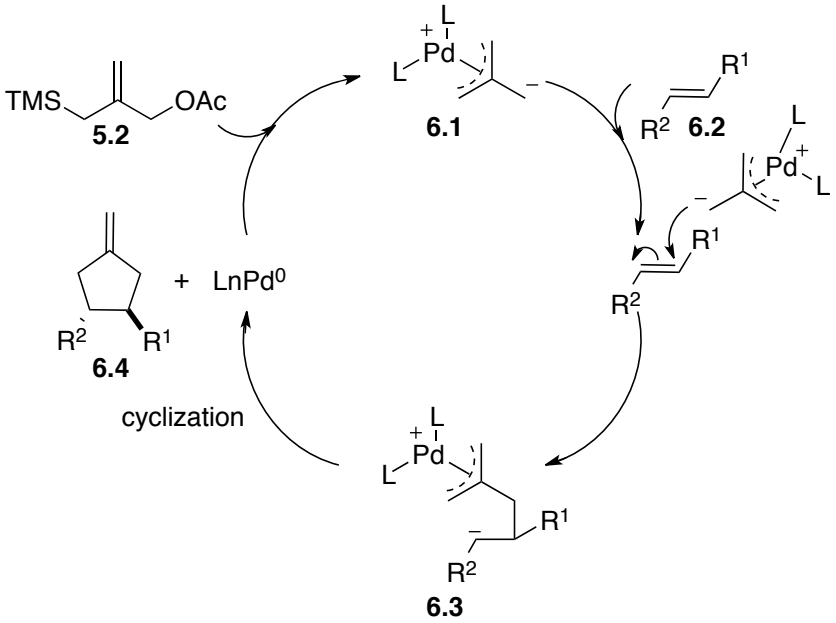
Trost and co-workers reported an enantioselective synthesis of carbocycles by an asymmetric trimethylenemethane cycloaddition. Their protocol involves an enantioselective [3+2] cycloaddition of trimethylenemethane with electron deficient olefins, using a pyrrolidine phosphoramidite ligand (**5.3**). Steric factors of the ligand system control the enantioselectivity.



Scheme 5

The catalytic cycle for the trimethylenemethane (TMM) reaction of silyl allylic acetate (**5.2**) involves the generation of zwitterionic Pd-TMM intermediate (**6.1**) by a metal-promoted ionization of the allylic acetate, followed by desilylation. Addition of the nucleophilic Pd-TMM complex to the olefin **6.2** gives the intermediate **6.3**. The collapse of this intermediate via an intramolecular

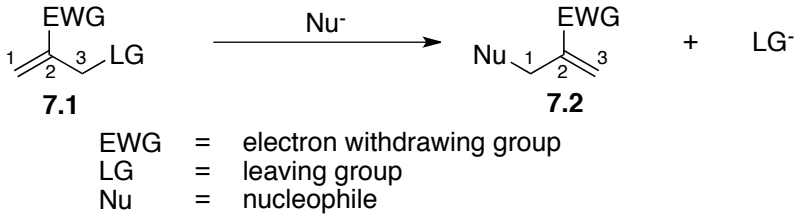
attack of the soft carbon nucleophile onto the π-allylpalladium affords the desired product **6.4** (Scheme 6).[4]



Scheme 6

1.3 Intermolecular and intramolecular conjugate displacement

Seebach and co-workers reported[5] that the presence of an electron-withdrawing group (EWG) at C-2 of an allylic system carrying a leaving group at C-3 increases the rate of S_N2' displacement; such systems were investigated by Lawton and co-workers[6] for cross-linking various chains.

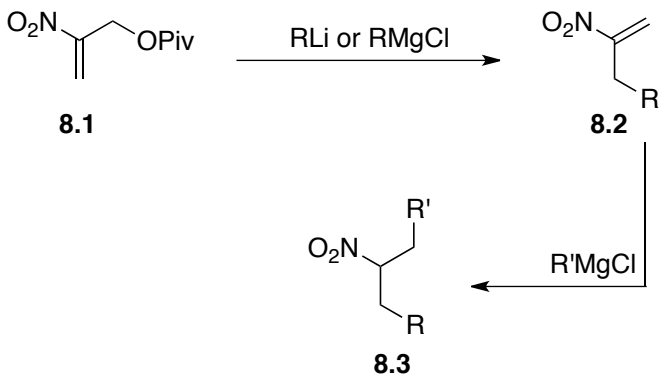


Scheme 7

Although, much research has been conducted on *intermolecular* versions of these S_N2' reactions using this EWG-activated allylic theme,[7] the intramolecular version of this process was not widely appreciated and only a few examples of protein cross linking[8] and synthesis of macrocycles[9] had been reported.[10] The general utility in complex molecule synthesis does not appear to have been appreciated. In the past few years, research from this laboratory has demonstrated the usefulness of this intramolecular reaction using carbon,[11] nitrogen[12] and sulphur[13] nucleophiles, and the method has also been applied in the construction of the core structures of several complex natural products.[14] The starting materials for these reactions are usually derived from Morita-Baylis-Hillman alcohols.[7]

1.3.1 Intermolecular conjugate displacement

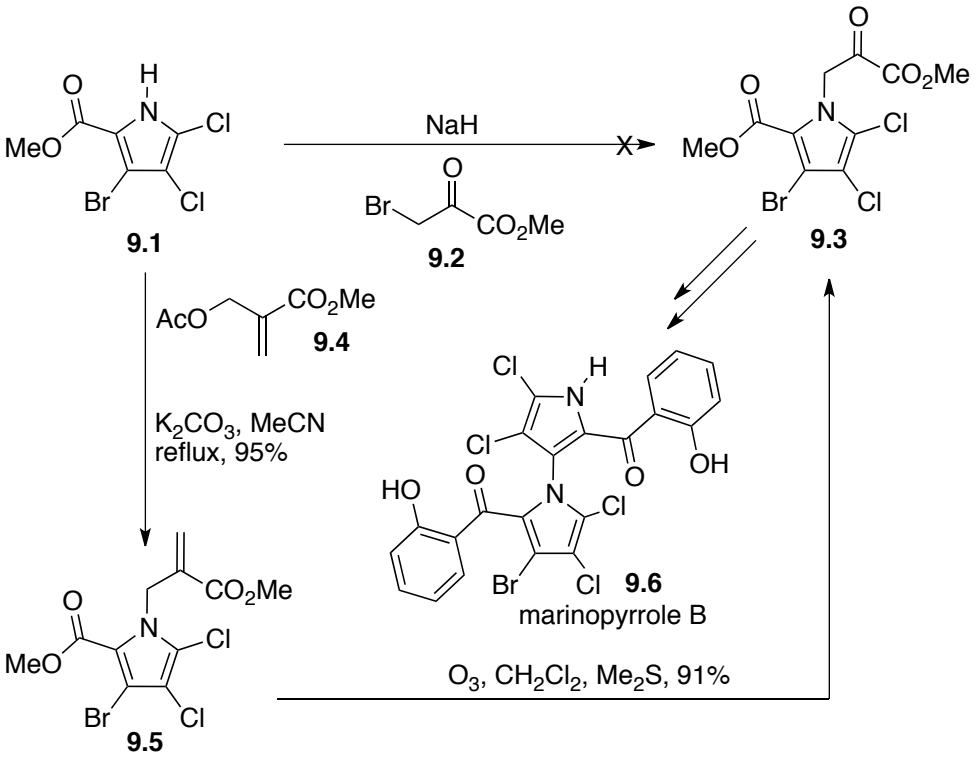
The type of reaction represented in Scheme 7, is formally a hybrid of the classical Michael addition and an S_N2' displacement.[11b] Seebach and co-workers in 1981 reported[6a,b] an early example of this type (Scheme 8).



Scheme 8

Reaction of the 2-nitroallyl pivaloate **8.1** with Grignard reagents or organolithium reagents gave the product **8.2**. From the results obtained, Seebach concluded that the reactivity of the substrate **8.1** was higher in the presence of the pivaloyloxy group (leaving group) than in its absence. The product **8.2**, which is a Michael acceptor, is less reactive than the starting material **8.1**, and was isolated and then subjected to a classical Michael addition to get the product **8.3**.[6a,b]

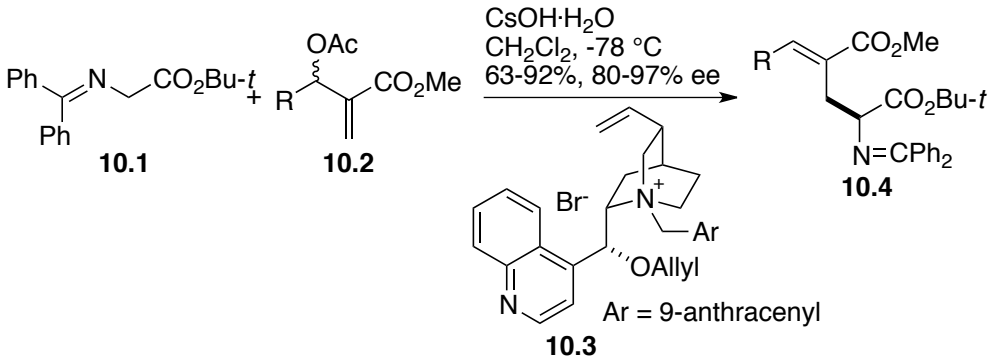
The fact that a Michael acceptor with an allylic leaving group is more reactive than one without the leaving group, was used in this laboratory during the synthesis of the marine natural product marinopyrrole B (**9.6**).[15] The extra reactivity allowed an alkylation to be done that was unsuccessful with less reactive reagents (Scheme 9).



Scheme 9

Reaction of **9.1** with ethyl bromopyruvate **9.2**, did not give any of the desired product (**9.3**). However, on treatment of **9.1** with the allylic acetate **9.4** and K_2CO_3 in refluxing MeCN, the desired conjugate displacement occurred and **9.5** was obtained in 95% yield.[15] Cleavage of the terminal double bond by ozonolysis gave **9.3**, which was then converted to marinopyrrole B.

Ramachandran and co-workers reported[16] an enantioselective S_N2' displacement for the synthesis of glutamic acid derivatives under phase transfer catalyst (PTC) conditions between benzophenone imine **10.1** and Morita-Baylis-Hillman acetate **10.2**. Catalyst **10.3**, derived from cinchonidine, was used as a PTC catalyst and the products were isolated with 80-97% *ee* (Scheme 10).



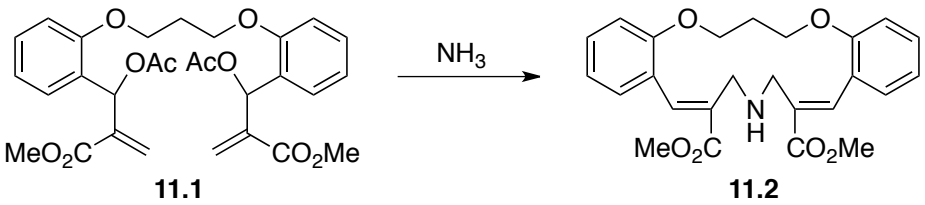
Scheme 10

Intermolecular reactions using Morita-Baylis-Hillman adducts have been extensively reviewed;[15] therefore, the rest of my introduction deals mainly with the intramolecular version.

1.3.2 Intramolecular conjugate displacement (ICD)

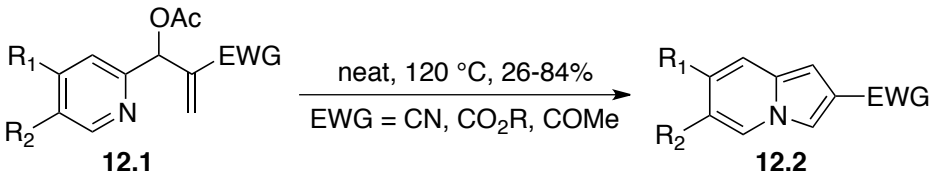
1.3.2.1 ICD reactions reported by other groups

The Foucaud group reported[17] one of the early examples of ICD reactions in 1989 and 1994, during their synthesis of cyclophanes and cryptophanes, using nitrogen nucleophiles. The reaction between Morita-Baylis-Hillman adduct **11.1** and ammonia gave the desired intramolecular conjugate displacement product **11.2** (Scheme 11).

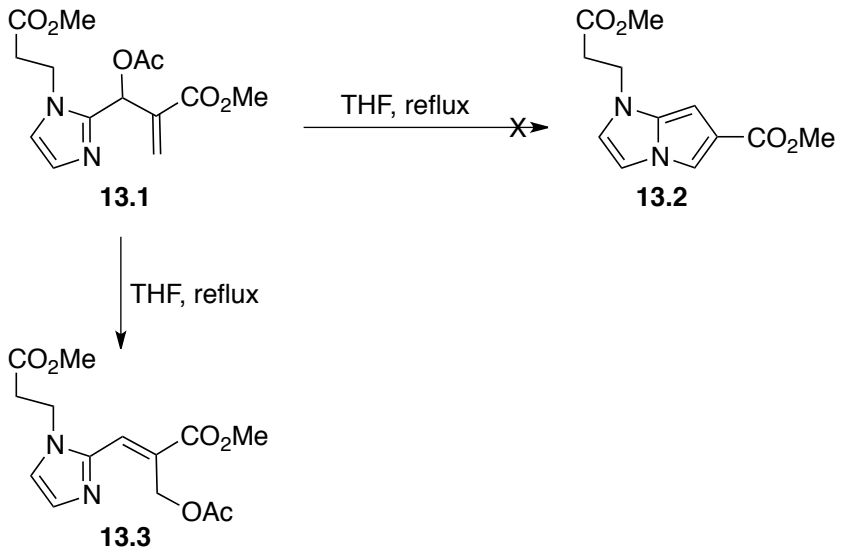


Scheme 11

Kaye's group in 1990 reported[18] the synthesis of indolizines from 2-pyridyl derivatives via an addition-elimination process using nitrogen as the nucleophile. But the mechanism proposed by Kaye's group contravenes Baldwin's rules for ring closure (5-*endo-trig*, disfavored, Scheme 12). In contrast, when Drewes and co-workers heated the imidazole substrate **13.1** in THF (Scheme 13), they isolated only the allylic rearrangement product **13.3**, and none of the ICD product **13.2** was obtained.



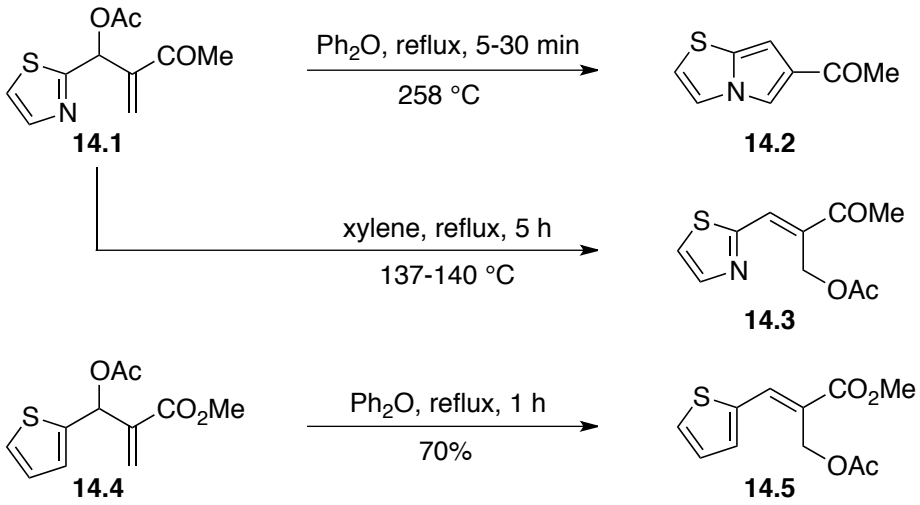
Scheme 12



Scheme 13

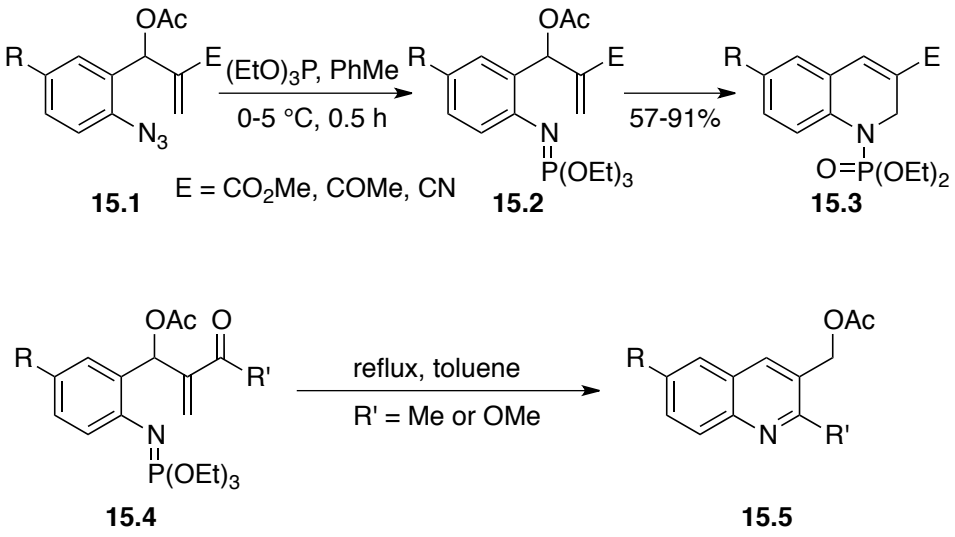
In a similar kind of experiment, Lee and co-workers observed[19] that allylic rearrangement could occur at a lower temperature than ring closure. Treatment of **14.1** in refluxing xylene (~140 °C) gave only **14.3**, which is a rearrangement product, whereas when the temperature was raised to 258 °C, the product isolated was the cyclized one **14.2** (Scheme 14).

Therefore, for those substrates in which the ICD reactions are disfavored by Baldwin's rules, the products are possibly formed by an allylic rearrangement followed by an S_N2 displacement.



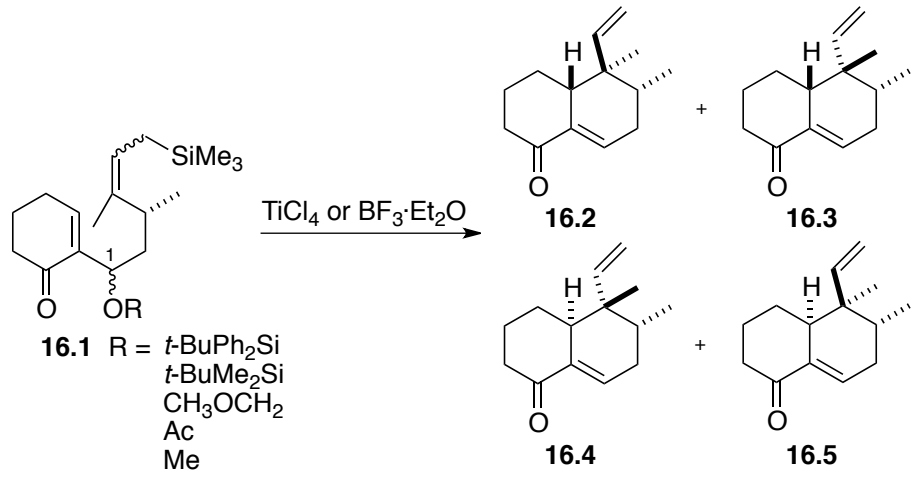
Scheme 14

Lee and co-workers have reported[20] the use of an iminophosphorane unit as a nucleophile for ICD reactions and they synthesized several 1,2-dihydroquinoline derivatives with such nucleophiles. Iminophosphoranes **15.2** were prepared by reaction between Morita-Baylis-Hillman acetates **15.1** and $(EtO)_3P$. Refluxing of a solution of **15.2** in toluene gave the dihydroquinoline **15.3** (Scheme 15). When the electron-withdrawing group was CO_2Me or COMe, a combination of aza-Wittig reaction and allylic shift occurred, resulting in the formation of **15.5**.



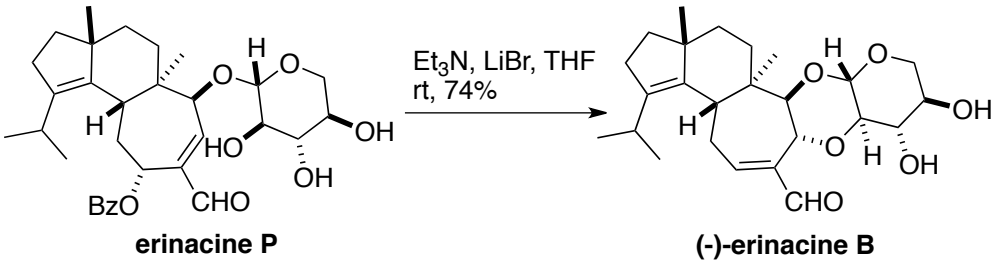
Scheme 15

In 1994, Tokoroyama and co-workers studied the effect of oxy-substituents at C-1 for altering the diastereoselectivity of cyclization of compound **16.1**.[21] In their studies the carbocycles were formed via an intramolecular conjugate displacement promoted by a Lewis acid. During these ICD reactions, they isolated 3-4 diastereomers (depending on the substrate) but there was no correlation between the stereochemistry of the cyclized product and the stereochemistry of the C-1 substituent.



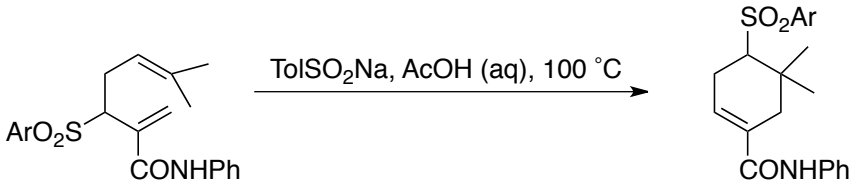
Scheme 16

Use of oxygen as a nucleophile for what we would call an ICD reaction can be seen during conversion of erinacine P to erinacine B by Sassa and co-workers.[22a] Treatment of erinacine P with Et_3N-LiBr resulted in the 1,4-addition of the hydroxyl group to the enal and elimination of acetate to give erinasine B. Nakada's group also used the same transformation during their enantioselective synthesis of (−)-erinacine B.[22b]



Scheme 17

Whitham's group observed a radical mediated process that can be classified as an ICD during their studies on radical induced cyclisation of allylic sulfones containing an electron-withdrawing group β to a sulfone group.[23] Heating $TolSO_2Na$ in aqueous acetic acid produces the sulfone radical which then attacks the substrate **18.1** to give **18.2**.

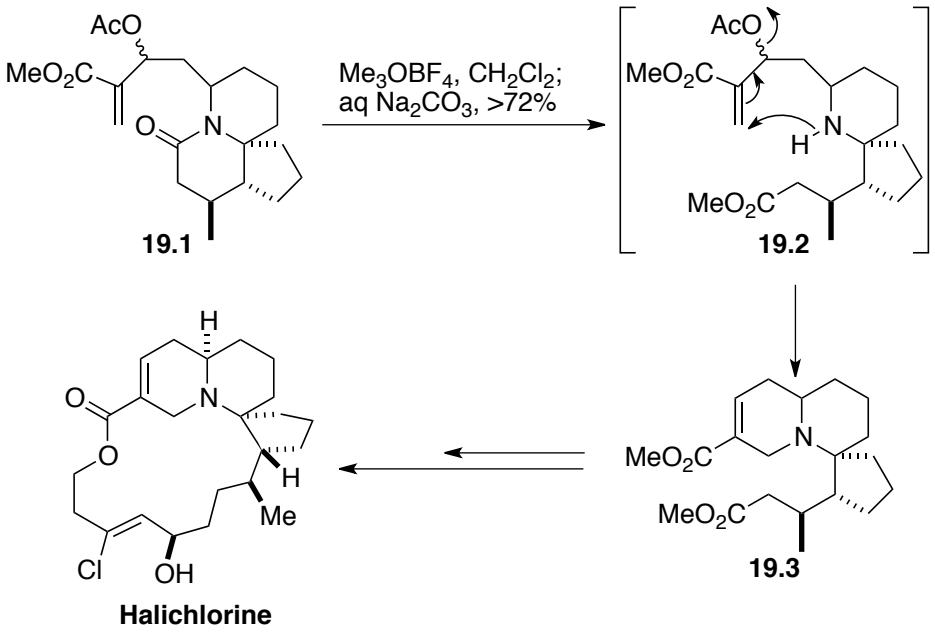


18.1 **18.2**

Scheme 18

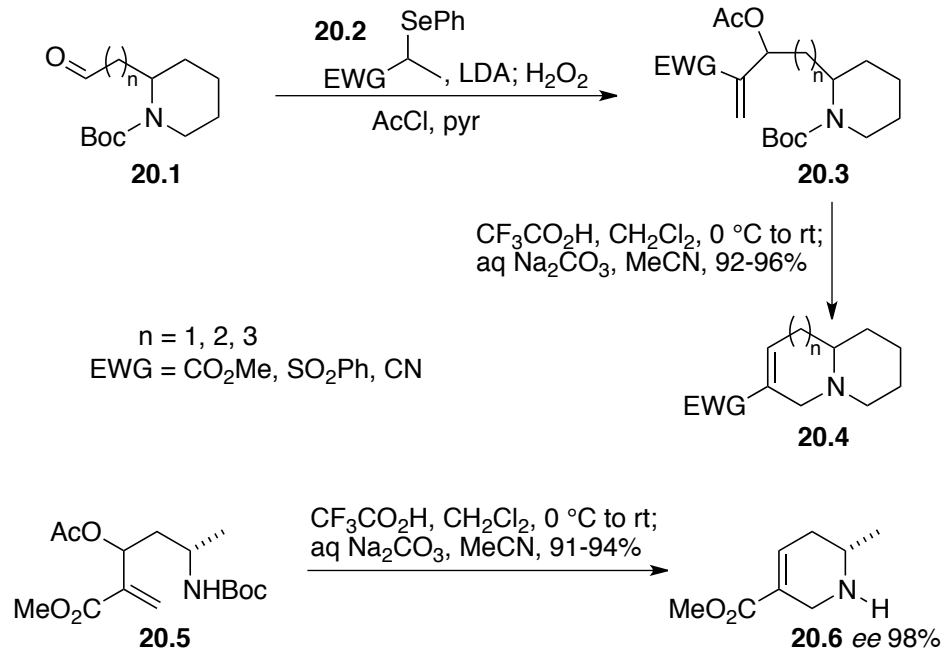
1.3.2.2 ICD reaction - prior work from the Clive group

The concept of ICD reactions emerged in this group during the total synthesis[12a,14a] of the marine alkaloid halichlorine (Scheme 19) as a method of forming a ring, and only later were the related literature precedents found in the earlier work of Lawton[6,8] and Foucauld.[9] Treatment of **19.1** with Meerwein's salt resulted in the opening of the lactam and subsequent treatment of the resulting amine with Na_2CO_3 gave the tricyclic core structure **19.3** of halichlorine. This substance was then elaborated into the natural product.



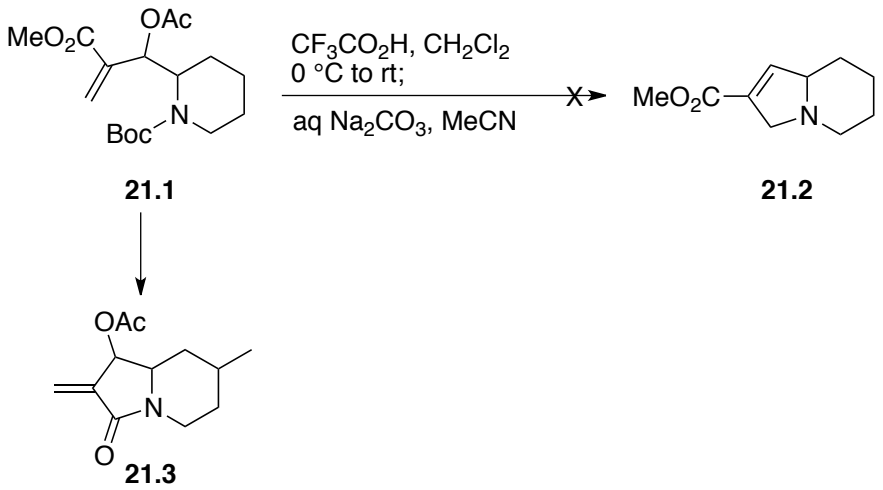
Scheme 19

The previous group members Dr. M. Yu and Dr. Z. Li generalized this methodology and showed that bicyclic amines with nitrogen at the bridgehead could be readily synthesized by ICD reaction in excellent yields.[12b] The precursors for these ICD reactions were synthesized either by Morita-Baylis-Hillman reaction or by condensation of aldehydes with selenium-stabilized carbanions followed by oxidation and acetylation (Scheme 20). They also showed that the ICD reaction occurred with preservation of stereochemistry α to the nitrogen (**20.5→20.6**).



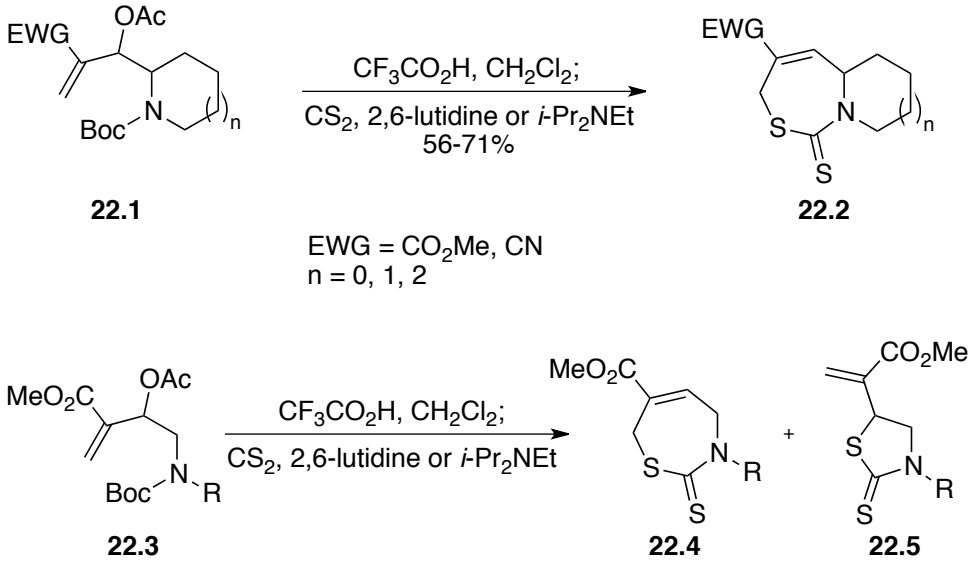
Scheme 20

Encouraged by the very high yields of this ICD reaction, Dr. Yu also tried to synthesize compound **21.2** via an 5-*endo-trig* cyclization, which is disfavored by Baldwin's rules. However, no desired product was found and, instead, the reaction gave the amide **21.3** by attack of nitrogen on the methyl ester (Scheme 21).[12b] It should be pointed out that intermolecular conjugate addition, followed by cyclization via an S_N2 displacement could have generated **21.2**. It is not clear why attack by nitrogen on the CO_2Me group was preferred over attack at the acetate carbonyl. In any event, the experimental observations indicate that ICD reactions are unfavorable when the ring that would be formed is five-membered, in accord with Baldwin's rules.



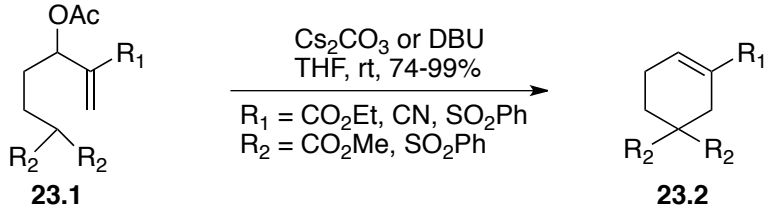
Scheme 21

Dr. Z. Chen took advantage of this fact by introducing an unsaturated electrophile X=Y, which could easily be attacked by the nitrogen to generate a nucleophilic species N-X-Y^- which, in turn can, undergo the ICD reaction by a 7-*endo-dig* pathway without violating Baldwin's rules.[13] Examination of several potential electrophiles (PhNCO, PhNCS, SO_2, $BnN{=}CH_2$, $(Cl_3C)_2C{=}NBn$, CO_2, CS_2, H_2NCN), showed that CS_2 is satisfactory and gave the desired products. During these reactions, in some cases Dr. Chen observed the formation of a 5-membered side product as well (e.g. **22.5**). The amount of side product depends on several factors: cyanide as the electron-withdrawing group increases the amount of 5-membered ring compared to a CO_2Me group. The amount of 5-membered ring formation was higher in acyclic precursors than in cyclic precursors in which the reacting arms are attached to an existing ring.



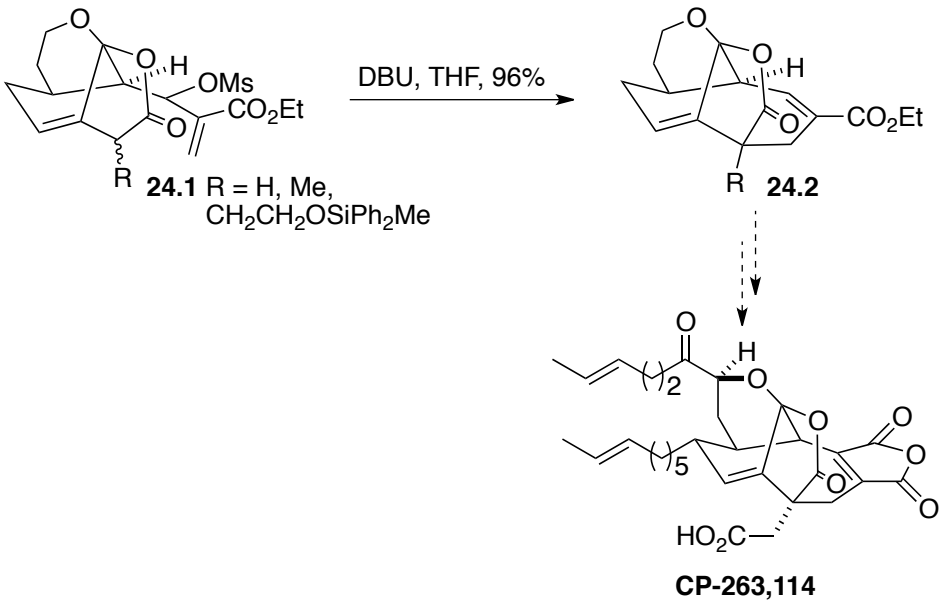
Scheme 22

In 2007, Dr. Prabhudas developed the ICD reaction for the synthesis of carbocycles.[11a] Later on, Dr. L. Wang conducted a detailed study on the all-carbon ICD reaction,[11b] the results of which showed that ICD reactions occurred under mild conditions and could be used for the synthesis six-, seven- and eight-membered carbocycles. Dr. Wang's results (Scheme 23) also showed that ICD reactions are compatible with different electron withdrawing groups (-CO_2R, -SO_2Ph, -CN), and also with different acidifying groups (-CO_2R, -NO_2, -COR, -SO_2Ph).



Scheme 23

The synthetic potential of all-carbon ICD reactions was illustrated during synthetic studies on the complex natural products CP-225, 917 and CP-263, 114.[14b] The core structure of these natural products was synthesized in this laboratory by an all-carbon ICD process using **24.1** with DBU as a base (Scheme 24).

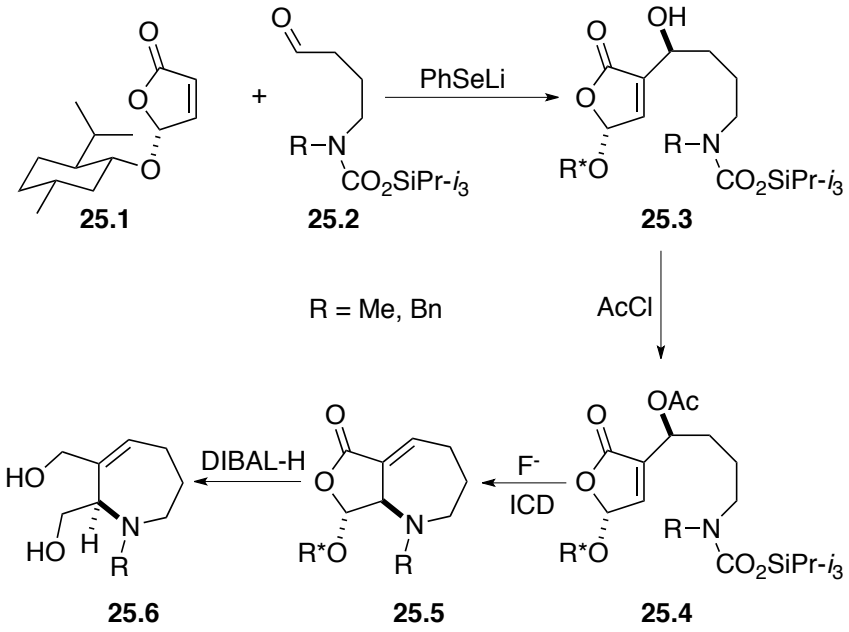


Scheme 24

Dr. Wang studied the mechanism of these all-carbon-ICD reactions and proposed that they involve a stepwise pathway, at least in those cases where there is a poor leaving group. He also tried to trap the carbanionic intermediate by using protic solvents, but trapping proved impossible.[11b]

During work on my project on asymmetric synthesis of carbocycles using ICD, another group member, Dr. P. Cheng, was studying the synthesis of optically

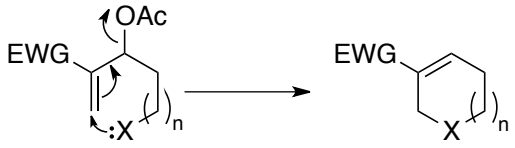
pure cyclic amines using same principle. Dr. Cheng was able to prepare optically pure six- or seven-membered cyclic amines possessing a stereogenic center α to the nitrogen, by using a chiral auxiliary approach.[12c] The chiral auxiliary can be removed at the end of the sequence by reduction with DIBAL-H so as to release an optically pure amine (Scheme 25).



Scheme 25

2. Results and Discussion[24]

After the successful implementation of intramolecular conjugate displacement (ICD) for the synthesis of carbocycles and heterocycles from this laboratory [see Scheme 26], the objective of my research was to develop this chemistry for the synthesis of optically pure carbocycles.

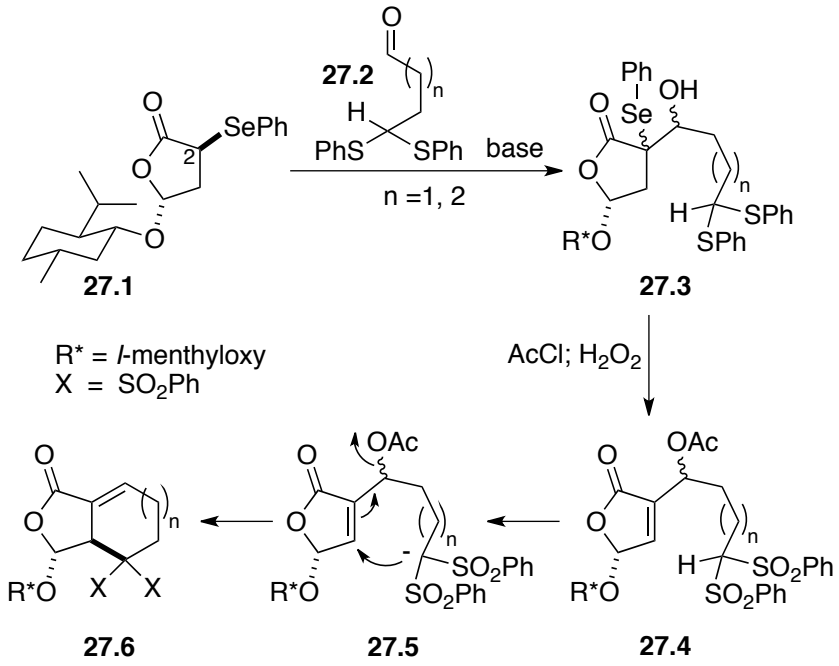


EWG = electron-withdrawing group, X = N, S, C.

Scheme 26

The principle behind my project was to attach a chiral auxiliary at the proper position of the acceptor double bond, so that the ICD occurs from the less hindered face of the double bond as shown in Scheme 27.

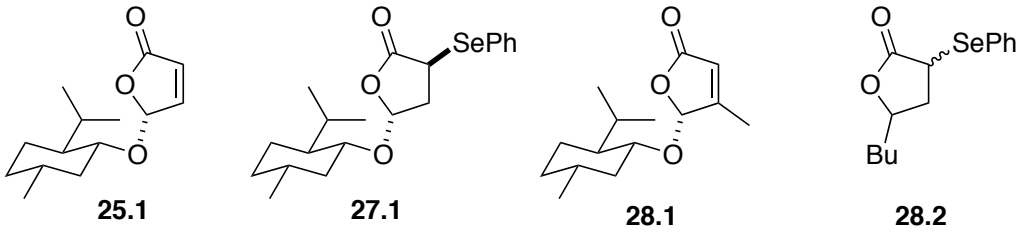
As indicated in the Scheme, the starting chiral lactone **27.1**, undergoes an aldol reaction with aldehyde **27.2**, which carries a geminal phenylthio group, to give alcohols **27.3**. Acetylation of the hydroxyl group, followed by oxidative removal of selenium would give the ICD precursor **27.4**. Treatment of **27.4** with a base should result in the formation of optically pure **27.6** by an ICD pathway. Finally, removal of the chiral auxiliary and desulfonylation should afford the optically pure carbocycles.



Scheme 27

2.1 Synthesis of chiral lactones

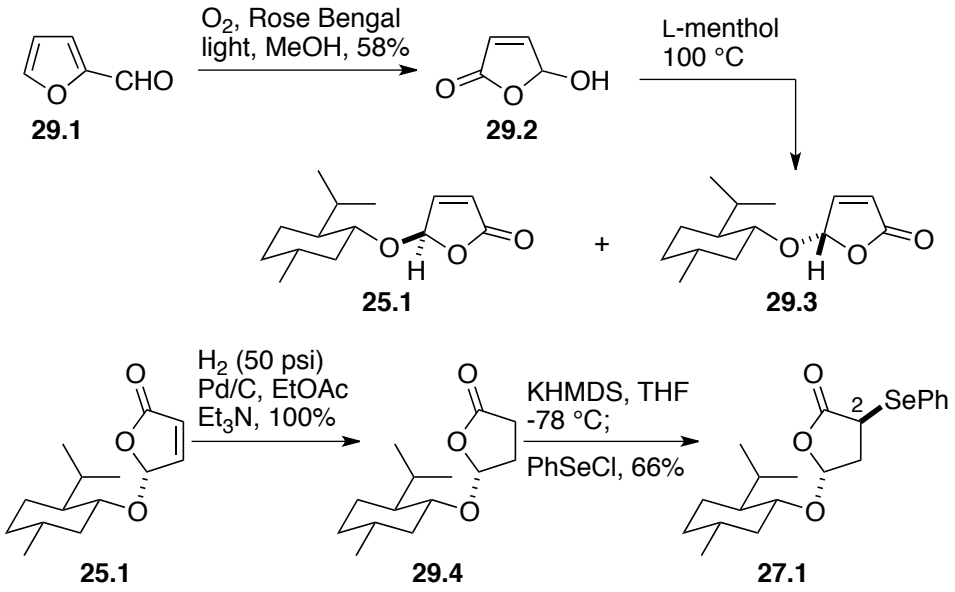
The chiral lactones used for this study are shown in Scheme 28.



Scheme 28

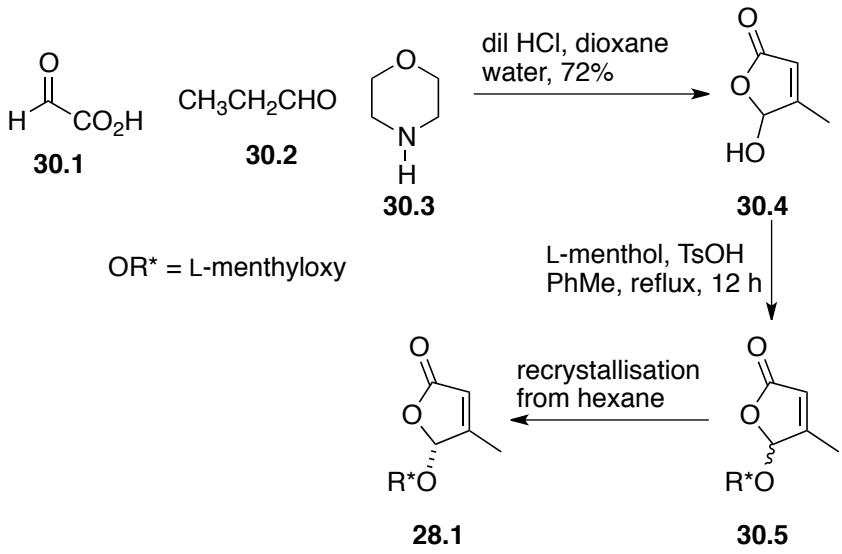
The chiral lactones **25.1**[25] and **27.1** were synthesized as described below. Photooxygenation of furfural (**29.1**), mediated by Rose Bengal in MeOH, gave the hydroxy lactone **29.2** by a Diels-Alder pathway. The racemic **29.2** was coupled

with L-menthol to give a diastereomeric mixture of **29.3** and **29.4** which, after recrystallization from hexane, gave[25] the desired single isomer **25.1**. Hydrogenation of lactone **25.1**, followed by deprotonation and selenation with PhSeCl, gave the selenolactone **27.1**, as the major isomer. The stereochemistry at C-2 was confirmed by Dr. Cheng using single crystal X-ray analysis.[10b]



Scheme 29

The chiral lactone **28.1** was prepared according to the literature method.[26] Acid catalyzed reaction between glyoxylic acid (**30.1**), morpholine (**30.3**) and propionaldehyde (**30.2**) gave the methyl-substituted hydroxy lactone **30.4**, which was then coupled with L-menthol to form **30.5** as a mixture of diastereomers. Recrystallization of **30.5** from hexane afforded the single isomer **28.1**.

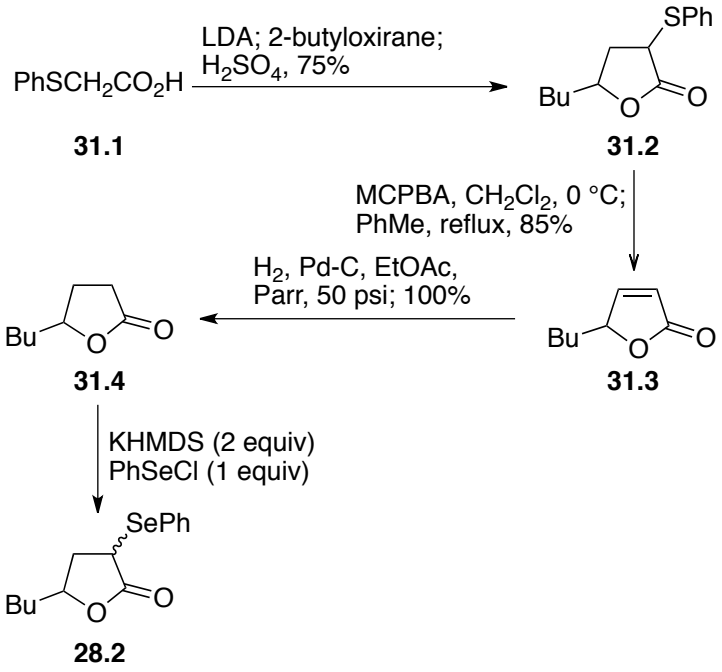


30.1 **30.2** **30.3** **30.4** **28.1** **30.5**

Scheme 30

Racemic γ-butyrolactone **28.2** was prepared by phenylselenation of the parent lactone **31.4**, using KHMDS and PhSeCl. The synthesis of **31.4** was carried-out as described in the literature.[27d] Reaction of (phenylthio)acetic acid with LDA and 2-butyloxirane, followed by treatment with H_2SO_4, gave α-(phenylthio)-γ-butyrolactone **31.2**. Oxidative elimination then produced the α,β-unsaturated γ-butyrolactone **31.3**, which was hydrogenated to give **31.4**.

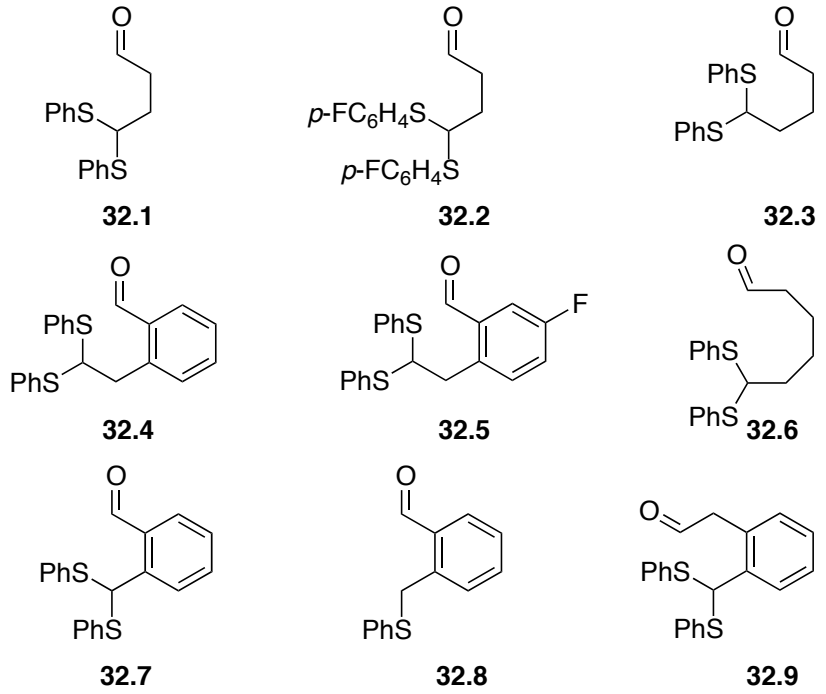
Both enantiomers of the lactone **31.4** are known[27a-c] and the enantiomers of **25.1**, **27.1** and **28.1** should be accessible by using D-menthol instead of L-menthol.



Scheme 31

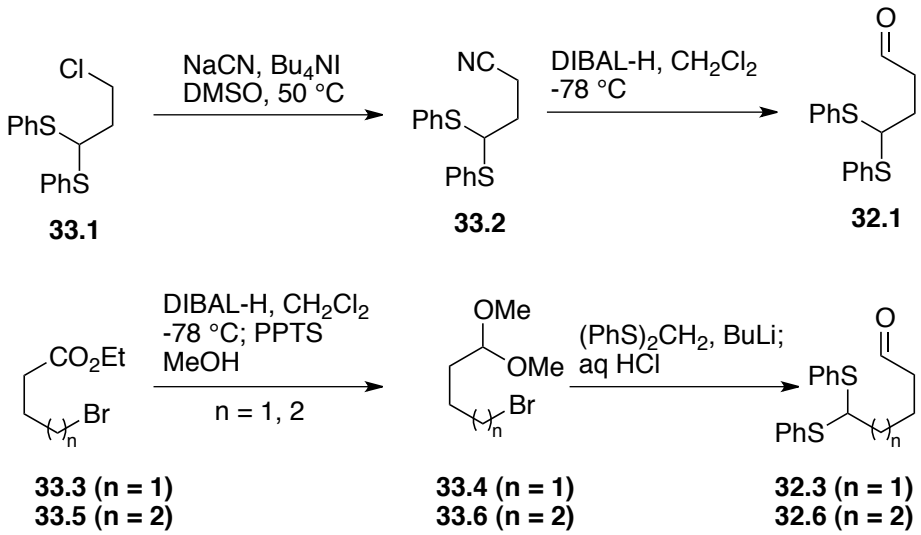
2.2 Synthesis of aldehydes for aldol reactions

The aldehydes **27.2**, used for the aldol reactions are shown in Scheme 32.



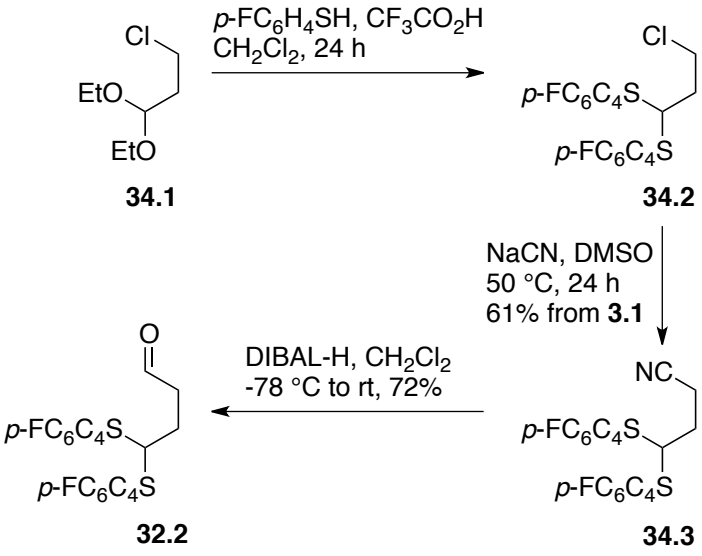
Scheme 32

Of these, **32.1**, **32.3** and **32.6** are known and were made by literature methods,[11b] as summarized in Scheme 33.



Scheme 33

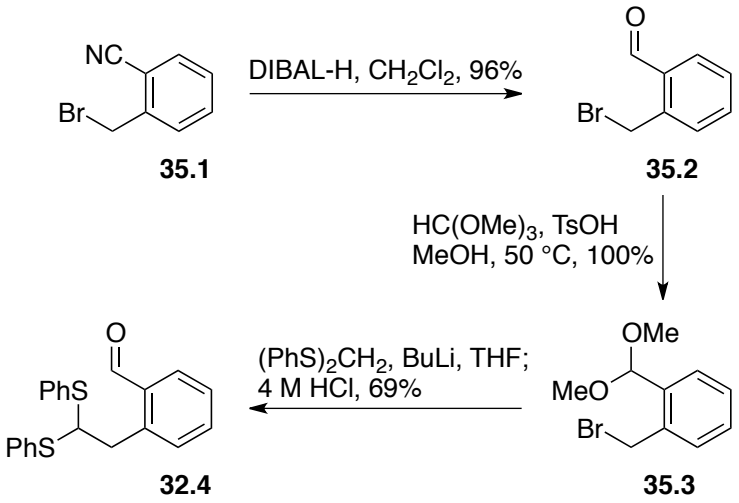
Synthesis of aldehyde **32.2** started (Scheme 34) from commercially available 3-chloropropionaldehyde diethyl acetal (**34.1**). Treatment of **34.1** with *p*-FC_6H_4SH and TFA resulted in acetal exchange with *p*-FC_6H_4S- groups to give **34.2**. This was then subjected to nucleophilic displacement of the chlorine with cyanide, using NaCN in DMSO at 50 °C to release **34.3** in 61% yield over two steps. Reduction of the nitrile using DIBAL-H gave the desired aldehyde **32.2** in 72% yield.



Scheme 34

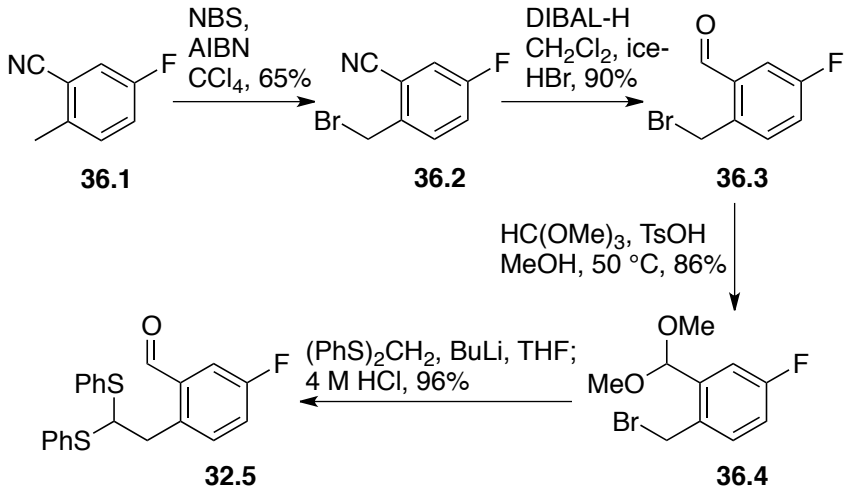
Aldehyde **32.4** was synthesized from commercial 2-(bromomethyl)-benzonitrile. DIBAL-H reduction of the nitrile group (Scheme 35) to the aldehyde level was done according to the literature procedure.[28] The stipulated use of hydrobromic acid in the workup of this reaction is crucial to avoid loss of the benzylic bromine and to prevent the formation of side products. The aldehyde

was then protected as an acetal using $(MeO)_3CH$ and a catalytic amount of $TsOH.H_2O$ in methanol. The resulting bromo acetal **35.3** was then alkylated with the anion derived from bis(phenylthio)methane. Finally, acid hydrolysis of the acetal group gave the desired aldehyde **32.4**.



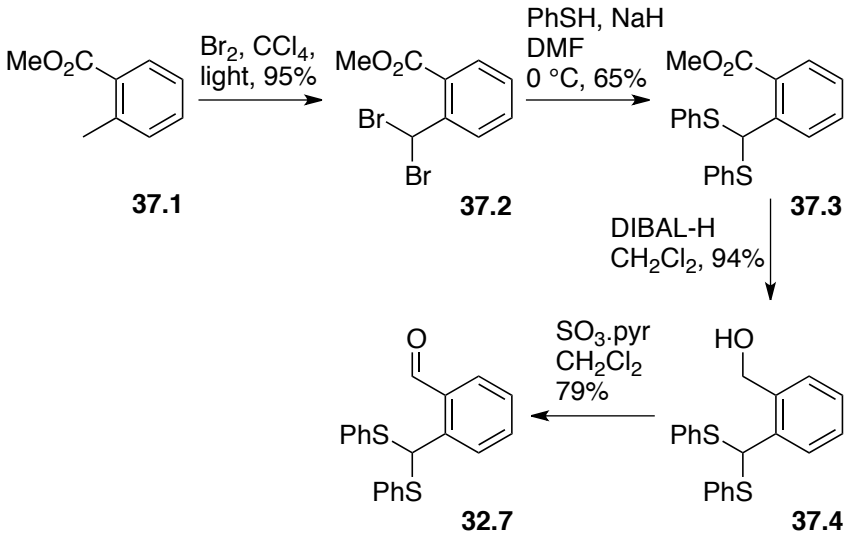
Scheme 35

Aldehyde **32.5** was also prepared (Scheme 36) by following the same sequence as above.[29,30] Commercially available 2-methyl-5-fluorobenzonitrile (**36.1**), was first subjected to radical bromination using *N*-bromosuccinimide and AIBN. Reduction of the nitrile group to an aldehyde, followed by acetal protection, gave **36.4**. Displacement of bromide by the anion of bis(phenylthio)methane and subsequent deprotection of the acetal released aldehyde **32.5**.



Scheme 36

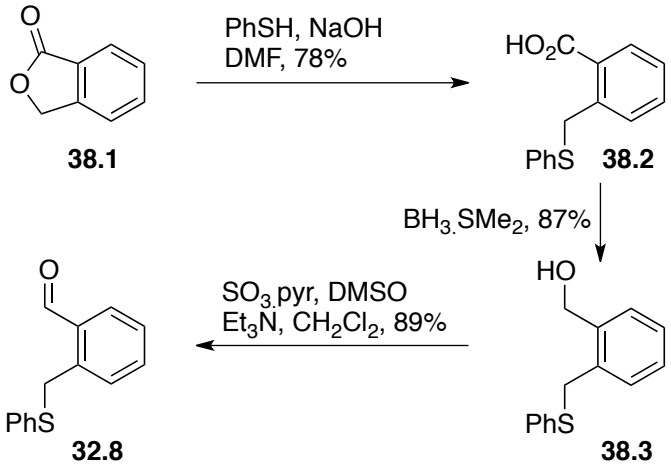
Benzylic bromination of methyl *o*-methylbenzoate under standard conditions[31] using bromine and light gave the geminal dibromide **37.2** (Scheme 37). Double nucleophilic displacement of bromine with PhSNa (generated from PhSH and NaH) in DMF, followed by reduction of the ester with DIBAL-H,



Scheme 37

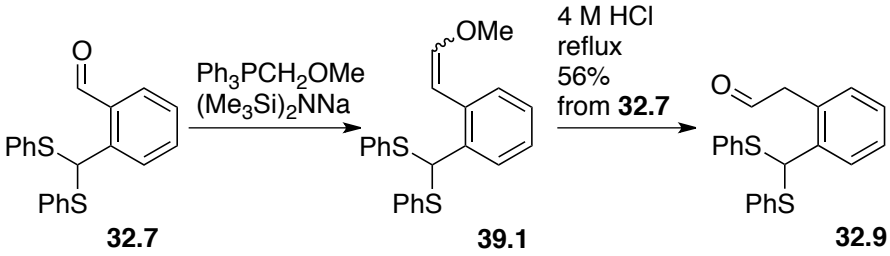
produced the alcohol **37.4** in 94% yield. Parikh-Doering oxidation then generated aldehyde **32.7** in 79% yield.

The mono(phenylthio) aldehyde **32.8** was prepared from phthalide (**38.1**). Ring opening of phthalide with PhSNa by a known procedure[32] gave acid **38.2** in 78% yield (Scheme 38). Reduction of the acid to an alcohol with $BH_3.SMe_2$,[33] followed by oxidation using SO_3.Py-DMSO, gave the desired aldehyde **32.8**.



Scheme 38

Aldehyde **32.9** was made from aldehyde **32.7** by Wittig olefination with $Ph_3P{=}CH(OMe)$ and acid hydrolysis (Scheme 39).



Scheme 39

2.3 Condensation of the chiral lactones with the aldehydes and synthesis of the ICD precursors

After the synthesis of the starting materials (Scheme 28) the next step was to condense the aldehydes with the lactones. Of course, these steps were studied after each aldehyde became available, but it is convenient to deal with all the aldehyde preparations together, and to treat the subsequent steps in a similar way.

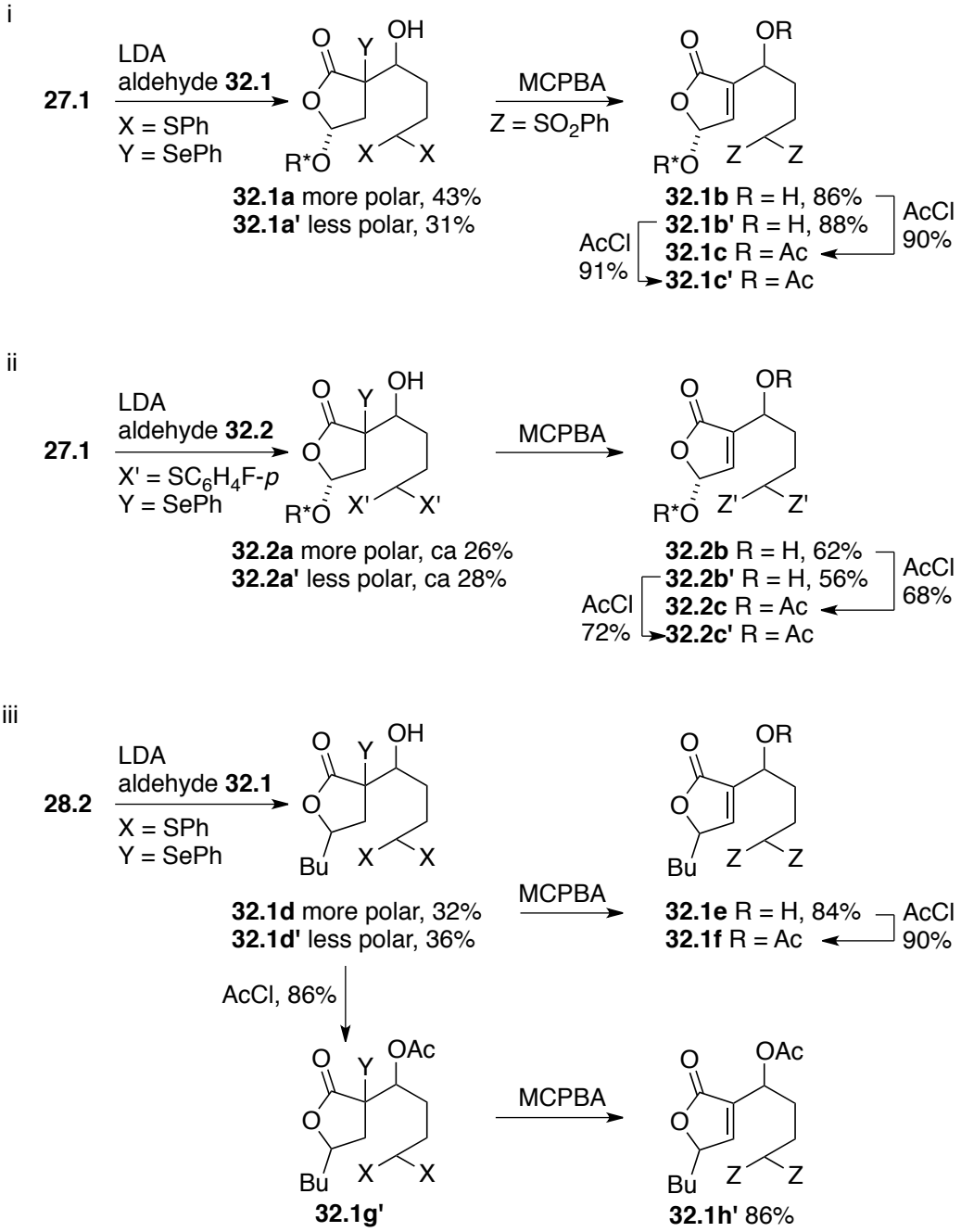
Two different procedures were used for condensing the aldehydes with the lactones. In the first approach the α,β-unsaturated chiral lactone **25.1** was allowed to react with the aldehydes under conditions reported by Jauch, using lithium phenyl selenide.[34] When Jauch attempted to do similar Morita-Baylis-Hillman reactions using standard conditions (catalytic DABCO) the desired product was not formed. But, by changing the nucleophile from DABCO to the more nucleophilic and less basic lithium phenyl selenide, he was able to carry out the reactions in good yield.[34a]

During our studies (Scheme 40), we observed that the aromatic aldehydes (**32.4**, **32.5**, **32.7** and **32.8**) react efficiently by the Jauch method. In contrast, the aliphatic aldehydes (**32.1**, **32.2**, **32.3** and **32.6**) reacted smoothly with the anion generated by deprotonation of the selenium-containing lactones **28.2** and **27.1**. The best conditions for deprotonation of the lactones involved adding a freshly prepared LDA solution slowly to a solution of the lactone in THF at −78 °C and stirring for another 1 h. Then a solution of the aldehyde was added dropwise. Reversing the order of addition, *i.e.* adding the lactones to the LDA or fast addition of LDA to the lactone resulted in extensive deselenation; however, the

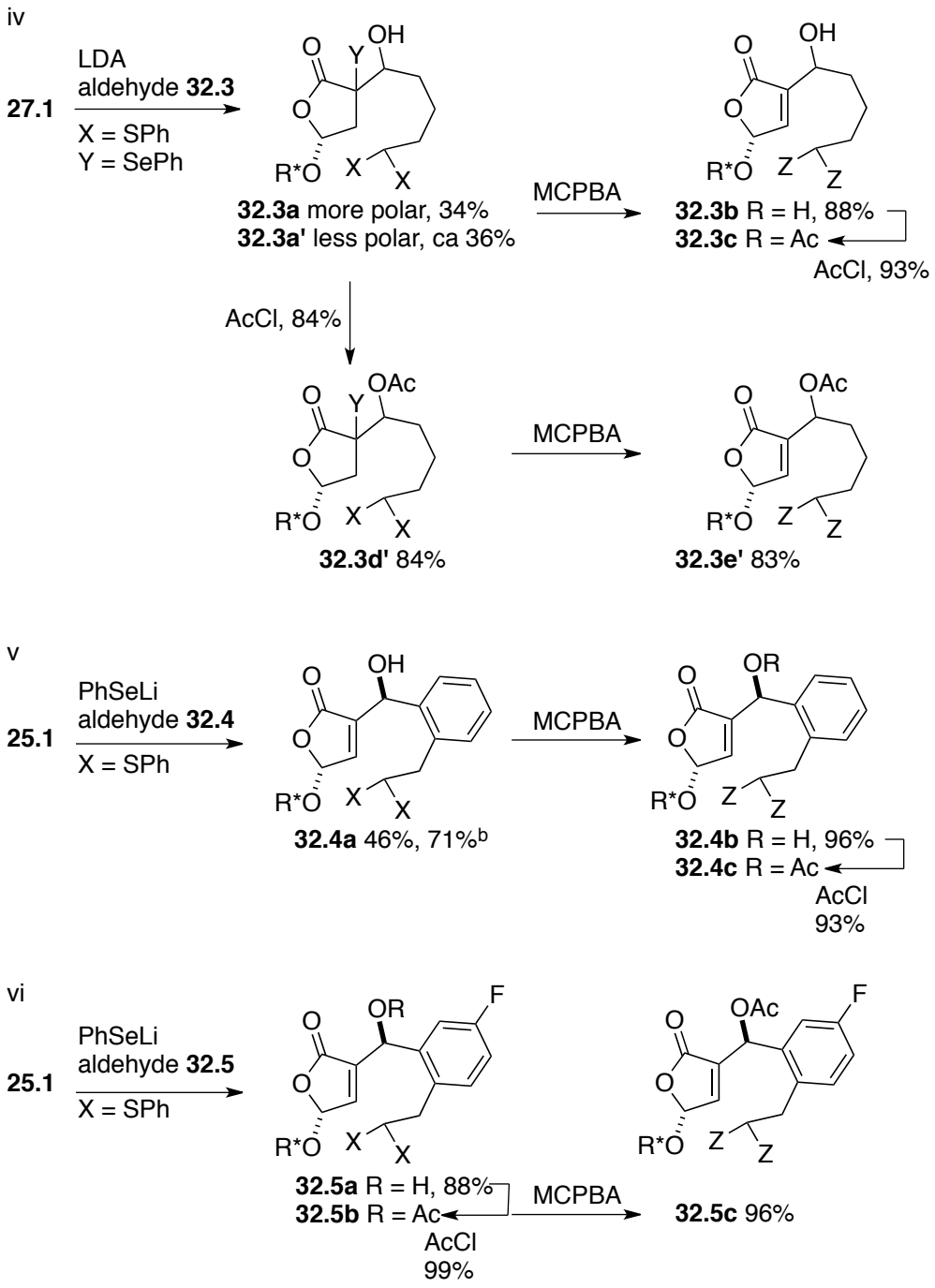
optimized procedure gave yields close to 70% with the aliphatic aldehydes. In a few experiments the use of $(Me_3Si)_2NK$ for deprotonation was also examined, but the yields were lower. During these aldol reactions, two diastereomers were separated; these are epimeric at the hydroxyl-bearing carbon. The fact that two diastereomers were formed is inconsequential, however.

Oxidative removal of selenium using MCPBA generated the required α,β-unsaturated lactone and also converted the phenylthio groups to phenylsulfonyl groups. This feature makes the use of phenylthio groups in the starting aldehydes especially convenient because the presence of a very acidic hydrogen [e.g. as in $C\mathbf{H}(SO_2Ph)_2$] at an earlier stage would probably interfere in the reaction of the carbanion with the aldehyde and, in fact, such interference was observed with the malonate system $C\mathbf{H}(CO_2Me)_2$ (see below, page 45).

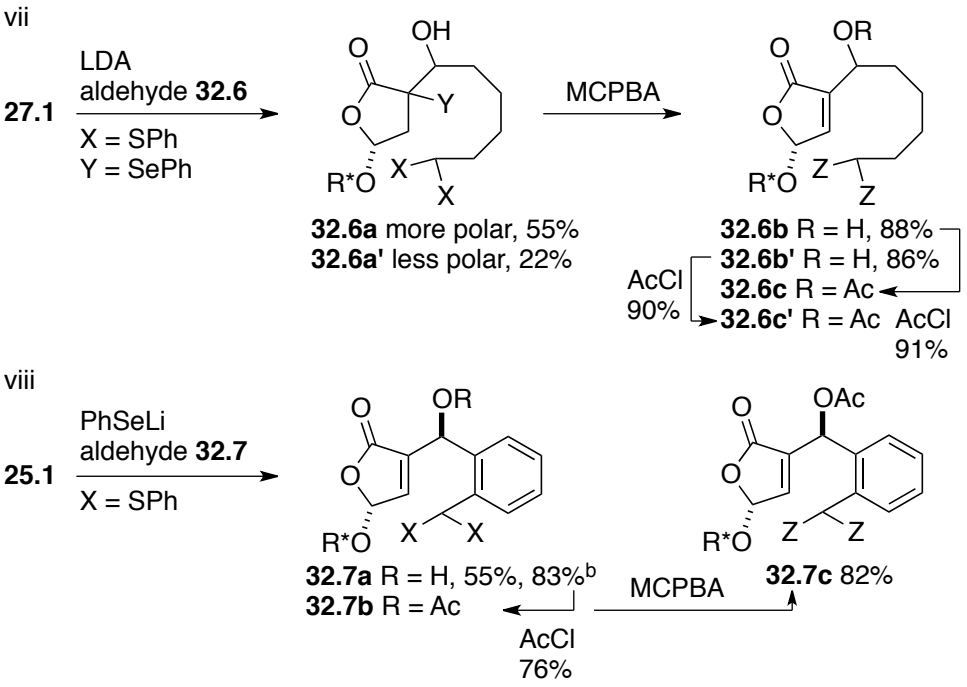
In the following Schemes R*O = L-menthyloxy, X = SPh, Y = SePh, Z = SO_2Ph, Z' = $SO_2C_6H_4F$-*p*.



Scheme 40 (part 1)

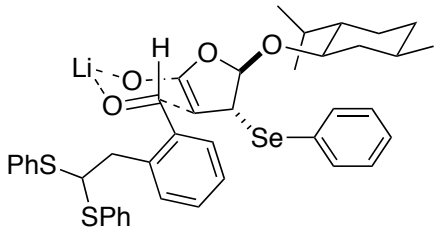


Scheme 40 (part 2)



Scheme 40 (part 3)

Condensation of aldehydes by the Jauch method using lithium phenyl selenide (entries v, vi and viii) resulted in the isolation of only a single isomer. The stereochemistry of the product was determined by X-ray analysis of suitable crystals obtained by recrystallization of **32.5c** (Figure 1). Jauch rationalized this outcome through the Zimmerman-Traxler model for the transition state in the aldol step (Scheme 41).[34a]



Scheme 41

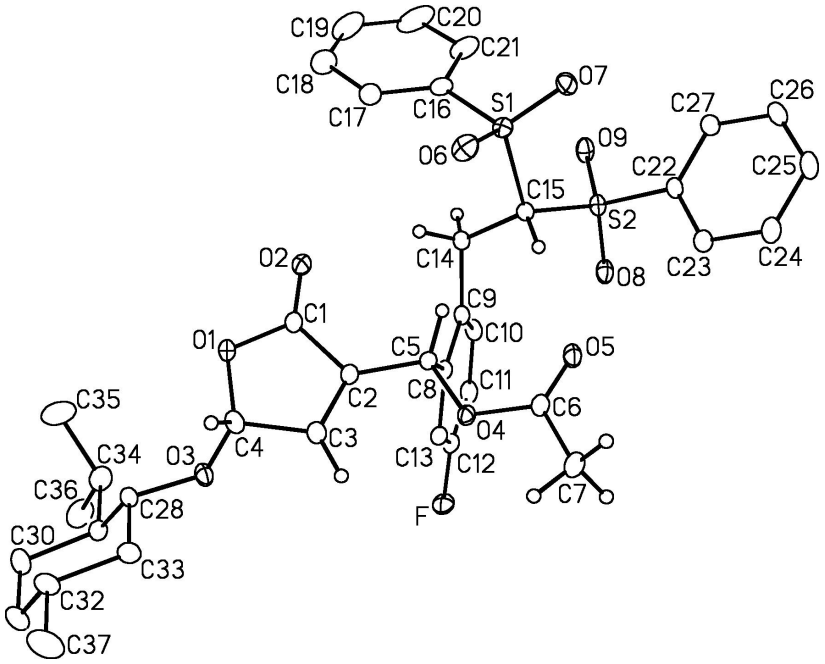
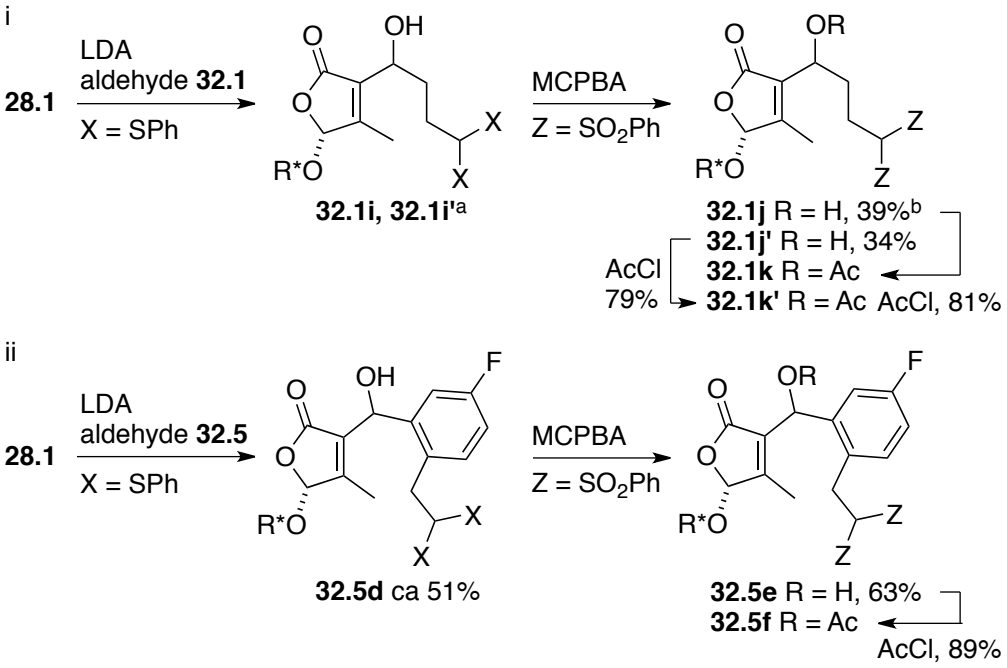


Figure 1. ORTEP diagram of compound 32.5c

The condensation of chiral lactone **28.1** (Scheme 42), in which the double bond carries a methyl substituent, was done as follows. Treatment of the lactone with LDA in THF at –78 °C for 1 h, followed by addition of an aldehyde, gave the desired alcohol as a mixture of diastereomers which are epimeric at the hydroxyl-bearing carbon. The reaction occurred at the α-position to the lactone carbonyl (Scheme 42).



[a]More polar 10%, less polar 12%, mixture of both 40%.
[b]More polar isomer.

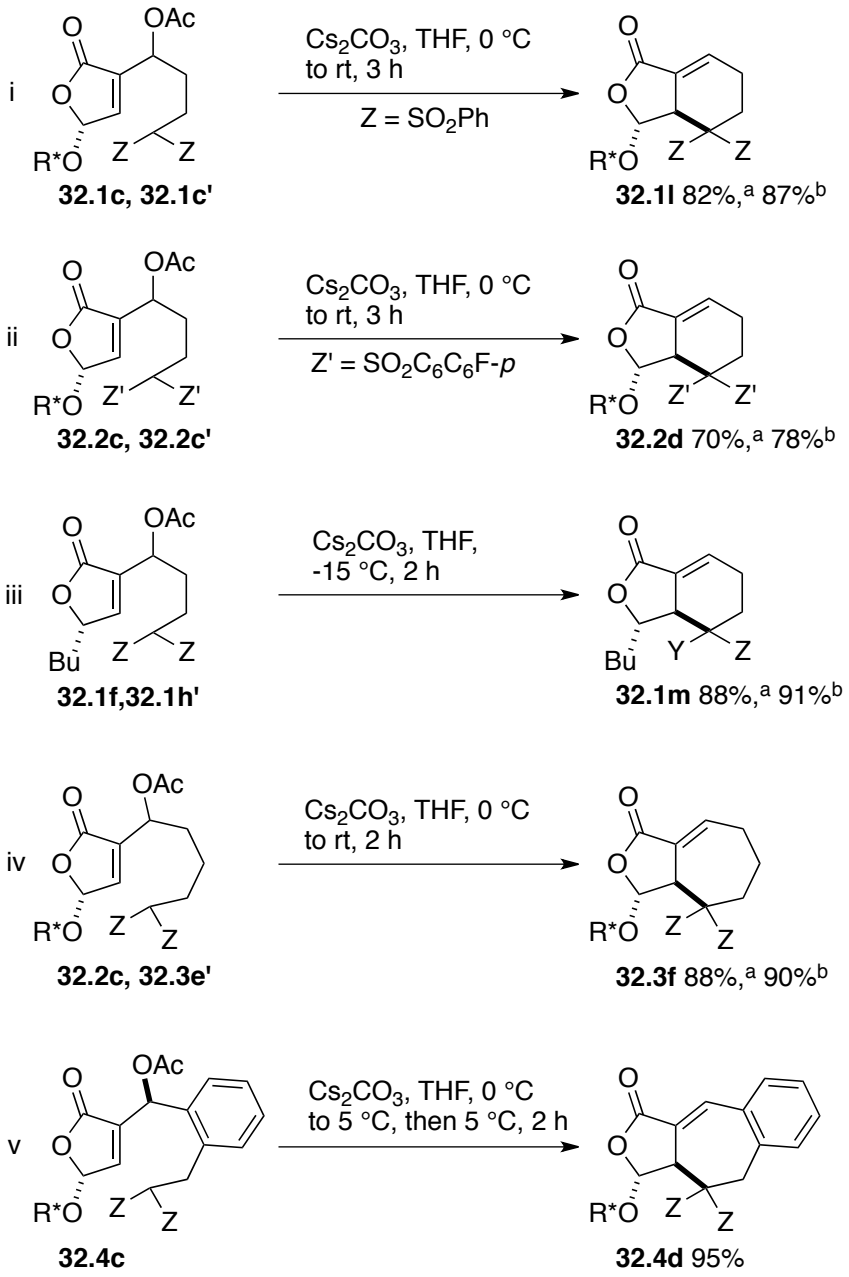
Scheme 42

The ICD precursors are prepared (Schemes 40 and 42) from the corresponding alcohols in very good yields, either by oxidation (MCPBA) followed by acetylation (AcCl, pyridine, DMAP) or by reversing the order of this sequence.

2.4 Ring closure by intramolecular conjugate displacement

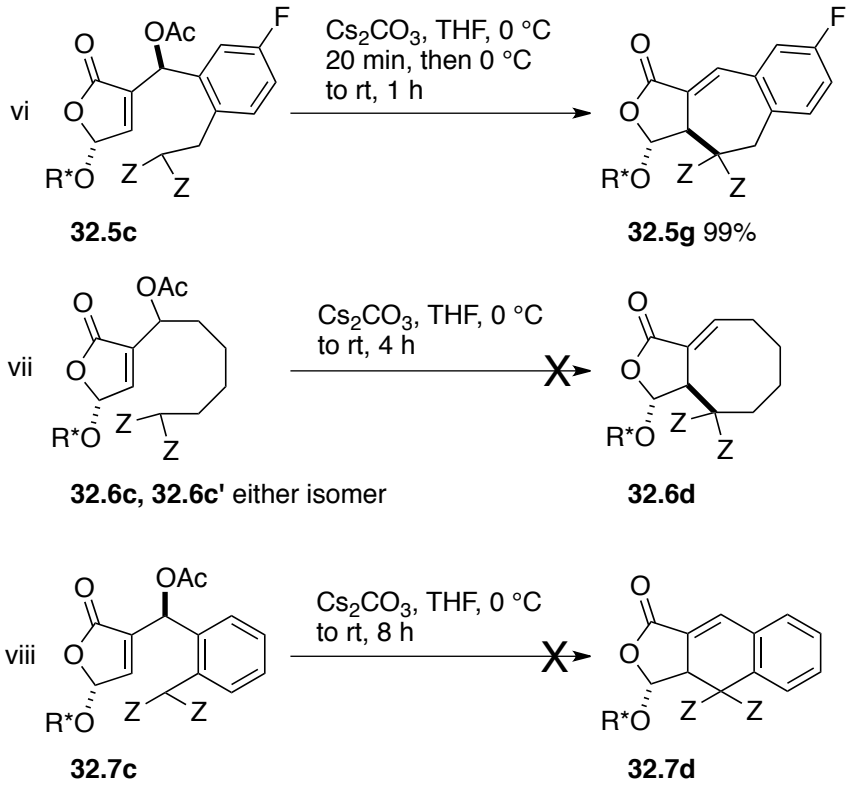
After the synthesis of the ICD precursors, the next step was to carry out the key intramolecular conjugate displacement so as to form optically pure carbocycles. For this, we used Cs_2CO_3 as the base in THF at 0 °C to room

temperature (Scheme 43), as these conditions had previously been found to work well.[11b]



[a]Acetate derived from more polar alcohol; [b]Acetate derived from less polar alcohol.

Scheme 43 (part 1)



Scheme 43 (part 2)

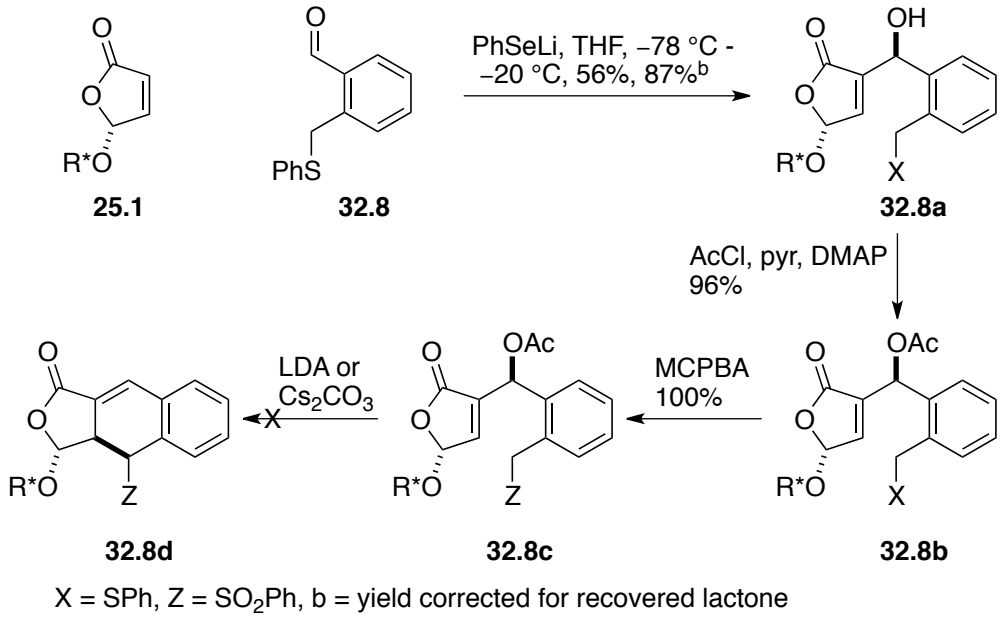
In those cases where we obtained two separable isomers of the ICD precursors (Scheme 43, entry i-iv), both gave the identical product. This indicates that attack of the intermediate carbanion on the β-carbon of the unsaturated lactone unit occurs smoothly both *syn* and *anti* to the acetate leaving group, and the stereochemistry at the newly-formed asymmetric center is not controlled by the stereochemistry of the acetoxy-bearing carbon.

Formation of six membered rings (Scheme 43, entry i and ii), irrespective of the nature of the acidifying groups (-SO_2Ph, -$SO_2C_6H_4F$-*p*), proceeded smoothly at 0 °C and gave the desired product in very good yields (70-87%) as a single isomer. It had previously been reported[35] from this laboratory that *p*-

fluorophenyl sulfones are desulfonylated faster than phenyl sulfones, hence the use of the $SO_2C_6H_4F$-*p* group.

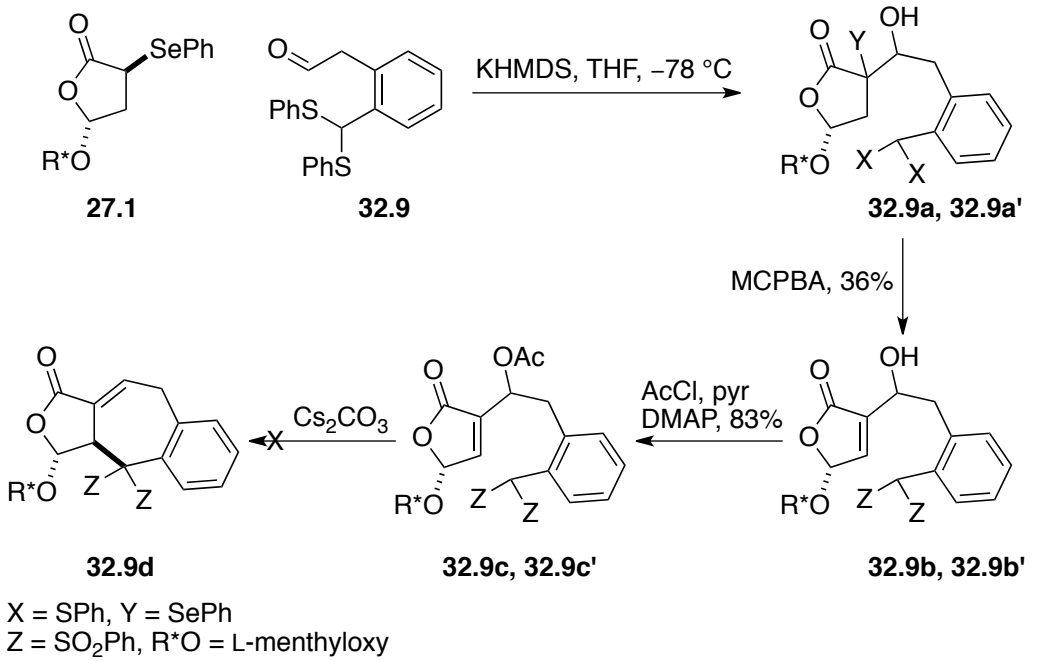
Changing the bulky L-menthyloxy group to butyl (Scheme 43, entry iii) produced a minor amount of a second isomer at 0 °C, but on decreasing the temperature to –15 °C, we solved this problem, and isolated only one isomer. Formation of a seven-membered ring (Scheme 43, entry iv) also proceeded smoothly to give the desired product in 90% yield as a single isomer. However, when we attempted to form an eight-membered ring (Scheme 43, entry vii), conjugate displacement did not occur and the main pathway appeared to be the result of elimination of acetate.

Seven-membered rings fused onto a benzene ring (Scheme 43, entries v and vi) are easily formed and very high yields were obtained. In these cases the carbanionic center was one carbon atom removed from the benzylic position. On the other hand, when the carbanionic center was benzylic (Scheme 43, entry viii), we did not isolate any of the expected ICD product; likewise, the corresponding experiment in the nitrogen series was also unsuccessful.[10b] We suspected that possibly the bulk of the two sulfone groups was preventing cyclization and so we prepared the ICD precursor **32.8c**, which contains only one sulfone group. Unfortunately, treatment of **32.8c** either with LDA or with Cs_2CO_3 did not give any ICD product (Scheme 44).



Scheme 44

At this point, we thought that there might be some unfavorable factors (such as the accessible approach angle of the nucleophile) that prevents the formation of six-membered rings from the benzylic position. In order to test this we prepared the ICD precursors **32.9c** and **32.9c'** (Scheme 45); however these did not cyclize either. Therefore, we concluded that a nucleophilic benzylic position (either as a carbanion or as an aniline[12c]) is not suitable for ICD reactions.



27.1 **32.9** **32.9a, 32.9a'** **32.9b, 32.9b'** **32.9c, 32.9c'** **32.9d**

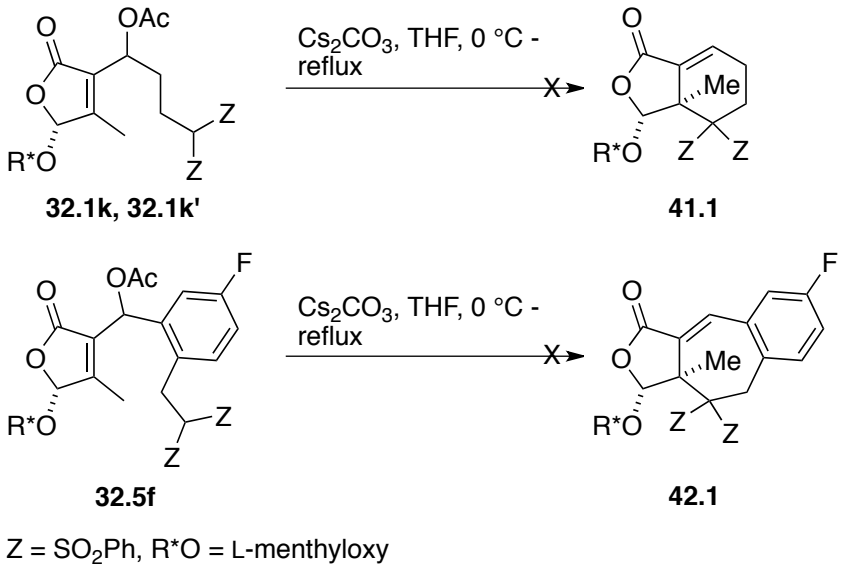
Scheme 45

The possibility that other acidifying groups might not be subject to this restriction, was explored briefly, but our attempts to prepare the ICD precursor using the ester **40.1**[36] or the malonate **40.2**[11b] (Scheme 46) were unsuccessful: with the ester, the initial adduct underwent spontaneous lactonization and with the malonate, the presence of the acidic hydrogen [C**H**$(CO_2Me)_2$] prevented addition of the carbanion from **27.1** to the aldehyde, even when the carbanion was used in excess.

40.1 **40.2**

Scheme 46

A limitation to the ICD process is that substitution at the carbon being attacked is not tolerated and we found that compounds **32.1k**, **32.1k'** and **32.5f** failed to undergo the ICD ring closure (Scheme 47); they were recovered unchanged at room temperature, and the ICD pathway was not followed at a higher temperature.



Scheme 47

2.5 Stereochemistry of ICD adducts

The ICD ring closure always occurs from the opposite side to the chiral auxiliary in the all-carbon series. For the fluorine-substituted 7-membered ICD product **32.5g**, the stereochemistry at the newly created stereogenic center was established by single crystal X-ray analysis (Figure 2).

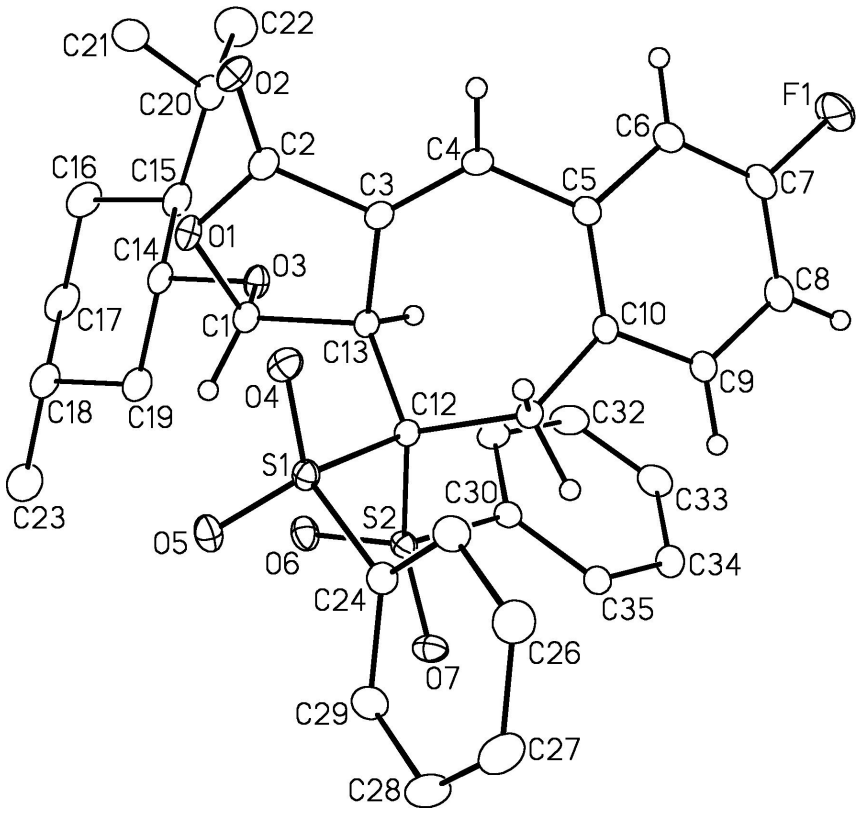


Figure 2. ORTEP diagram of compound 32.5g

The coupling constant for the signal of the acetal hydrogen (O-C**H**-O) of **32.5g** at δ 6.46 is < 1 Hz and the value for the same hydrogen (δ 6.53) of **32.4d** is 1 Hz. This is possible only if the relevant dihedral angles in both these compounds at the newly-created asymmetric center are very similar. Therefore, by analogy, we assign the same stereochemistry to **32.4d**. Similarly, for the 7-membered ICD product **32.3f**, the acetal signal at δ 6.78 is a doublet with J = 1.3 Hz, a value consistent only with the indicated stereochemistry, and we conclude that in all these cases, ICD formation occurred from the opposite side to chiral auxiliary, as expected on the basis of steric considerations.

For the six-membered ICD products **32.1l**, **32.2d** and **32.1m**, assignment of stereochemistry was important because in the nitrogen series, formation of a six-membered ring resulted in an anomalous stereochemistry.[12c] In that case the nitrogen nucleophile approached from the same face as the auxiliary group – an unexpected outcome that was established by single crystal X-ray analysis of the ICD product.[12c] But in my project, we were able to get satisfactory crystals of **32.1l** (Figure 3), and X-ray analysis established the indicated geometry, *i.e.*, the ICD pathway occurred from the opposite side to chiral auxiliary. The stereochemistry for the other two examples in which a six-membered ring (**32.2d** and **32.1m**) is formed were assigned by analogy. Evidently, the factors responsible for the anomalous outcome in the nitrogen series for the production of a six-membered ring (nitrogen adds *syn* to the R*O group) do not operate in the all-carbon ICD series or else the steric bulk of the two-sulfone groups prevents this unusual outcome.

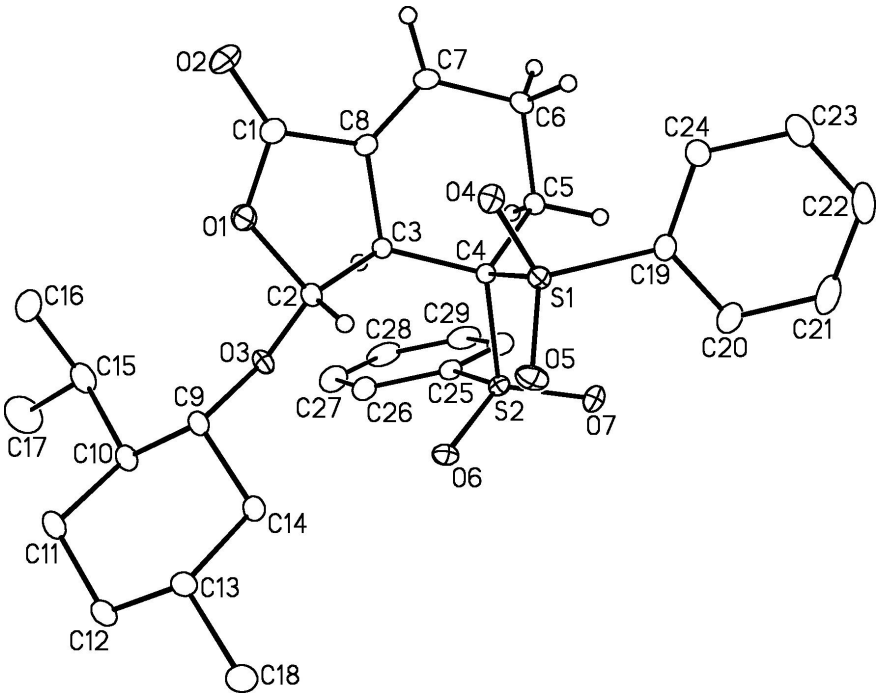
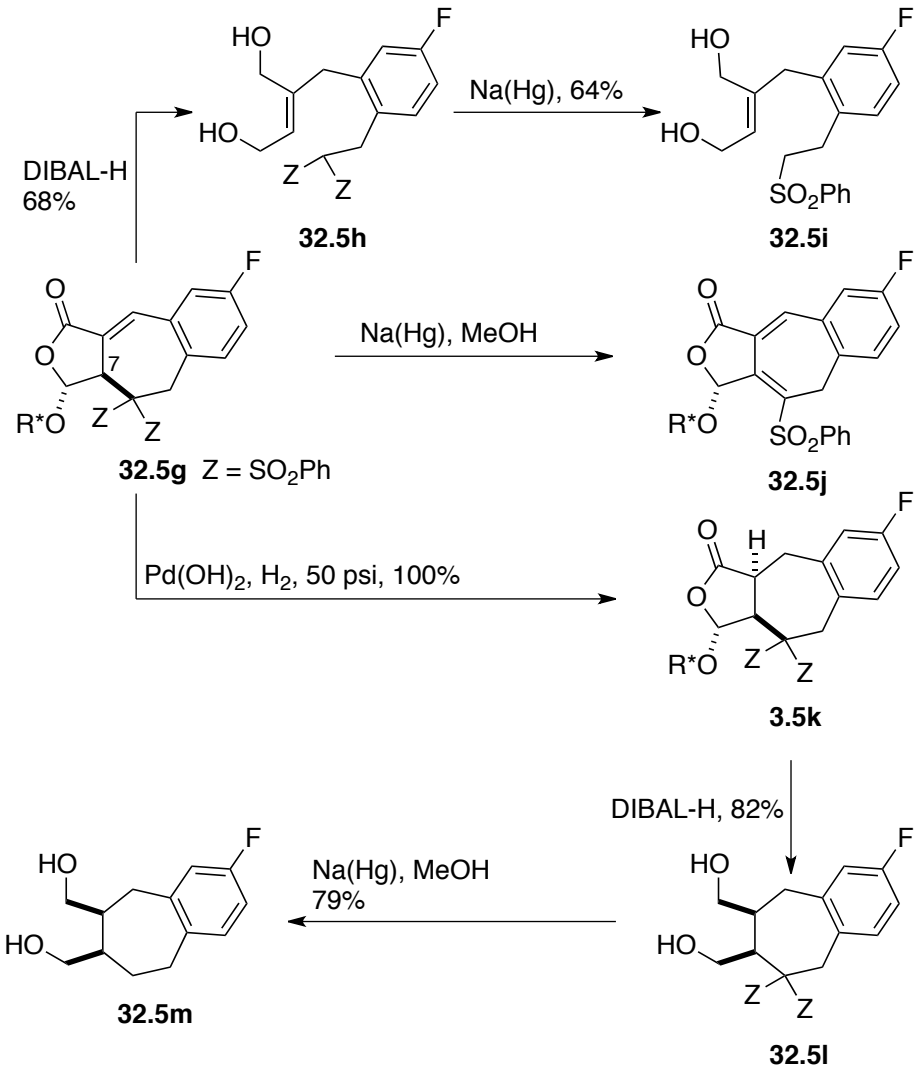


Figure 3. ORTEP diagram of compound 32.1l

2.6 Removal of the chiral auxiliary

In the nitrogen series, where the nucleophile for the ICD reaction is nitrogen, the chiral auxiliary was easily removed by DIBAL-H reduction, and the pure cyclic amines were obtained in good yields.[12c] But in the present project, this process was initially very troublesome. In order to study this step, we used **32.5g** as a test case (Scheme 48). Treatment of with DIBAL-H opened the ring that had been formed by ICD, and the resulting product, on treatment with Na(Hg), undergoes mono-desulfonylation[37] to give diol **32.5i**. Single crystal X-ray analysis of this compound confirmed the structure (Figure 4).



Scheme 48

Mechanistically, the formation of **32.5h** (see Scheme 49) must have occurred by conjugate reduction of the unsaturated carbonyl system to generate an enolate equivalent (**32.5n**), which displaced the germinal bis(sulfone) unit to give **32.5o**. An unsaturated lactone was reformed, and was then again reduced initially to lactol **32.5p** and then to diol **32.5h**. Periodic analysis of the DIBAL-H reduction mixture by HRMS revealed the generation of substances with molecular

formulas corresponding to the intermediates **32.5o** and **32.5p**. Situations in which displacements of the type **32.5n→32.5o** are observed must be rare as a search of the Reaxys database served to identify only a single close precedent.[38]

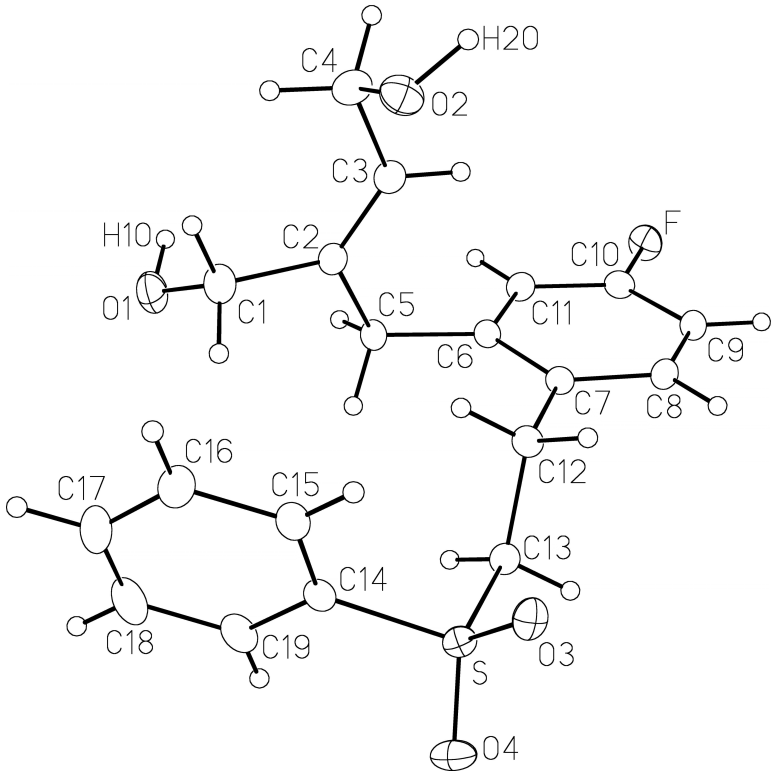
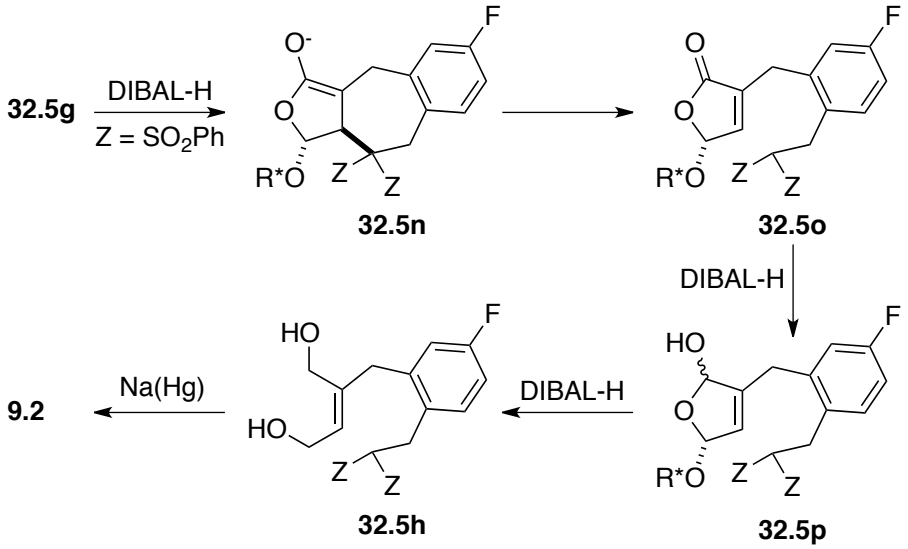


Figure 4. ORTEP diagram of compound 32.5i



Scheme 49

At this point we tried to remove the sulfone groups of **32.5g** before reducing the lactone, but found that elimination of one of the sulfonyl groups occurred to give **32.5j** (see Scheme 48); presumably, the electron-withdrawing sulfone groups acidified the allylic C-7 hydrogen sufficiently to permit elimination[39] in the basic reaction medium.

Once these characteristics of **32.5g** were established we found that stereoselective hydrogenation of **32.5g** over Pearlman's catalyst gave the hydrogenated product **32.5k** in quantitative yield (when we tried the hydrogenation with Pd-C and H_2, the yield was either very low or no reaction occurred). The hydrogenation occurred from the less crowded face and the resulting stereochemistry was confirmed by single crystal X-ray analysis of **32.5k** (Figure 5). DIBAL-H reduction of **32.5k**, followed by desulfonylation, gave the desired optically pure carbocycle **32.5m** in good yield.

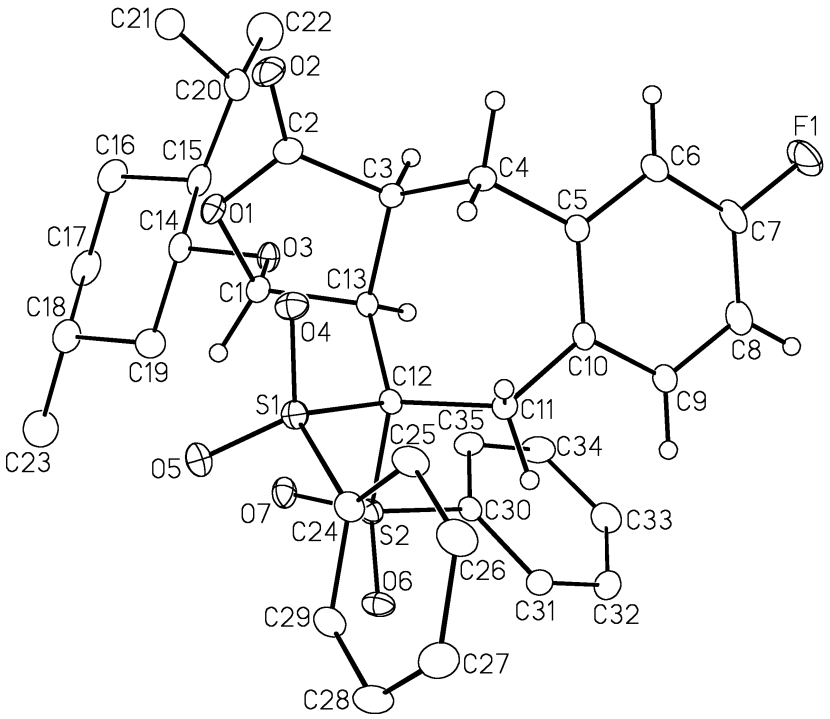


Figure 4. ORTEP diagram of compound 32.5k

3 Conclusion

During this project, we were able to show that intramolecular conjugate displacement (ICD) can be successfully used for the synthesis of optically pure carbocycles. The precursors for the ICD reactions were made either by PhSeLi-mediated Morita-Baylis-Hillman condensation of chiral lactones with aldehydes or by an aldol reaction between selenium-containing chiral lactones with aldehydes. Both six-membered and seven-membered optically pure carbocycles were synthesized in good yield. A limitation is that the nucleophilic carbon atom must not be benzylic and the acceptor double bond should be unsubstituted. The method works well, especially for benzo-fused carbocycles, and either enantiomer is accessible because both enantiomers of the chiral auxiliary[25] are readily available. The aldehyde components are made by simple reactions, at least in the examples we have studied. The stereochemistry of the key compounds was confirmed by NMR measurements and X-ray analysis. Our research, together with the prior work from this laboratory completes the study of the ionic ICD process.

4 EXPERIMENTAL SECTION

General Procedures. Unless stated to the contrary, the following conditions apply: 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 x 42 cm) of R3-11 catalyst[40] and then through a similar column of Drierite. All solvents for reactions were dried, as described below. Glassware was dried in an oven for at least 3 h before use (120 °C) and either cooled in desiccators over Drierite, or assembled quickly, sealed with rubber septa, and allowed to cool under a slight static pressure of Ar. Reaction mixtures were stirred with Teflon-coated magnetic stirring bars.

Solvents used for chromatography was distilled before use.

Products were isolated from solution by evaporation under water aspirator vacuum at room temperature, using a rotary evaporator and the residue was then kept under oil pump vacuum.

Microliter syringes were washed with water and acetone using a suction device to draw the solvents through. Then air was sucked through for 1 min. The solution to be dispensed was drawn up and expelled, and this operation was repeated several times before drawing up the sample to be used. Cannula transfers were always done under slight pressure (Ar), not by suction.

Commercial thin layer chromatography (TLC) plates (silica gel, Merck 60F-254) were used. Spots were detected by spraying the plate with a solution of phosphomolybdic acid,[41] followed by charring on a hot plate, or by examination

under UV light. Silica gel for flash chromatography was Merck type 60 (230-400 mesh).

Dry solvents were prepared under an inert atmosphere and transferred by dry syringes fitted with oven-dried needles, or cannula. Dry THF was distilled from sodium benzophenone ketyl. Dry Et_3N, *i*-Pr_2NH, CH_2Cl_2, and pyridine were distilled from CaH_2. All other solvents were used as purchased. Commercial (Aldrich) solutions of *n*-BuLi (in hexanes) were titrated and found to have the stated molarity.

FTIR measurements were recorded on a Nicolet 7000 FTIR instrument. Measurements were made as casts from specified solvent.

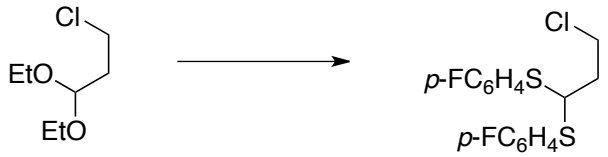
^1H Nuclear magnetic resonance spectra were recorded with Varian INOVA-300 (at 300 MHz), Varian INOVA-400 (at 400 MHz), Varian INOVA-500 (at 500 MHz) spectrometers in the specified deuterated solvent. ^{13}C spectra were recorded with Varian INOVA-400 (at 100 MHz), Varian INOVA-500 (at 125 MHz). The symbols s, d, t, and q used for ^{13}C NMR signals indicate 0, 1, 2, or 3 attached hydrogens, respectively, which are assigned based on the APT experiment.

Mass spectra were recorded with Agilent Technologies 6220 oaTOF or Agilent technologies 5975C MSD single quadrupole mass spectrometers. Low resolution LC-mass spectra were measured with an Agilent 1100MSD single quadrupole mass spectrometer with electrospray ionization.

Solvent mixtures specified as x% A-B indicate that X mL of A were mixed with (100-X) mL of B.

Compounds isolated by flash chromatography were pure by TLC and, unless otherwise stated, also as judged by high field ^{1}H and ^{13}C NMR spectra.

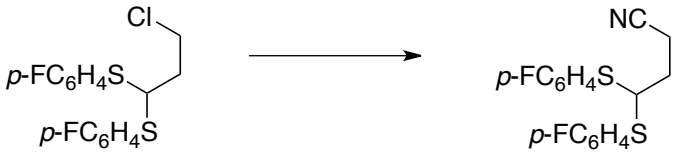
1-({3-Chloro-1-[(4-fluorophenyl)sulfanyl]propyl}sulfanyl)-4-fluoro-benzene (34.2).



34.1 **34.2**

4-Fluorothiophenol (3.6 g, 28.15 mmol) and CF_3CO_2H (2.38 g, 21.11 mmol) were added to a stirred solution of **34.1** (1.17 g, 7.03 mmol) in CH_2Cl_2 (30 mL) at room temperature and stirring was continued for 24 h. The reaction mixture was quenched with water (20 mL) and extracted with CH_2Cl_2 (2 x 30 mL). The combined organic extracts were washed with aqueous NaOH (10 w/v) 2 x 10 mL) and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (4 x 15 cm), using 8% Et_2O-hexane, gave **34.2** which was used directly for the next step.

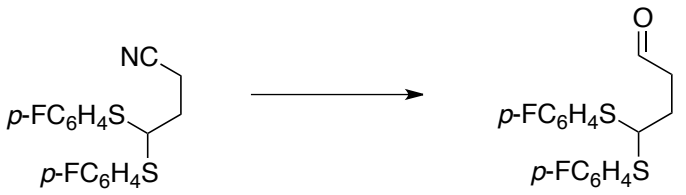
4,4-Bis[(4-fluorophenyl)sulfanyl]butanenitrile (34.3).



34.2 **34.3**

A solution of **34.2** (2.13 g, 6.44 mmol) in DMSO (2.5 mL) was added to a stirred mixture of NaCN (1.58 g, 32.23 mmol) and Bu_4NI (475 mg, 1.28 mmol) in DMSO (25 mL), and the resulting mixture was stirred at 50 °C for 24 h, cooled to room temperature, diluted with water (20 mL) and extracted with Et_2O (2 x 100 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (4 x 15 cm), using 20% Et_2O-hexane, gave **34.3** (1.37 g, 61% over two steps) as an oil: FTIR ($CDCl_3$, cast) 3094, 3067, 2856, 2248, 1589, 1489, 1443, 1420 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.49-7.45 (m, 4 H), 7.07-7.02 (m, 4 H), 4.27 (t, J = 7.1 Hz, 1 H), 2.68 (t, J = 7.1 Hz, 2 H), 2.10 (q, J = 7.1 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.1 (**C**F, d, $^1J_{CF}$ = 249.9 Hz), 136.1 (**C**CCF, d, $^3J_{CF}$ = 8.4 Hz), 127.5 (**C**CCCF, d, $^4J_{CF}$ = 3.5 Hz), 118.4 (s), 116.4 (**C**CF, d, $^2J_{CF}$ = 21.9 Hz), 58.5 (d), 31.0 (t), 15.2 (t); exact mass (electrospray) m/z calcd for $C_{16}H_{13}F_2NNaS_2$ (M + Na) 344.0350, found 344.0358.

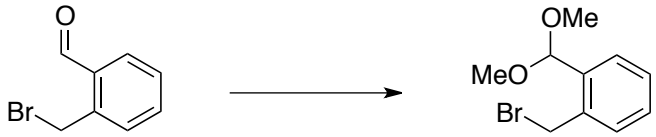
4,4-Bis[(4-fluorophenyl)sulfanyl]butanal (32.2).



34.3 **32.2**

DIBAL-H (1 M in PhMe, 3.1 mL, 3.11 mmol) was added by syringe pump over 20 min to a stirred and cooled (-78 °C) solution of **34.3** (500 mg, 1.55 mmol) in CH_2Cl_2 (16 mL). After the addition, stirring at -78 °C was continued for 1 h and then the cold bath was replaced by an ice bath. Stirring at 0 °C was continued for 30 min and the mixture was quenched with water (0.56 mL, 31 mmol) and NaF[42] (1.34 g, 31 mmol). The ice bath was removed, the mixture was diluted with Et_2O (50 mL), stirred vigorously for 1 h and then filtered through a pad of Celite (1 x 3 cm diameter) using Et_2O. Evaporation of the filtrate and flash chromatography of the residue over silica gel (2 x 15 cm), using 20% Et_2O-hexane, gave **32.2** (359 mg, 72%) as an oil: FTIR ($CDCl_3$, cast) 3067, 2927, 2849, 2726, 1724, 1589, 1490, 1443, 1443 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.80 (br s, 1 H), 7.49-7.45 (m, 4 H), 7.07-7.02 (m, 4 H), 4.30 (t, J = 6.8 Hz, 1 H), 2.83 (td, J = 7.1, 1.0 Hz, 2 H), 2.14 (q, J = 7.0 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.6 (s), 162.9 (**C**F, $^1J_{CF}$ = 249.0 Hz), 135.7 (**C**CCF, $^3J_{CF}$ = 8.3 Hz), 128.3 (**C**CCCF, $^4J_{CF}$ = 3.5 Hz), 116.2 (**C**CF, $^2J_{CF}$ = 21.9 Hz), 59.2 (d), 41.1 (t), 27.9 (t); exact mass (electrospray) m/z calcd for $C_{16}H_{14}F_2NaOS_2$ (M + Na) 347.0346, found 347.0346.

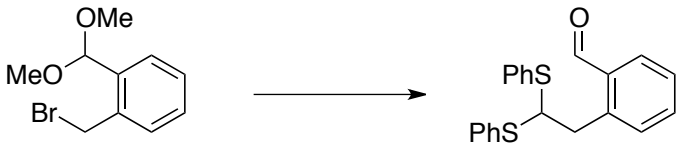
1-(Bromomethyl)-2-(dimethoxymethyl)benzene (35.3).



35.2 **35.3**

$CH(OMe)_3$ (2.54 mL, 23.23 mmol) was added to a solution of **35.2**[28] (925 mg, 4.65 mmol) and $TsOH.H_2O$ (88 mg, 0.46 mmol) in anhydrous MeOH (23 mL), and the mixture was heated at 50 °C for 12 h., cooled, and quenched with Et_3N (3 mL). The MeOH was evaporated under reduced pressure and the residue was diluted with water (20 mL) and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (4 x 15 cm), using 6% Et_2O-hexane, gave **35.3** (1.10 g, 100%) as a colorless oil: FTIR ($CDCl_3$, cast) 3064, 2991, 2953, 2904, 2829, 1488, 1455 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.60-7.56 (m, 1 H), 7.40-7.37 (m, 1 H), 7.34-7.30 (m, 2 H), 5.64 (s, 1 H), 4.69 (s, 2 H), 3.35 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.2 (s), 135.7 (s), 131.1 (d), 129.0 (d), 128.4 (d), 127.4 (d), 101.1 (d), 53.3 (q), 30.7 (t); exact mass (electrospray) *m/z* calcd for $C_{10}H_{13}{}^{79}BrNaO_2$ (M + Na) 266.9991, found 266.9989.

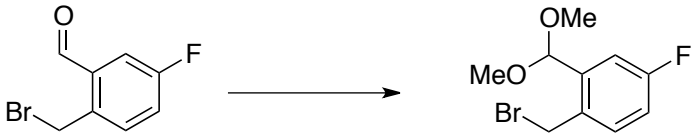
2-[2,2-Bis(phenylsulfanyl)ethyl]benzaldehyde (32.4).



35.3 **32.4**

BuLi (2.5 M in hexane, 0.63 mL, 1.57 mmol) was added dropwise to a stirred and cooled (0 °C) solution of $(PhS)_2CH_2$ (335 mg, 1.45 mmol) in THF (4 mL). Stirring at 0 °C was continued for 10 min and the mixture was then cooled to -78 °C. A solution of **35.3** (300 mg, 1.20 mmol) in THF (6 mL) was added rapidly in one portion and stirring at -78 °C was continued for 30 min and then at 0 °C (ice bath) for 10 min. Hydrochloric acid (4 M, 3 mL) was added, the cold bath was removed and stirring was continued for 3 h. The mixture was diluted with water (20 mL) and extracted with Et_2O (50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 8% Et_2O-hexane, gave **32.4** (289 mg, 69%) as a colorless oil: FTIR ($CDCl_3$, cast) 3055, 2861, 2832, 2742, 1699, 1598, 1574, 1480, 1451 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 10.03 (br s, 1 H), 7.76 (dd, *J* = 7.6, 1.4 Hz, 1 H), 7.51 (td, *J* = 7.5, 1.5 Hz, 1 H), 7.41 (td, *J* = 7.5, 1.1 Hz, 1 H), 7.36-7.34 (m, 4 H), 7.31-7.24 (m, 7 H), 4.71 (t, *J* = 7.5 Hz, 1 H), 3.60 (d, *J* = 7.5 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.4 (d), 139.9 (s), 134.2 (s), 134.1 (d), 133.5 (d), 133.0 (d), 132.9 (d), 132.9 (d), 128.9 (d), 127.9 (d), 127.6 (d), 59.5 (d), 39.7 (t); exact mass (EI) *m/z* calcd for $C_{21}H_{18}OS_2$ 350.0799, found 350.0796.

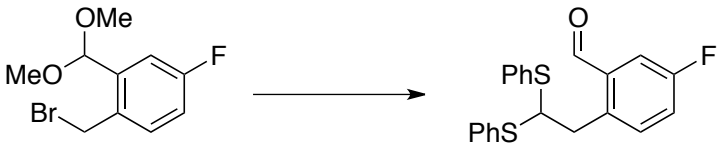
1-(Bromomethyl)-2-(dimethoxymethyl)-4-fluorobenzene (36.4).



36.3 **36.4**

$CH(OMe)_3$ (4.2 mL, 38.35 mmol) was added to a solution of **36.3**[29,30] (1.67 g, 7.67 mmol) and $TsOH.H_2O$ (146 mg, 0.77 mmol) in anhydrous MeOH (30 mL) and the mixture was heated at 50 °C for 1 h. The reaction mixture quenched with Et_3N (3 mL) and the MeOH was evaporated under reduced pressure. The residue was partitioned between water (20 mL) and Et_2O (50 mL), and the organic phase was washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (4 x 15 cm), using 5% Et_2O-hexane, gave **36.4** (1.75 g, 86%) as a colorless oil: FTIR ($CDCl_3$, cast) 3081, 2993, 2956, 2936, 2907, 2831, 1611, 1595, 1495, 1447, 1423 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37-7.32 (m, 2 H), 7.01 (td, J = 8.2, 2.8 Hz, 1 H), 5.63 (s, 1 H), 4.64 (s, 2 H), 3.35 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.6 (**C**F, $^1J_{CF}$ = 248.5 Hz), 139.0 (**C**CCF, $^3J_{CF}$ = 7.3 Hz), 132.8 (**C**CCF, $^3J_{CF}$ = 8.3 Hz), 131.6 (**C**CCCF, $^4J_{CF}$ = 3.6 Hz), 115.8 (**C**CF, $^2J_{CF}$ = 21.7 Hz), 114.9 (**C**CF, $^2J_{CF}$ = 23.4 Hz), 99.9 (**C**F, $^4J_{CF}$ = 1.8 Hz), 53.1 (q), 29.8 (t); exact mass (electrospray) *m/z* calcd for $C_{10}H_{12}{}^{79}BrFNaO_2$ (M + Na) 284.9897, found 284.9896.

2-[2,2-Bis(phenylsulfanyl)ethyl]-5-fluorobenzaldehyde (32.5).

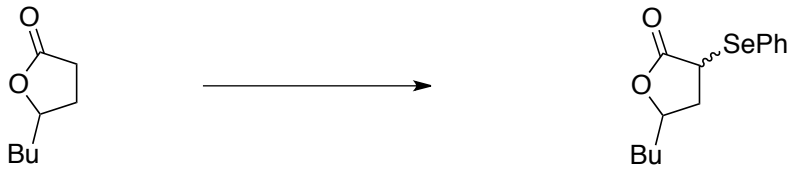


36.4 **32.5**

BuLi (2.5 M in hexane, 1.2 mL, 2.84 mmol) was added dropwise to a stirred and cooled (0 °C) solution of $(PhS)_2CH_2$ (660 mg, 2.84 mmol) in THF (20 mL). Stirring at 0 °C was continued for 10 min and the mixture was then cooled to -78 °C. A solution of **36.4** (630 mg, 2.36 mmol) in THF (6 mL) was added rapidly in one portion and stirring at -78 °C was continued for another 30 min and then at 0 °C (ice bath) for 10 min. Hydrochloric acid (4 M, 3 mL) was added, the cold bath was removed and stirring was continued for 3 h. The mixture was diluted with water (20 mL) and extracted with Et_2O (50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 15 cm), using 10% Et_2O-hexane, gave **32.5** (839 mg, 96%) as a colorless oil: FTIR ($CDCl_3$, cast) 3059, 3019, 2923, 2866, 2736, 1695, 1609, 1582, 1494, 1479, 1439, 1419 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 10.00 (d, *J* = 1.7 Hz, 1 H), 7.49 (dd, *J* = 8.7, 2.8 Hz, 1 H), 7.40-7.37 (m, 4 H), 7.32-7.29 (m, 7 H), 7.23 (td, *J* = 8.1, 2.8 Hz, 1 H), 4.63 (t, *J* = 7.4 Hz, 1 H), 3.58 (d, *J* = 7.4 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.5 (d), 161.9 (**C**F, $^1J_{CF}$ = 248.7 Hz), 135.8 (s), 135.8 (s), 135.8 (s), 134.6 (**C**CCF, $^3J_{CF}$ = 7.3 Hz), 133.9 (s), 133.0 (d), 129.0 (d), 128.0 (d), 120.6 (**C**CF, $^2J_{CF}$ = 21.4 Hz),

117.7 (**C**CF, $^2J_{CF}$ = 22.0 Hz), 60.0 (s), 38.5 (t); exact mass (electrospray) *m*/*z* calcd for $C_{21}H_{17}FNaOS_2$ (M + Na) 391.0597, found 391.0590.

5-Butyl-3-(phenylselanyl)oxolan-2-one (28.2).



31.4 **28.2**

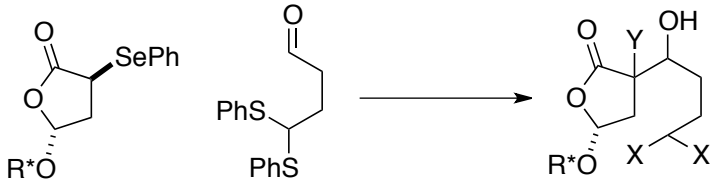
$(Me_3Si)_2NK$ (0.5 M in PhMe, 1.29 mL, 0.65 mmol) was added dropwise to a stirred and cooled (-78 °C) solution 5-butyloxolan-2-one[27,43] **(31.4)** (92 mg, 0.64 mmol) in THF (4 mL). Stirring at -78 °C was continued for 45 min. Then a solution of PhSeCl (62 mg, 0.324 mmol) in THF (1 mL) was injected rapidly in ONE PORTION (this mode of addition is important) and stirring at -78 °C was continued for 20 min. Saturated aqueous NH_4Cl (ca 3 mL) was added and the mixture was extracted with EtOAc. The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 14% Et_2O-hexane, gave **28.2** as a mixture of diastereomers which was separated into three fractions (more polar, 24 mg, 25%; less polar, 28 mg, 29%; mixture, 20.2 mg, 21%).

The more polar selenide had: FTIR ($CDCl_3$, cast) 3057, 2956, 2933, 2862, 1764, 1578, 1478, 1466, 1438 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.67-7.65 (m,

2 H), 7.38-7.30 (m, 3 H), 4.41-4.35 (m, 1 H), 4.01 (t, *J* = 9.6 Hz, 1 H), 2.71 (ddd, *J* = 13.5, 9.4, 6.5 Hz, 1 H), 1.93 (ddd, *J* = 13.5, 9.8, 8.6 Hz, 1 H), 1.63-1.56 (m, 1 H), 1.49-1.42 (m, 1 H), 1.36-1.21 (m, 4 H), 0.87 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.8 (s), 135.6 (d), 129.3 (d), 128.8 (d), 127.1 (s), 79.3 (d), 37.6 (d), 36.0 (t), 35.1 (t), 27.1 (t), 22.3 (t), 13.8 (q); exact mass (electrospray) calcd for $C_{14}H_{18}NaO_2{}^{80}Se$ (M + Na) 319.0375, found 319.0374.

The less polar selenide had: FTIR ($CDCl_3$, cast) 3057, 2956, 2932, 2862, 1770, 1578, 1478, 1467, 1438 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69-7.67 (m, 2 H), 7.40-7.31 (m, 3 H), 4.35-4.29 (m, 1 H), 3.95 (dd, *J* = 7.8, 3.1 Hz, 1 H), 2.37-2.27 (m, 2 H), 1.73-1.66 (m, 1 H), 1.58-1.51 (m, 1 H), 1.42-1.26 (m, 4 H), 0.89 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.7 (s), 135.7 (d), 129.4 (d), 129.1 (d), 126.9 (s), 79.5 (d), 37.2 (d), 36.7 (t), 34.9 (t), 27.2 (t), 22.3 (t), 13.9 (q); exact mass (electrospray) *m*/*z* calcd for $C_{14}H_{18}NaO_2{}^{80}Se$ (M + Na) 319.0375, found 319.0375.

(5*R*)-3-[1-Hydroxy-4,4-bis(phenylsulfanyl)butyl]-5-{[(1*R*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy}-3-(phenylselanyl)oxolan-2-one (32.1a, 32.1a').



27.1 **32.1** **32.1a, 32.1a'**, Y = SePh, X = SPh

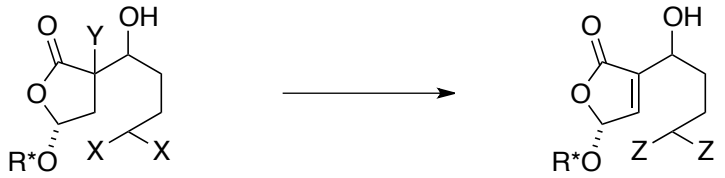
A stock solution of LDA was prepared as follows: BuLi (2.5 M in hexanes, 0.75 mL, 1.89 mmol) was added to a stirred and cooled (-78 °C) solution of *i*-Pr_2NH (0.30 mL, 1.88 mmol) in THF (8 mL), and stirring was continued for 30 min at -78 °C. A portion (1.81 mL, 0.37 mmol LDA) of this stock solution was added dropwise (over ca 10 min, added manually by syringe) to a stirred and cooled (-78 °C) solution of lactone **27.1** (120 mg, 0.302 mmol) in THF (4 mL). Stirring at -78 °C was continued for 45 min and then HMPA (0.5 mL) was added dropwise. Stirring was continued for 5 min, and then a solution of aldehyde **32.1**[11b] (139 mg, 0.48 mmol) in THF (2 mL) was added at a fast dropwise rate. Stirring at -78 °C was continued for 20-30 min (TLC control, silica, Et_2O-hexane, disappearance of aldehyde monitored). Then saturated aqueous NH_4Cl (ca 3 mL) was added and the mixture was extracted with Et_2O. The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 30% Et_2O-hexane, gave **32.1a** and **32.1a'** as separable isomers: more polar **32.1a** (88 mg, 43%) and less polar **32.1a'** (66 mg, 31%), each as an oil:

The more polar alcohol **32.1a** had: FTIR ($CDCl_3$, cast) 3367, 3072, 3058, 2953, 2923, 2868, 1762, 1582, 1477, 1455, 1438 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.60-7.58 (m, 2 H), 7.49-7.44 (m, 4 H), 7.39-7.27 (m, 7 H), 7.25-7.21 (m, 2 H), 5.68 (d, *J* = 5.9 Hz, 1 H), 4.43 (t, *J* = 6.5 Hz, 1 H), 3.63-3.56 (m, 2 H), 2.91 (dd, *J* = 14.6, 6.4 Hz, 1 H), 2.60-2.50 (m, 1 H), 2.20-2.03 (m, 3 H), 2.02-1.93 (m, 2 H), 1.80-1.65 (m, 3 H), 1.56-1.48 (m, 1 H), 1.44-1.36 (m, 1 H), 1.31-1.21 (m, 1 H), 1.06-0.75 (m, 12 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.8 (s), 138.0 (d),

134.1 (s), 134.0 (s), 132.7 (d), 132.5 (d), 129.7 (d), 128.9 (d), 128.9 (d), 127.7 (d), 127.7 (d), 125.4 (s), 97.8 (d), 77.3 (d), 71.4 (d), 57.8 (d), 50.0 (s), 47.7 (d), 39.4 (t), 34.8 (t), 34.3 (t), 32.8 (t), 31.4 (d), 28.2 (t), 24.9 (d), 22.7 (t), 22.2 (q), 21.1 (q), 15.4 (q); exact mass (electrospray) calcd for $C_{36}H_{44}NaO_4S_2{}^{78}Se$ (M + Na) 705.1755, found 705.1755.

The less polar alcohol **32.1a'** had: FTIR ($CDCl_3$, cast) 3495, 3057, 3018, 2953, 2923, 2868, 1763, 1582, 1476, 1454, 1438 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 8.1, 1.2 Hz, 2 H), 7.44-7.41 (m, 5 H), 7.34-7.25 (m, 8 H), 5.67 (dd, *J* = 6.5, 1.3 Hz, 1 H), 4.40 (t, *J* = 6.5 Hz, 1 H), 3.59-3.54 (m, 2 H), 2.86 (br s, 1 H), 2.71 (dd, *J* = 15.3, 6.5 Hz, 1 H), 2.48-2.42 (m, 1 H), 2.17-2.07 (m, 2 H), 2.05-1.98 (m, 1 H), 1.91-1.81 (m, 2 H), 1.70-1.62 (m, 3 H), 1.43-1.34 (m, 1 H), 1.30-1.22 (m, 1 H), 1.06-0.76 (m, 12 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.1 (s), 138.1 (d), 133.9 (s), 133.9 (s), 132.8 (d), 132.8 (d), 129.9 (d), 129.1 (d), 128.9 (d), 127.7 (d), 127.7 (d), 125.9 (s), 97.8 (d), 77.4 (d), 71.9 (d), 58.0 (d), 53.1 (s), 47.8 (d), 39.5 (t), 36.7 (t), 34.3 (t), 32.7 (t), 31.4 (d), 28.7 (t), 25.0 (d), 22.8 (t), 22.2 (q), 21.1 (q), 15.6 (q); exact mass (electrospray) *m/z* calcd for $C_{36}H_{44}NaO_4S_2{}^{80}Se$ (M + Na) 707.1740, found 707.1727.

(5*R*)-3-[4,4-Bis(benzenesulfonyl)-1-hydroxybutyl]-5-{[(1*R*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy}-3-(pheylselanyl)-2,5-dihydrofuran-2-one (32.1b, 32.1b').



32.1a, 32.1a', X = SPh

32.1b, 32.1b', Z = SO_2Ph

Use of 32.1a'

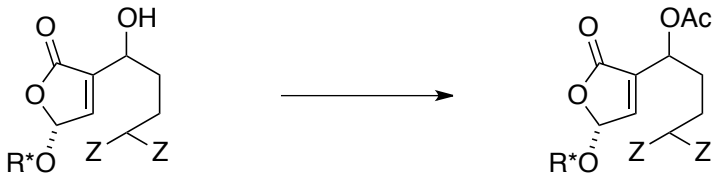
MCPBA (70%, 309 mg, 1.25 mmol) was added to a stirred and cooled (0 °C) solution of **32.1a'** (43 mg, 0.062 mmol) in CH_2Cl_2 (4 mL). The ice bath was left in place but not recharged and stirring was continued for 12 h. The reaction mixture was quenched with a mixture of saturated aqueous $NaHCO_3$ (2 mL) and saturated aqueous $Na_2S_2O_3$ (2 mL) and extracted with CH_2Cl_2. The combined organic extracts were washed with water and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 30% EtOAc-hexane, gave **32.1b'** (32.4 mg, 88%) as a colorless oil: FTIR ($CDCl_3$, cast) 3516, 3067, 2955, 2925, 2870, 1761, 1584, 1448 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.95-7.93 (m, 4 H), 7.71-7.67 (m, 2 H), 7.59-7.55 (m, 4 H), 6.96 (s, 1 H), 5.99 (s, 1 H), 4.77 (t, *J* = 5.6 Hz, 1 H), 4.52-4.50 (m, 1 H), 3.63 (td, *J* = 10.7, 4.3 Hz, 1 H), 2.68 (br s, 1 H), 2.35 (q, *J* = 6.5 Hz, 2 H), 2.17-2.07 (m, 3 H), 2.01-1.94 (m, 1 H), 1.69-1.64 (m, 2 H), 1.44-1.36 (m, 1 H), 1.28-1.22 (m, 1 H), 1.06-0.77 (m, 12 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 170.2 (s), 143.9 (d), 139.0 (s), 137.7 (s), 137.7 (s), 134.7 (d), 134.6 (d), 129.7 (d), 129.6 (d), 129.2 (d), 129.2 (d), 99.4 (d), 82.7 (d), 79.4 (d), 66.6 (d), 47.7 (d), 40.4 (t), 34.2 (t), 32.3 (t),

31.5 (d), 25.3 (d), 23.1 (t), 22.2 (q), 21.9 (t), 20.9 (q), 15.8 (q); exact mass (electrospray) *m/z* calcd for $C_{30}H_{38}NaO_8S_2$ (M + Na) 613.1900, found 613.1892.

Use of 32.1a

MCPBA (70%, 382 mg, 1.55 mmol) was added to a stirred and cooled (0 °C) solution of **32.1a** (53 mg, 0.077 mmol) in CH_2Cl_2 (4 mL). The ice bath was left in place but not recharged and stirring was continued for 12 h. The reaction mixture was quenched with a mixture of saturated aqueous $NaHCO_3$ (2 mL) and saturated aqueous $Na_2S_2O_3$ (2 mL) and extracted with CH_2Cl_2. The combined organic extracts were washed with water and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 40% EtOAc-hexane, gave **32.1b** (39.0 mg, 86%) as a colorless oil: FTIR ($CDCl_3$, cast) 3513, 3097, 3067, 2955, 2925, 2870, 1760, 1584, 1448 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.95-7.94 (m, 4 H), 7.71-7.68 (m, 2 H), 7.57 (t, *J* = 7.6 Hz, 4 H), 6.94 (t, *J* = 1.4 Hz, 1 H), 5.99 (t, *J* = 1.1 Hz, 1 H), 4.75 (t, *J* = 5.5 Hz, 1 H), 4.50-4.48 (m, 1 H), 3.63 (td, *J* = 10.7, 4.3 Hz, 1 H), 2.86 (br s, 1 H), 2.44-2.32 (m, 2 H), 2.17-2.07 (m, 3 H), 2.03-1.96 (m, 1 H), 1.70-1.64 (m, 2 H), 1.45-1.36 (m, 1 H), 1.28-1.23 (m, 1 H), 1.06-0.78 (m, 12 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4 (s,), 143.5 (d), 138.8 (s), 137.7 (s), 137.7 (s), 134.6 (d), 134.6 (d), 129.6 (d), 129.6 (d), 129.1 (d), 129.1 (d), 99.4 (d), 82.7 (d), 79.5 (d), 66.4 (d), 47.7 (d), 40.4 (t), 34.2 (t), 32.4 (t), 31.5 (d), 25.2 (d), 23.1 (t), 22.2 (q), 22.0 (t), 20.9 (q), 15.8 (q); exact mass (electrospray) *m/z* calcd for $C_{30}H_{38}NaO_8S_2$ (M + Na) 613.1900, found 613.1891.

4,4-Bis(benzenesulfonyl)-1-[(5*R*)-5-{[(1*R*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy}-2-oxo-2,5-dihydrofuran-3-yl]butyl acetate (32.1c, 32.1c').



32.1b, 32.1b' **32.1c, 32.1c'**, Z = SO_2Ph

Use of 32.1b'

DMAP (1.2 mg, 0.01 mmol) was added to a stirred solution of **32.1b'** (32 mg, 0.05 mmol) in CH_2Cl_2 (3 mL). The mixture was then cooled to 0 °C, and AcCl (0.02 mL, 0.27 mmol) and pyridine (0.04 mL, 0.37 mmol) were added sequentially. The ice bath was left in place but not recharged and stirring was continued for 3 h, during which time the cold bath reached room temperature. The reaction mixture was quenched with saturated aqueous $CuSO_4$ (2 mL) and water (5 mL), and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 50% EtOAc-hexane, gave **32.1c'** (31 mg, 91%) as a colorless foam: FTIR (neat) 3067, 2955, 2926, 2870, 1766, 1653, 1584, 1478, 1448 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.93-7.90 (m, 4 H), 7.71-7.68 (m, 2 H), 7.59-7.55 (m, 4 H), 6.94 (t, *J* = 1.2 Hz, 1 H), 6.00 (s, 1 H), 5.61-5.59 (m, 1 H), 4.50 (dd, *J* = 6.0, 5.0 Hz, 1 H), 3.61 (td, *J* = 10.7, 4.3 Hz, 1 H), 2.30-2.08 (m, 9 H), 1.69-1.63 (m, 2 H), 1.43-1.37 (m, 1 H),

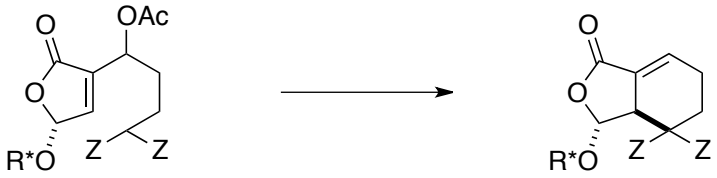
1.27-1.21 (m, 1 H), 1.02-0.78 (m, 12 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9 (s), 168.9 (s), 145.4 (d), 137.9 (s), 137.9 (s), 136.1 (s), 134.9 (d), 134.9 (d), 129.8 (d), 129.9 (d), 129.4 (d), 99.3 (d), 82.9 (d), 79.5 (d), 67.5 (d), 47.9 (d), 40.7 (t), 34.4 (t), 31.7 (q), 30.5 (t), 25.4 (d), 23.3 (t), 22.4 (d), 21.2 (t), 21.1 (q), 21.1 (q), 15.9 (q); exact mass (electrospray) *m/z* calcd for $C_{32}H_{40}NaO_9S_2$ (M + Na) 655.2006, found 655.1999.

Use of 32.1b

DMAP (0.8 mg, 0.007 mmol) was added to a stirred solution of **32.1b** (44 mg, 0.07 mmol) in CH_2Cl_2 (2 mL). The mixture was then cooled to 0 °C, and AcCl (0.026 mL, 0.37 mmol) and pyridine (0.042 mL, 0.52 mmol) were added sequentially. The ice bath was left in place but not recharged and stirring was continued for 3 h, during which time the cold bath reached room temperature. The reaction mixture was quenched with saturated aqueous $CuSO_4$ (2 mL) and water (5 mL), and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 50% EtOAc-hexane, gave **32.1c** (42 mg, 90%) as a colorless foam: FTIR (neat) 3066, 2955, 2926, 2870, 1766, 1653, 1584, 1448 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95-7.92 (m, 4 H), 7.71-7.68 (m, 2 H), 7.59-7.55 (m, 4 H), 6.90 (t, *J* = 1.1 Hz, 1 H), 5.97 (s, 1 H), 5.52-5.50 (m, 1 H), 4.51 (t, *J* = 5.4 Hz, 1 H), 3.63 (td, *J* = 10.7, 4.3 Hz, 1 H), 2.30-2.22 (m, 3 H), 2.16-2.10 (m, 6 H), 1.70-1.64 (m, 2 H), 1.44-1.37 (m, 1 H), 1.29-1.23 (m, 1 H), 1.06-0.78 (m, 12 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ

169.7 (s), 168.6 (s), 144.7 (d), 137.7 (s), 137.6 (s), 135.9 (s), 134.7 (d), 134.6 (d), 129.6 (d), 129.6 (d), 129.1 (d), 99.0 (d), 82.5 (d), 79.6 (d), 67.2 (d), 47.7 (d), 40.5 (t), 34.1 (t), 31.5 (q), 30.6 (t), 25.2 (d), 23.1 (t), 22.2 (d), 21.3 (t), 20.9 (q), 20.8 (q), 15.7 (q); exact mass (electrospray) *m/z* calcd for $C_{32}H_{40}NaO_9S_2$ (M + Na) 655.2006, found 655.2001.

(3*R*,3a*R*)-4,4-Bis(benzenesulfonyl)-3-{[(1*R*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy}-1,3,3a,4,5,6-hexahydro-2-benzofuran-1-one (32.1l).



32.1c, 32.1c' **32.1l**, Z = SO_2Ph

Use of 32.1c'

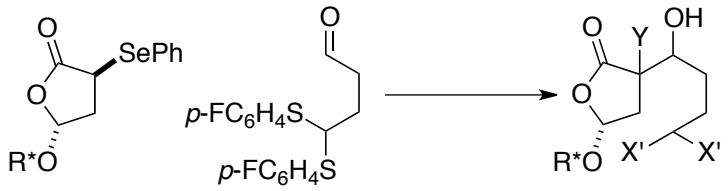
Cs_2CO_3 (77.3 mg, 0.23 mmol) was added to a stirred and cooled (0 °C) solution of **32.1c'** (30 mg, 0.047 mmol) in THF (3 mL). The ice bath was left in place but not recharged and stirring was continued for 2 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (2 mL) and extracted with EtOAc (20 mL). The combined organic extracts were washed with water and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 50% EtOAc-hexane, gave **32.1l** (23.5 mg, 87%) as a single diastereoisomer.

Use of 32.1c

Cs_2CO_3 (61 mg, 0.19 mmol) was added to a stirred and cooled (0 °C) solution of **32.1c** (24 mg, 0.037 mmol) in THF (3 mL). The ice bath was left in place but not recharged and stirring was continued for 2 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (2 mL) and extracted with EtOAc (20 mL). The combined organic extracts were washed with water and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 50% EtOAc-hexane, gave **32.1l** (23.5 mg, 82%) as a single diastereoisomer: FTIR (neat) 3066, 2954, 2927, 2869, 1768, 1692, 1583, 1478, 1448 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.15-8.07 (m, 4 H), 7.76-7.70 (m, 2 H), 7.63-7.54 (m, 4 H), 6.84 (q, *J* = 3.6 Hz, 1 H), 6.54 (d, *J* = 4.5 Hz, 1 H), 3.78 (td, *J* = 10.7, 4.1 Hz, 1 H), 3.25 (dt, *J* = 7.6, 3.7 Hz, 1 H), 2.71-2.56 (m, 2 H), 2.44-2.37 (m, 1 H), 2.27-2.18 (m, 2 H), 1.91 (ddd, *J* = 14.6, 9.0, 7.6 Hz, 1 H), 1.70-1.67 (m, 2 H), 1.44-1.35 (m, 2 H), 1.11-0.85 (m, 12 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.9 (s), 138.7 (s), 135.3 (s), 135.1 (d), 135.0 (d), 134.7 (d), 131.9 (d), 131.3 (d), 129.0 (d), 128.7 (d), 126.6 (s), 98.7 (d), 87.5 (s), 77.1 (d), 48.1 (d), 46.4 (d), 38.3 (t), 34.3 (t), 31.4 (d), 27.9 (t), 25.7 (d), 24.3 (t), 23.3 (t), 22.3 (q), 21.0 (q), 15.9 (q); exact mass (electrospray) *m/z* calcd for $C_{30}H_{36}NaO_7S_2$ (M + Na) 595.1795, found 595.1788.

For X-ray analysis crystals of **32.1l** were grown by slow vapor diffusion of hexanes into a solution of the compound in CH_2Cl_2: mp 210-212 °C.

(5*R*)-3-{4,4-Bis[(4-fluorophenyl)sulfanyl]-1-hydroxybutyl}-5-{[(1*R*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy}-3-(phenylselanyl)-oxolan-2-one (32.2a, 32.2a').

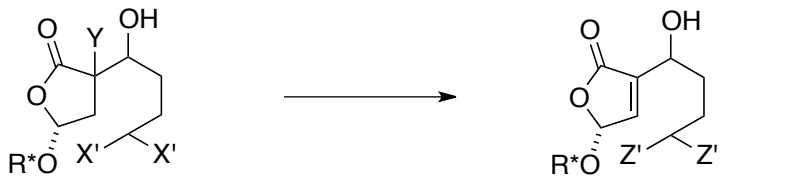


27.1 **32.2** **32.2a, 32.2a'**, X' = SC_6H_4F-*p*

A solution of LDA was prepared as follows: BuLi (2.5 M in hexanes, 2.58 mL, 6.45 mmol) was added to a stirred and cooled (-78 °C) solution of *i*-Pr_2NH (0.98 mL, 7 mmol) in THF (20 mL), and stirring was continued for 30 min at -78 °C. A portion (4.71 mL) of this stock solution was then taken up into a syringe and added dropwise (over ca 10 min, added manually by syringe) to a stirred and cooled (-78 °C) solution of lactone **27.1** (427 mg, 1.078 mmol) in THF (3 mL). Stirring at -78 °C was continued for 45 min and then HMPA (1 mL) was added dropwise. Stirring was continued for 5 min and then a solution of aldehyde **32.2** (524 mg, 1.61 mmol) in THF (2 mL) was added at a fast dropwise rate. Stirring at -78 °C was continued for 20-30 min (TLC control, disappearance of aldehyde monitored). Then saturated aqueous NH_4Cl (5 mL) was added and the mixture was extracted with Et_2O. The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (4 x 15 cm), using 40% Et_2O-hexane gave two diastereoisomers which were partially separated

[more polar isomer **32.2a** (187 mg, 26%); less polar isomer **32.2a'** (200 mg, 28%)] as oils. Neither isomer was pure and so the material was used without characterization for the next step.

(5*R*)-3-{4,4-Bis[(4-fluorobenzene)sulfonyl]-1-hydroxybutyl}-5-{[(1*R*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy}-2,5-dihydrofuran-2-one (32.2b, 32.2b').



32.2a, 32.2a', X' = SC_6H_4F-*p* **32.2b, 32.2b'**, Z' = $SO_2C_6H_4F$-*p*

Use of 32.2a'

MCPBA (70%, 512 mg, 2.08 mmol) was added to a stirred and cooled (0 °C) solution of **32.2a'** (100 mg, 0.14 mmol) in CH_2Cl_2 (5 mL). The ice bath was left in place but not recharged and stirring was continued for 4 h. The reaction mixture was quenched with a mixture of saturated aqueous $NaHCO_3$ (2 mL) and saturated aqueous $Na_2S_2O_3$ (2 mL), and extracted with CH_2Cl_2. The combined organic extracts were washed with water and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 40% Et_2O-hexane, gave **32.2b'** (48 mg, 56%) as a colorless oil: FTIR ($CDCl_3$, cast) 3510, 3107, 2956, 2926, 2871, 1761, 1591, 1493, 1456, 1406 cm^{-1};

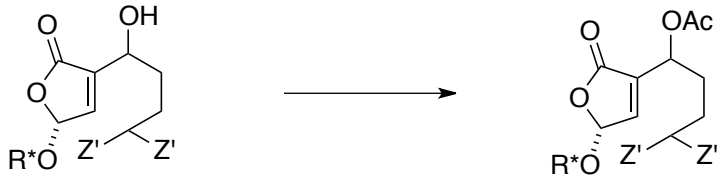
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04-8.01 (m, 4 H), 7.31-7.28 (m, 4 H), 7.01 (t, *J* = 1.4 Hz, 1 H), 6.04 (s, 1 H), 4.80 (t, *J* = 5.7 Hz, 1 H), 4.58 (m, 1 H), 3.67 (td, *J* = 10.7, 4.3 Hz, 1 H), 2.37-2.32 (m, 2 H), 2.23-2.00 (m, 4 H), 1.73-1.66 (m, 2 H), 1.47-1.41 (m, 1 H), 1.31-1.24 (m, 2 H), 1.07-0.82 (m, 12 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2 (s), 166.5 (**C**F, $^1J_{CF}$ = 258.7 Hz), 143.9 (d), 139.1 (s), 133.5 (s), 132.8 (**C**CCF, $^3J_{CF}$ = 10.2 Hz), 132.8 (**C**CCF, $^3J_{CF}$ = 10.2 Hz), 116.6 (**C**CF, $^2J_{CF}$ = 22.9 Hz), 99.4 (d), 82.9 (d), 79.5 (d), 66.7 (d), 47.8 (d), 40.4 (t), 34.2 (t), 32.2 (t), 31.5 (d), 25.3 (d), 23.1 (t), 22.2 (q), 22.1 (t), 20.9 (q), 15.8 (q); exact mass (electrospray) *m/z* calcd for $C_{30}H_{36}F_2NaO_8S_2$ (M + Na) 649.1712, found 649.1701.

Use of 32.2a

MCPBA (70%, 960 mg, 3.89 mmol) was added to a stirred and cooled (0 °C) solution of **32.2a** (187 mg, 0.26 mmol) in CH_2Cl_2 (5 mL). The ice bath was left in place but not recharged and stirring was continued for 3 h. The reaction mixture was quenched with a mixture of saturated aqueous $NaHCO_3$ (2 mL) and saturated aqueous $Na_2S_2O_3$ (2 mL), extracted with CH_2Cl_2. The combined organic extracts were washed with water and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 50% Et_2O-hexane, gave **32.2b** (101 mg, 62%) as a colorless oil: FTIR ($CDCl_3$, cast) 3514, 3107, 2956, 2926, 2871, 1760, 1591, 1493, 1456, 1406 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05-8.02 (m, 4 H), 7.32-7.28 (m, 4 H), 6.98 (t, *J* = 1.4 Hz, 1 H), 6.04 (t, *J* = 1.2 Hz, 1 H), 4.78 (t, *J* = 5.7 Hz, 1 H), 4.57 (dt, *J* = 8.6, 1.6 Hz, 1 H), 3.67 (dt, *J* = 10.7, 5.3 Hz, 1 H), 2.42-2.32 (m, 2 H), 2.23-2.02 (m, 4 H), 1.73-1.68 (m, 2 H),

1.45-1.40 (m, 1 H), 1.32-1.24 (m, 2 H), 1.07-0.81 (m, 12 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4 (s), 166.5 (**C**F, $^1J_{CF}$ = 258.6 Hz), 143.6 (d), 138.8 (s), 133.5 (s), 132.8 (**C**CCF, $^3J_{CF}$ = 10.1 Hz), 116.6 (**C**CF, $^2J_{CF}$ = 23.0 Hz), 99.4 (d), 82.9 (d), 79.6 (d), 66.4 (d), 47.7 (d), 40.4 (t), 34.2 (t), 32.4 (t), 31.5 (d), 25.3 (q), 23.1 (t), 20.9 (q), 15.8 (q); exact mass (electrospray) *m/z* calcd for $C_{30}H_{36}F_2NaO_8S_2$ (M + Na) 649.1712, found 649.1710.

4,4-Bis[(4-fluorobenzene)sulfonyl]-1-[(5*R*)-5-{[(1*R*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy}-2-oxo-2,5-dihydrofuran-3-yl]butyl acetate (32.2c, 32.2c').



32.2b, 32.2b' **32.2c, 32.2c',** Z' = $SO_2C_6H_4F$-*p*

Use of 32.2b'

DMAP (1.2 mg, 0.01 mmol) was added to a stirred solution of **32.2b'** (50 mg, 0.079 mmol) in CH_2Cl_2 (2 mL). The mixture was then cooled to 0 °C, and AcCl (0.028 mL, 0.39 mmol) and pyridine (0.046 mL, 0.55 mmol) were added sequentially. The ice bath was left in place but not recharged and stirring was continued for 3 h, during which time the cold bath reached room temperature. The reaction mixture was quenched with saturated aqueous $CuSO_4$ (2 mL) and

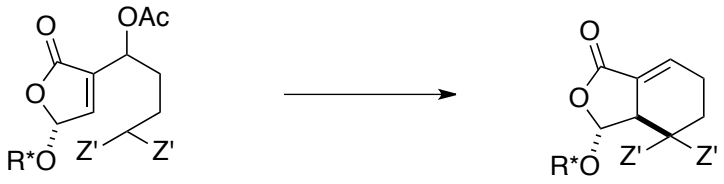
water (5 mL), and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 30% EtOAc-hexane, gave **32.2c'** (38 mg, 72%) as a colorless foam: FTIR ($CDCl_3$, cast) 3106, 2956, 2926, 2871, 1765, 1591, 1493, 1456, 1406 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.03-8.00 (m, 4 H), 7.32-7.28 (m, 4 H), 6.99 (t, *J* = 1.3 Hz, 1 H), 6.04 (s, 1 H), 5.66-5.63 (m, 1 H), 4.54 (dd, *J* = 6.2, 5.1 Hz, 1 H), 3.66 (td, *J* = 10.7, 4.3 Hz, 1 H), 2.35-2.09 (m, 9 H), 1.75-1.68 (m, 2 H), 1.46-1.44 (m, 1 H), 1.31-1.24 (m, 1 H), 1.06-0.81 (m, 12 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.7 (s), 168.8 (s), 166.5 (**C**F, $^1J_{CF}$ = 258.8 Hz), 145.2 (d), 135.8 (s), 133.4 (**C**CF, $^2J_{CF}$ = 17.3 Hz), 132.7 (**C**CCF, $^3J_{CF}$ = 10.2 Hz), 116.6 (**C**CF, $^2J_{CF}$ = 23.9 Hz), 99.1 (s), 82.8 (s), 79.4 (s), 67.1 (s), 47.7 (s), 40.4 (t), 34.2 (t), 31.5 (q), 30.3 (t), 25.2 (d), 23.1 (t), 22.2 (d), 21.1 (d), 20.9 (q), 20.9 (q), 15.7 (d); exact mass (electrospray) *m/z* calcd for $C_{32}H_{38}F_2NaO_9S_2$ (M + Na) 691.1818, found 691.1809.

Use of 32.2b

DMAP (1.2 mg, 0.01 mmol) was added to a stirred solution of **32.2b** (35 mg, 0.05 mmol) in CH_2Cl_2 (2 mL). The solution was then cooled to 0 °C, and AcCl (0.019 mL, 0.28 mmol) and pyridine (0.031 mL, 0.39 mmol) were added sequentially. The ice bath was left in place but not recharged and stirring was continued for 3 h, during which time the cold bath reached room temperature. The reaction mixture was quenched with saturated aqueous $CuSO_4$ (2 mL) and water (5 mL), and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic

extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 30% EtOAc-hexane, gave **32.2c** (25 mg, 68%) as a colorless foam: FTIR ($CDCl_3$, cast) 3106, 2956, 2926, 2871, 1767, 1591, 1493, 1456, 1406 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.04-7.99 (m, 4 H), 7.31-7.27 (m, 4 H), 6.93 (t, *J* = 1.3 Hz, 1 H), 6.01 (t, *J* = 1.2 Hz, 1 H), 5.57-5.54 (m, 1 H), 4.54 (ddd, *J* = 6.5, 4.7, 2.0 Hz, 1 H), 3.67 (td, *J* = 10.7, 4.3 Hz, 1 H), 2.34-2.10 (m, 9 H), 1.70-1.67 (m, 2 H), 1.45-1.41 (m, 1 H), 1.31-1.25 (m, 1 H), 1.09-0.82 (m, 12 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.8 (s), 168.7 (s), 166.47 (**C**F, $^1J_{CF}$ = 258.7 Hz), 144.8 (d), 135.9 (s), 133.4 (**C**CCCF, $^4J_{CF}$ = 3.3 Hz), 132.8 (**C**CCF, $^3J_{CF}$ = 5.2 Hz), 132.8 (**C**CCF, $^3J_{CF}$ = 5.2 Hz), 116.6 (**C**CF, $^2J_{CF}$ = 22.9 Hz), 99.1 (d), 82.8 (d), 79.7 (d), 67.1 (d), 47.7 (d), 40.5 (t), 34.1 (t), 31.5 (t), 30.6 (t), 25.3 (d), 23.1 (t), 22.2 (d), 21.3 (t), 20.9 (q), 20.8 (q), 15.7 (q); exact mass (electrospray) *m/z* calcd for $C_{32}H_{38}F_2NaO_9S_2$ (M + Na) 691.1818, found 691.1804.

(3*R*,3a*R*)-4,4-Bis[(4-fluorobenzene)sulfonyl]-3-{[(1*R*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy}-1,3,3a,4,5,6-hexahydro-2-benzofuran-1-one (32.2d).



32.2c, 32.2c' **32.2d**, Z' = $SO_2C_6H_4F$-*p*

Use of 32.2c'

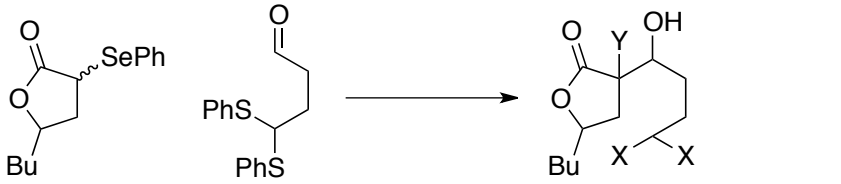
Cs_2CO_3 (49 mg, 0.15 mmol) was added to a stirred and cooled (0 °C) solution of **32.2c'** (20 mg, 0.03 mmol) in THF (2 mL). The ice bath was left in place but not recharged and stirring was continued for 3 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (2 mL) and extracted with EtOAc (20 mL). The combined organic extracts were washed with water and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 50% EtOAc-hexane, gave **32.2d** (14 mg, 78%).

Use of 32.2c

Cs_2CO_3 (44 mg, 0.13 mmol) was added to a stirred and cooled (0 °C) solution of **32.2c** (18 mg, 0.026 mmol) in THF (2 mL). The ice bath was left in place but not recharged and stirring was continued for 2 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (2 mL) and extracted with EtOAc (20 mL). The combined organic extracts were washed with water and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 50% EtOAc-hexane, gave **32.2d** (11 mg, 70%): FTIR ($CDCl_3$, cast) 3106, 2955, 2927, 2870, 1769, 1692, 1590, 1493, 1456, 1406 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.17-8.08 (m, 4 H), 7.31-7.20 (m, 4 H), 6.88 (q, *J* = 3.7 Hz, 1 H), 6.47 (d, *J* = 4.5 Hz, 1 H), 3.76 (td, *J* = 10.7, 4.1 Hz, 1 H), 3.20 (dt, *J* = 7.7, 3.7 Hz, 1 H), 2.75-2.66 (m, 1 H), 2.57 (ddd, *J* = 14.6, 6.6, 2.1 Hz, 1 H), 2.49-2.42 (m, 1 H), 2.23-2.14 (m, 2 H), 1.91 (ddd, *J* = 14.7, 9.0, 7.3 Hz, 1 H), 1.71-1.67 (m, 2 H), 1.43-1.29 (m, 2 H), 1.08-0.82 (m, 12 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ

166.7 (**C**F, $^{1}J_{CF}$= 258.3 Hz), 165.7 (s), 135.01 (**C**CCF, $^{3}J_{CF}$ = 4.2 Hz), 135.0 (s), 134.5 (d), 134.4 (d), 131.1 (**C**CCCF, $^{4}J_{CF}$ = 3.4 Hz), 126.5 (s), 116.5 (**C**CF, $^{2}J_{CF}$, *J* = 22.7 Hz), 116.2 (**C**CF, $^{2}J_{CF}$ = 22.8 Hz), 98.5 (d), 87.8 (s), 76.5 (d), 48.2 (d), 46.5 (d), 38.4 (t), 34.3 (t), 31.4 (d), 28.0 (t), 25.8 (d), 24.3 (t), 23.3 (t), 22.4 (q), 21.1 (q), 16.0 (q); exact mass (electrospray) *m/z* calcd for $C_{30}H_{34}F_2NaO_7S_2$ (M + Na) 631.1606, found 631.1600.

5-Butyl-3-[1-hydroxy-4,4-bis(phenylsulfanyl)butyl]-3-(phenylselanyl)-oxoan-2-one (32.1d, 32.1d').



28.2 **32.1** **32.1d, 32.1d'**, X = SPh

A stock solution of LDA was prepared as follows: BuLi (2.5 M in hexanes, 0.63 mL, 1.59 mmol) was added to a stirred and cooled (-78 °C) solution of *i*-Pr_2NH (0.24 mL, 1.73 mmol) in THF (20 mL), and stirring was continued for 30 min at -78 °C. A portion (2.1 mL, 0.15 mmol LDA) of this stock solution was added dropwise (over ca 10 min, added manually by syringe) to a stirred and cooled (-78 °C) solution of lactone **28.2** (43 mg, 0.145 mmol) in THF (4 mL). Stirring at -78 °C was continued for 45 min and then HMPA (0.4 mL) was added dropwise. Stirring was continued for 5 min and then a solution of aldehyde

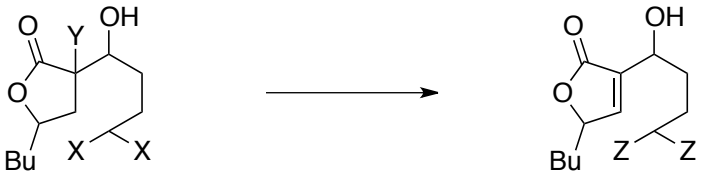
32.1[11b] (41.6 mg, 0.148 mmol) in THF (2 mL) was added at a fast dropwise rate. Stirring at -78 °C was continued for 20-30 min (TLC control, silica, Et_2O-hexane, disappearance of aldehyde monitored). Then saturated aqueous NH_4Cl (ca 3 mL) was added and the mixture was extracted with Et_2O. The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 30% Et_2O-hexane, gave the less polar isomer **32.1d'** (32 mg, 36%) and the more polar isomer **32.1d** (26 mg, 32%) (57.6 mg in all, 68%) as oils.

The more polar alcohol **32.1d** had: FTIR ($CDCl_3$, cast) 3459, 3057, 2954, 2930, 2861, 1753, 1582, 1476, 1438 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.62-7.60 (m, 2 H), 7.50-7.46 (m, 4 H), 7.39 (ddt, *J* = 8.0, 6.9, 1.2 Hz, 1 H), 7.34-7.24 (m, 8 H), 4.48-4.40 (m, 2 H), 3.71 (dd, *J* = 10.7, 1.5 Hz, 1 H), 2.85 (dd, *J* = 14.4, 8.9 Hz, 1 H), 2.49 (dddd, *J* = 13.9, 10.2, 5.6, 1.8 Hz, 1 H), 2.18-2.11 (m, 2 H), 1.88-1.73 (m, 3 H), 1.66-1.58 (m, 1 H), 1.53-1.26 (m, 5 H), 0.90 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.5 (s), 137.9 (d), 134.1 (s), 134.0 (s), 132.8 (d), 132.6 (d), 129.9 (d), 129.1 (d), 128.9 (d), 127.8 (d), 127.8 (d), 125.6 (s), 78.3 (d), 72.5 (d), 57.9 (d), 52.8 (s), 35.7 (t), 33.5 (t), 32.7 (t), 28.8 (t), 27.7 (t), 22.3 (t), 13.9 (q); exact mass (electrospray) calcd for $C_{30}H_{34}NaO_3S_2{}^{78}Se$ (M + Na) 607.1021, found 607.1024.

The less polar alcohol **32.1d'** had: FTIR ($CDCl_3$, cast) 3477, 3057, 2955, 2931, 2861, 1753, 1582, 1476, 1438 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.66 (dt, *J* = 8.1, 1.5 Hz, 2 H), 7.51-7.41 (m, 5 H), 7.36-7.23 (m, 8 H), 4.44 (t, *J* = 6.5 Hz, 1 H), 4.39-4.34 (m, 1 H), 3.68 (dd, *J* = 9.9, 2.0 Hz, 1 H), 2.92 (br s, 1 H), 2.67 (dd, *J*

= 14.8, 8.6 Hz, 1 H), 2.19-2.12 (m, 1 H), 1.98-1.85 (m, 3 H), 1.80-1.75 (m, 1 H), 1.65-1.58 (m, 1 H), 1.43-1.18 (m, 5 H), 0.88 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6 (s), 138.0 (d), 133.9 (s), 133.9 (s), 132.8 (d), 132.8 (d), 129.9 (d), 128.9 (d), 128.9 (d), 127.8 (d), 127.7 (d), 126.0 (s), 78.2 (d), 72.9 (d), 58.0 (d), 55.4 (s), 35.6 (t), 35.3 (t), 32.8 (t), 29.4 (t), 27.4 (t), 22.3 (t), 13.9 (q); exact mass (electrospray) calcd for $C_{30}H_{34}NaO_3S_2{}^{78}Se$ (M + Na) 607.1021, found 607.1024.

3-[4,4-Bis(benzenesulfonyl)-1-hydroxybutyl]-5-butyl-2,5-dihydro-furan-2-one (32.1e).



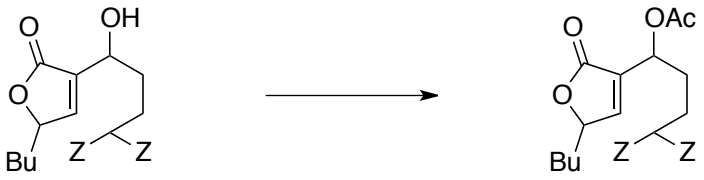
32.1d, X = SPh **32.1e**, Z = SO_2Ph

Use of 32.1d

MCPBA (70%, 288 mg, 1.67 mmol) was added to a stirred and cooled (0 °C) solution of **32.1d** (49 mg, 0.083 mmol) in CH_2Cl_2 (4 mL). The ice bath was left in place but not recharged and stirring was continued for 12 h. The mixture was quenched with a mixture of saturated aqueous $NaHCO_3$ (2 mL) and saturated aqueous $Na_2S_2O_3$ (2 mL), and extracted with CH_2Cl_2. The combined organic extracts were washed with water and brine, dried (Na_2SO_4) and evaporated. Flash

chromatography of the residue over silica gel (1 x 15 cm), using 50% EtOAc-hexane, gave **32.1e** (34 mg, 84%) as a colorless oil: FTIR ($CDCl_3$, cast) 3513, 3067, 2957, 2931, 2872, 1745, 1584, 1479, 1448 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.96-7.94 (m, 4 H), 7.72-7.68 (m, 2 H), 7.57 (t, *J* = 7.7 Hz, 4 H), 4.96-4.92 (m, 1 H), 4.81-4.78 (m, 1 H), 4.52-4.50 (m, 1 H), 2.91 (br s, 1 H), 2.36 (q, *J* = 6.5 Hz, 2 H), 2.19-2.11 (m, 1 H), 2.06-1.96 (m, 1 H), 1.77-1.60 (m, 2 H), 1.45-1.33 (m, 4 H), 0.91 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4 (s), 149.3 (d), 137.7 (s), 137.7 (s), 135.3 (s), 134.6 (d), 129.6 (d), 129.6 (d), 129.2 (d), 129.2 (d), 82.7 (d), 82.0 (d), 66.6 (d), 32.9 (t), 32.5 (t), 27.1 (t), 22.4 (t), 21.9 (t), 13.8 (q); exact mass (electrospray) *m/z* calcd for $C_{24}H_{28}NaO_7S_2$ (M + Na) 515.1169, found 515.1164.

4,4-Bis(benzenesulfonyl)-1-(5-butyl-2-oxo-2,5-dihydrofuran-3-yl)butyl acetate (32.1f).



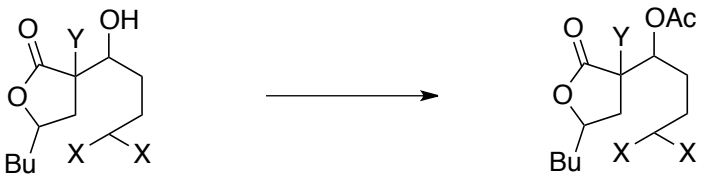
32.1e **32.1f**, Z = SO_2Ph

Use of 32.1e

DMAP (1.1 mg, 0.01 mmol) was added to a stirred solution of **32.1e** (45 mg, 0.09 mmol) in CH_2Cl_2 (3 mL). The mixture was then cooled to 0 °C and

AcCl (0.033 mL, 0.46 mmol) and pyridine (0.051 mL, 0.64 mmol) were added sequentially. The ice bath was left in place but not recharged and stirring was continued for 3 h, during which time the cold bath reached room temperature. The mixture was quenched with saturated $CuSO_4$ (2 mL) and water (5 mL), and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 50% EtOAc-hexane, gave **32.1f** (45 mg, 90%) as a colorless oil: FTIR ($CDCl_3$, cast) 3068, 2958, 2933, 2873, 1753, 1584, 1479, 1448 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.96-7.93 (m, 4 H), 7.72 (td, *J* = 7.5, 0.7 Hz, 2 H), 7.61-7.57 (m, 4 H), 7.25 (t, *J* = 1.4 Hz, 1 H), 5.58-5.56 (m, 1 H), 4.96 (t, *J* = 6.5 Hz, 1 H), 4.56 (t, *J* = 5.4 Hz, 1 H), 2.34-2.17 (m, 4 H), 2.11 (s, 3 H), 1.79-1.72 (m, 1 H), 1.69-1.62 (m, 1 H), 1.47-1.35 (m, 4 H), 0.93 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8 (s), 169.8 (s), 150.8 (d), 137.8 (s), 137.6 (s), 134.7 (d), 134.7 (d), 132.1 (s), 129.5 (d), 129.5 (d), 129.2 (d), 82.6 (d), 81.7 (d), 67.6 (d), 32.9 (t), 30.3 (t), 27.1 (t), 22.4 (t), 21.1 (t), 20.9 (q), 13.8 (q); exact mass (electrospray) *m/z* calcd for $C_{26}H_{30}NaO_8S_2$ (M + Na) 557.1274, found 557.1268.

1-[5-Butyl-2-oxo-3-(phenylselanyl)oxolan-3-yl]-4,4-bis(phenylsulfanyl)butyl acetate (32.1g').



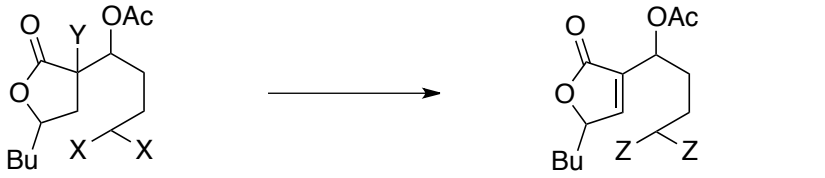
32.1d', X = SPh **32.1g'**

Use of 32.1d'

DMAP (1.1 mg, 0.01 mmol) was added to a stirred solution of **32.1d'** (35 mg, 0.06 mmol) in CH_2Cl_2 (2 mL). The mixture was then cooled to 0 °C and AcCl (0.022 mL, 0.29 mmol) and pyridine (0.039 mL, 0.48 mmol) were added sequentially. The ice bath was left in place but not recharged and stirring was continued for 3 h, during which time the cold bath reached room temperature. The reaction mixture was quenched with saturated $CuSO_4$ (2 mL) and water (5 mL), and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 50% Et_2O-hexane, gave **32.1g'** (32 mg, 86%) as a colorless oil: FTIR ($CDCl_3$, cast) 3058, 2956, 2932, 2861, 1761, 1582, 1477, 1439 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.65-7.63 (m, 2 H), 7.48-7.40 (m, 5 H), 7.35-7.28 (m, 8 H), 5.26 (dd, *J* = 10.5, 2.6 Hz, 1 H), 4.38 (dd, *J* = 7.5, 6.1 Hz, 1 H), 4.28-4.23 (m, 1 H), 2.55 (dd, *J* = 14.7, 8.0 Hz, 1 H), 2.22-2.07 (m, 2 H), 2.01 (dd, *J* = 14.7, 6.7 Hz, 1 H), 1.95 (s, 3 H), 1.88-1.72 (m, 2 H), 1.51-1.43 (m, 1 H), 1.30-1.14 (m, 5 H), 0.85 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.8 (s), 170.2 (s), 138.0 (d), 133.6 (s), 133.5 (s), 133.2 (d), 133.0 (d), 129.9 (d), 129.3 (d), 128.9 (d), 127.9 (d), 127.9 (d), 126.2 (s), 78.1 (d), 74.8 (d),

57.5 (d), 53.2 (s), 37.3 (t), 35.4 (t), 31.9 (t), 28.6 (t), 27.2 (t), 22.3 (t), 20.7 (q), 13.8 (q); exact mass (electrospray) calcd for $C_{32}H_{36}NaO_4S_2{}^{78}Se$ (M + Na) 649.1127, found 649.1133.

4,4-Bis(benzenesulfonyl)-1-(5-butyl-2-oxo-2,5-dihydrofuran-3-yl)butyl acetate (32.1h').



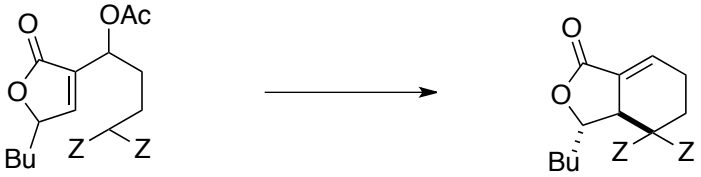
32.1g', X = SPh **32.1h'**, Z = SO_2Ph

Use of 32.1g'

MCPBA (70%, 112 mg, 0.45 mmol) was added to a stirred and cooled (0 °C) solution of **32.1g'** (19 mg, 0.030 mmol) in CH_2Cl_2 (4 mL). The ice bath was left in place but not recharged and stirring was continued for 12 h. The reaction mixture was quenched with a mixture of saturated aqueous $NaHCO_3$ (2 mL) and saturated aqueous $Na_2S_2O_3$ (2 mL), and extracted with CH_2Cl_2. The combined organic extracts were washed with water and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 50% EtOAc-hexane, gave **32.1h'** (18 mg, 86%) as a colorless oil: FTIR ($CDCl_3$, cast) 3069, 2958, 2932, 2873, 1753, 1584, 1448 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.95-7.91 (m, 4 H), 7.72-7.68 (m, 2 H), 7.59-7.56 (m, 4 H), 7.24

(t, *J* = 1.4 Hz, 1 H), 5.56-5.54 (m, 1 H), 4.94 (ddt, *J* = 7.4, 5.6, 1.7 Hz, 1 H), 4.52 (td, *J* = 5.5, 3.5 Hz, 1 H), 2.31-2.17 (m, 4 H), 2.10 (s, 3 H), 1.76-1.60 (m, 2 H), 1.46-1.33 (m, 4 H), 0.92 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8 (s), 169.8 (s), 150.7 (d), 137.7 (s), 137.6 (s), 134.7 (d), 134.6 (d), 132.2 (s), 129.6 (d), 129.5 (d), 129.2 (d), 82.6 (d), 81.6 (d), 67.6 (d), 32.9 (t), 30.4 (t), 27.1 (t), 22.4 (t), 21.1 (t), 20.9 (q), 13.8 (q); exact mass (electrospray) *m/z* calcd for $C_{26}H_{30}NaO_8S_2$ (M + Na) 557.1274, found 557.1280.

(3*S*,3a*R*)-*rel*-4,4-Bis(benzenesulfonyl)-3-butyl-1,3,3a,4,5,6-hexahydro-2-benzofuran-1-one (32.1m).



32.1f, 32.1h' **32.1m**, Z = SO_2Ph

Use of 32.1h'

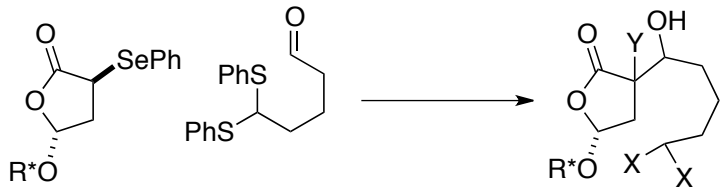
Cs_2CO_3 (115 mg, 0.36 mmol) was tipped into a stirred and cooled (-15 °C) solution of **32.1h'** (38 mg, 0.034 mmol) in dry THF (2 mL), and stirring at -15 °C was continued for 2 h. The mixture was quenched with saturated aqueous NH_4Cl (2 mL) and extracted with EtOAc (20 mL). The combined organic extracts were washed with water and brine, dried (Na_2SO_4) and evaporated. Flash

chromatography of the residue over silica gel (1 x 15 cm), using 50% EtOAc-hexane, gave **32.1m** (30 mg, 91%).

Use of 32.1f

Cs_2CO_3 (91.5 mg, 0.28 mmol) was added to a stirred and cooled (0 °C) solution of **32.1f** (30 mg, 0.056 mmol) in THF (2 mL). The ice bath was left in place but not recharged and stirring was continued for 2 h. The mixture was quenched with saturated aqueous NH_4Cl (2 mL) and extracted with EtOAc (20 mL). The combined organic extracts were washed with water and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 50% EtOAc-hexane, gave **32.1m** (23 mg, 88%): FTIR ($CDCl_3$, cast) 3067, 3021, 2958, 2930, 2871, 1760, 1690, 1583, 1477, 1467, 1448 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.6 Hz, 2 H), 7.89 (d, *J* = 7.7 Hz, 2 H), 7.76 (t, *J* = 7.5 Hz, 1 H), 7.71 (t, *J* = 7.5 Hz, 1 H), 7.63 (t, *J* = 7.9 Hz, 2 H), 7.56 (t, *J* = 7.9 Hz, 2 H), 6.75 (q, *J* = 3.3 Hz, 1 H), 4.93 (t, *J* = 8.3 Hz, 1 H), 3.61 (dq, *J* = 6.3, 3.1 Hz, 1 H), 2.49-2.35 (m, 4 H), 2.30-2.24 (m, 1 H), 1.68-1.60 (m, 1 H), 1.54-1.45 (m, 1 H), 1.44-1.25 (m, 3 H), 0.90 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.3 (s), 138.4 (s), 136.6 (s), 136.0 (d), 135.3 (d), 135.0 (d), 131.7 (d), 130.7 (d), 129.1 (d), 128.9 (d), 126.2 (s), 89.7 (s), 79.9 (d), 43.6 (d), 35.8 (t), 27.8 (t), 27.3 (t), 24.4 (t), 22.0 (t), 13.9 (q); exact mass (electrospray) *m/z* calcd for $C_{24}H_{26}NaO_6S_2$ (M + Na) 497.1063, found 497.1058.

(5*R*)-3-[1-Hydroxy-5,5-bis(phenylsulfanyl)pentyl]-5-{[(1*R*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy}-3-(phenylselanyl)oxolan-2-one (32.3a, 32.3a').



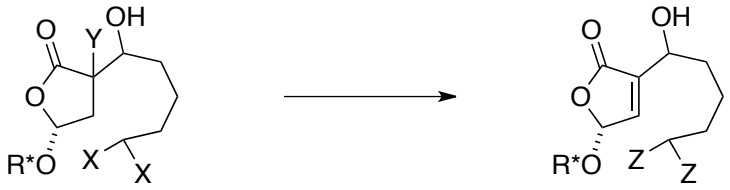
27.1 **32.3** **32.3a, 32.3a'**, X = SPh

A solution of LDA was prepared as follows: BuLi (2.5 M in hexanes, 0.15 mL, 0.38 mmol) was added to a stirred and cooled (-78 °C) solution of *i*-Pr_2NH (0.06 mL, 0.42 mmol) in THF (2 mL), and stirring was continued for 30 min at -78 °C. This LDA solution was then taken up into a syringe and added dropwise (over ca 10 min, added manually by syringe) to a stirred and cooled (-78 °C) solution of lactone **27.1** (120 mg, 0.30 mmol) in THF (2 mL). Stirring at -78 °C was continued for 45 min and then HMPA (0.4 mL) was added dropwise. Stirring was continued for 5 min and then a solution of aldehyde **32.3**[11b] (165 mg, 0.55 mmol) in THF (1 mL) was added at a fast dropwise rate. Stirring at -78 °C was continued for 20-30 min (TLC control, silica, 40% Et_2O-hexane, disappearance of aldehyde monitored). Then saturated aqueous NH_4Cl (3 mL) was added and the mixture was extracted with Et_2O. The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 40% Et_2O-hexane, gave **32.3a**, and **32.3a'** (150 mg, 70%) as an

oil that was a mixture of diastereoisomers [more polar isomer **32.3a**, 73 mg, 34%; less polar isomer **32.3a'**, 77 mg (not pure), ca 36%]. Only the more polar isomer **32.3a** could be separated in pure form, and the crude less polar isomer **32.3a'** (containing some **27.1**) was acetylated and then purified.

The more polar alcohol **32.3a** had: FTIR ($CDCl_3$, cast) 3457, 3073, 3058, 2951, 2923, 2868, 1763, 1582, 1477, 1455, 1438 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.63-7.61 (m, 2 H), 7.47-7.39 (m, 5 H), 7.34-7.27 (m, 8 H), 5.67 (d, *J* = 5.9 Hz, 1 H), 4.38 (t, *J* = 6.5 Hz, 1 H), 3.64 (dd, *J* = 10.4, 0.2 Hz, 1 H), 3.58 (td, *J* = 10.7, 4.1 Hz, 1 H), 2.88 (dd, *J* = 14.5, 6.4 Hz, 1 H), 2.51 (dtd, *J* = 14.0, 7.0, 2.7 Hz, 1 H), 2.20-2.11 (m, 2 H), 1.99-1.90 (m, 2 H), 1.85-1.75 (m, 2 H), 1.70-1.65 (m, 2 H), 1.60-1.51 (m, 2 H), 1.44-1.36 (m, 1 H), 1.30-1.19 (m, 2 H), 1.06-0.79 (m, 12 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.9 (s), 137.9 (d), 134.17 (s), 134.14 (s), 132.80 (d), 132.77 (d), 129.8 (d), 129.00 (d), 128.9 (d), 128.9 (d), 127.8 (d), 125.6 (s), 97.8 (d), 77.3 (d), 71.5 (d), 58.4 (d), 50.2 (q), 47.8 (t), 39.5 (t), 35.4 (t), 35.0 (t), 34.4 (t), 31.4 (s), 30.1 (t), 25.0 (d), 23.9 (t), 22.7 (t), 22.3 (q), 21.1 (q), 15.5 (q); exact mass (electrospray) *m/z* calcd for $C_{37}H_{46}NaO_4S_2{}^{78}Se$ (M + Na) 719.1911, found 719.1901.

(5*R*)-3-[5,5-Bis(benzenesulfonyl)-1-hydroxypentyl]-5-{[(1*R*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy}-2,5-dihydrofuran-2-one (32.3b).



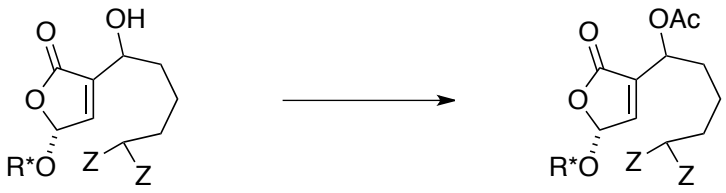
32.3a **32.3b**, Z = SO_2Ph

Use of 32.3a

MCPBA (70%, 232 mg, 0.94 mmol) was added to a stirred and cooled (0 °C) solution of **32.3a** (33 mg, 0.047 mmol) in CH_2Cl_2 (3 mL). The ice bath was left in place but not recharged and stirring was continued for 12 h. The reaction mixture was quenched with a mixture of saturated aqueous $NaHCO_3$ (2 mL) and saturated aqueous $Na_2S_2O_3$ (2 mL), and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extracts were washed with water and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 50% EtOAc-hexane, gave **32.3b** (25.0 mg, 88%) as a colorless oil: FTIR ($CDCl_3$, cast) 3518, 3097, 2956, 2925, 2870, 1760, 1584, 1448 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.5 Hz, 4 H), 7.70 (t, *J* = 7.4 Hz, 2 H), 7.58 (t, *J* = 7.8 Hz, 4 H), 6.90 (t, *J* = 1.2 Hz, 1 H), 6.00 (s, 1 H), 4.47-4.44 (m, 2 H), 3.64 (td, *J* = 10.7, 4.3 Hz, 1 H), 2.61 (br s, 1 H), 2.23 (q, *J* = 6.6 Hz, 2 H), 2.14-2.08 (m, 2 H), 1.85-1.72 (m, 3 H), 1.69-1.60 (m, 3 H), 1.45-1.37 (m, 1 H), 1.28-1.23 (m, 1 H), 1.06-0.78 (m, 12 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5 (s), 143.2 (d), 139.5 (s), 137.8 (s), 137.7 (s), 134.6 (d), 129.6 (d), 129.6 (d), 129.2 (d), 99.3 (d), 83.2 (d), 79.4 (d), 66.1 (d), 47.7 (d), 40.4 (t), 34.2 (t), 34.1 (t), 31.5 (d), 25.3 (d),

25.1 (t), 23.7 (t), 23.1 (t), 22.2 (q), 20.9 (q), 15.8 (q); exact mass (electrospray) *m/z* calcd for $C_{31}H_{40}NaO_8S_2$ (M + Na) 627.2057, found 627.2049.

5,5-Bis(benzenesulfonyl)-1-[(5*R*)-5-{[(1*R*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy}-2-oxo-2,5-dihydrofuran-3-yl]pentyl acetate (32.3c).

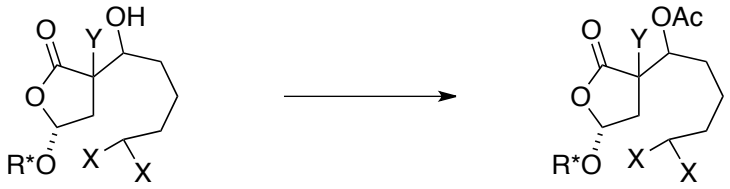


32.3b **32.3c**, Z = SO_2Ph

DMAP (1.3 mg, 0.01 mmol) was added to a stirred solution of crude **32.3b** (65 mg, 0.107 mmol) in CH_2Cl_2 (3 mL). The mixture was then cooled to 0 °C, and AcCl (0.038 mL, 0.53 mmol) and pyridine (0.069 mL, 0.72 mmol) were added sequentially. The ice bath was left in place but not recharged and stirring was continued for 3 h, during which time the cold bath reached room temperature. The reaction mixture was quenched with saturated aqueous $CuSO_4$ (2 mL) and water (5 mL), and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 50% EtOAc-hexane, gave **32.3c** (64.6 mg, 93%) as a colorless foam: FTIR ($CDCl_3$, cast) 3067, 2955, 2926, 2870, 1766, 1584, 1448 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.95-7.93 (m, 4 H), 7.70 (td, *J* = 7.5, 0.5 Hz, 2 H), 7.60-7.56 (m, 4 H), 6.86 (t, *J* =

1.4 Hz, 1 H), 5.97 (t, *J* = 1.3 Hz, 1 H), 5.51-5.49 (m, 1 H), 4.39 (t, *J* = 5.7 Hz, 1 H), 3.63 (td, *J* = 10.7, 4.3 Hz, 1 H), 2.21-2.16 (m, 2 H), 2.14-2.09 (m, 5 H), 1.88-1.81 (m, 1 H), 1.77-1.63 (m, 5 H), 1.44-1.36 (m, 1 H), 1.28-1.21 (m, 1 H), 1.06-0.79 (m, 12 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.7 (s), 168.8 (s), 144.3 (d), 137.8 (s), 137.7 (s), 136.6 (s), 134.6 (d), 129.6 (d), 129.2 (d), 98.9 (d), 83.1 (d), 79.5 (d), 67.8 (d), 47.7 (d), 40.5 (t), 34.2 (t), 31.8 (t), 31.5 (d), 25.3 (d), 25.1 (t), 23.4 (t), 23.1 (t), 22.2 (d), 20.9 (q), 20.8 (q), 15.8 (q); exact mass (electrospray) *m/z* calcd for $C_{33}H_{42}NaO_9S_2$ (M + Na) 669.2162, found 669.2154.

5,5-Bis(benzenesulfonyl)-1-[(5*R*)-5-{[(1*R*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy}-2-oxo-3-(phenylselanyl)oxolan-3-yl]pentyl acetate (32.3d').



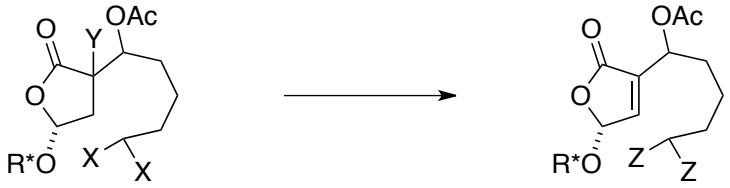
32.3a' **32.3d'**, X = SPh

Use of 32.3a'

DMAP (1.37 mg, 0.01 mmol) was added to a stirred solution of **32.3a'** (40 mg, 0.057 mmol) in CH_2Cl_2 (3 mL). The mixture was then cooled to 0 °C, and Ac_2O (0.028 mL, 0.29 mmol) and Et_3N (0.048 mL, 0.343 mmol) were added sequentially. The ice bath was left in place but not recharged and stirring was continued for 3 h, during which time the cold bath reached room temperature.

The reaction mixture was quenched with saturated aqueous NH_4Cl (2 mL) and water (5 mL), and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 30% Et_2O-hexane, gave **32.3d'** (35.4 mg, 84%) as a colorless oil: FTIR ($CDCl_3$, cast) 3058, 2952, 2924, 2868, 1766, 1746, 1582, 1477, 1455, 1438 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.66-7.64 (m, 2 H), 7.44-7.40 (m, 5 H), 7.35-7.27 (m, 8 H), 5.60 (dd, *J* = 6.5, 2.6 Hz, 1 H), 5.22 (dd, *J* = 9.7, 2.7 Hz, 1 H), 4.31 (t, *J* = 6.8 Hz, 1 H), 3.52 (td, *J* = 10.7, 4.2 Hz, 1 H), 2.67 (dd, *J* = 15.3, 6.5 Hz, 1 H), 2.32-2.25 (m, 1 H), 2.14-2.03 (m, 5 H), 1.89-1.76 (m, 2 H), 1.69-1.56 (m, 6 H), 1.40-1.34 (m, 1 H), 1.26-1.19 (m, 1 H), 1.04-0.78 (m, 12 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4 (s), 170.2 (s), 138.2 (d), 134.1 (s), 134.2 (s), 132.8 (d), 132.8 (d), 129.8 (d), 129.0 (d), 128.9 (d), 128.9 (d), 127.7 (d), 127.7 (d), 126.3 (s), 97.8 (d), 77.5 (d), 74.6 (d), 58.1 (d), 51.1 (s), 47.7 (d), 39.5 (t), 38.0 (t), 35.6 (t), 34.3 (t), 31.4 (q), 30.4 (t), 24.9 (d), 23.6 (t), 22.8 (t), 22.3 (d), 21.1 (q), 20.9 (q), 15.6 (q); exact mass (electrospray) *m/z* calcd for $C_{39}H_{48}NaO_5S_2{}^{80}Se$ (M + Na) 761.2018, found 761.2016.

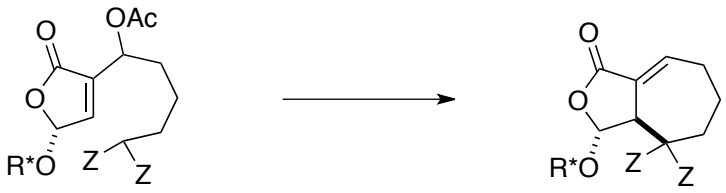
5,5-Bis(benzenesulfonyl)-1-[(5*R*)-5-{[(1*R*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy}-2-oxo-2,5-dihydrofuran-3-yl]pentyl acetate (32.3e').



32.3d', X = SPh **32.3e'**, Z = SO_2Ph

MCPBA (70%, 266 mg, 1.08 mmol) was added to a stirred and cooled (0 °C) solution of **32.3d'** (40 mg, 0.054 mmol) in CH_2Cl_2 (3 mL). The ice bath was left in place but not recharged and stirring was continued for 12 h. The mixture was quenched with a mixture of saturated aqueous $NaHCO_3$ (2 mL) and saturated aqueous $Na_2S_2O_3$ (2 mL), and extracted with CH_2Cl_2. The combined organic extracts were washed with water and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 40% EtOAc-hexane, gave **32.3e'** (28.9 mg, 83%) as a colorless foam: FTIR ($CDCl_3$, cast) 3096, 3067, 2955, 2926, 2870, 1766, 1584, 1448 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.94-7.92 (m, 4 H), 7.70 (tq, *J* = 7.5, 1.6 Hz, 2 H), 7.60-7.56 (m, 4 H), 6.92 (t, *J* = 1.3 Hz, 1 H), 6.01 (s, 1 H), 5.60-5.58 (m, 1 H), 4.40 (t, *J* = 5.7 Hz, 1 H), 3.62 (td, *J* = 10.7, 4.2 Hz, 1 H), 2.25-2.08 (m, 7 H), 1.87-1.75 (m, 2 H), 1.69-1.62 (m, 4 H), 1.44-1.36 (m, 1 H), 1.27-1.22 (m, 1 H), 1.06-0.78 (m, 12 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.7 (s), 168.9 (s), 144.9 (d), 137.8 (s), 137.7 (s), 136.3 (d), 134.6 (d), 129.6 (d), 129.2 (d), 99.0 (d), 83.0 (d), 79.2 (d), 67.9 (d), 47.7 (d), 40.5 (t), 34.2 (t), 31.5 (q), 31.4 (t), 25.2 (d), 25.1 (t), 23.1 (t), 23.1 (t), 22.2 (d), 20.9 (q), 20.9 (q), 15.7 (q); exact mass (electrospray) *m/z* calcd for $C_{33}H_{42}NaO_9S_2$ (M + Na) 669.2162, found 669.2153.

(3*R*,3a*R*)-4,4-Bis(benzenesulfonyl)-3-{[(1*R*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy}-1*H*,3*H*,3a*H*,4*H*,5*H*,6*H*,7*H*-cyclohepta[*c*]furan-1-one (32.3f).



32.3e', 32.3c **32.3f**, Z = SO_2Ph

Use of 32.3e'

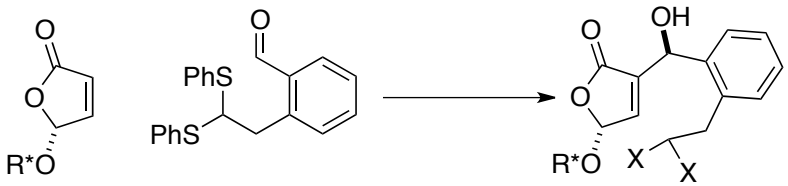
Cs_2CO_3 (55 mg, 0.17 mmol) was added to a stirred and cooled (0 °C) solution of **32.3e'** (22 mg, 0.034 mmol) in THF (2 mL). The ice bath was left in place but not recharged and stirring was continued for 2 h. The mixture was quenched with saturated aqueous NH_4Cl (2 mL) and extracted with EtOAc (20 mL). The combined organic extracts were washed with water and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 50% EtOAc-hexane, gave **32.3f** (17.9 mg, 90%).

Use of 32.3c

Cs_2CO_3 (121 mg, 0.37 mmol) was added to a stirred and cooled (0 °C) solution of **32.3c** (48 mg, 0.074 mmol) in THF (4 mL). The ice bath was left in place but not recharged and stirring was continued for 2 h. The mixture was quenched with saturated aqueous NH_4Cl (2 mL) and extracted with EtOAc (20

mL). The combined organic extracts were washed with water and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 50% EtOAc-hexane, gave **32.3f** (38 mg, 88%): FTIR ($CDCl_3$, cast) 3066, 2955, 2927, 2870, 1766, 1682, 1583, 1448 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.16 (dd, *J* = 8.4, 1.0 Hz, 2 H), 7.98-7.97 (m, 2 H), 7.76-7.69 (m, 2 H), 7.60 (dt, *J* = 11.4, 7.9 Hz, 4 H), 6.78 (br signal including d, *J* = 1.3 Hz, 2 H), 3.88 (t, *J* = 1.7 Hz, 1 H), 3.74 (td, *J* = 10.7, 4.1 Hz, 1 H), 2.45-2.32 (m, 1 H), 2.26-2.16 (m, 3 H), 2.13-2.07 (m, 1 H), 1.71-1.65 (m, 2 H), 1.45-1.37 (m, 1 H), 1.34-1.16 (m, 3 H), 1.09-0.82 (m, 12 H), 0.56-0.47 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.8 (s), 138.3 (d), 137.5 (s), 136.2 (s), 135.2 (d), 134.8 (d), 132.0 (d), 131.1 (d), 129.7 (d), 128.6 (d), 125.8 (s), 96.9 (d), 91.1 (s), 76.6 (d), 48.2 (d), 46.3 (d), 39.0 (t), 34.4 (t), 31.8 (t), 31.5 (t), 31.5 (d), 25.5 (d), 23.3 (t), 22.3 (q), 21.0 (q), 18.4 (t), 15.8 (q); exact mass (electrospray) *m/z* calcd for $C_{31}H_{38}NaO_7S_2$ (M + Na) 609.1951, found 609.1942.

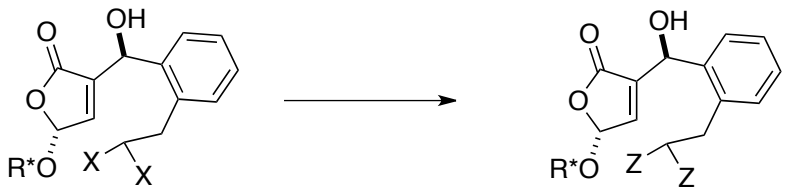
(5*R*)-3-[(*S*)-{2-[2,2-Bis(phenylsulfanyl)ethyl]phenyl}(hydroxy)methyl]-5-{[(1*R*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy}-2,5-dihydrofuran-2-one (32.4a).



25.1 **32.4** **32.4a**, X = SPh

BuLi (2.5 M in hexane, 0.941 mL, 0.255 mmol) was added dropwise to a stirred and cooled (-20 °C) solution of PhSeSePh (721 mg, 2.312 mmol) in THF (4 mL). After 10 min, the mixture was cooled to -45 °C, a mixture of **25.1** (275.0 mg, 1.156 mmol) and **32.4** (289 mg, 0.8257 mmol) in THF (9 mL) was added dropwise, and stirring was continued for 8 h at -45 °C. Then BnBr (0.28 mL, 2.312 mmol) and Bu_4NI (30.4 mg, 0.0825 mmol) were added and stirring was continued for another 8 h at -45 °C to -20 °C. The mixture was quenched with saturated aqueous NH_4Cl (3 mL) and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 2:3 Et_2O-hexanes, gave **32.4a** [(223 mg, 46 %, or 71% corrected for recovered **25.1** (85 mg)] as an oil: FTIR ($CDCl_3$, cast) 3439, 3059, 2955, 2925, 2897, 1765, 1582, 1480, 1450, 1439 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.44-7.25 (m, 14 H), 6.70 (t, *J* = 1.4 Hz, 1 H), 5.99 (s, 1 H), 5.51 (s, 1 H), 4.62 (dd, *J* = 7.8, 6.7 Hz, 1 H), 3.65 (td, *J* = 10.7, 4.3 Hz, 1 H), 3.35-3.26 (m, 2 H), 2.98 (s, 1 H), 2.13-2.09 (m, 2 H), 1.72-1.65 (m, 2 H), 1.44-1.39 (m, 1 H), 1.31-1.24 (m, 1 H), 1.09-0.81 (m, 12 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1 (s), 144.2 (d), 139.4 (s), 137.9 (s), 135.7 (s), 134.0 (s), 133.9 (s), 133.3 (d), 132.9 (d), 131.5 (d), 130.9 (d), 129.0 (d), 129.0 (d), 128.4 (d), 128.1 (d), 128.0 (d), 127.9 (d), 127.5 (d), 99.2 (d), 79.3 (d), 65.6 (d), 60.2 (d), 47.7 (d), 40.4 (t), 39.2 (t), 34.2 (t), 31.5 (d), 25.5 (d), 23.3 (s), 22.2 (q), 20.8 (q), 15.9 (q); exact mass (electrospray) *m/z* calcd for $C_{35}H_{40}NaO_4S_2$ (M + Na) 611.2260, found 611.2258.

(5*R*)-3-[(*S*)-{2-[2,2-Bis(benzenesulfonyl)ethyl]phenyl}(hydroxy)-methyl]-5-{[(1*R*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy}-2,5-dihydro-furan-2-one (32.4b).

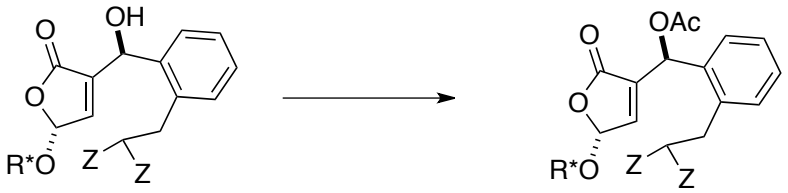


32.4a, X = SPh **32.4b**, Z = SO_2Ph

MCPBA (70%, 197 mg, 0.79 mmol) was added to a stirred and cooled (0 °C) solution of **32.4a** (47 mg, 0.079 mmol) in CH_2Cl_2 (3 mL). The ice bath was left in place but not recharged and stirring was continued for 12 h. The reaction mixture was quenched with a mixture of saturated aqueous $NaHCO_3$ (2 mL) and saturated aqueous $Na_2S_2O_3$ (2 mL), and extracted with CH_2Cl_2. The combined organic extracts were washed with water and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 60% Et_2O-hexane, gave **32.4b** (50 mg, 96%) as a colorless oil: FTIR ($CDCl_3$, cast) 3497, 3065, 2955, 2925, 2870, 1757, 1584, 1491, 1479, 1448 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.88-7.86 (m, 2 H), 7.75-7.73 (m, 2 H), 7.67-7.64 (m, 1 H), 7.61-7.57 (m, 1 H), 7.53-7.50 (m, 2 H), 7.45-7.42 (m, 2 H), 7.27-7.17 (m, 4 H), 7.07 (t, *J* = 1.5 Hz, 1 H), 6.05 (t, *J* = 1.4 Hz, 1 H), 5.89 (t, *J* = 1.7 Hz, 1 H), 5.40 (dd, *J* = 7.9, 4.2 Hz, 1 H), 3.87-3.74 (m, 2 H), 3.64 (td, *J* = 10.7, 4.2 Hz, 1 H), 3.08 (d, *J* = 3.8 Hz, 1 H), 2.14-2.03 (m, 2 H), 1.70-1.64 (m, 2 H), 1.42-1.35

(m, 1 H), 1.30-1.24 (m, 1 H), 1.05-0.76 (m, 12 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.9 (s), 143.9 (d), 1396 (s), 138.6 (s), 138.2 (s), 137.7 (s), 134.6 (d), 134.3 (d), 134.1 (s), 131.3 (d), 129.6 (d), 129.1 (d), 129.1 (d), 128.9 (d), 128.7 (d), 128.2 (d), 127.9 (d), 99.5 (d), 84.4 (d), 79.4 (d), 65.7 (d), 47.7 (d), 40.4 (t), 34.2 (t), 31.5 (d), 28.2 (t), 25.6 (d), 23.4 (t), 22.2 (q), 20.8 (q), 16.1 (q); exact mass (electrospray) *m*/*z* calcd for $C_{35}H_{40}NaO_8S_2$ (M + Na) 675.2057, found 675.2049.

(*S*)-{2-[2,2-Bis(benzenesulfonyl)ethyl]phenyl}[(5*R*)-5-{[(1*R*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy}-2-oxo-2,5-dihydrofuran-3-yl]methyl acetate (32.4c).

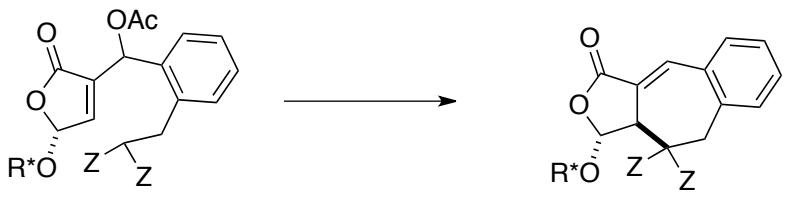


32.4b **32.4c**, Z = SO_2Ph

DMAP (1.8 mg, 0.015 mmol) was added to a stirred solution of **32.4b** (50 mg, 0.09 mmol) in CH_2Cl_2 (2 mL). The mixture was then cooled to 0 °C, and AcCl (0.033 mL, 0.46 mmol) and pyridine (0.049 mL, 0.61 mmol) were added sequentially. The ice bath was left in place but not recharged and stirring was continued for 3 h, during which time the cold bath reached room temperature. The reaction mixture was quenched with saturated aqueous $CuSO_4$ (2 mL) and water (5 mL), and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic

extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 60% Et_2O-hexane, gave **32.4c** (49 mg, 93%) as a colorless foam: FTIR ($CDCl_3$, cast) 3065, 2955, 2926, 2870, 1764, 1585, 1493, 1480, 1448 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.96-7.89 (m, 3 H), 7.61-7.58 (m, 2 H), 7.49-7.46 (m, 4 H), 7.42 (dd, *J* = 7.6, 1.1 Hz, 1 H), 7.28-7.18 (m, 3 H), 7.13 (t, *J* = 1.4 Hz, 1 H), 6.82 (t, *J* = 1.7 Hz, 1 H), 6.21 (t, *J* = 5.8 Hz, 1 H), 6.03 (t, *J* = 1.4 Hz, 1 H), 4.05 (dd, *J* = 15.8, 5.7 Hz, 1 H), 3.88 (dd, *J* = 15.8, 5.9 Hz, 1 H), 3.63 (td, *J* = 10.6, 4.3 Hz, 1 H), 2.13-2.03 (m, 5 H), 1.69-1.64 (m, 2 H), 1.42-1.36 (m, 1 H), 1.32-1.20 (m, 2 H), 1.03-0.76 (m, 12 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.4 (s), 168.6 (s), 144.4 (d), 138.3 (s), 138.1 (s), 137.1 (s), 135.2 (s), 134.3 (s), 134.1 (d), 134.1 (d), 133.4 (d), 128.7 (d), 128.7 (d), 128.6 (d), 128.2 (d), 127.6 (d), 99.2 (d), 81.6 (d), 79.4 (d), 67.2 (d), 47.7 (d), 40.5 (t), 34.2 (t), 31.5 (d), 28.7 (t), 25.4 (d), 23.3 (t), 22.2 (d), 20.9 (q), 20.8 (q), 15.9 (q); exact mass (electrospray) *m/z* calcd for $C_{37}H_{42}NaO_9S_2$ (M + Na) 717.2162, found 717.2150.

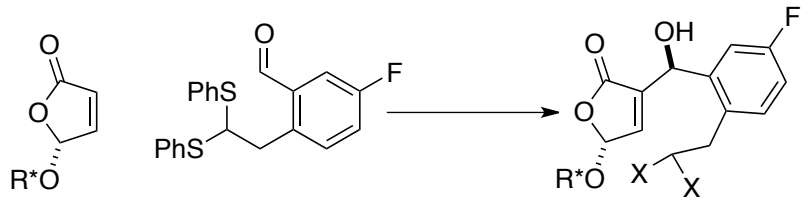
(6*R*,7*R*)-8,8-Bis(benzenesulfonyl)-6-{[(1*R*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyloxy}-5-oxatricyclo[8.4.0.0^{3,7}]tetradeca-1(14),2,10,12-tetraen-4-one (32.4d).



32.4c **32.4d**, Z = SO_2Ph

Cs_2CO_3 (56.3 mg, 0.17 mmol) was added to a stirred and cooled (0 °C) solution of **32.4c** (26 mg, 0.035 mmol) in THF (1.5 mL). The ice bath was left in place but not recharged and stirring was continued for 1 h, by which time the temperature had reached 5 °C. The mixture was quenched with saturated aqueous NH_4Cl (2 mL) and extracted with EtOAc (20 mL). The combined organic extracts were washed with water and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 60% Et_2O-hexane, gave **32.4d** (21 mg, 95%) whose ^1H NMR spectrum indicted the presence of ca 2% of an impurity: FTIR ($CDCl_3$, cast) 3065, 2955, 2926, 2869, 1769, 1660, 1583, 1478, 1448 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.17-8.08 (m, 3 H), 7.76 (tt, *J* = 7.5, 1.4 Hz, 1 H), 7.70-7.53 (m, 6 H), 7.33-7.26 (m, 2 H), 7.10 (td, *J* = 7.4, 1.6 Hz, 1 H), 6.98-6.95 (m, 1 H), 6.54 (d, *J* = 1.1 Hz, 1 H), 3.68-3.62 (m, 2 H), 3.53 (d, *J* = 14.9 Hz, 1 H), 3.05 (d, *J* = 14.9 Hz, 1 H), 2.05-1.96 (m, 2 H), 1.67-1.61 (m, 3 H), 1.35-1.28 (m, 1 H), 1.18-1.12 (m, 1 H), 1.05-0.72 (m, 11 H), 0.52 (q, *J* = 11.7 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6 (s), 137.5 (s), 137.2 (s), 136.8 (d), 135.7 (s), 135.1 (d), 134.9 (d), 133.7 (s), 133.1 (d), 132.2 (d), 132.1 (d), 130.2 (d), 129.2 (d), 129.1 (d), 128.8 (s), 128.7 (d), 127.8 (d), 102.8 (s), 96.6 (d), 76.1 (d), 48.8 (d), 47.7 (d), 38.4 (t), 37.7 (t), 34.4 (t), 31.3 (d), 25.3 (d), 23.1 (t), 22.3 (q), 20.9 (q), 15.7 (q); exact mass (electrospray) *m/z* calcd for $C_{35}H_{38}NaO_7S_2$ (M + Na) 657.1951, found 657.1949.

(4*R*)-2-[(*S*)-{2-[2,2-Bis(phenylsulfanyl)ethyl]-5-fluorophenyl}-(hydroxy)methyl]-4-{[(1*R*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy}-cyclopent-2-en-1-one (32.5a).

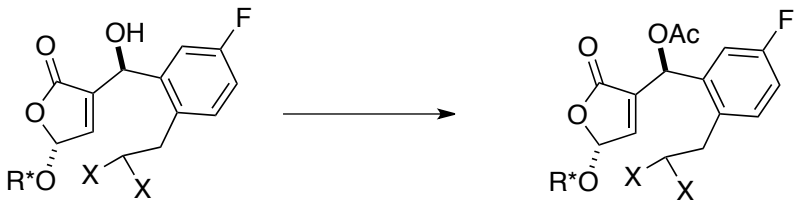


25.1 **32.5** **32.5a**, X = SPh

BuLi (2.5 M in hexane, 0.17 mL, 0.42 mmol) was added dropwise to a stirred and cooled (-20 °C) solution of PhSeSePh (130.6 mg, 0.42 mmol) in THF (6 mL). After 10 min, the mixture was cooled to -60 °C and a mixture of **25.1** (166 mg, 0.697 mmol) and **32.5** (385 mg, 1.05 mmol) in THF (6 mL) was added dropwise. Stirring was continued for 8 h, during which time the temperature of the cold bath rose to -20 °C. The reaction mixture was then quenched with saturated aqueous NH_4Cl (3 mL) and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 30% Et_2O-hexanes, gave **32.5a** (371 mg, 88%) as an oil: FTIR ($CDCl_3$, cast) 3460, 3060, 2955, 2925, 2870, 1766, 161, 1590, 1497, 1479, 1455, 1439 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.45-7.43 (m, 2 H), 7.37-7.20 (m, 9 H), 7.10 (dd, *J* = 9.8, 2.7 Hz, 1 H), 6.97 (td, *J* = 8.2, 2.7 Hz, 1 H), 6.66 (s, 1 H), 6.00 (s, 1 H), 5.43 (s, 1 H), 4.53 (t, *J* = 7.2 Hz, 1 H), 3.66 (td, *J* = 10.7, 4.2 Hz, 1 H), 3.24 (dd, *J* = 7.0, 5.0 Hz, 2

H), 3.08 (d, J = 2.8 Hz, 1 H), 2.14-2.07 (m, 2 H), 1.70 (dq, J = 10.0, 3.5 Hz, 2 H), 1.45-1.40 (m, 1 H), 1.32-1.26 (m, 1 H), 1.06-0.79 (m, 12 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0 (s), 162.1 (**C**F, $^1J_{CF}$ = 246.6 Hz), 144.4 (d), 140.2 (s), 140.1 (s), 138.9 (s), 133.9 (s), 133.8 (s), 133.3 (d), 133.2 (d), 133.1 (d), 133.0 (d), 131.3 (s), 131.2 (s), 129.1 (d), 129.1 (d), 128.2 (**C**CCF, $^3J_{CF}$ = 7.1 Hz), 115.4 (**C**CF, $^2J_{CF}$ = 21.3 Hz), 114.1 (**C**CF, $^2J_{CF}$ = 22.5 Hz), 99.2 (d), 79.4 (d), 65.2 (d), 60.4 (d), 47.7 (d), 40.3 (t), 38.5 (t), 34.2 (t), 31.5 (d), 25.5 (d), 23.3 (t), 22.2 (q), 20.8 (q), 15.9 (q); exact mass (electrospray) m/z calcd for $C_{35}H_{39}FNaO_4S_2$ (M + Na) 629.2166, found 629.2163.

(*S*)-{2-[2,2-Bis(phenylsulfanyl)ethyl]-5-fluorophenyl}[(5*R*)-5-{[(1*R*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy}-2-oxo-2,5-dihydro-furan-3-yl]methyl acetate (32.5b).

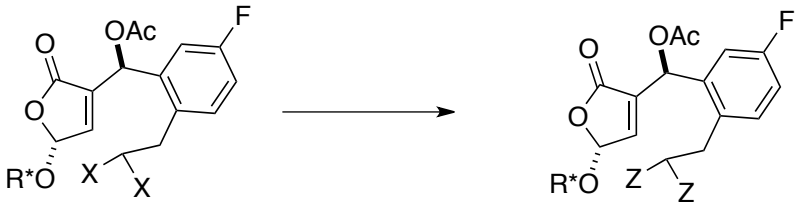


32.5a **32.5b**, X = SPh

DMAP (5.5 mg, 0.045 mmol) was added to a stirred solution of **32.5a** (274 mg, 0.45 mmol) in CH_2Cl_2 (5 mL). The mixture was then cooled to 0 °C, and AcCl (0.19 mL, 2.71 mmol) and pyridine (0.29 mL, 3.61 mmol) were added sequentially. The ice bath was left in place but not recharged and stirring was

continued for 3 h, during which time the cold bath reached room temperature. The reaction mixture was quenched with saturated aqueous $CuSO_4$ (5 mL) and water (5 mL), and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 40% Et_2O-hexane, gave **32.5b** (292 mg, 99%) as a colorless foam: FTIR ($CDCl_3$, cast) 3060, 2956, 2925, 2870, 1774, 1612, 1592, 1500, 1479, 1456, 1439 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.47-7.45 (m, 2 H), 7.39-7.37 (m, 2 H), 7.29-7.23 (m, 7 H), 7.02-6.94 (m, 2 H), 6.65 (t, *J* = 1.4 Hz, 1 H), 6.42 (d, *J* = 1.2 Hz, 1 H), 5.95 (t, *J* = 1.1 Hz, 1 H), 4.88 (t, *J* = 7.3 Hz, 1 H), 3.60 (td, *J* = 10.7, 4.2 Hz, 1 H), 3.27 (d, *J* = 7.4 Hz, 2 H), 2.11-2.03 (m, 5 H), 1.69-1.63 (m, 2 H), 1.41-1.36 (m, 1 H), 1.26-1.20 (m, 1 H), 1.04-0.77 (m, 12 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.0 (s), 167.9 (s), 162.0 (**C**F, $^1J_{CF}$ = 246.6 Hz), 145.9 (d), 137.0 (s), 137.0 (s), 136.5 (s), 134.0 (s), 133.8 (d), 133.7 (d), 133.7 (s), 133.4 (d), 132.7 (d), 131.9 (s), 131.9 (s), 129.0 (d), 128.9 (d), 128.0 (d), 127.7 (d), 115.7 (**C**CF, $^2J_{CF}$ = 21.1 Hz), 114.5 (**C**CF, $^2J_{CF}$ = 22.7 Hz), 98.6 (d), 79.4 (d), 66.0 (d), 58.0 (d), 47.7 (d), 40.4 (t), 38.7 (t), 34.2 (t), 31.5 (q), 25.4 (d), 23.3 (t), 22.2 (d), 20.8 (q), 20.8 (q), 15.9 (q); exact mass (electrospray) *m/z* calcd for $C_{37}H_{41}FNaO_5S_2$ (M + Na) 671.2272, found 671.2261.

(*S*)-{2-[2,2-Bis(benzenesulfonyl)ethyl]-5-fluorophenyl}[(5*R*)-5-{[(1*R*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy}-2-oxo-2,5-dihydro-furan-3-yl]methyl acetate (32.5c).

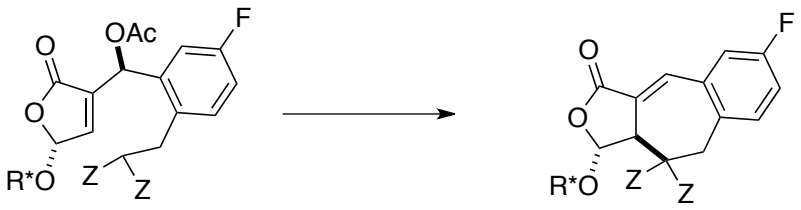


32.5b, X = SPh **32.5c**, Z = SO_2Ph

MCPBA (70%, 1.37 g, 5.54 mmol) was added to a stirred and cooled (0 °C) solution of **32.5b** (360 mg, 0.55 mmol) in CH_2Cl_2 (8 mL). The ice bath was left in place but not recharged and stirring was continued for 7 h. The reaction mixture was quenched with a mixture of saturated aqueous $NaHCO_3$ (2 mL) and saturated aqueous $Na_2S_2O_3$ (2 mL), and extracted with CH_2Cl_2. The combined organic extracts were washed with water and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 60% Et_2O-hexane, gave **32.5c** (383 mg, 96%) as a solid: FTIR ($CDCl_3$, cast) 3066, 2956, 2927, 2871, 1764, 1613, 1593, 1502, 1479, 1448 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.95-7.91 (m, 4 H), 7.62 (td, *J* = 7.5, 0.9 Hz, 2 H), 7.52-7.48 (m, 4 H), 7.43 (dd, *J* = 8.6, 5.7 Hz, 1 H), 7.18 (t, *J* = 1.4 Hz, 1 H), 6.98-6.90 (m, 2 H), 6.81 (d, *J* = 1.5 Hz, 1 H), 6.19 (t, *J* = 5.7 Hz, 1 H), 6.05 (s, 1 H), 4.00 (dd, *J* = 15.9, 5.7 Hz, 1 H), 3.88 (dd, *J* = 15.9, 5.7 Hz, 1 H), 3.64 (td, *J* = 10.7, 4.2 Hz, 1 H), 2.13-2.03 (m, 5 H), 1.70-1.65 (m, 2 H), 1.42-1.37 (m, 1 H), 1.31-1.25 (m, 1 H), 1.07-0.77 (m, 12 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.4 (s), 168.6 (s), 162.3 (**C**F, $^1J_{CF}$ = 247.3 Hz), 144.7 (d), 138.1 (s), 138.0 (s), 137.6 (s), 137.5 (s), 136.7 (s), 135.4 (d), 135.4 (d), 134.2 (d), 130.3 (s), 130.3 (s), 129.8 (d), 129.7 (d), 128.8 (d), 128.8 (d), 115.9 (**C**CF, $^2J_{CF}$ = 21.0 Hz), 114.2 (**C**CF, $^2J_{CF}$ = 22.7 Hz),

99.3 (d), 81.5 (d), 79.6 (d), 67.0 (d), 47.7 (d), 40.5 (t), 34.2 (t), 31.5 (q), 28.1 (t), 25.5 (d), 23.4 (t), 22.2 (d), 20.9 (q), 20.8 (q), 16.0 (q); exact mass (electrospray) *m*/*z* calcd for $C_{37}H_{41}FNaO_9S_2$ (M + Na) 735.2068, found 735.2057.

(6*R*,7*R*)-8,8-Bis(benzenesulfonyl)-13-fluoro-6-{[(1*R*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)-cyclohexyl]oxy}-5-oxatricyclo[8.4.0.0^{3,7}]tetradeca-1(14),2,10,12-tetraen-4-one (32.5g).

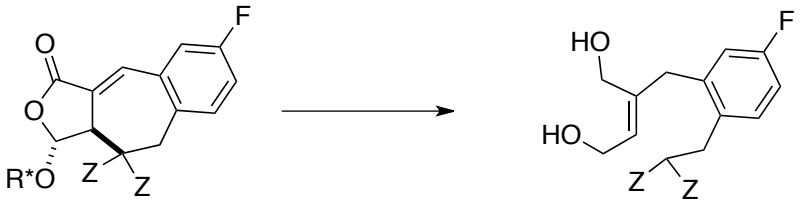


32.5c **32.5g**, Z = SO_2Ph

Cs_2CO_3 (876 mg, 2.69 mmol) was added to a stirred and cooled (0 °C) solution of **32.5c** (383 mg, 0.54 mmol) in THF (10 mL) and stirring at 0 °C was continued for 20 min. The cold bath was removed and stirring was continued for 1 h. The mixture was quenched with saturated aqueous NH_4Cl (2 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were washed with water and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 60% Et_2O-hexane, gave **32.5g** (348 mg, 99%) as a solid: mp 135-137 °C; FTIR ($CDCl_3$, cast) 3069, 2955, 2927, 2869, 1770, 1668, 1581, 1502, 1494, 1479, 1448 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14-8.12 (m, 2 H), 8.07-8.05 (m, 2 H), 7.75 (tt, *J* = 7.5, 1.4 Hz, 1 H),

7.67 (tt, *J* = 7.5, 1.4 Hz, 1 H), 7.62-7.59 (m, 3 H), 7.56-7.53 (m, 2 H), 7.00-6.94 (m, 2 H), 6.79 (td, *J* = 8.3, 2.7 Hz, 1 H), 6.46 (d, *J* = 1.0 Hz, 1 H), 3.63-3.58 (m, 2 H), 3.45 (d, *J* = 15.0 Hz, 1 H), 3.04 (d, *J* = 15.0 Hz, 1 H), 1.98-1.92 (m, 2 H), 1.65-1.58 (m, 2 H), 1.33-1.25 (m, 1 H), 1.15-1.09 (m, 1 H), 1.02-0.73 (m, 11 H), 0.44 (q, *J* = 11.7 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.3 (s), 161.9 (**C**F, $^1J_{CF}$ = 249.0 Hz), 137.5 (s), 137.0 (s), 135.6 (d), 135.2 (d), 135.1 (d), 134.9 (d), 134.8 (d), 132.2 (d), 132.1 (d), 130.2 (s), 129.5 (s), 129.3 (d), 128.8 (d), 116.5 (**C**CF, $^2J_{CF}$ = 22.1 Hz), 116.1 (**C**CF, $^2J_{CF}$ = 21.4 Hz), 102.7 (s), 96.5 (d), 76.0 (d), 48.8 (d), 47.7 (d), 38.3 (t), 37.0 (t), 34.4 (t), 31.3 (t), 25.4 (d), 23.2 (t), 22.3 (q), 20.9 (q), 15.7 (q); exact mass (electrospray) *m*/*z* calcd for $C_{35}H_{37}FNaO_7S_2$ (M + Na) 675.1857, found 675.1854.

(2*Z*)-2-({2-[2,2-Bis(benzenesulfonyl)ethyl]-5-fluorophenyl}methyl)but-2-ene-1,4-diol (32.5h).

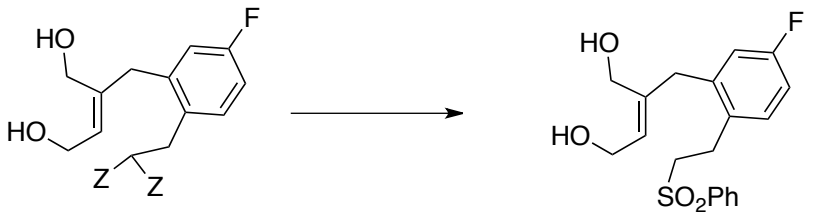


32.5g **32.5h**, Z = SO_2Ph

DIBAL-H (1 M solution in PhMe, 0.61 mL, 0.61 mmol) was added by syringe pump over 20 min to a stirred and cooled (-78 °C) solution of **32.5g** (40 mg, 0.061 mmol) in PhMe. After the addition, stirring at -78 °C was continued

for 1 h. The cold bath was replaced by an ice bath and stirring at 0 °C was continued for 1 h. Finally the ice bath was removed and stirring was continued for 2 h. The reaction mixture was quenched with water (1.226 mmol, 0.022 mL) and NaF[42] (51 mg, 1.2 mmol), diluted with Et_2O (50 mL), stirred vigorously for 1 h at room temperature, and then filtered through a pad of Celite (1 x 1 cm), using Et_2O as a rinse. Evaporation o the filtrate and flash chromatography of the residue over silica gel (1 x 15 cm), using 80% EtOAc-hexane, gave **32.5h** (21 mg, 68%) as an oil: FTIR ($CDCl_3$, cast) 3524, 3378, 3069, 2858, 2926, 2855, 1588, 1498, 1448 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 8.4, 1.1 Hz, 4 H), 7.67-7.64 (m, 2 H), 7.52-7.49 (m, 4 H), 7.23 (dd, *J* = 8.5, 5.8 Hz, 1 H), 6.84-6.79 (m, 2 H), 5.28 (t, *J* = 6.8 Hz, 1 H), 5.10 (t, *J* = 6.3 Hz, 1 H), 4.18 (d, *J* = 6.7 Hz, 2 H), 4.13 (s, 2 H), 3.59 (d, *J* = 6.3 Hz, 2 H), 3.51 (s, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.1 (**C**F, $^1J_{CF}$ = 246.8 Hz), 141.7 (s), 139.5 (s), 139.4 (s), 138.1 (s), 134.6 (d), 133.0 (d), 133.0 (d), 129.7 (s), 129.7 (s), 129.4 (d), 129.1 (d), 128.7 (d), 117.4 (**C**CF, $^2J_{CF}$ = 21.3 Hz), 113.7 (**C**CF, $^2J_{CF}$ = 21.2 Hz), 83.7 (d), 60.5 (t), 58.4 (t), 37.9 (t), 28.4 (t); exact mass (electrospray) *m/z* calcd for $C_{25}H_{25}FNaO_6S_2$ (M + Na) 527.0969, found 527.0958.

(2*Z*)-2-({2-[2-(Benzenesulfonyl)ethyl]-5-fluorophenyl}methyl)but-2-ene-1,4-diol (32.5i).

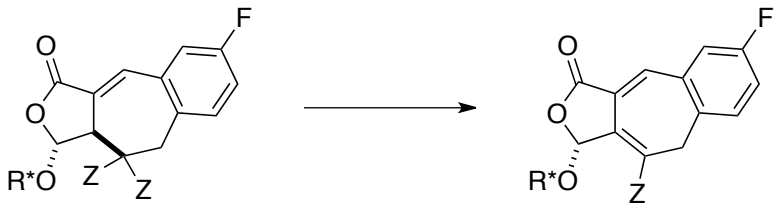


32.5h, Z = SO_2Ph **32.5i**

6% Na(Hg) (80 mg) was added to a stirred and cooled (0 °C) solution of **32.5h** (5 mg, 0.009 mmol) and Na_2HPO_4 (14 mg, 0.099 mmol) in MeOH (2 mL). Stirring at 0 °C was continued for 30 min. The ice bath was removed and stirring was continued for 2 h. The reaction mixture was quenched with water (2 mL) and the MeOH was evaporated under reduced pressure. The residue was extracted with EtOAc (20 mL) and the combined organic extracts were washed with water and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 100% EtOAc, gave **32.5i** (2.3 mg, 64%) as a solid: FTIR ($CDCl_3$, cast) 3415, 3064, 2926, 2855, 1611, 1590, 1499, 1477 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.94 (dt, *J* = 8.3, 1.6 Hz, 2 H), 7.68 (tt, *J* = 7.5, 1.5 Hz, 1 H), 7.60-7.57 (m, 2 H), 7.04 (dd, *J* = 8.3, 5.8 Hz, 1 H), 6.89-6.84 (m, 2 H), 5.30 (t, *J* = 6.8 Hz, 1 H), 4.21 (d, *J* = 6.9 Hz, 2 H), 4.16 (s, 2 H), 3.48 (s, 2 H), 3.32-3.28 (m, 2 H), 3.03 (dt, *J* = 7.9, 4.2 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.7 (**C**F, $^1J_{CF}$ = 246.1 Hz), 141.7 (s), 139.2 (s), 139.1 (s), 138.9 (s), 134.0 (d), 132.0 (s), 132.0 (s), 131.0 (d), 130.9 (d), 129.5 (d), 128.5 (d), 128.0 (d), 117.9 (**C**CF, $^2J_{CF}$ = 21.2 Hz), 114.0 (**C**CF, $^2J_{CF}$ = 21.1 Hz), 60.4 (t), 58.4 (t), 56.9 (t), 38.4 (t), 24.5 (t); exact mass (electrospray) *m/z* calcd for $C_{19}H_{21}FNaO_4S$ (M + Na) 387.1037, found 387.1028.

For X-ray analysis crystals of **32.5i** were grown by slow vapor diffusion of hexanes into a solution of the compound in Et_2O.

(6*R*)-8-(Benzenesulfonyl)-13-fluoro-6-{[(1*R*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy}-5-oxatricyclo[8.4.0.0^{3,7}]tetradeca-1(14),2,7,10,12-pentaen-4-one (32.5j).

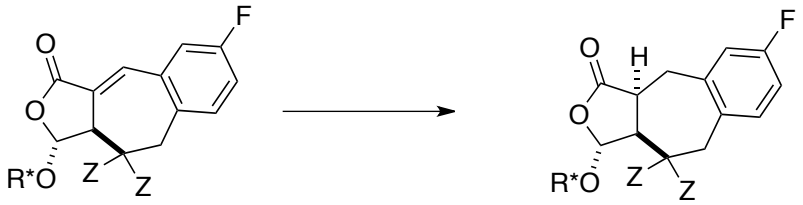


32.5g **32.5j**, Z = SO_2Ph

6% Na(Hg) (100 mg) and Na_2HPO_4 (37 mg, 0.026 mmol) were added to a stirred and cooled (0 °C) solution of **32.5g** (17 mg, 0.026 mmol) in MeOH (1 mL), and stirring at 0 °C was continued for 30 min. The ice bath was removed and stirring was continued for 2 h. The mixture was quenched with water (2 mL) and the MeOH was evaporated under reduced pressure. The residue was extracted with EtOAc (10 mL) and the organic layer was washed with water and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 80% EtOAc, gave **32.5j** (6 mg, 45%) as an oil: FTIR ($CDCl_3$, cast) 3065, 2955, 2925, 2869, 1776, 1644, 1613, 1571, 1494, 1448 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (s, 1 H), 8.01 (d, *J* = 7.2 Hz, 2 H), 7.61 (t, *J* =

7.4 Hz, 1 H), 7.53 (t, *J* = 7.7 Hz, 2 H), 7.17 (dd, *J* = 8.8, 2.6 Hz, 1 H), 7.07 (td, *J* = 8.2, 2.7 Hz, 1 H), 6.95 (s, 1 H), 6.70 (dd, *J* = 8.4, 5.2 Hz, 1 H), 3.77 (td, *J* = 10.7, 4.2 Hz, 1 H), 3.69 (d, *J* = 15.0 Hz, 1 H), 3.13 (d, *J* = 14.8 Hz, 1 H), 2.47 (d, *J* = 13.8 Hz, 1 H), 2.00-1.94 (m, 1 H), 1.67-1.63 (m, 2 H), 1.41-1.38 (m, 1 H), 1.24-1.20 (m, 1 H), 1.08-0.77 (m, 12 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.3 (s), 161.6 (**C**F, $^{1}J_{CF}$ = 246.3 Hz), 142.4 (d), 140.1 (s), 140.0 (s), 135.0 (s), 134.9 (s), 134.0 (d), 131.6 (s), 130.4 (d), 130.3 (d), 129.3 (d), 128.9 (s), 128.4 (d), 125.3 (d), 120.6 (**C**CF, $^{2}J_{CF}$ = 21.8 Hz), 116.7 (**C**CF, $^{2}J_{CF}$ = 21.9 Hz), 96.4 (d), 77.9 (d), 48.0 (d), 38.8 (t), 34.3 (t), 34.1 (t), 31.6 (d), 25.3 (d), 23.3 (t), 22.3 (q), 21.0 (q), 15.6 (q); exact mass (electrospray) *m/z* calcd for $C_{29}H_{31}NaO_5S$ (M + Na) 533.1768, found 533.1767.

(3*S*,6*R*,7*R*)-8,8-Bis(benzenesulfonyl)-13-fluoro-6-{[(1*R*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy}-5-oxatricyclo[8.4.0.0^{3,7}]tetradeca-1(14),10,12-trien-4-one (32.5k).

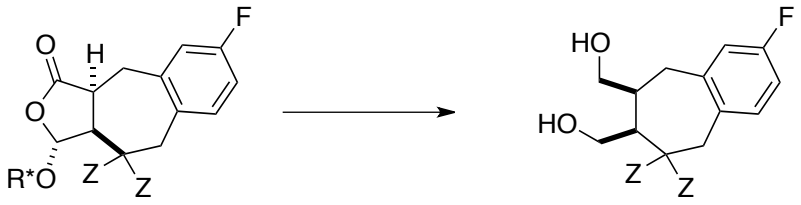


32.5g **32.5k**, Z = SO_2Ph

10% $Pd(OH)_2$-charcoal (50 mg) was added to a solution of **32.5g** (100 mg, 0.153 mmol) in EtOAc (10 mL) and AcOH (1 mL). The mixture was

hydrogenated in a Parr apparatus (50 psi) at room temperature for 36 h and then filtered through a pad of Celite, using EtOAc (50 mL) as a rinse. Evaporation of the filtrate and flash chromatography of the residue over silica gel (1 x 15 cm), using 80% EtOAc-hexane, gave **32.5k** (100 mg, 100%): FTIR ($CDCl_3$, cast) 3067, 2955, 2927, 2870, 1790, 1613, 1595, 1583, 1498, 1447 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.24 (d, *J* = 7.5 Hz, 2 H), 7.97 (d, *J* = 7.4 Hz, 2 H), 7.75 (t, *J* = 7.5 Hz, 1 H), 7.69 (t, *J* = 7.5 Hz, 1 H), 7.62 (t, *J* = 7.9 Hz, 2 H), 7.57 (t, *J* = 7.8 Hz, 2 H), 6.91 (dd, *J* = 8.7, 2.5 Hz, 1 H), 6.58 (s, 1 H), 6.54 (td, *J* = 8.4, 2.6 Hz, 1 H), 6.42 (dd, *J* = 8.3, 5.6 Hz, 1 H), 3.75 (d, *J* = 16.3 Hz, 1 H), 3.53 (td, *J* = 10.7, 4.0 Hz, 1 H), 3.38 (t, *J* = 13.0 Hz, 1 H), 3.31-3.25 (m, 1 H), 3.18-3.11 (m, 2 H), 3.04 (d, *J* = 9.2 Hz, 1 H), 2.00-1.93 (m, 2 H), 1.65-1.60 (m, 2 H), 1.34-1.21 (m, 1 H), 1.15-1.10 (m, 1 H), 0.99-0.75 (m, 11 H), 0.56 (q, *J* = 11.7 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.3 (s), 162.3 (**C**F, $^1J_{CF}$ = 248.2 Hz), 141.3 (s), 141.2 (s), 137.6 (s), 136.8 (s), 135.2 (d), 135.1 (d), 132.8 (d), 132.4 (d), 132.3 (d), 131.8 (d), 129.6 (d), 128.6 (d), 126.6 (s), 126.6 (s), 115.1 (**C**CF, $^2J_{CF}$ = 21.8 Hz), 113.3 (**C**CF, $^2J_{CF}$ = 21.2 Hz), 97.6 (d), 87.9 (s), 76.2 (d), 48.3 (d), 47.9 (d), 41.8 (d), 38.9 (t), 35.3 (t), 34.4 (t), 31.3 (d), 30.4 (t), 25.5 (d), 22.8 (t), 22.2 (q), 21.1 (q), 15.3 (q); exact mass (electrospray) *m/z* calcd for $C_{35}H_{39}FNaO_7S_2$ (M + Na) 677.2013, found 677.2008.

(7*R*,8*S*)-6,6-Bis(benzenesulfonyl)-2-fluoro-8-(hydroxymethyl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-7-yl]methanol (32.5l).

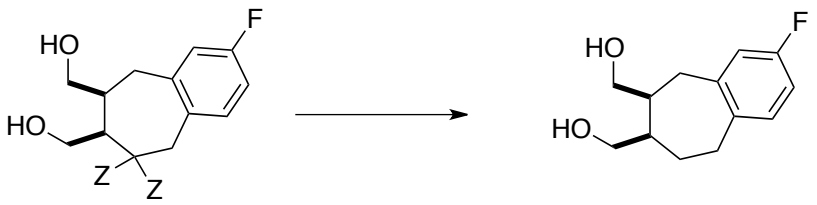


32.5k **32.5l**, Z = SO_2Ph

DIBAL-H (1 M in PhMe, 1.5 mL, 1.53 mmol) was added manually dropwise over 5 min. by syringe to a stirred and cooled (0 °C) solution of **32.5k** (50 mg, 0.076 mmol) in PhMe (4 mL). After the addition stirring at 0 °C was continued for 1 h. The cold bath was removed and stirring was continued for 8 h. The mixture was quenched with MeOH (0.052 mL, 1.52 mmol), water (0.028 mL, 1.52 mmol) and NaF[42] (64 mg, 1.52 mmol). The mixture was diluted with EtOAc (20 mL), stirred vigorously at room temperature for 1 h, and then filtered through a pad of Celite, using Et_2O as a rinse. Evaporation of the filtrate and flash chromatography of the residue over silica gel (1 x 15 cm), using 80% EtOAc-hexane, gave **32.5l** (32 mg, 82%) as an oil: FTIR ($CDCl_3$, cast) 3354, 3103, 3068, 2928, 1613, 1584, 1502, 1477, 1448 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, *J* = 7.7 Hz, 2 H), 7.72-7.68 (m, 3 H), 7.62 (tt, *J* = 7.5, 1.1 Hz, 1 H), 7.57 (t, *J* = 7.9 Hz, 2 H), 7.40 (t, *J* = 8.0 Hz, 2 H), 6.75 (dd, *J* = 9.5, 2.7 Hz, 1 H), 6.60 (td, *J* = 8.2, 2.6 Hz, 1 H), 6.36 (s, 1 H), 4.31 (dd, *J* = 12.0, 4.1 Hz, 1 H), 4.23-4.18 (m, 1 H), 3.89 (d, *J* = 16.4 Hz, 1 H), 3.74-3.69 (m, 1 H), 3.60-3.56 (m, 1 H), 3.46 (dd, *J* = 16.6, 11.5 Hz, 1 H), 3.38-3.30 (m, 2 H), 3.19 (br s, 1 H), 2.42-2.34 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.0 (**C**F, $^1J_{CF}$ = 247.3 Hz), 142.6 (s), 142.5 (s), 138.5 (s), 137.1 (s), 134.9 (d), 134.7 (d), 134.6 (d), 134.4 (d), 132.0 (d), 131.5 (d),

128.9 (d), 128.2 (d), 126.6 (s), 116.3 (**C**CF, $^2J_{CF}$ = 21.1 Hz), 112.6 (**C**CF, $^2J_{CF}$ = 21.1 Hz), 97.8 (s), 64.9 (t), 59.4 (t), 45.7 (d), 39.5 (d), 36.2 (t), 33.2 (t); exact mass (electrospray) *m*/*z* calcd for $C_{25}H_{25}FNaO_6S_2$ (M + Na) 527.0969, found 527.0965.

[(7*R*,8*S*)-2-Fluoro-8-(hydroxymethyl)-6,7,8,9-tetrahydro-5*H*-benzo[7]-annulen-7-yl]methanol (32.5m).

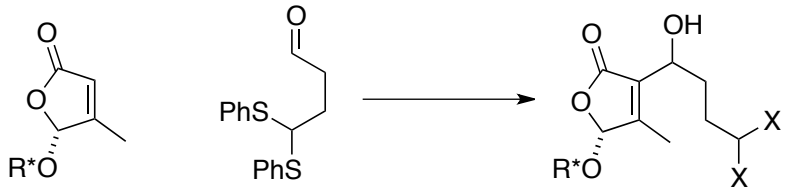


32.5l, Z = SO_2Ph **32.5m**

6% Na(Hg) (300 mg) and Na_2HPO_4 (56 mg, 0.396 mmol) were added to a stirred and cooled (0 °C) solution of **32.5l** (20 mg, 0.039 mmol) in MeOH (5 mL), and stirring at 0 °C was continued for 30 min. The ice bath was removed and stirring was continued for 2 h. The mixture was quenched with water (2 mL) and the MeOH was evaporated under reduced pressure. The residue was extracted with EtOAc (20 mL) and the combined organic extracts were washed with water and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 100% EtOAc, gave **32.5m** (7 mg, 79%) as an oil: FTIR ($CDCl_3$, cast) 3315, 2926, 2881, 1611, 1592, 1498, 1443, 1422 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.02 (dd, *J* = 8.1, 5.9 Hz, 1 H), 6.82-6.76 (m, 2 H),

3.70-3.64 (m, 2 H), 3.42 (dd, J = 10.9, 4.6 Hz, 1 H), 3.31 (dd, J = 10.6, 8.6 Hz, 1 H), 2.89-2.85 (m, 2 H), 2.82-2.72 (m, 2 H), 2.33-2.29 (m, 1 H), 2.11-2.05 (m, 1 H), 1.76-1.71 (m, 1 H), 1.53-1.44 (m, 1 H), 1.26 (s, 1 H), 0.89-0.86 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.2 (**C**F, $^1J_{CF}$ = 243.5 Hz), 141.0 (**C**CCF, $^3J_{CF}$ = 7.9 Hz), 138.1 (**C**CCCF, $^4J_{CF}$ = 3.3 Hz), 130.0 (**C**CCF, $^3J_{CF}$ = 8.0 Hz), 116.5 (**C**CF, $^2J_{CF}$ = 20.9 Hz), 112.6 (**C**CF, $^2J_{CF}$ = 20.5 Hz), 66.6 (t), 62.4 (t), 47.4 (d), 39.5 (d), 38.3 (t), 34.1 (t), 26.4 (t); exact mass (electrospray) m/z calcd for $C_{13}H_{17}FNaO_2$ (M + Na) 247.1105, found 247.1102.

(5*R*)-3-[1-Hydroxy-4,4-bis(phenylsulfanyl)butyl]-4-methyl-5-{[(1*R*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy}-2,5-dihydrofuran-2-one (32.1i, 32.1i').



28.1 **32.1** **32.1i, 32.1i'**, X = SPh

BuLi (2.5 M in hexanes, 0.38 mL, 0.95 mmol) was added to a stirred and cooled (-78 °C) solution of *i*-Pr_2NH (0.15 mL, 1.11 mmol) in THF (3 mL), and stirring was continued for 30 min at -78 °C. A solution of **28.1**[26] (200 mg, 0.79 mmol) in THF (2 mL) was then added dropwise and stirring at -78 °C was continued for 50 min. A solution of aldehyde **32.1**[11b] (274 mg, 0.95 mmol) in

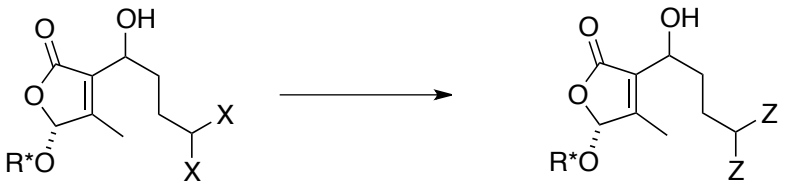
THF (2 mL) was added at a fast dropwise rate and stirring at -78 °C was continued for 30 min. Saturated aqueous NH_4Cl (ca 3 mL) was added and the mixture was extracted with Et_2O. The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 50% Et_2O-hexane, gave an oil, which was separated into three fractions: less polar alcohol **32.1i'** (41 mg, 10 %), more polar alcohol **32.1i** (52 mg, 12%), and a mixture of both isomers (172 mg, 40%).

The more polar alcohol **32.1i** had: FTIR ($CDCl_3$, cast) 3476, 3058, 2954, 2923, 2869, 1756, 1686, 1583, 1480, 1455, 1439 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.48-7.46 (m, 4 H), 7.33-7.26 (m, 6 H), 5.63 (s, 1 H), 4.46-4.41 (m, 2 H), 3.61 (td, *J* = 10.7, 4.3 Hz, 1 H), 2.84 (d, *J* = 9.1 Hz, 1 H), 2.15-1.81 (m, 9 H), 1.70-1.64 (m, 2 H), 1.44-1.39 (m, 1 H), 1.27-1.21 (m, 1 H), 1.03-0.78 (m, 12 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3 (s), 155.6 (s), 133.9 (s), 133.9 (s), 132.9 (d), 132.9 (d), 130.2 (s), 129.0 (d), 129.0 (d), 127.9 (d), 127.9 (d), 100.8 (d), 79.6 (d), 66.4 (d), 58.0 (d), 47.8 (d), 40.5 (t), 34.2 (t), 33.8 (t), 31.7 (t), 31.5 (d), 25.2 (d), 23.1 (t), 22.3 (q), 20.9 (q), 15.8 (q), 11.5 (q); exact mass (electrospray) *m*/*z* calcd for $C_{31}H_{40}NaO_4S_2$ (M + Na) 563.2260, found 563.2251.

The less polar alcohol **32.1i'** had: FTIR ($CDCl_3$, cast) 3477, 3058, 2954, 2923, 2869, 1755, 1687, 1583, 1480, 1455, 1439 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.50-7.48 (m, 4 H), 7.36-7.29 (m, 6 H), 5.68 (s, 1 H), 4.49-4.44 (m, 2 H), 3.64 (td, *J* = 10.7, 4.3 Hz, 1 H), 2.84 (d, *J* = 9.2 Hz, 1 H), 2.18-1.88 (m, 9 H), 1.73-1.67 (m, 2 H), 1.46-1.41 (m, 1 H), 1.30-1.25 (m, 1 H), 1.08-0.82 (m, 12 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4 (s), 155.6 (s), 133.9 (s), 133.9 (s), 132.9 (d),

132.9 (d), 130.3 (s), 129.0 (d), 129.0 (d), 127.9 (d), 127.9 (d), 101.1 (d), 79.8 (d), 66.6 (d), 58.1 (d), 47.7 (d), 40.6 (t), 34.2 (t), 33.9 (t), 31.8 (t), 31.5 (d), 25.2 (d), 23.1 (t), 22.3 (q), 20.9 (q), 15.8 (q), 11.6 (q); exact mass (electrospray) *m*/*z* calcd for $C_{31}H_{40}NaO_4S_2$ (M + Na) 563.2260, found 563.2255.

(5*R*)-3-[4,4-Bis(benzenesulfonyl)-1-hydroxybutyl]-4-methyl-5-{[(1*R*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy}-2,5-dihydrofuran-2-one (32.1j, 32.1j').



32.1i, 32.1i', X = SPh **32.1j, 32.1j'**, Z = SO_2Ph

MCPBA (70%, 1.18 g, 4.77 mmol) was added to a stirred and cooled (0 °C) solution of a mixture of **32.1i** and **32.1i'** (172 mg, 0.318 mmol) in CH_2Cl_2 (4 mL). The ice bath was removed and stirring was continued for 3 h. The mixture was quenched with a mixture of saturated aqueous $NaHCO_3$ (3 mL) and saturated aqueous $Na_2S_2O_3$ (3 mL), and extracted with CH_2Cl_2 (2 x 30 mL). The combined organic extracts were washed with water and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 80% Et_2O-hexane, gave a separable mixture of isomers (140 mg, 73%):

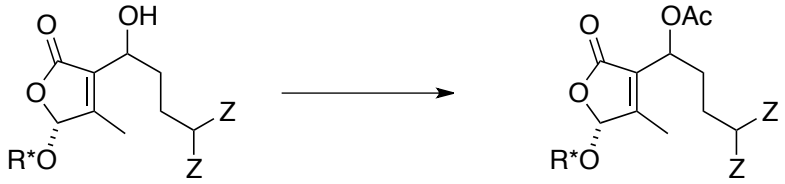
more polar sulfone alcohol **32.1j** (74 mg, 39%) and the less polar sulfone alcohol **32.1j'** (66 mg, 34%).

The more polar alcohol **32.1j** had: FTIR ($CDCl_3$, cast) 3517, 3065, 2955, 2924, 2870, 1753, 1687, 1585, 1448 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.97-7.94 (m, 4 H), 7.70 (t, *J* = 7.5 Hz, 2 H), 7.58 (t, *J* = 7.9 Hz, 4 H), 5.69 (s, 1 H), 4.65 (t, *J* = 5.8 Hz, 1 H), 4.48 (td, *J* = 8.4, 3.8 Hz, 1 H), 3.61 (td, *J* = 10.7, 4.3 Hz, 1 H), 2.89 (d, *J* = 8.2 Hz, 1 H), 2.46-2.25 (m, 2 H), 2.14-1.91 (m, 7 H), 1.70-1.64 (m, 2 H), 1.44-1.38 (m, 1 H), 1.27-1.21 (m, 1 H), 1.06-0.78 (m, 12 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3 (s), 156.3 (s), 137.9 (s), 137.7 (s), 134.7 (d), 134.7 (d), 129.7 (d), 129.5 (d), 129.2 (d), 129.2 (d), 101.0 (d), 82.8 (d), 79.8 (d), 66.3 (d), 47.8 (d), 40.5 (t), 34.2 (t), 33.8 (t), 31.5 (d), 25.2 (d), 23.1 (t), 22.3 (t), 22.3 (q), 20.9 (q), 15.8 (q), 11.6 (q); exact mass (electrospray) *m/z* calcd for $C_{31}H_{40}NaO_8S_2$ (M + Na) 627.2057, found 627.2050.

The less polar alcohol **32.1j'** had: FTIR ($CDCl_3$, cast) 3514, 3066, 2955, 2924, 2870, 1754, 1686, 1585, 1448 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.98-7.94 (m, 4 H), 7.72-7.68 (m, 2 H), 7.60-7.56 (m, 4 H), 5.69 (s, 1 H), 4.66 (t, *J* = 5.8 Hz, 1 H), 4.47 (td, *J* = 9.0, 3.9 Hz, 1 H), 3.61 (td, *J* = 10.7, 4.3 Hz, 1 H), 2.85 (d, *J* = 8.6 Hz, 1 H), 2.39 (ddt, *J* = 15.2, 9.2, 5.8 Hz, 1 H), 2.29 (ddt, *J* = 15.3, 9.0, 6.3 Hz, 1 H), 2.14-1.91 (m, 7 H), 1.70-1.64 (m, 2 H), 1.45-1.36 (m, 1 H), 1.28-1.22 (m, 1 H), 1.06-0.76 (m, 12 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3 (s), 156.3 (s), 137.9 (s), 137.7 (s), 134.7 (d), 134.7 (d), 129.7 (d), 129.6 (d), 129.2 (d), 129.2 (d), 101.2 (d), 82.8 (d), 79.9 (d), 66.5 (d), 47.7 (d), 40.6 (t), 34.2 (t), 34.1 (t), 31.5 (d), 25.2 (d), 23.1 (t), 22.4 (t), 22.3 (q), 21.0 (q), 15.7 (q), 11.7 (q); exact

mass (electrospray) *m/z* calcd for $C_{31}H_{40}NaO_8S_2$ (M + Na) 627.2057, found 627.2050.

4,4-Bis(benzenesulfonyl)-1-[(5*R*)-4-methyl-5-{[(1*R*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy}-2-oxo-2,5-dihydrofuran-3-yl]butyl acetate (32.1k, 32.1k').



32.1j, 32.1j', Z = SO_2Ph **32.1k, 32.1k'**

Use of 32.1j'

DMAP (1.2 mg, 0.01 mmol) was added to a stirred solution of **32.1j'** (12 mg, 0.0198 mmol) in CH_2Cl_2 (1 mL). The mixture was then cooled to 0 °C, and AcCl (8.5 μL, 0.11 mmol) and pyridine (0.0128 mL, 0.16 mmol) were added sequentially. The ice bath was left in place but not recharged and stirring was continued for 3 h, during which time the cold bath reached room temperature. The reaction mixture was quenched with saturated aqueous $CuSO_4$ (2 mL) and water (5 mL), and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 80% Et_2O-hexane, gave **32.1k'** (10.1 mg, 79%) as a colorless foam: FTIR ($CDCl_3$, cast)

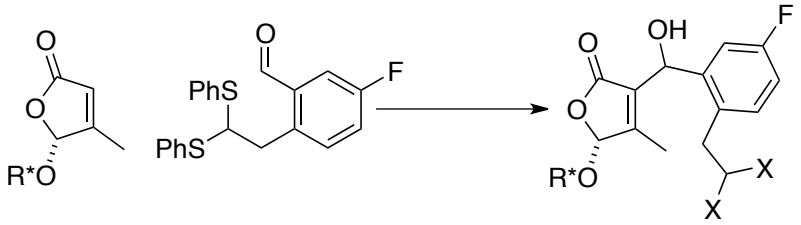
3065, 3023, 2955, 2925, 2870, 1760, 1670, 1584, 1448 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.99-7.97 (m, 4 H), 7.76-7.73 (m, 2 H), 7.62 (t, *J* = 7.8 Hz, 4 H), 5.72 (s, 1 H), 5.58 (dd, *J* = 8.9, 4.5 Hz, 1 H), 4.54 (t, *J* = 5.8 Hz, 1 H), 3.64 (td, *J* = 10.6, 4.2 Hz, 1 H), 2.46-2.39 (m, 1 H), 2.29-2.10 (m, 11 H), 1.73-1.69 (m, 2 H), 1.48-1.42 (m, 1 H), 1.32-1.26 (m, 1 H), 1.10-0.84 (m, 12 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2 (s), 169.4 (s), 159.5 (s), 137.8 (s), 137.6 (s), 134.7 (d), 134.7 (d), 129.7 (d), 129.6 (d), 129.2 (d), 129.2 (d), 126.8 (s), 100.6 (d), 82.6 (d), 79.8 (d), 66.6 (d), 47.7 (d), 40.5 (t), 34.2 (t), 31.5 (q), 30.1 (t), 25.1 (d), 23.1 (t), 22.3 (d), 21.6 (t), 20.9 (q), 20.8 (q), 15.7 (q), 12 (q); exact mass (electrospray) *m/z* calcd for $C_{33}H_{42}NaO_9S_2$ (M + Na) 669.2162, found 669.2156.

Use of 32.1j

DMAP (1.2 mg, 0.01 mmol) was added to a stirred solution of **32.1j** (12 mg, 0.0198 mmol) in CH_2Cl_2 (1 mL). The mixture was then cooled to 0 °C, and AcCl (8.5 μL, 0.11 mmol) and pyridine (0.0128 mL, 0.16 mmol) were added sequentially. The ice bath was left in place but not recharged and stirring was continued for 3 h, during which time the cold bath reached room temperature. The reaction mixture was quenched with saturated aqueous $CuSO_4$ (2 mL) and water (5 mL), and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 80% Et_2O-hexane, gave **32.1k** (10.3 mg, 81%) as a colorless foam: FTIR ($CDCl_3$, cast) 3067, 3025, 2955, 2925, 2870, 1761, 1690, 1584, 1448 cm^{-1}; ^1H NMR (500 MHz,

$CDCl_3$) δ 7.95-7.93 (m, 4 H), 7.70 (t, *J* = 7.5 Hz, 2 H), 7.58 (t, *J* = 7.6 Hz, 4 H), 5.66 (s, 1 H), 5.55 (dt, *J* = 8.8, 4.5 Hz, 1 H), 4.53 (t, *J* = 5.8 Hz, 1 H), 3.61 (td, *J* = 10.7, 4.3 Hz, 1 H), 2.34-2.04 (m, 12 H), 1.69-1.65 (m, 2 H), 1.44-1.37 (m, 1 H), 1.29-1.23 (m, 1 H), 1.07-0.80 (m, 12 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1 (s), 169.4 (s), 158.9 (s), 137.8 (s), 137.6 (s), 134.7 (d), 134.7 (d), 129.7 (d), 129.6 (d), 129.2 (d), 129.2 (d), 127.0 (s), 100.6 (d), 82.5 (d), 80.0 (d), 66.6 (d), 47.7 (d), 40.6 (t), 34.2 (t), 31.5 (q), 30.1 (t), 25.2 (d), 23.1 (t), 22.3 (d), 21.6 (t), 20.9 (q), 20.8 (q), 15.8 (q), 11.8 (q); exact mass (electrospray) *m*/*z* calcd for $C_{33}H_{42}NaO_9S_2$ (M + Na) 669.2162, found 669.2150.

(5*R*)-3-({2-[2,2-Bis(phenylsulfanyl)ethyl]-5-fluorophenyl}(hydroxy)-methyl)-4-methyl-5-{[(1*R*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy}-2,5-dihydrofuran-2-one (32.5d).

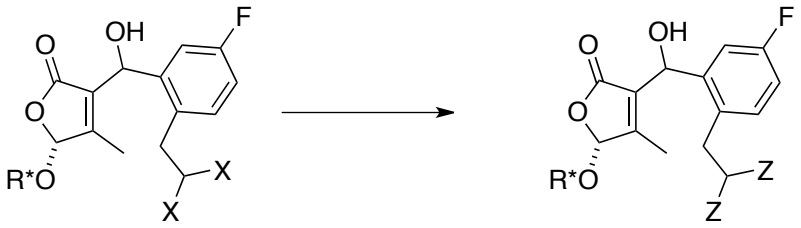


28.1 **32.5** **32.5d**, X = SPh

BuLi (2.5 M in hexanes, 0.46 mL, 1.14 mmol) was added to a stirred and cooled (-78 °C) solution of *i*-Pr_2NH (0.18 mL, 1.30 mmol) in THF (5 mL), and stirring was continued for 30 min. A solution of **28.1** (273 mg, 1.08 mmol) in

THF (3 mL) was then added dropwise and stirring at -78 °C was continued for 50 min. A solution of aldehyde **32.5** (200 mg, 0.54 mmol) in THF (2 mL) was added at a fast dropwise rate and stirring at -78 °C was continued for 30 min. Then saturated aqueous NH_4Cl (ca 5 mL) was added and the mixture was extracted with Et_2O. The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 50% Et_2O-hexane, gave crude **32.5d** (171 mg, 51%) which could not be purified by flash chromatography and was used directly for next step.

(5*R*)-3-({2-[2,2-Bis(benzenesulfonyl)ethyl]-5-fluorophenyl}(hydroxy)-methyl)-4-methyl-5-{[(1*R*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy}-2,5-dihydrofuran-2-one (32.5e).

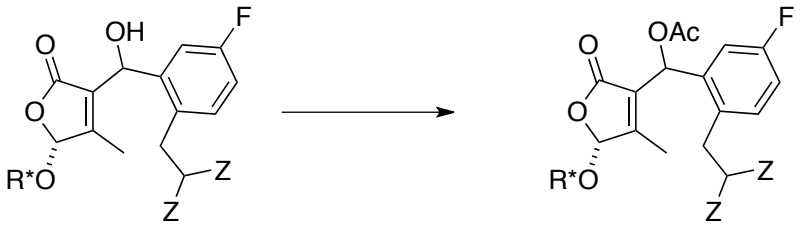


32.5d, X = SPh **32.5e**, Z = SO_2Ph

MCPBA (70%, 465 mg, 1.88 mmol) was added to a stirred and cooled (0 °C) solution of crude **32.5d** (117 mg, ca 0.188 mmol) in CH_2Cl_2 (5 mL). The ice bath was removed and stirring was continued for 4 h. The mixture was quenched with a mixture of saturated aqueous $NaHCO_3$ (3 mL) and saturated aqueous

$Na_2S_2O_3$ (3 mL), and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were washed with water and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 60% Et_2O-hexane, gave **32.5e** (81 mg, 63%) as an inseparable mixture of diastereomers: FTIR ($CDCl_3$, cast) 3502, 3066, 3021, 2956, 2924, 2871, 1749, 1689, 1613, 1592, 1501, 1499, 1479, 1448 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.86-7.83 (m, 2 H), 7.77-7.73 (m, 2 H), 7.66-7.61 (m, 2 H), 7.52-7.46 (m, 4 H), 7.30-7.26 (m, 1 H), 6.96-6.88 (m, 2 H), 5.96 (s, 1 H), 5.80 (s, 1 H), 5.55 (t, *J* = 6.1 Hz, 1 H), 3.95 (dd, *J* = 15.8, 6.1 Hz, 1 H), 3.75 (dd, *J* = 15.8, 6.2 Hz, 1 H), 3.67 (td, *J* = 10.7, 4.3 Hz, 1 H), 3.61 (s, 1 H), 2.15-2.04 (m, 5 H), 1.73-1.69 (m, 2 H), 1.47-1.26 (m, 2 H), 1.12-0.82 (m, 12 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6 (s), 162.2 (**C**F, $^1J_{CF}$ = 247.6 Hz), 157.6 (s), 141.6 (s), 141.6 (s), 138.4 (s), 138.2 (s), 134.4 (d), 134.4 (d), 133.5 (d), 133.5 (d), 129.9 (s), 129.9 (d), 129.2 (d), 129.2 (d), 129.0 (d), 129.0 (d), 128.8 (s), 115.5 (**C**CF, $^2J_{CF}$ = 21.3 Hz), 114.6 (**C**CF, $^2J_{CF}$ = 22.5 Hz), 101.3 (d), 83.7 (d), 79.8 (d), 66.1 (d), 47.7 (d), 40.4 (t), 34.2 (t), 31.5 (d), 27.7 (t), 25.4 (d), 23.3 (t), 22.3 (q), 20.8 (q), 15.9 (q), 12 (q); exact mass (electrospray) *m*/*z* calcd for $C_{36}H_{41}FNaO_8S_2$ (M + Na) 707.2119, found 707.2111.

{2-[2,2-Bis(benzenesulfonyl)ethyl]-5-fluorophenyl}[(5*R*)-4-methyl-5-{[(1*R*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy}-2-oxo-2,5-dihydro-furan-3-yl]methyl acetate (32.5f).

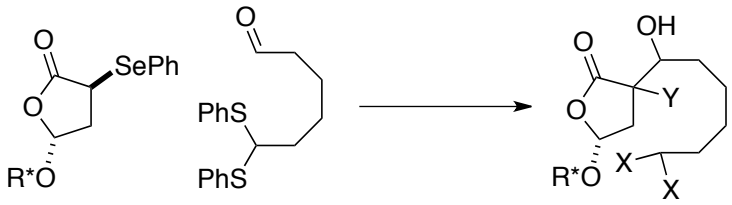


32.5e **32.5f**, Z = SO_2Ph

DMAP (1.2 mg, 0.01 mmol) was added to a stirred solution of **32.5e** (13.5 mg, 0.0197 mmol) in CH_2Cl_2 (1 mL). The mixture was then cooled to 0 °C, and AcCl (0.0084 mL, 0.11 mmol) and pyridine (0.0128 mL, 0.16 mmol) were added sequentially. The ice bath was left in place but not recharged and stirring was continued for 3 h, during time the cold bath reached room temperature. The reaction mixture was quenched with saturated aqueous $CuSO_4$ (2 mL) and water (5 mL), and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 50% Et_2O-hexane, gave **32.5f** (12.7 mg, 89%) as a colorless foam: FTIR ($CDCl_3$, cast) 3068, 2956, 2926, 2871, 1759, 1685, 1613, 1592, 1501, 1448 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.92-7.89 (m, 3 H), 7.63-7.35 (m, 7 H), 7.01 (dd, *J* = 9.6, 2.7 Hz, 1 H), 6.91-6.84 (m, 2 H), 6.16-6.11 (m, 1 H), 5.70 (s, 1 H), 3.93 (d, *J* = 6.1 Hz, 2 H), 3.61 (td, *J* = 10.7, 4.3 Hz, 1 H), 2.34-2.01 (m, 9 H), 1.71-1.65 (m, 2 H), 1.43-1.39 (m, 1 H), 1.31-1.24 (m, 1 H), 1.05-0.73 (m, 12 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.6 (s), 169.2 (s), 162.2 (**C**F, $^1J_{CF}$ = 247.1 Hz), 157.4 (s), 138.4 (s), 138.2 (s), 134.8 (d), 134.8 (d), 134.1 (d), 129.6 (d), 128.8 (d), 127.4 (s), 115.7 (**C**CF, $^2J_{CF}$ = 21.3 Hz),

114.8 (**C**CF, $^2J_{CF}$ = 22.5 Hz), 101.1 (d), 81.6 (d), 79.9 (d), 68.1 (d), 47.7 (d), 40.5 (t), 34.2 (t), 31.5 (q), 27.8 (t), 25.4 (d), 23.3 (t), 22.3 (d), 20.9 (q), 20.8 (q), 15.9 (q), 12.5 (q); exact mass (electrospray) *m/z* calcd for $C_{38}H_{43}FNaO_9S_2$ (M + Na) 749.2225, found 749.2218.

(5*R*)-3-[1-Hydroxy-6,6-bis(phenylsulfanyl)hexyl]-5-{[(1*R*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy}-3-(phenylselanyl)oxolan-2-one (32.6a, 32.6a').



27.1 **32.6** **32.6a, 32.6a'**, X = SPh

A solution of LDA was prepared as follows: BuLi (2.5 M in hexanes, 0.625 mL, 1.57 mmol) was added to a stirred and cooled (-78 °C) solution of *i*-Pr_2NH (0.25 mL, 1.76 mmol) in THF (5 mL), and stirring was continued for 30 min at -78 °C. A portion (1.18 mL, 0.32 mmol) of this stock solution was then taken up into a syringe and added manually dropwise over ca 10 min, to a stirred and cooled (-78 °C) solution of lactone **27.1** (100 mg, 0.25 mmol) in THF (2 mL). Stirring at -78 °C was continued for 45 min and then HMPA (0.5 mL) was added dropwise. Stirring was continued for 5 min and then a solution of aldehyde **32.6**[11b] (127 mg, 0.55 mmol) in THF (2 mL) was added at a fast dropwise rate.

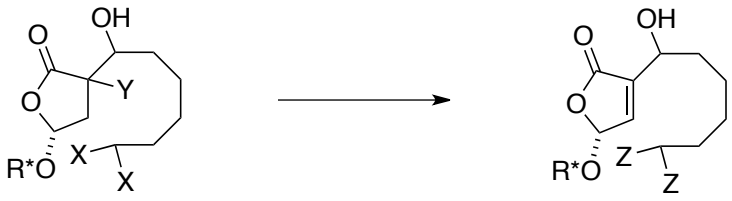
Stirring at -78 °C was continued for 20-30 min (TLC control, silica, Et_2O-hexane, disappearance of aldehyde monitored). Then saturated aqueous NH_4Cl (3 mL) was added and the mixture were extracted with Et_2O. The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 30% Et_2O-hexane, gave **32.6a** (more polar isomer, 98 mg, 55%) and **32.6a'** (less polar isomer, 40 mg, 22%) as oils.

The more polar alcohol **32.6a** had: FTIR ($CDCl_3$, cast) 3452, 3073, 3058, 2949, 2925, 2866, 1764, 1582, 1478, 1455, 1438 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64-7.62 (m, 2 H), 7.47-7.43 (m, 5 H), 7.40-7.37 (m, 1 H), 7.33-7.26 (m, 7 H), 5.67 (d, *J* = 5.8 Hz, 1 H), 4.39 (t, *J* = 6.6 Hz, 1 H), 3.65 (dd, *J* = 10.1, 3.9 Hz, 1 H), 3.58 (td, *J* = 10.7, 4.1 Hz, 1 H), 2.88 (dd, *J* = 14.6, 6.4 Hz, 1 H), 2.54-2.47 (m, 1 H), 2.17-2.10 (m, 2 H), 1.95-1.92 (m, 2 H), 1.87-1.83 (m, 2 H), 1.70-1.56 (m, 5 H), 1.51-1.35 (m, 3 H), 1.30-0.80 (m, 13 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2 (s), 138.2 (d), 134.6 (s), 134.5 (s), 133.0 (d), 132.9 (d), 130.0 (d), 129.2 (d), 129.2 (d), 129.1 (d), 129.1 (d), 127.9 (s), 127.9 (d), 125.9 (d), 98.1 (d), 71.8 (d), 58.6 (d), 50.5 (s), 48.0 (d), 39.7 (t), 36.0 (t), 35.2 (t), 34.6 (t), 31.7 (d), 30.7 (t), 27.0 (t), 26.0 (t), 25.2 (d), 23.0 (t), 22.5 (d), 21.4 (t), 15.7 (q); exact mass (electrospray) *m/z* calcd for $C_{38}H_{48}NaO_4S_2{}^{80}Se$ (M + Na) 735.2051, found 735.2050.

The less polar alcohol **32.6a'** had: FTIR ($CDCl_3$, cast) 3500, 3073, 3058, 2951, 2925, 2867, 1764, 1582, 1477, 1455, 1438 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 8.1, 1.2 Hz, 2 H), 7.43-7.23 (m, 13 H), 5.66 (dd, *J* = 6.3,

1.2 Hz, 1 H), 4.34 (t, *J* = 6.7 Hz, 1 H), 3.59-3.54 (m, 2 H), 2.81 (s, 1 H), 2.70 (dd, *J* = 15.3, 6.5 Hz, 1 H), 2.46-2.39 (m, 1 H), 2.11-2.07 (m, 1 H), 1.98 (dd, *J* = 15.3, 1.5 Hz, 1 H), 1.82-1.78 (m, 2 H), 1.69-1.65 (m, 2 H), 1.60-1.46 (m, 4 H), 1.43-1.34 (m, 1 H), 1.30-1.21 (m, 3 H), 1.03-0.77 (m, 12 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1 (s), 138.1 (d), 134.2 (s), 132.7 (d), 129.9 (d), 129.1 (d), 128.8 (d), 127.6 (d), 125.8 (s), 97.7 (d), 77.3 (d), 71.9 (d), 58.2 (d), 53.4 (s), 47.8 (d), 39.5 (t), 36.6 (t), 35.6 (t), 34.3 (t), 31.4 (d), 31.1 (t), 26.9 (t), 26.0 (t), 25.0 (d), 22.8 (t), 22.3 (q), 21.1 (q), 15.6 (q); exact mass (electrospray) *m/z* calcd for $C_{38}H_{48}NaO_4S_2{}^{80}Se$ (M + Na) 735.2051, found 735.2047.

(5*R*)-3-[6,6-Bis(benzenesulfonyl)-1-hydroxyhexyl]-5-{[(1*R*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy}-2,5-dihydrofuran-2-one (32.6b, 32.6b').



32.6a, 32.6a', X = SPh **32.6b, 32.6b'**, Z = SO_2Ph

Use of 32.6a'

MCPBA (70%, 276 mg, 1.12 mmol) was added to a stirred and cooled (0 °C) solution of **32.6a'** (40 mg, 0.056 mmol) in CH_2Cl_2 (4 mL). The ice bath was left in place but not recharged and stirring was continued for 3 h. The reaction

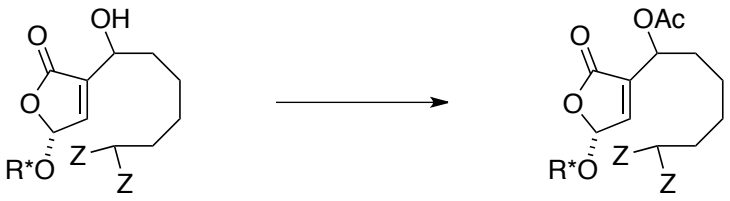
mixture was quenched with a mixture of saturated aqueous $NaHCO_3$ (2 mL) and saturated aqueous $Na_2S_2O_3$ (2 mL), and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were washed with water and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 40% EtOAc-hexane, gave **32.6b'** (29.7 mg, 86%) as a colorless oil: FTIR ($CHCl_3$, cast) 3525, 3020, 2953, 2925, 2869, 2848, 1761, 1448 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.7 Hz, 4 H), 7.70 (t, *J* = 7.5 Hz, 2 H), 7.58 (t, *J* = 7.9 Hz, 4 H), 6.91 (t, *J* = 1.3 Hz, 1 H), 6.01 (s, 1 H), 4.46 (dd, *J* = 8.4, 3.5 Hz, 1 H), 4.39 (t, *J* = 5.6 Hz, 1 H), 3.64 (td, *J* = 10.7, 4.2 Hz, 1 H), 2.41 (br s, 1 H), 2.19-2.07 (m, 4 H), 1.76-1.55 (m, 6 H), 1.49-1.32 (m, 3 H), 1.29-1.23 (m, 1 H), 1.07-0.80 (m, 12 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4 (s), 143.2 (d), 139.9 (s), 137.8 (s), 134.6 (d), 129.6 (d), 129.1 (d), 99.2 (d), 83.5 (d), 79.2 (d), 66.7 (d), 47.7 (d), 40.4 (t), 34.4 (t), 34.2 (t), 31.5 (d), 27.6 (t), 25.4 (t), 25.3 (d), 24.5 (t), 23.1 (t), 22.2 (q), 20.9 (q), 15.8 (q); exact mass (electrospray) *m/z* calcd for $C_{32}H_{42}NaO_8S_2$ (M + Na) 641.2213, found 641.2206.

Use of 32.6a

MCPBA (70%, 678 mg, 2.75 mmol) was added to a stirred and cooled (0 °C) solution of **32.6a** (98 mg, 0.14 mmol) in CH_2Cl_2 (5 mL). The ice bath was left in place but not recharged and stirring was continued for 2 h. The reaction mixture was quenched with a mixture of saturated aqueous $NaHCO_3$ (2 mL) and saturated aqueous $Na_2S_2O_3$ (2 mL), and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were washed with water and brine, dried (Na_2SO_4) and

evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 40% EtOAc-hexane, gave **32.6b** (74 mg, 88%) as a colorless oil: FTIR ($CHCl_3$, cast) 3526, 3065, 2954, 2920, 2869, 2848, 1761, 1455, 1448, 1438 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.96-7.93 (m, 4 H), 7.71-7.68 (m, 2 H), 7.59-7.55 (m, 4 H), 6.88 (t, *J* = 1.4 Hz, 1 H), 5.99 (t, *J* = 1.2 Hz, 1 H), 4.44-4.43 (m, 1 H), 4.39 (t, *J* = 5.6 Hz, 1 H), 3.63 (td, *J* = 10.7, 4.3 Hz, 1 H), 2.58 (br s, 1 H), 2.18-2.07 (m, 4 H), 1.74-1.56 (m, 6 H), 1.49-1.34 (m, 3 H), 1.28-1.23 (m, 1 H), 1.06-0.82 (m, 12 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5 (s), 143.0 (d), 139.7 (s), 137.8 (s), 134.6 (d), 129.6 (d), 129.1 (s), 99.3 (d), 83.5 (d), 79.4 (d), 66.4 (d), 47.7 (d), 40.4 (t), 34.4 (t), 34.2 (t), 31.5 (d), 27.6 (t), 25.4 (t), 25.3 (d), 24.5 (t), 23.2 (t), 22.2 (q), 20.9 (q), 15.8 (q); exact mass (electrospray) *m/z* calcd for $C_{32}H_{42}NaO_8S_2$ (M + Na) 641.2213, found 641.2204.

6,6-Bis(benzenesulfonyl)-1-[(5*R*)-5-{[(1*R*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy}-2-oxo-2,5-dihydrofuran-3-yl]hexyl acetate (32.6c, 32.6c').



32.6b, 32.6b', Z = SO_2Ph **32.6c, 32.6c'**

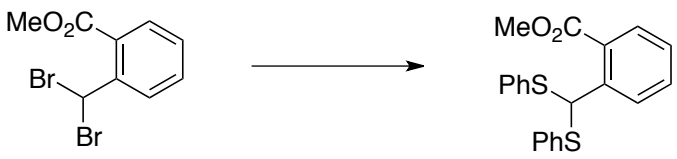
Use of 32.6b'

DMAP (1.2 mg, 0.01 mmol) was added to a stirred solution of **32.6b'** (27 mg, 0.044 mmol) in CH_2Cl_2 (3 mL). The mixture was then cooled to 0 °C, and AcCl (0.016 mL, 0.22 mmol) and pyridine (0.28 mL, 0.35 mmol) were added sequentially. The ice bath was left in place but not recharged and stirring was continued for 3 h, during which time the cold bath reached room temperature. The reaction mixture was quenched with saturated aqueous $CuSO_4$ (2 mL) and water (5 mL), and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 30% EtOAc-hexane, gave **32.6c'** (25.8 mg, 90%) as a colorless foam: FTIR ($CHCl_3$, cast) 3065, 2954, 2926, 2870, 1766, 1448 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.95-7.93 (m, 4 H), 7.72-7.69 (m, 2 H), 7.60-7.56 (m, 4 H), 6.91 (t, *J* = 1.3 Hz, 1 H), 6.01 (s, 1 H), 5.60-5.58 (m, 1 H), 4.35 (t, *J* = 5.6 Hz, 1 H), 3.62 (td, *J* = 10.7, 4.3 Hz, 1 H), 2.17-2.09 (m, 7 H), 1.85-1.64 (m, 4 H), 1.62-1.55 (m, 2 H), 1.44-1.37 (m, 1 H), 1.31-1.22 (m, 3 H), 1.06-0.79 (m, 12 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.7 (s), 168.9 (s), 144.5 (d), 137.9 (s), 137.8 (s), 136.8 (s), 134.6 (d), 129.6 (d), 129.6 (d), 129.1 (d), 98.9 (d), 83.6 (d), 79.2 (d), 68.2 (d), 47.7 (d), 40.5 (t), 34.2 (t), 32.0 (t), 31.5 (q), 27.7 (t), 25.4 (t), 25.2 (d), 24.4 (t), 23.1 (t), 22.2 (q), 20.9 (q), 20.9 (q), 15.7 (q); exact mass (electrospray) *m/z* calcd for $C_{34}H_{44}NaO_9S_2$ (M + Na) 683.2319, found 683.2312.

Use of 32.6b

DMAP (1.2 mg, 0.01 mmol) was added to a stirred solution of **32.6b** (57 mg, 0.092 mmol) in CH_2Cl_2 (3 mL). The mixture was then cooled to 0 °C, and AcCl (0.033 mL, 0.46 mmol) and pyridine (0.060 mL, 0.74 mmol) were added sequentially. The ice bath was left in place but not recharged and stirring was continued for 3 h, during which time the cold bath reached room temperature. The reaction mixture was then quenched with saturated aqueous $CuSO_4$ (2 mL) and water (5 mL), and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 30% EtOAc-hexane, gave **32.6c** (55 mg, 91%) as a colorless foam: FTIR (neat) 3096, 3067, 2954, 2926, 2870, 1767, 1448 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.96-7.94 (m, 4 H), 7.72-7.68 (m, 2 H), 7.59-7.56 (m, 4 H), 6.85 (t, *J* = 1.4 Hz, 1 H), 5.97 (t, *J* = 1.4 Hz, 1 H), 5.51 (tdd, *J* = 5.6, 2.6, 1.5 Hz, 1 H), 4.36 (t, *J* = 5.6 Hz, 1 H), 3.63 (td, *J* = 10.7, 4.3 Hz, 1 H), 2.16-2.07 (m, 7 H), 1.84-1.54 (m, 6 H), 1.44-1.22 (m, 4 H), 1.06-0.80 (m, 12 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.8 (s), 168.9 (s), 144.0 (d), 137.9 (s), 137.8 (s), 137.0 (s), 134.6 (d), 129.6 (d), 129.6 (d), 129.1 (d), 129.1 (d), 98.9 (d), 83.6 (d), 79.5 (d), 68.2 (d), 47.7 (d), 40.5 (t), 34.2 (t), 32.3 (t), 31.5 (q), 27.7 (t), 25.4 (t), 25.4 (d), 24.6 (t), 23.2 (t), 22.2 (d), 20.9 (q), 20.8 (q), 15.9 (q); exact mass (electrospray) *m/z* calcd for $C_{34}H_{44}NaO_9S_2$ (M + Na) 683.2319, found 683.2310.

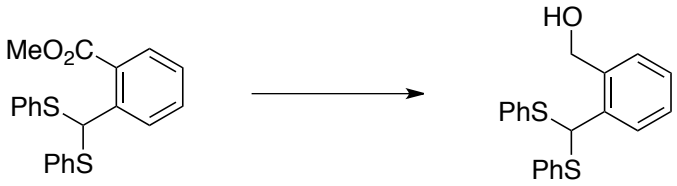
Methyl 2-[bis(phenylsulfanyl)methyl]benzoate (37.3).



37.2 **37.3**

NaH (60%, 1.58 g, 39.32 mmol) was added slowly to a stirred and cooled (0 °C) solution of PhSH (3.9 mL, 38.04 mmol) in DMF (60 mL). Stirring was continued for 10 min, a solution of **37.2** (4.68 g, 15.21 mmol) in DMF (10 mL) was then added, and stirring was continued for 12 h. The mixture was quenched with hydrochloric acid (1 M, 5 mL) and extracted with Et_2O (2 x 100 mL). The combined organic extracts were washed with aqueous NaOH (10%, 20 mL) to remove unreacted PhSH, and the organic phase was washed with water and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (4 x 15 cm), using 5% Et_2O-hexane, gave **37.3** (3.5 g, 65%) as an oil: FTIR (cast film) 3057, 3019, 2948, 2926, 1715, 1598, 1581, 1480, 1438 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.87-7.83 (m, 2 H), 7.47 (dddd, *J* = 7.9, 7.4, 1.5, 0.4 Hz, 1 H), 7.39-7.36 (m, 4 H), 7.30-7.21 (m, 7 H), 7.06 (s, 1 H), 3.82 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.4 (s), 141.2 (s), 134.4 (d), 132.4 (d), 132.3 (d), 130.4 (d), 129.7 (d), 128.8 (d), 128.1 (s), 127.6 (d), 127.6 (d), 54.7 (q), 52.2 (d); exact mass (electrospray) *m/z* calcd for $C_{21}H_{18}NaO_2S_2$ (M + Na) 389.0640, found 389.0642.

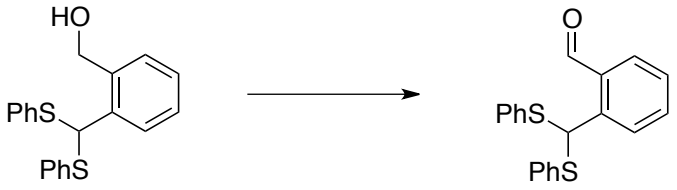
{2-[Bis(phenylsulfanyl)methyl]phenyl}methanol (37.4).



37.3 **37.4**

DIBAL-H (1 M solution in PhMe, 24.6 mL, 24.6 mmol) was added by syringe pump over 20 min to a stirred and cooled (-78 °C) solution of **37.3** (3.49 g, 9.85 mmol) in CH_2Cl_2 (100 mL). After the addition stirring at -78 °C was continued for 1 h and then the cold bath was replaced by an ice bath and stirring was continued for 1 h. The reaction was quenched with water (3.5 mL, 197 mmol) and NaF[42] (8.27 g, 197 mmol) at 0 °C, diluted with Et_2O (100 mL), stirred vigorously for 1 h at room temperature, and filtered through a pad of Celite using Et_2O. Evaporation of the filtrate and flash chromatography of the residue over silica gel (4 x 15 cm), using 40% Et_2O-hexane, gave **37.4** (3.13 g, 94%) as an oil: FTIR (neat) 3396, 3059, 3016, 3003, 2922, 2883, 1602, 1582, 1480, 1452, 1439 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.71-7.68 (m, 1 H), 7.40-7.22 (m, 13 H), 5.94 (s, 1 H), 4.66 (s, 2 H), 1.70 (br s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.0 (s), 137.4 (s), 134.2 (s), 132.8 (d), 129.1 (d), 129.0 (d), 128.9 (d), 128.6 (d), 128.3 (d), 128.0 (d), 63.4 (t), 56.8 (d); exact mass (electrospray) *m/z* calcd for $C_{20}H_{18}NaOS_2$ (M + Na) 361.0691, found 361.0697.

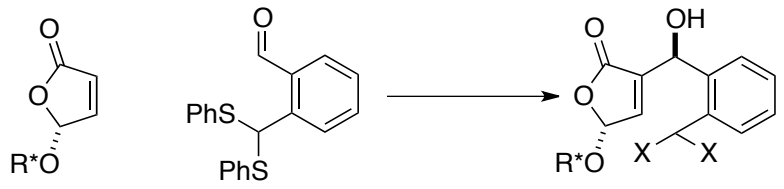
2-[Bis(phenylsulfanyl)methyl]benzaldehyde (32.7).



37.4 **32.7**

Et_3N (4.2 mL, 30 mmol) and DMSO (4.2 mL, 60 mmol) were added to a stirred and cooled (0 °C) solution of **37.4** (1.01 g, 3 mmol) in CH_2Cl_2 (30 mL). Stirring was continued for 5 min and then SO_3.py (1.4 g, 9 mmol) was added and stirring was continued for 12 h, the ice bath being left in place but not recharged. The reaction mixture was quenched with water (5 mL) and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were washed with water and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (3 x 15 cm), using 20% Et_2O-hexane, gave **32.7** (798 mg, 79%) as an oil: FTIR ($CHCl_3$, cast) 3057, 3017, 2834, 2745, 1696, 1597, 1581, 1573, 1480, 1449, 1438 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 10.12 (s, 1 H), 7.85 (d, *J* = 7.7 Hz, 1 H), 7.71 (dd, *J* = 7.6, 1.5 Hz, 1 H), 7.55-7.51 (m, 1 H), 7.43 (td, *J* = 7.5, 1.2 Hz, 1 H), 7.39-7.35 (m, 4 H), 7.24-7.21 (m, 6 H), 6.97 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.7 (d), 141.5 (s), 134.1 (d), 134.0 (s), 133.9 (d), 132.6 (d), 132.3 (s), 129.9 (d), 128.9 (d), 128.3 (d), 127.9 (d), 54.1 (d); exact mass (electrospray) *m/z* calcd for $C_{20}H_{16}NaOS_2$ (M + Na) 359.0535, found 359.0538.

(5*R*)-3-[(*S*)-{2-[Bis(phenylsulfanyl)methyl]phenyl}(hydroxy)methyl]-5-{[(1*R*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy}-2,5-dihydrofuran-2-one (32.7a).

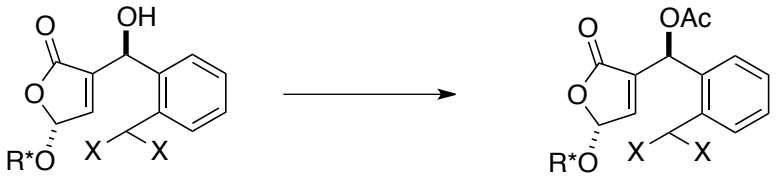


25.1 **32.7** **32.7a**, X = SPh

BuLi (2.5 M in hexane, 0.52 mL, 1.29 mmol) was added dropwise to a stirred and cooled (-20 °C) solution of PhSeSePh (367 mg, 1.17 mmol) in THF (5 mL). After 10 min, the mixture was cooled to -45 °C, a mixture of **25.1** (140 mg, 0.59 mmol) and **32.7** (198 mg, 0.59 mmol) in THF (4 mL) was added dropwise, and stirring was continued for 8 h at -45 °C. Then BnBr (0.18 mL, 1.47 mmol) and Bu_4NI (217 mg, 0.589 mmol) were added and stirring was continued for 8 h at -45 °C to -20 °C. The mixture was quenched with saturated aqueous NH_4Cl (5 mL) and extracted with Et_2O (2 x 20 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 40% Et_2O-hexanes, gave **32.7a** [183 mg, 55 %, 83% after correction for recovered **25.1** (75 mg)]: FTIR ($CHCl_3$, cast) 3423, 3060, 3020, 2955, 2925, 2869, 1766, 1582, 1480, 1453, 1439 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 6.2 Hz, 1 H), 7.43-7.22 (m, 13 H), 6.71 (dd, *J* = 1.6, 1.3 Hz, 1 H), 5.90 (s, 1 H), 5.88 (t, *J* = 1.2 Hz, 1 H), 5.79 (s, 1 H), 3.60 (td, *J*

= 10.7, 4.3 Hz, 1 H), 2.09-2.04 (m, 2 H), 1.69-1.61 (m, 2 H), 1.34-1.18 (m, 2 H), 1.02-0.75 (m, 13 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3 (s), 145.2 (d), 138.4 (s), 137.2 (s), 134.1 (s), 133.6 (s), 133.2 (d), 132.8 (d), 129.3 (d), 128.9 (d), 128.9 (d), 128.9 (d), 128.5 (d), 128.3 (d), 128.0 (d), 99.4 (d), 79.3 (d), 66.1 (d), 47.7 (d), 40.4 (t), 34.2 (t), 31.4 (d), 25.3 (d), 23.1 (t), 22.2 (d), 20.8 (q), 15.8 (q); exact mass (electrospray) *m/z* calcd for $C_{34}H_{38}NaO_4S_2$ (M + Na) 597.2104, found 597.2102.

(S)-{2-[Bis(phenylsulfanyl)methyl]phenyl}[(5*R*)-5-{[(1*R*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy}-2-oxo-2,5-dihydrofuran-3-yl]methyl acetate (32.7b).

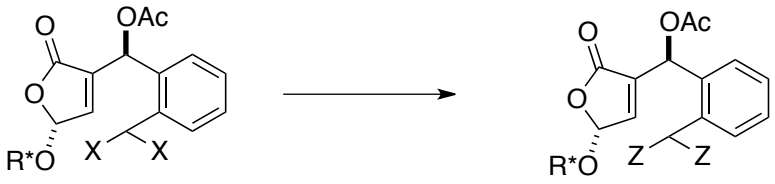


32.7a **32.7b**, X = SPh

DMAP (0.5 mg, 0.005 mmol) was added to a stirred solution of **32.7a** (28 mg, 0.049 mmol) in CH_2Cl_2 (2 mL). The mixture was then cooled to 0 °C, and AcCl (0.0104 mL, 0.146 mmol) and pyridine (0.0196 mL, 0.24 mmol) were added sequentially. The ice bath was left in place but not recharged and stirring was continued for 3 h, during which time the cold bath reached room temperature. The reaction mixture was then quenched with saturated aqueous $CuSO_4$ (2 mL)

and water (2 mL), and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 40% Et_2O-hexane, gave **32.7b** (23 mg, 76%): FTIR ($CHCl_3$, cast) 3060, 3022, 2955, 2924, 2869, 1774, 1745, 1582, 1481, 1454, 1439 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.75-7.73 (m, 1 H), 7.38-7.21 (m, 13 H), 6.94 (s, 1 H), 6.65 (t, *J* = 1.4 Hz, 1 H), 5.96 (s, 1 H), 5.87 (t, *J* = 1.1 Hz, 1 H), 3.59 (td, *J* = 10.7, 4.3 Hz, 1 H), 2.07-1.99 (m, 5 H), 1.67-1.60 (m, 2 H), 1.39-1.33 (m, 1 H), 1.22-1.15 (m, 1 H), 1.01-0.69 (m, 12 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.4 (s), 168.4 (s), 146.7 (d), 137.1 (s), 136.3 (s), 134.1 (s), 133.8 (s), 133.4 (s), 132.7 (d), 132.4 (d), 129.6 (d), 129.2 (d), 128.9 (d), 128.9 (d), 128.4 (d), 128.1 (d), 128.0 (d), 127.7 (d), 98.7 (d), 79.0 (d), 66.3 (d), 55.9 (d), 47.7 (d), 40.4 (t), 34.2 (t), 31.4 (q), 25.2 (d), 23.1 (t), 22.2 (d), 20.8 (q), 15.7 (q); exact mass (electrospray) *m/z* calcd for $C_{36}H_{40}NaO_5S_2$ (M + Na) 639.2209, found 639.2214.

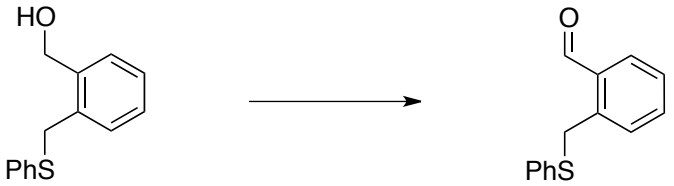
(S)-{2-[Bis(benzenesulfonyl)methyl]phenyl}[(5*R*)-5-{[(1*R*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy}-2-oxo-2,5-dihydrofuran-3-yl]methyl acetate (32.7c).



32.7b, X = SPh **32.7c**, Z = SO_2Ph

MCPBA (70%, 58 mg, 0.26 mmol) was added to a stirred and cooled (0 °C) solution of **32.7b** (16 mg, 0.026 mmol) in CH_2Cl_2 (3 mL). The ice bath was left in place but not recharged and stirring was continued for 6 h. The reaction mixture was quenched with a mixture of saturated aqueous $NaHCO_3$ (2 mL) and saturated aqueous $Na_2S_2O_3$ (2 mL), and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extracts were washed with water and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 40% EtOAc-hexane, gave **32.7c** (14 mg, 82%) as a colorless oil: FTIR ($CHCl_3$, cast) 3067, 3024, 2955, 2926, 2870, 1768, 1584, 1478, 1446 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.92-7.79 (m, 5 H), 7.65-7.60 (m, 2 H), 7.52-7.44 (m, 6 H), 7.34-7.30 (m, 1 H), 6.86 (t, *J* = 1.4 Hz, 1 H), 6.68 (s, 1 H), 6.43 (s, 1 H), 6.01 (t, *J* = 1.2 Hz, 1 H), 3.62 (td, *J* = 10.7, 4.3 Hz, 1 H), 2.13-2.07 (m, 5 H), 1.67-1.61 (m, 2 H), 1.40-1.35 (m, 1 H), 1.26-1.19 (m, 1 H), 1.00-0.74 (m, 12 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.6 (s), 168.4 (s), 146.7 (d), 138.2 (s), 137.6 (s), 137.6 (s), 136.1 (s), 134.6 (d), 134.4 (d), 133.7 (d), 131.6 (d), 130.8 (d), 130.2 (d), 130.1 (d), 130.0 (d), 129.8 (d), 129.1 (d), 128.9 (d), 128.8 (d), 128.8 (d), 128.3 (d), 124.0 (s), 99.1 (d), 82.6 (d), 79.5 (d), 65.7 (d), 47.7 (d), 40.6 (t), 34.1 (t), 31.4 (q), 30.9 (d), 25.2 (d), 23.1 (t), 22.2 (q), 20.9 (q), 15.8 (q); exact mass (electrospray) *m/z* calcd for $C_{36}H_{40}NaO_5S_2$ (M + Na) 703.2006, found 703.2001.

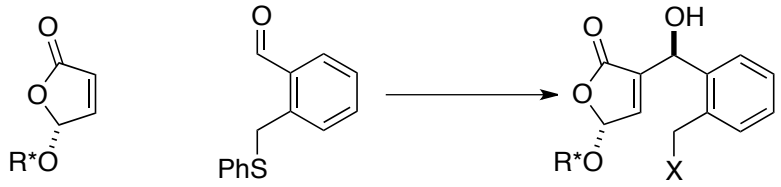
2-[(Phenyl-sulfanyl)methyl]benzaldehyde (32.8).



38.3 **32.8**

Et_3N (2.16 mL, 15.5 mmol) and DMSO (2.2 mL, 31.04 mmol) were added to a stirred and cooled (0 °C) solution of **38.3**[33] (388 mg, 1.55 mmol) in CH_2Cl_2 (11 mL). Stirring was continued for 5 min and then SO_3.py (988 mg, 6.21 mmol) was added. Stirring was continued for 12 h, the ice bath being left in place but not recharged. The reaction mixture was then quenched with water (5 mL) and extracted with CH_2Cl_2 (2 x 20 mL), and the combined organic extracts were washed with water and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 15% Et_2O-hexane, gave **32.8** (343 mg, 89%) as an oil: FTIR ($CDCl_3$, cast) 3059, 3019, 2932, 2836, 2744, 1696, 1598, 1575, 1481, 1451, 1439, 1402 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.23 (s, 1 H), 7.85-7.83 (m, 1 H), 7.49-7.41 (m, 2 H), 7.34-7.21 (m, 6 H), 4.53 (s, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.0 (d), 139.8 (s), 135.3 (s), 133.7 (s), 133.6 (d), 132.8 (d), 131.3 (d), 131.2 (d), 128.9 (d), 127.8 (d), 127.1 (d), 36.3 (t); exact mass (EI) *m/z* calcd for $C_{14}H_{12}OS$ (M) 228.0608, found 228.0610.

(5*R*)-3-[(*S*)-Hydroxy({2-[(phenylsulfanyl)methyl]phenyl})methyl]-5-{[(1*R*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy}-2,5-dihydrofuran-2-one (32.8a).

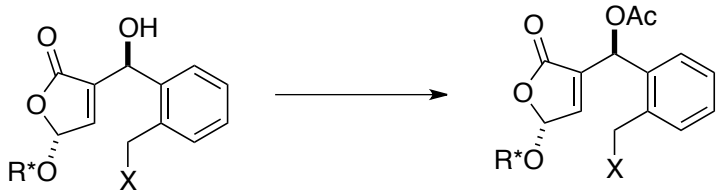


25.1 **32.8** **32.8a**, X = SPh

BuLi (2.5 M in hexane, 80 μL, 0.20 mmol) was added dropwise to a stirred and cooled (-20 °C) solution of PhSeSePh (63 mg, 0.20 mmol) in THF (2 mL). After 10 min, the mixture was cooled to -45 °C, a mixture of **25.1** (78 mg, 0.33 mmol) and **32.8** (90 mg, 0.39 mmol) in THF (2 mL) was added dropwise, and stirring was continued for 8 h at -45 °C. Then BnBr (44 μL, 0.36 mmol) and Bu_4NI (12 mg, 0.036 mmol) were added and stirring was continued for 8 h at -45 °C to -20 °C. The mixture was quenched with saturated aqueous NH_4Cl (5 mL) and extracted with Et_2O (2 x 20 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 40% Et_2O-hexanes, gave **32.8a** [78 mg, 56%, 87% after correction for recovered **25.1** (32 mg)]: FTIR (microscope) 3452, 3060, 2954, 2924, 2869, 1768, 1584, 1481, 1454, 1439 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (dd, *J* = 7.7, 1.2 Hz, 1 H), 7.34-7.17 (m, 8 H), 6.88 (t, *J* = 1.5 Hz, 1 H), 6.02 (t, *J* = 1.3 Hz, 1 H), 5.93 (s, 1 H), 4.36 (d, *J* = 12.6 Hz, 1 H), 4.15 (d, *J* =

12.7 Hz, 1 H), 3.64 (td, *J* = 10.7, 4.3 Hz, 1 H), 3.16 (s, 1 H), 2.14-2.04 (m, 2 H), 1.70-1.63 (m, 2 H), 1.44-1.21 (m, 2 H), 1.07-0.76 (m, 12 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2 (s), 144.5 (d), 139.2 (s), 138.3 (s), 135.2 (s), 134.7 (s), 130.9 (d), 130.8 (d), 129.0 (d), 128.5 (d), 128.2 (d), 127.6 (d), 127.1 (d), 99.3 (d), 79.2 (d), 65.8 (d), 47.7 (d), 40.4 (t), 37.1 (t), 34.2 (t), 31.5 (d), 25.5 (d), 23.3 (t), 22.2 (q), 20.8 (q), 15.9 (q); exact mass (electrospray) *m/z* calcd for $C_{28}H_{34}NaO_4S$ (M + Na) 489.207, found 489.2070.

(*S*)-[(5*R*)-5-{[(1*R*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy}-2-oxo-2,5-dihydrofuran-3-yl]({2-[(phenylsulfanyl)methyl]phenyl})methyl acetate (32.8b).

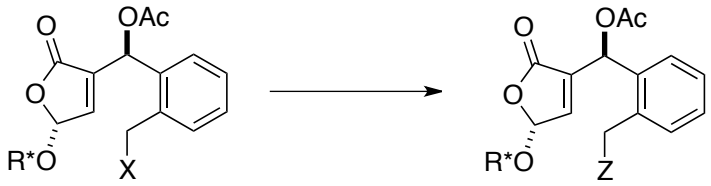


32.8a **32.8b**, X = SPh

DMAP (1.2 mg, 0.01 mmol) was added to a stirred solution of **32.8a** (20 mg, 0.043 mmol) in CH_2Cl_2 (2 mL). The mixture was then cooled to 0 °C, and AcCl (9.1 μL, 0.13 mmol) and pyridine (21 μL, 0.25 mmol) were added sequentially. The ice bath was left in place but not recharged and stirring was continued for 3 h, during which time the cold bath reached room temperature. The reaction mixture was quenched with saturated aqueous $CuSO_4$ (2 mL) and

water (5 mL), and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 40% Et_2O-hexane, gave **32.8b** (21 mg, 96%) as a colorless oil: FTIR ($CHCl_3$, cast) 3060, 2955, 2925, 2869, 1771, 1748, 1659, 1600, 1584, 1481, 1455, 1439 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.41 (dd, *J* = 7.6, 1.1 Hz, 1 H), 7.36-7.18 (m, 8 H), 6.94 (t, *J* = 1.3 Hz, 1 H), 6.83 (t, *J* = 1.4 Hz, 1 H), 6.03 (t, *J* = 1.2 Hz, 1 H), 4.36 (d, *J* = 13.0 Hz, 1 H), 4.31 (d, *J* = 13.0 Hz, 1 H), 3.64 (td, *J* = 10.7, 4.2 Hz, 1 H), 2.12-2.03 (m, 5 H), 1.69-1.62 (m, 2 H), 1.43-1.36 (m, 1 H), 1.26-1.20 (m, 1 H), 1.02-0.73 (m, 12 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.5 (s), 168.6 (s), 146.0 (d), 137.0 (s), 135.8 (s), 135.3 (s), 135.0 (s), 130.7 (d), 130.4 (d), 128.9 (d), 128.9 (d), 128.1 (d), 127.9 (d), 126.6 (d), 98.7 (d), 79.0 (d), 66.4 (d), 47.8 (d), 40.4 (t), 36.7 (t), 34.2 (t), 31.5 (q), 25.4 (d), 23.3 (t), 22.2 (d), 20.9 (q), 20.8 (q), 15.9 (q); exact mass (electrospray) *m/z* calcd for $C_{30}H_{36}NaO_5S$ (M + Na) 531.2175, found 531.2172.

(*S*)-{2-[(Benzenesulfonyl)methyl]phenyl}[(5*R*)-5-{[(1*R*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy}-2-oxo-2,5-dihydrofuran-3-yl]methyl acetate (32.8c).

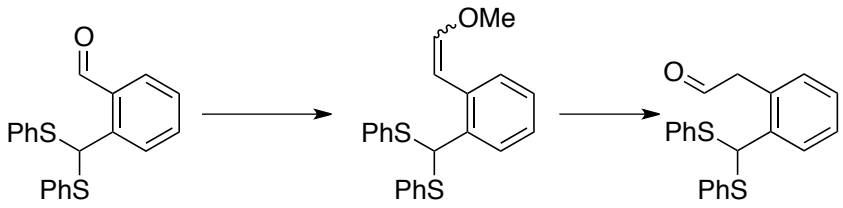


32.8b, X = SPh **32.8c**, Z = SO_2Ph

MCPBA (70%, 102 mg, 0.41 mmol) was added to a stirred and cooled (0 °C) solution of **32.8b** (21 mg, 0.041 mmol) in CH_2Cl_2 (3 mL). The ice bath was left in place but not recharged and stirring was continued for 4 h. The reaction mixture was quenched with a mixture of saturated aqueous $NaHCO_3$ (2 mL) and saturated aqueous $Na_2S_2O_3$ (2 mL), and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extracts were washed with water and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 60% Et_2O-hexane, gave **32.8c** (22 mg, 100%) as a colorless oil: FTIR (CH_2Cl_2, cast) 3065, 2955, 2926, 2870, 1768, 1585, 1496, 1448 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88-7.85 (m, 2 H), 7.67-7.52 (m, 4 H), 7.41 (td, *J* = 7.6, 1.4 Hz, 1 H), 7.31 (td, *J* = 7.5, 1.4 Hz, 1 H), 7.21 (dd, *J* = 7.8, 1.3 Hz, 1 H), 6.93 (t, *J* = 1.4 Hz, 1 H), 6.78 (t, *J* = 1.4 Hz, 1 H), 6.04 (t, *J* = 1.3 Hz, 1 H), 4.69 (d, *J* = 14.1 Hz, 1 H), 4.62 (d, *J* = 14.1 Hz, 1 H), 3.61 (td, *J* = 10.7, 4.3 Hz, 1 H), 2.12-2.01 (m, 5 H), 1.68-1.60 (m, 2 H), 1.43-1.32 (m, 1 H), 1.26-1.19 (m, 1 H), 1.01-0.70 (m, 12 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8 (s), 168.8 (s), 145.1 (d), 139.1 (s), 137.0 (s), 136.8 (s), 133.8 (d), 133.0 (d), 129.5 (d), 129.2 (d), 129.1 (d), 129.0 (d), 128.4 (d), 126.4 (s), 99.2 (d), 79.2 (d), 66.7 (d), 59.4 (t), 47.7 (d), 40.6 (t), 34.2 (t), 31.4 (q), 25.3 (d), 23.2 (t), 22.2 (d), 20.9 (q), 20.8 (q), 15.8 (q); exact

mass (electrospray) *m*/*z* calcd for $C_{30}H_{36}NaO_7S$ (M + Na) 563.2074, found 563.2074.

2-{2-[Bis(phenylsulfanyl)methyl]phenyl}acetaldehyde (32.9).



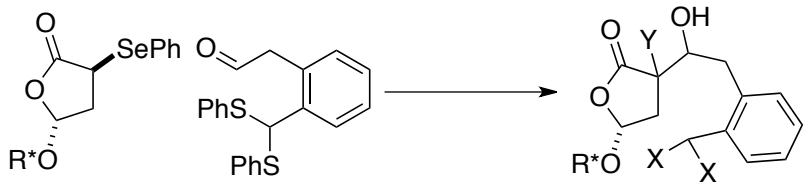
32.7 **39.1** **32.9**

$(Me_3Si)_2NNa$ (1 M in THF, 7.13 mL, 7.13 mmol) was added dropwise over 5 min to a stirred and cooled (-78 °C) solution of (methoxymethyl)triphenylphosphonium chloride (3.26 g, 9.5 mmol) in THF (20 mL). The resulting slurry was stirred for 90 min at -78 °C and then a solution of **32.7** (798 mg, 2.38 mmol) was added dropwise over 5 min. The cold bath was left in place but not recharged and stirring was continued for 12 h, during which time the cold bath reached room temperature. The reaction mixture was quenched with saturated aqueous NH_4Cl (ca 10 mL) and extracted with Et_2O. The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (3 x 15 cm), using 5% Et_2O-hexane, gave **39.1**, which was used for the next step.

Hydrochloric acid (4 M, 4 mL) was added to a solution of **39.1** in THF (15 mL) and the mixture was refluxed at 66 °C for 3 h, cooled, quenched with

saturated aqueous $NaHCO_3$ (ca 5 mL), diluted with water (20 mL) and extracted with Et_2O (50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 15 cm), using 10% Et_2O-hexane, gave **32.9** (464 mg, 56% over two steps) as an oil: FTIR ($CDCl_3$, cast) 3058, 3019, 2822, 2724, 1721, 1581, 1480, 1448, 1438, 1415 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.53 (t, *J* = 2.3 Hz, 1 H), 7.71 (d, *J* = 6.9 Hz, 1 H), 7.37-7.24 (m, 12 H), 7.15 (dd, *J* = 7.2, 1.8 Hz, 1 H), 5.54 (s, 1 H), 3.71 (d, *J* = 1.9 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.0 (d), 138.5 (s), 133.9 (s), 133.0 (d), 131.2 (d), 129.7 (s), 129.5 (d), 129.0 (d), 128.5 (d), 128.2 (d), 128.2 (d), 57.9 (d), 47.9 (t); exact mass (electrospray) *m/z* calcd for $C_{21}H_{18}NaOS_2$ (M + Na) 373.0691, found 373.0695.

(4*R*)-2-(2-{2-[Bis(benzenesulfonyl)methyl]phenyl}-1-hydroxyethyl)-4-{[(1*R*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy}-2-(phenylselanyl)-cyclopentan-1-one (32.9a, 32.9a').

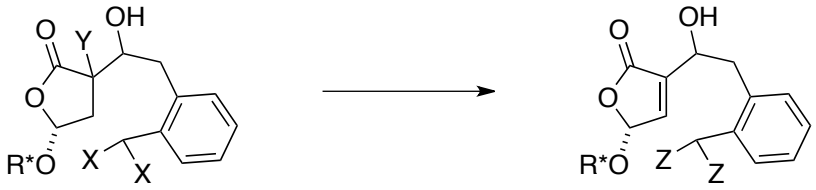


27.1 **32.9** **32.9a, 32.9a'**, X = SPh

$(Me_3Si)_2NK$ (0.5 M in PhMe, 0.92 mL, 0.46 mmol) was added dropwise (over ca 10 min) to a stirred and cooled (-78 °C) solution of lactone **27.1** (166 mg,

0.42 mmol) in THF (5 mL). Stirring at -78 °C was continued for 45 min and then a solution of aldehyde **32.9** (165 mg, 0.47 mmol) in THF (2 mL) was added. Stirring at -78 °C was continued for 20-30 min (TLC control, silica, 40% Et_2O-hexane, disappearance of aldehyde monitored). Then saturated aqueous NH_4Cl (3 mL) was added and the mixture was extracted with Et_2O. The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 40% Et_2O-hexane gave **32.9a** and **32.9a'** as an oil. This mixture of diastereoisomers was used directly for next step.

(4*R*)-2-[2-{2-[Bis(benzenesulfonyl)methyl]phenyl}-1-hydroxyethyl]-4-{[(1*R*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy}cyclopent-2-en-1-one (32.9b, 32.9b').



32.9a, 32.9a', X = SPh **32.9b, 32.9b'**, Z = SO_2Ph

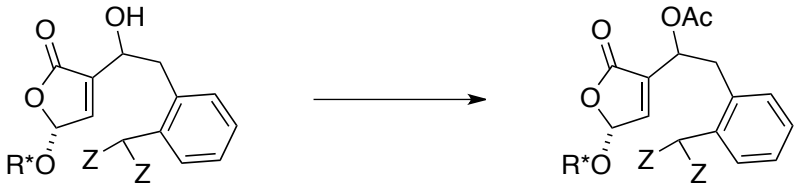
MCPBA (70%, 1.27 g, 5.1 mmol) was added to a stirred and cooled (0 °C) solution of **32.9a** and **32.9a'** (192 mg, 0.26 mmol) in CH_2Cl_2 (5 mL). The ice bath was left in place but not recharged and stirring was continued for 12 h. The reaction mixture was quenched with a mixture of saturated aqueous $NaHCO_3$ (2 mL) and saturated aqueous $Na_2S_2O_3$ (2 mL) and extracted with CH_2Cl_2. The

combined organic extracts were washed with water and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 60% Et_2O-hexane, gave a mixture of diastereomers which was separated into three fractions (more polar, 13 mg, 5%; less polar, 10 mg, 4%; mixture, 73 mg, 27%). The more polar alcohol **32.9b** had: FTIR ($CDCl_3$, cast) 3508, 3067, 2954, 2928, 2871, 1754, 1584, 1493, 1448 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.99 (dd, *J* = 7.9, 1.3 Hz, 1 H), 7.84-7.78 (m, 4 H), 7.66-7.62 (m, 2 H), 7.47 (t, *J* = 7.5 Hz, 4 H), 7.38 (td, *J* = 7.5, 1.4 Hz, 1 H), 7.31 (td, *J* = 7.6, 1.3 Hz, 1 H), 7.15 (dd, *J* = 7.6, 1.3 Hz, 1 H), 6.95 (t, *J* = 1.4 Hz, 1 H), 6.31 (s, 1 H), 6.02 (t, *J* = 1.4 Hz, 1 H), 4.60-4.58 (m, 1 H), 3.65 (td, *J* = 10.7, 4.3 Hz, 1 H), 2.77 (dd, *J* = 14.5, 2.6 Hz, 1 H), 2.42 (dd, *J* = 14.5, 9.0 Hz, 1 H), 2.16-2.10 (m, 2 H), 1.71-1.66 (m, 2 H), 1.41-1.37 (m, 1 H), 1.30-1.21 (m, 2 H), 1.05-0.82 (m, 12 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1 (s), 143.8 (s), 139.1 (s), 139.0 (s), 138.5 (s), 138.0 (s), 134.7 (s), 134.5 (s), 131.8 (s), 131.5 (s), 130.9 (s), 130.0 (s), 129.6 (s), 128.9 (s), 128.9 (s), 127.6 (s), 124.6 (s), 99.4 (s), 82.7 (s), 79.3 (s), 68.6 (s), 47.8 (s), 40.4 (s), 39.0 (s), 34.2 (s), 31.6 (s), 25.4 (s), 23.2 (s), 22.3 (s), 21.0 (s), 15.9 (q); exact mass (electrospray) *m/z* calcd for $C_{35}H_{40}NaO_8S_2$ (M + Na) 675.2057, found 675.2046.

The less polar alcohol **32.9b'** had: FTIR ($CDCl_3$, cast) 3503, 3067, 2955, 2928, 2870, 1753, 1599, 1584, 1493, 1448 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.99-7.94 (m, 1 H), 7.85-7.77 (m, 4 H), 7.66-7.57 (m, 3 H), 7.49-7.28 (m, 5 H), 7.14 (dd, *J* = 7.6, 1.3 Hz, 1 H), 6.96 (t, *J* = 1.4 Hz, 1 H), 6.39 (s, 1 H), 6.00 (s, 1 H), 4.61-4.59 (m, 1 H), 3.66 (td, *J* = 10.7, 4.3 Hz, 1 H), 2.84 (dd, *J* = 14.5, 2.7 Hz,

1 H), 2.43 (dd, *J* = 14.5, 9.1 Hz, 1 H), 2.16-2.11 (m, 2 H), 1.71-1.66 (m, 2 H), 1.42-1.38 (m, 1 H), 1.29-1.19 (m, 2 H), 1.08-0.81 (m, 12 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ^{13}C NMR ($CDCl_3$, 126 MHz) δ 170.1 (s), 144.1 (d), 139.1 (s), 139.0 (s), 138.5 (s), 137.9 (s), 135.4 (d), 134.6 (d), 134.5 (d), 133.7 (d), 131.7 (d), 131.5 (d), 130.8 (d), 130.0 (d), 129.6 (d), 128.9 (d), 128.9 (d), 128.8 (d), 128.3 (d), 127.5 (d), 124.6 (s), 99.3 (d), 82.7 (d), 79.2 (d), 68.6 (d), 47.8 (d), 40.3 (d), 38.5 (d), 34.2 (d), 31.5 (d), 25.4 (d), 23.2 (t), 22.2 (q), 20.9 (q), 15.9 (q); exact mass (electrospray) *m/z* calcd for $C_{35}H_{40}NaO_8S_2$ (M + Na) 675.2057, found 675.2058.

(1*S*)-2-{2-[Bis(benzenesulfonyl)methyl]phenyl}-1-[(3*R*)-3-{[(1*R*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl]oxy}-5-oxocyclopent-1-en-1-yl]ethyl acetate (32.9c, 32.9c').



32.9b, 32.9b' **32.9c**, **32.9c'** Z = SO_2Ph

DMAP (1.2 mg, 0.01 mmol) was added to a stirred solution of **32.9b** and **32.9b'** (73 mg, 0.11 mmol) in CH_2Cl_2 (3 mL). The mixture was then cooled to 0 °C, and AcCl (0.048 mL, 0.67 mmol) and pyridine (0.072 mL, 0.89 mmol) were added sequentially. The ice bath was left in place but not recharged and stirring was continued for 3 h, during which time the cold bath reached room temperature.

The reaction mixture was quenched with saturated aqueous $CuSO_4$ (2 mL) and water (5 mL), and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 50% EtOAc-hexane, gave as a mixture of diastereomers which was separated into two fractions (less polar, 22 mg, 28%; mixture, 42 mg, 55%). The less polar isomer **32.9c'** had: FTIR ($CDCl_3$, cast) 3066, 2954, 2928, 2870, 1758, 1748, 1584, 1491, 1448 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.16 (dd, *J* = 7.8, 1.3 Hz, 1 H), 7.94 (dd, *J* = 8.3, 1.0 Hz, 2 H), 7.71-7.64 (m, 3 H), 7.59-7.49 (m, 3 H), 7.40-7.28 (m, 4 H), 6.98 (dd, *J* = 7.5, 1.3 Hz, 1 H), 6.81 (t, *J* = 0.9 Hz, 1 H), 6.35 (s, 1 H), 5.86 (s, 1 H), 5.62 (t, *J* = 7.3 Hz, 1 H), 3.61 (td, *J* = 10.7, 4.3 Hz, 1 H), 2.87 (dd, *J* = 14.3, 7.3 Hz, 1 H), 2.50 (dd, *J* = 14.3, 7.4 Hz, 1 H), 2.12-2.04 (m, 5 H), 1.68-1.64 (m, 2 H), 1.41-1.34 (m, 1 H), 1.25-1.19 (m, 1 H), 1.00-0.75 (m, 12 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2 (s), 169.2 (s), 147.0 (d), 138.7 (s), 138.1 (s), 137.7 (s), 134.5 (d), 134.4 (d), 134.1 (s), 132.0 (d), 131.2 (d), 130.5 (d), 129.9 (d), 129.6 (d), 128.9 (d), 128.8 (d), 127.7 (d), 124.4 (s), 99.1 (d), 82.0 (d), 79.8 (d), 69.3 (d), 47.7 (d), 40.4 (t), 35.0 (t), 34.1 (t), 31.5 (q), 25.4 (d), 23.1 (t), 22.2 (d), 20.9 (q), 20.9 (q), 15.9 (q); exact mass (electrospray) *m/z* calcd for $C_{37}H_{42}NaO_9S_2$ (M + Na) 717.2162, found 717.2162.

The mixture of isomers (containing mainly the more polar) **32.9c** had: FTIR ($CDCl_3$, cast) 3067, 2955, 2928, 2870, 1807, 1758, 1748, 1584, 1492, 1448 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.15-7.97 (m, 3 H), 7.75-7.64 (m, 3 H), 7.62-7.31 (m, 7 H), 7.03-6.99 (m, 1 H), 6.85-6.83 (m, 1 H), 6.42-6.39 (m, 1 H), 5.99-

5.90 (m, 1 H), 5.73-5.65 (m, 1 H), 3.67-3.57 (m, 1 H), 2.91 (dd, *J* = 14.2, 7.6 Hz, 1 H), 2.64-2.51 (m, 1 H), 2.15-2.04 (m, 5 H), 1.72-1.66 (m, 2 H), 1.45-1.37 (m, 1 H), 1.29-1.20 (m, 1 H), 1.06-0.78 (m, 12 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2 (s), 169.3 (s), 147.5 (d), 139.0 (s), 138.8 (s), 138.1 (s), 137.8 (s), 137.7 (s), 137.5 (s), 135.4 (d), 134.6 (d), 134.5 (d), 134.5 (d), 134.4 (d), 134.2 (d), 133.9 (s), 132.0 (d), 131.9 (d), 131.3 (d), 131.3 (d), 130.8 (d), 130.5 (d), 130.5 (d), 130.0 (d), 129.9 (d), 129.9 (d), 129.7 (d), 129.7 (d), 129.6 (d), 128.9 (d), 128.9 (d), 128.9 (d), 128.8 (d), 128.8 (d), 128.7 (d), 128.7 (d), 128.7 (d), 128.7 (d), 127.7 (d), 127.7 (d), 124.4 (s), 124.4 (s), 99.1 (d), 98.7 (d), 82.1 (d), 82.0 (d), 79.8 (d), 78.5 (d), 69.4 (d), 69.4 (d), 47.7 (d), 47.7 (d), 40.5 (t), 40.1 (t), 35.0 (t), 34.9 (t), 34.2 (t), 34.2 (t), 31.5 (q), 31.5 (q), 25.4 (d), 25.3 (d), 23.1 (t), 22.2 (t), 22.2 (d), 21.0 (q), 21.0 (q), 20.9 (q), 20.9 (q), 15.9 (q); exact mass (electrospray) *m*/*z* calcd for $C_{37}H_{42}NaO_9S_2$ (M + Na) 717.2162, found 717.2163.

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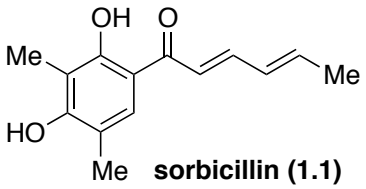
Chapter 2

Studies towards the total synthesis of the marine alkaloid sorbicillactone A

1. Introduction

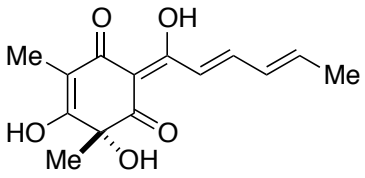
1.1 Isolation of sorbicillin

Sorbicillin (**1.1**) is a hexaketide isolated in 1948 by Cram and Tishler of Merck & Co. from the fungus *Pencillium notatum*.[1a,b] In 1953 Arima and co-workers in Japan reported isolation of this compound from *Penicillium chrysogenum*.[2] For several decades this remained the only example of a hexaketide in which cyclization had taken place on the carboxylate terminus (see later, Scheme 5).[3]

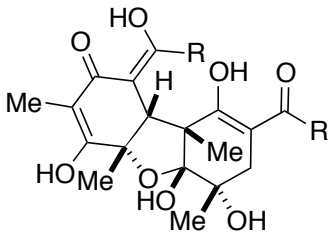


Scheme 1

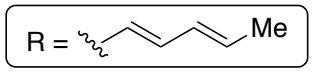
There are a number of natural products evidently derived from sorbicillin or by related biosynthetic pathways. All of these compounds can be categorized into monomeric, dimeric, trimeric, or polycyclic sorbicillinoids, vertinolides or nitrogen-containing sorbicillinoids.[3] The structures of several of these compounds are shown in Scheme 2.

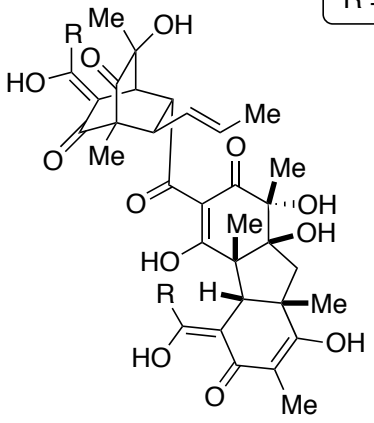


oxosorbicillinol (2.1)

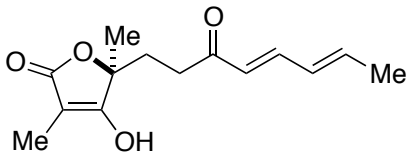


bisvertinol (2.2)





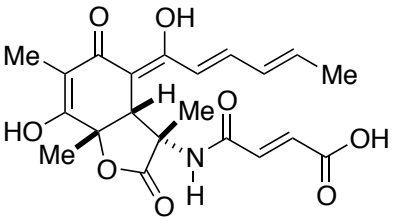
trisorbicillinone (2.3)



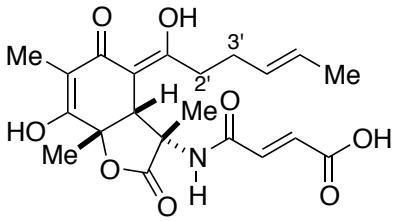
vertinolide (2.4)

Scheme 2

Sorbicillactone A (**3.1**) and its 2',3'-dihydro analogue, sorbicillactone B (**3.2**) are the first nitrogen-containing sorbicillinoids.



sorbicillactone A (3.1)



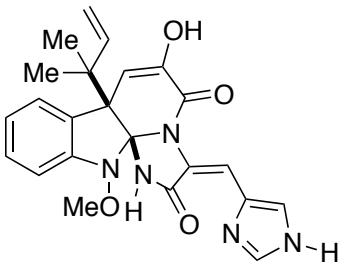
sorbicillactone B (3.2)

Scheme 3

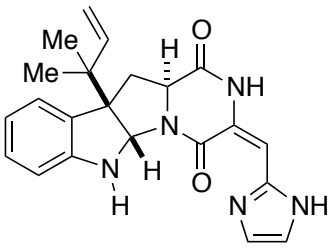
1.2 Isolation and structure determination of sorbicillactone A

In the search for new bioactive compounds from marine sponges and their associated microorganisms, Bringmann and co-workers in 2003 isolated novel alkaloids sorbicillactone A and sorbicillactone B.[4a,b] These compounds are produced by a saltwater culture of a *Pencillium chrysogenum* strain isolated from the Mediterranean sponge *Ircinia fasciculate*.

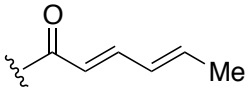
For investigation of the secondary metabolic profile, the fungus was propagated as a 10-L culture in a saline medium for 14 days. After this period, both the mycelium and culture broth were extracted with organic solvents, and the extracts were subjected to detailed chromatographic analysis. Two metabolites were identified as meleagrine (**4.1**) and roquefortine C (**4.2**) by comparing their UV spectra with a commercially available natural product database.[4a,b]



meleagrine (4.1)



roquefortine C (4.2)



4.3

Scheme 4

Besides these known compounds several other peaks were detected in the chromatograms. The most prominent of these peaks were thoroughly investigated using HPLC-NMR, and the evidence indicated the presence of a sorbyl residue (**4.3**). The UV spectrum of the compound containing this residue showed some similarity to the spectra of the so-called bisorbicillinoids (*e.g.* **2.2**).[4,5a,b] But HPLC-MS showed a molecular mass of 417 which was too low for the compound to belong to the bisorbicillinoids, and did not fit any of the few known monomeric sorbicillin-derived natural products.[4,6a,b]

Bringmann and coworkers isolated the new compounds by preparative HPLC on an RP-18 phase column and obtained 6 mg of the compound.[4a,b] Extensive 2D-NMR and mass spectrometry measurements were carried out in Bringmann's group and allowed the structure of the new compounds to be identified as sorbicillactone A **(3.1)** and sorbicillactone B **(3.2)**. The absolute configuration of the compounds was elucidated by quantum mechanical calculation of circular dichroism (CD) spectra and comparison with experimental measurements.

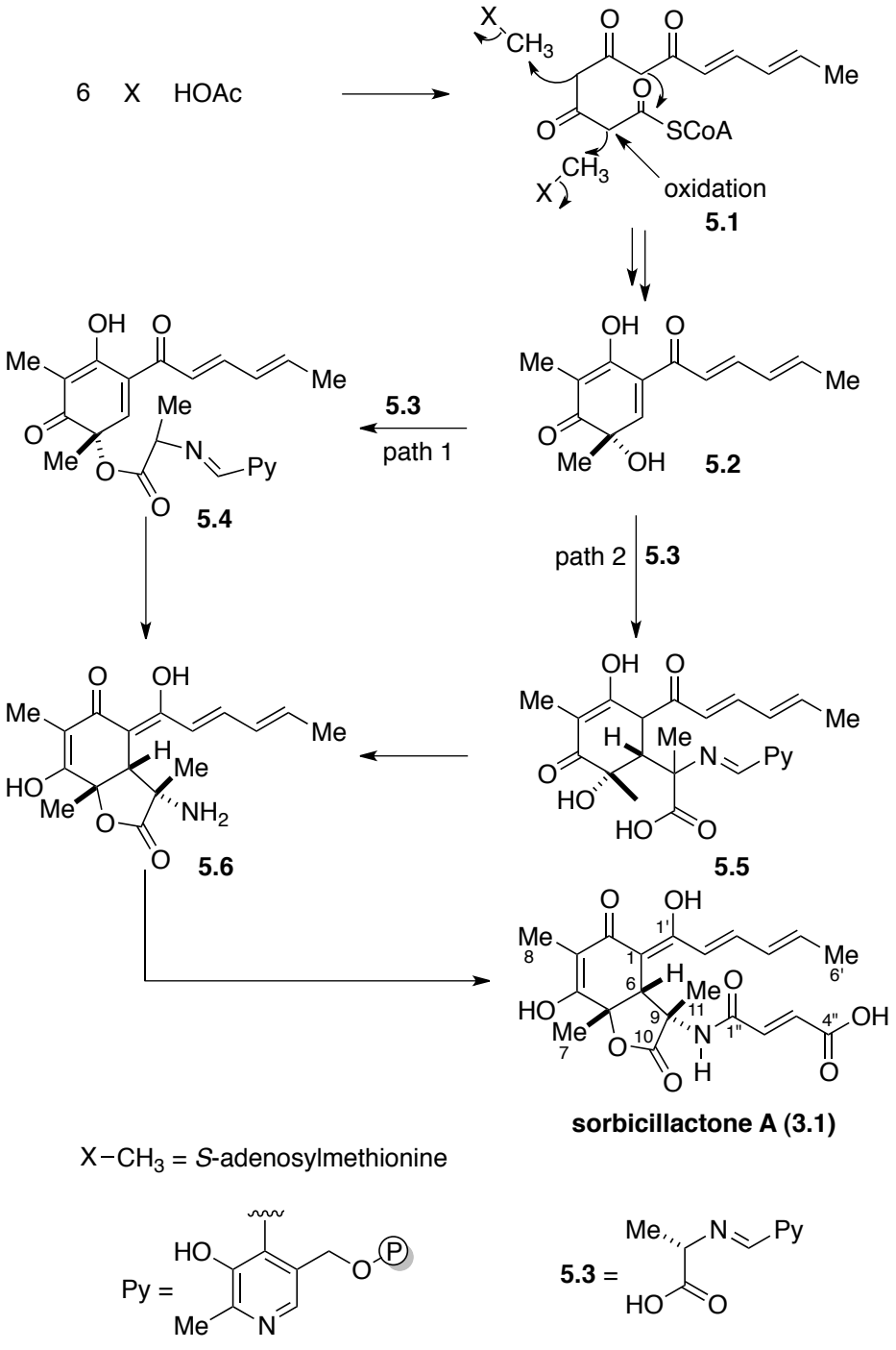
1.3 Biosynthesis of sorbicillactone A

There is little biosynthetic work published, but the general belief is that sorbicillactone A and sorbicillactone B are derived as shown in Scheme 5. After optimizing the growth conditions of the fungus *Pencillium chrysogenum* for the production of sorbicillactone A, Bringmann and co-workers carried out labeling experiments to study the biosynthesis of this molecule, the results of which are

discussed below, using the non-systematic skeletal numbering of his original publications.[4a]

Feeding experiment performed in Brigmann's group with [$^{13}C_2$]-acetate showed high incorporation of ^{13}C in all position of the six membered ring and the sorbyl chain, but no labeling at all at C-9, C-10 and C-11, nor at the methyl carbons C-7 and C-8. This observation firmly established the polyketide origin of this family of compounds. Administration of [$^{13}C_3$]-L-alanine to the fungus resulted in a significantly higher concentration of ^{13}C at the C-9, C-10 and C-11 positions. These results clearly indicated that the C_3 unit forming the lactone ring is derived directly from alanine (possibly activated by Schiff base formation with pyridoxal phosphate). Feeding of [methyl-^{13}C]-L-methionine led to a significant increase in the relative intensity of the C-7 and C-8 signals in the ^{13}C NMR spectrum of sorbicillactone A, which showed that the methyl carbons C-7 and C-8 are incorporated, presumably by methyl transfer from *S*-adenosylmethionine. But the fumaryl residue showed a weaker labeling pattern in all the above feeding experiments. Also, the labeling pattern of the amidic side chain was found to be non-symmetric, which clearly indicated that this residue, at least partially, was derived from an unsymmetrical compound. Furthermore, feeding of [$^{13}C_4$]-fumaric acid did not result in labeling of the fumaryl side chain and this fact indicated that fumaric acid itself is not the biosynthetic precursor of this side chain; however, it may be formed from a biosynthetic equivalent of fumaric acid. Results from the Abe group[7] and the Bringmann group[4a,b] showed the carbon skeleton of sorbicillactone A is derived from a sorbicillinol unit **(5.2)**. Based on

these feeding experiments, Bringmann and co-workers proposed the biosynthetic route to sorbicillactone A outlined in Scheme 5.



Scheme 5

1.4 Biological properties and biotechnological production of sorbicillactone A

The novel structural features of sorbicillactone A and sorbicillactone B made them attractive candidates for biological studies.[3,4a,b]

Bringmann and co-workers studied the biological properties of both sorbicillactone A and sorbicillactone B. Sorbicillactone A showed significant cytotoxic/cytostatic activity against murine leukemic lymphoblast L5178y cells with an IC_{50} value of 2.2 μg/mL. But against rat pheochromocytoma PC12 cells, human T lymphocyte H9 cells and human cervix carcinoma HeLa S3 cells its IC_{50} value was > 10 μg/mL. On the other hand, the structurally related sorbicillactone B exhibited a significantly lower activity than sorbicillactone A with IC_{50} values > 10 μg/mL for L5178y, PC13 and HeLa cells.

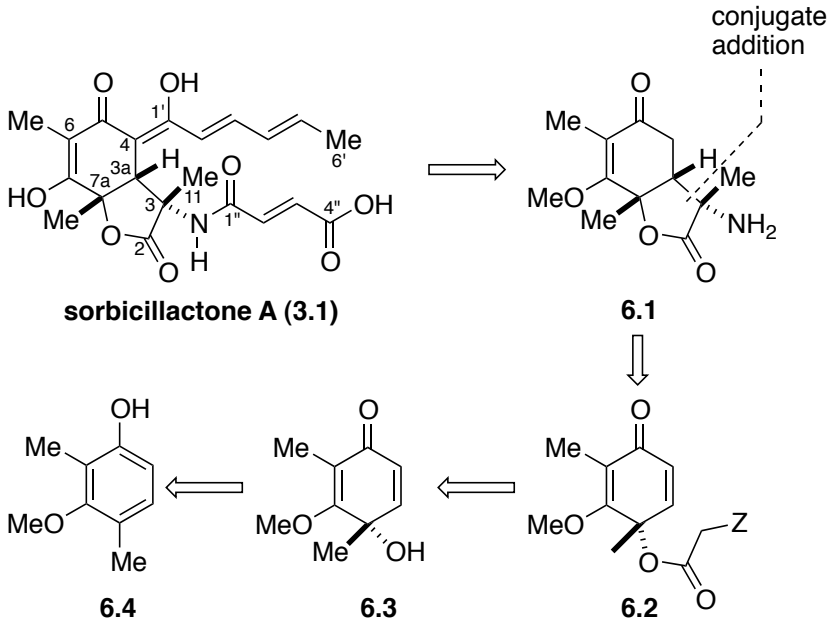
Besides its cytotoxicity, sorbicillactone A also showed high anti-HIV activity. In the concentration range between 0.3-3.0 mg/mL, sorbicillactone A protected human T lymphocytes (H9 cells) against the cytopathic effect of HIV-1 and inhibited the expression of viral proteins.[8,9] Results obtained from Bringmann's group on the effect of sorbicillactone A on calcium ion concentration in primary neurons after stimulation with serotonin showed that sorbicillactone A can be considered as a promising neuroprotective compound. Overall, the biological properties of sorbicillactone A include selective anti-leukemia activity without showing significant cytotoxicity, and also antiviral as well as neuroprotective properties. It could, therefore, be a potential new lead structure in medicinal chemistry.[4a,b]

The initial amount of sorbicillactone A produced was approximately 4 mg/L (range 2-6 mg/L).[10] In order to increase the yield and to adapt the production to amounts sufficient for preclinical and clinical studies, the Bringmann group in 2007 developed an efficient process for the biotechnological large scale production of sorbicillactone A. By this procedure they were able to isolate 100 g of pure sorbicillactone A for ongoing preclinical studies on this potential antitumor drug.[10]

1.5 Synthetic studies of sorbicillactone A reported in the literature

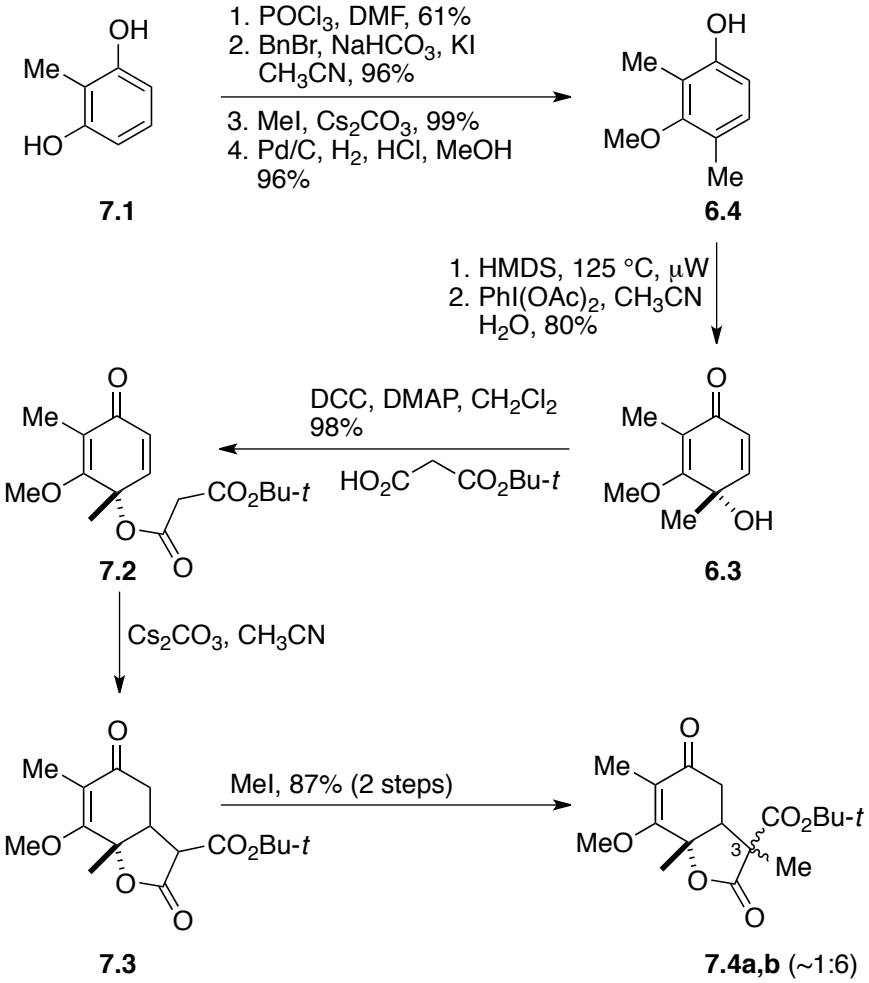
1.5.1 Harned's synthesis of racemic sorbicillactone A

So far, there is only one total synthesis of sorbicillactone A (racemic) reported in the literature by Harned's group in 2011.[11]



Scheme 6

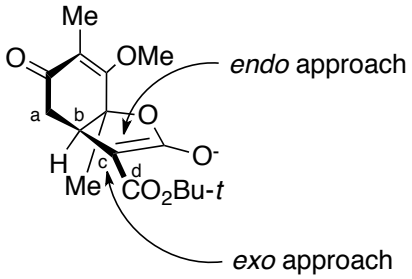
The synthetic plan used by Harned's group is depicted in Scheme 6, in which the sorbyl side chain was installed at a late stage through the use of a bicyclic intermediate similar to **6.1**. The key bond formation, C3-C3a, was established through an intramolecular conjugate displacement of activated (by "Z-group") dienone **6.2** which, in turn, can be synthesized from **6.3**. Based on this strategy, phenol **6.4** was chosen as the starting material.



Scheme 7

The synthesis in Harned's group began with commercially available 2-methylresorcinol (**7.1**). Vilsmeier-Haack reaction to introduce a formyl group adjacent to one hydroxyl, selective *O*-benzylation and methylation of both hydroxyl groups, followed by aldehyde reduction and exhaustive hydrogenolysis resulted in the formation of **6.4** from **7.1**. Oxidative dearomatization of **6.4** produced quinol **6.3** in 80% yield. Acylation of the quinol using a malonic acid monoester then produced dienone **7.2**. Harned's group used a malonic acid unit as an activating group for a Michael addition and also as a masked amine group that could be revealed later through a Curtius rearrangement. Malonate **7.2** was cyclized to provide bicyclic lactone **7.3** in the presence of Cs_2CO_3.

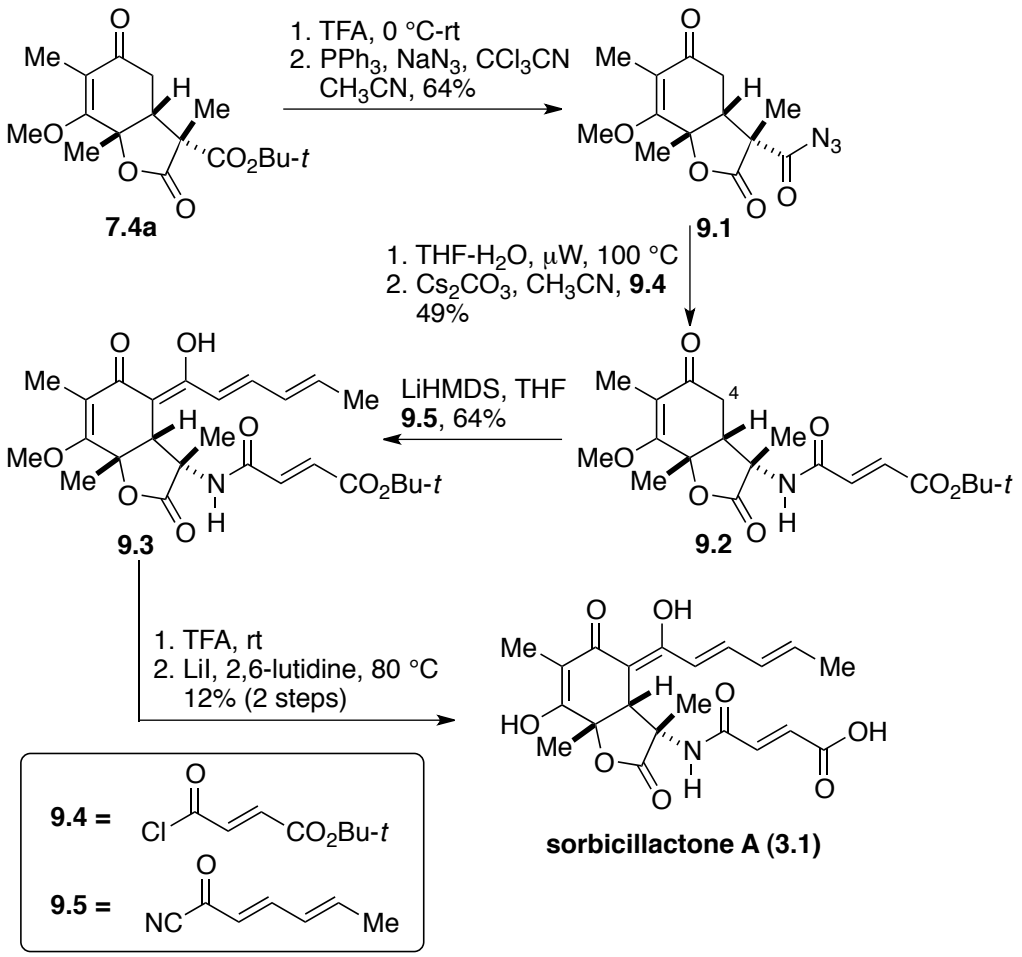
The critical alkylation of the bicyclic lactone was carried out by using MeI, but the desired isomer [**7.4a**, with an *exo* methyl group at C-3] for the synthesis of sorbicillactone A was obtained only in poor yield. Very recently, Harned has reported an explanation for this unusual stereochemical outcome.[12] According to his explanation, alkylation involving methyl iodide proceeds from the concave (*endo*) face of the bicyclo[4.3.0]nonene ring system, whereas carbon-based electrophiles larger than methyl iodide approach from the convex (*exo*) face (Scheme 8). Computational studies, using M06-2X and B3LYP methods, have revealed that the observed stereoselectivity is due to a subtle energetic difference between a staggered transition state with less torsional strain and an unfavorable steric interaction with the cyclohexenone ring.[12]



Scheme 8

When the electrophile approaches from the *endo* face, the dihedral angle between Ca-Cb-Cc-Cd is ~ 75º, whereas for *exo* approach this angle is only 15º. Compression of this dihedral angle creates a torsional strain in the system for the *exo* approach. Therefore, the small electrophile methyl iodide approaches from the *endo* face. On the other hand, in the case of larger electrophiles steric hindrance experienced from the cyclohexenone ring in approach from the *endo* face is severe, and outweighs the unfavorable factors that otherwise impede approach from the *exo* face.

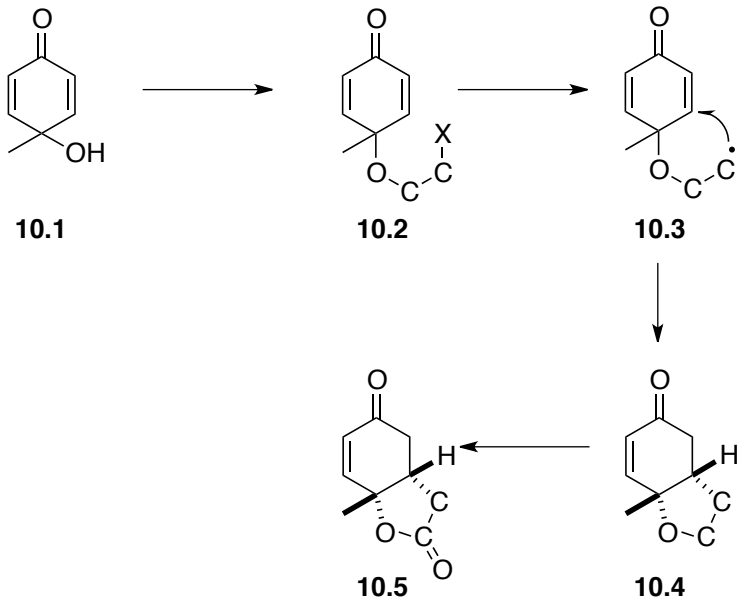
To finish the synthesis of sorbicillactone A, Harned and co-workers converted the *tert*-butyl ester in **7.4a** into acyl azide **9.1**. Curtius rearrangement of **9.1**, followed by acylation of the resulting amine, gave amide **9.2**, which was then subjected to *C*-acylation at C-4 to produce compound **9.3**. Finally, cleavage of the methyl ether and *tert*-butyl ester completed the total synthesis of sorbicillactone A **(3.1)**. Even though Harned's group was able to finish the synthesis of racemic sorbicillactone A, their product was stated to be impure and the yield in the last two last steps was only 12%. As indicated above, the yield of the desired isomer in the critical methylation was 15%.



Scheme 9

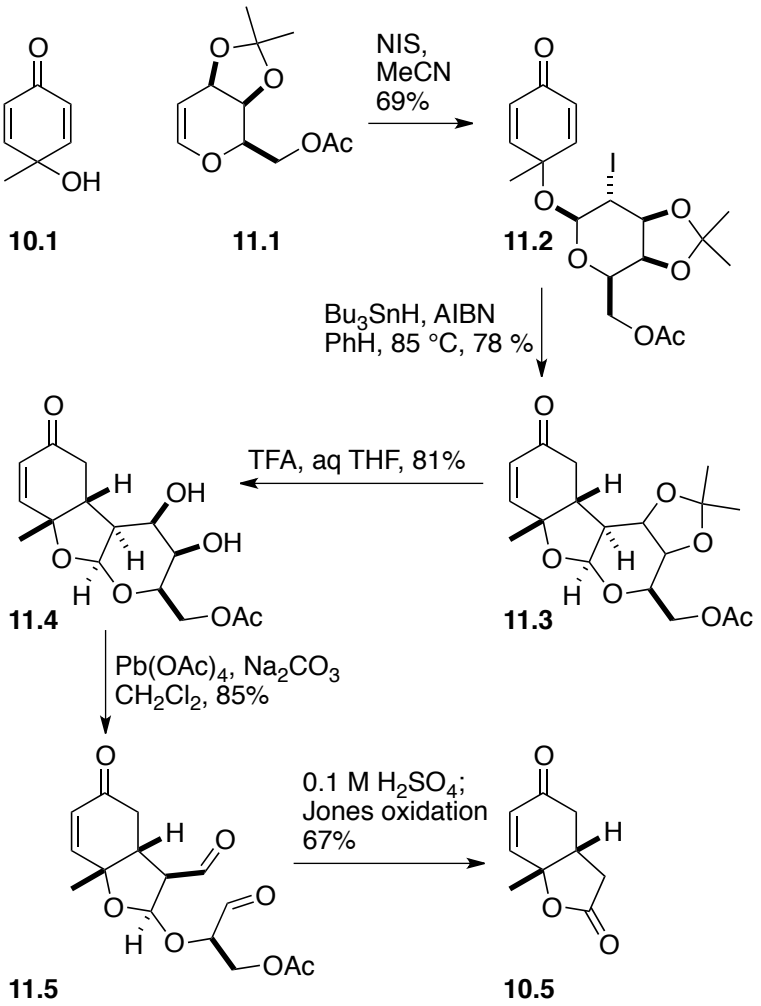
1.5.2 The Clive synthesis of optically pure bicyclic γ-lactones

In 2010, Clive and Sunasee described a desymmetrization process whereby the symmetrical dienone **10.1** was converted into optically pure lactone **10.5** using a free radical cyclization (Scheme 10).[13] The product had the absolute configuration corresponding to that of the core of sorbicillactone A.



Scheme 10

In this desymmetrization strategy stereoinduction occurs via a covalently bonded chiral sugar moiety. In the presence of NIS, the tertiary alcohol **10.1** reacted with glycal **11.1** to provide a single iodo-ether **11.2**, which underwent stannane-mediated radical cyclization to gave the cyclized product **11.3** as a single isomer. Acid hydrolysis of **11.3** released the diol **11.4**; this was then cleaved by treatment with $Pb(OAc)_4$ in the presence of Na_2CO_3 to dialdehyde **11.5**. The dialdehyde was subjected to acid hydrolysis with dilute H_2SO_4, followed by Jones oxidation of the resulting crude product, to give lactone **10.5** as a single isomer.[13]



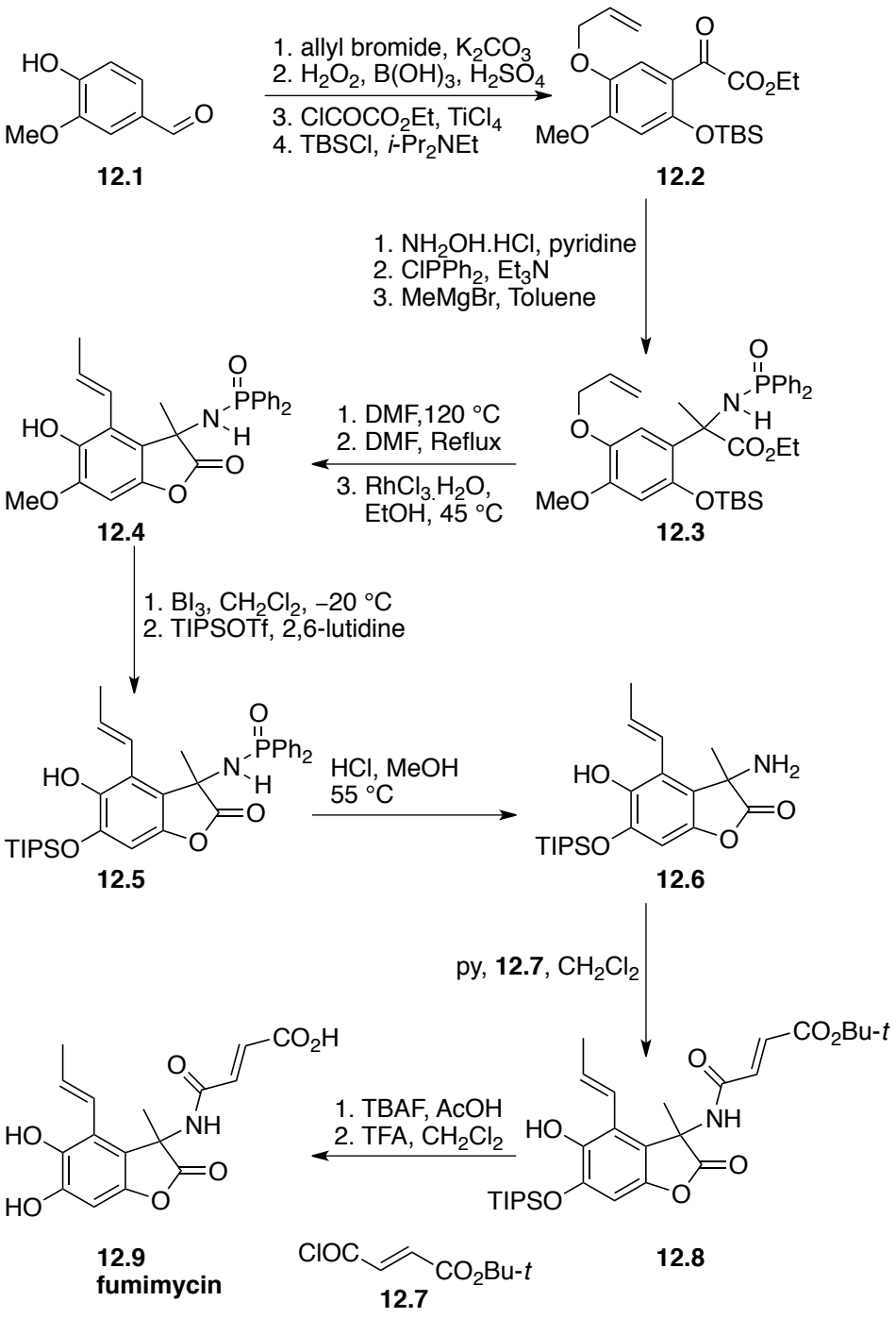
Scheme 11

Apart from this work and that of the Harned group, there have been no reports on synthetic activity in this field, although the synthesis of a compound called (±)-fumimycin (**12.9**) that has some resemblance to sorbicillactone A was reported by Bräse and co-workers in 2010.[14]

1.5.3 Total synthesis of fumimycin

Both sorbicillactone A and fumimycin possess a six-membered ring fused to a five-membered lactone as a skeleton and have an α-trisubstituted amine linked to a fumaric acid moiety. The total synthesis of fumimycin by the Bräse group is summarized in Scheme 12.[14]

The Bräse group started their synthesis with vanillin (**12.1**), which was first allylated, then subjected to Dakin oxidation, followed by Friedel-Crafts acylation and silylation to give ketone **12.2**. The ketone was then subjected to oxime formation, diphenylphosphinic amide formation and selective 1,2-addition with MeMgBr to provide phosphinic amide **12.3**. Thermal lactonization of **12.3**, followed by Claisen rearrangement and subsequent isomerization of the terminal double bond, gave olefin **12.4** (*trans*/*cis* 10:1). The isomers were separated by column chromatography. Cleavage of the methyl ether and selective silylation of the hydroxyl group, followed by deprotection of the amide, gave amine **12.6**. Finally, acylation of the amine, using acid chloride **12.7**, and cleavage of the silyl ether and *tert*-butyl ester completed the total synthesis of fumimycin (**12.9**).

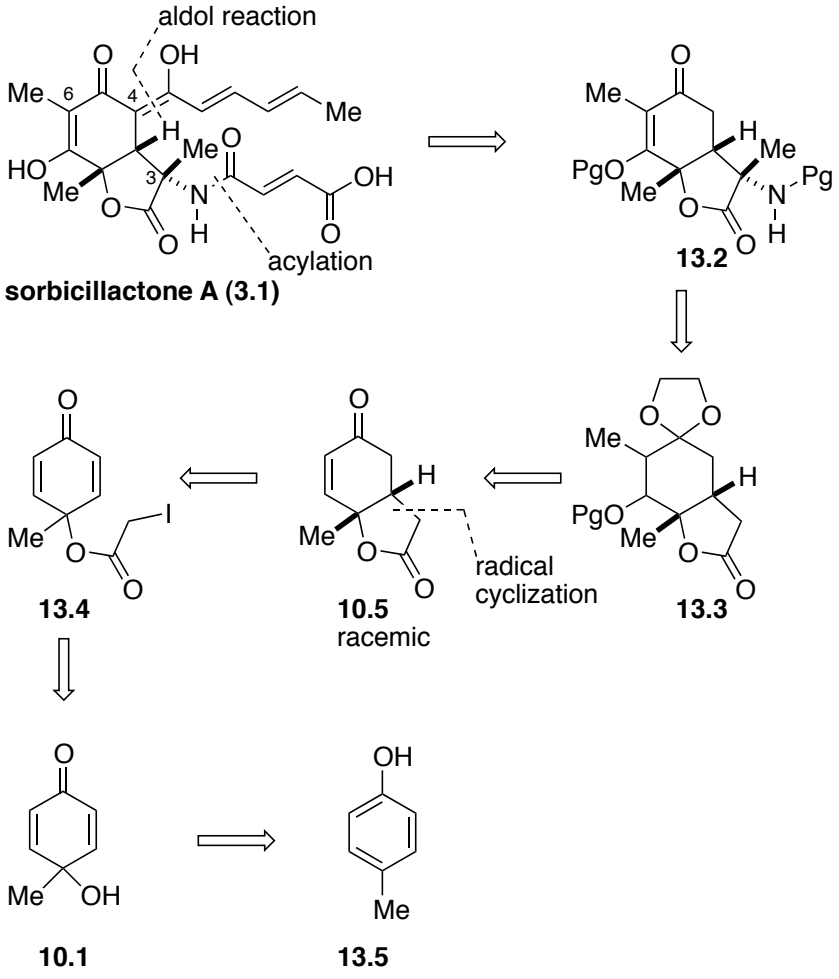

1. allyl bromide, K2CO3
2. H2O2, B(OH)3, H2SO4
3. ClCOCO2Et, TiCl4
4. TBSCl, i-Pr2NEt
12.1
12.2
1. NH2OH.HCl, pyridine
2. ClPPh2, Et3N
3. MeMgBr, Toluene
1. DMF,120 °C
2. DMF, Reflux
3. RhCl3.H2O, EtOH, 45 °C
12.3
12.4
1. BI3, CH2Cl2, −20 °C
2. TIPSOTf, 2,6-lutidine
HCl, MeOH
55 °C
12.5
12.6
py, 12.7, CH2Cl2
1. TBAF, AcOH
2. TFA, CH2Cl2
12.8
12.9
fumimycin
12.7

Scheme 12

2. Results and Discussion

The aim of my project was to make racemic sorbicillactone A from racemic **10.5**, and then to apply the same route to optically pure **10.5**, which can be synthesized as shown in Scheme 11, and thus achieve the synthesis of (-)-sorbicillactone A.

2.1 Retrosynthetic analysis of sorbicillactone A

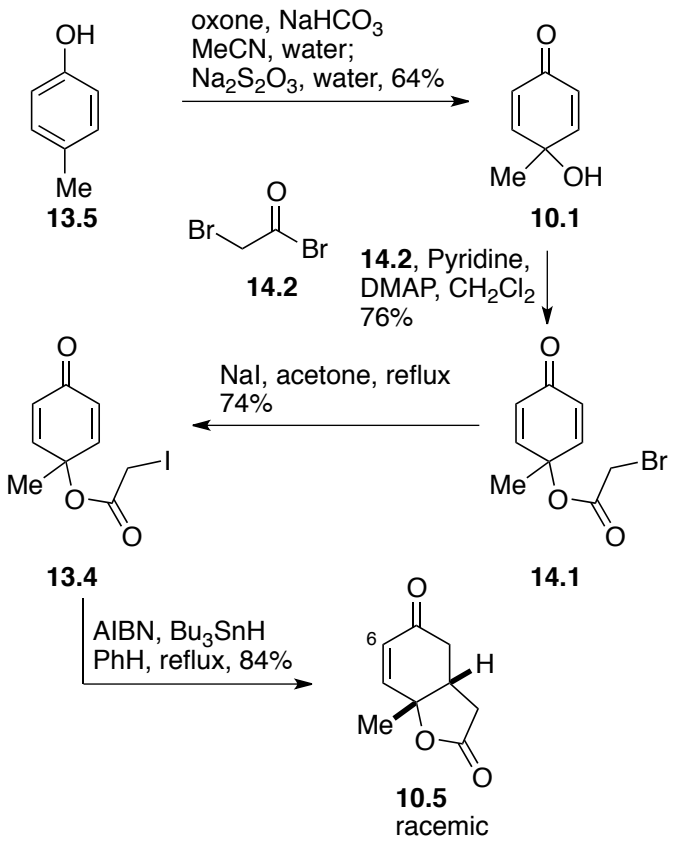


Scheme 13

In principle, sorbicillactone A can be synthesized from **13.2** by attaching the side chains by *N*-acylation and an aldol reaction. Compound **13.2**, in turn, should be available from **13.3** by α-amination followed by α-alkylation. Functional group manipulation of **10.5** can give **13.3**. The core **10.5** is the result of a radical cyclization of compound **13.4**, which can be synthesized from **10.1** by *O*-acylation. The dienone **10.1** has been prepared from *p*-cresol (**13.5**).

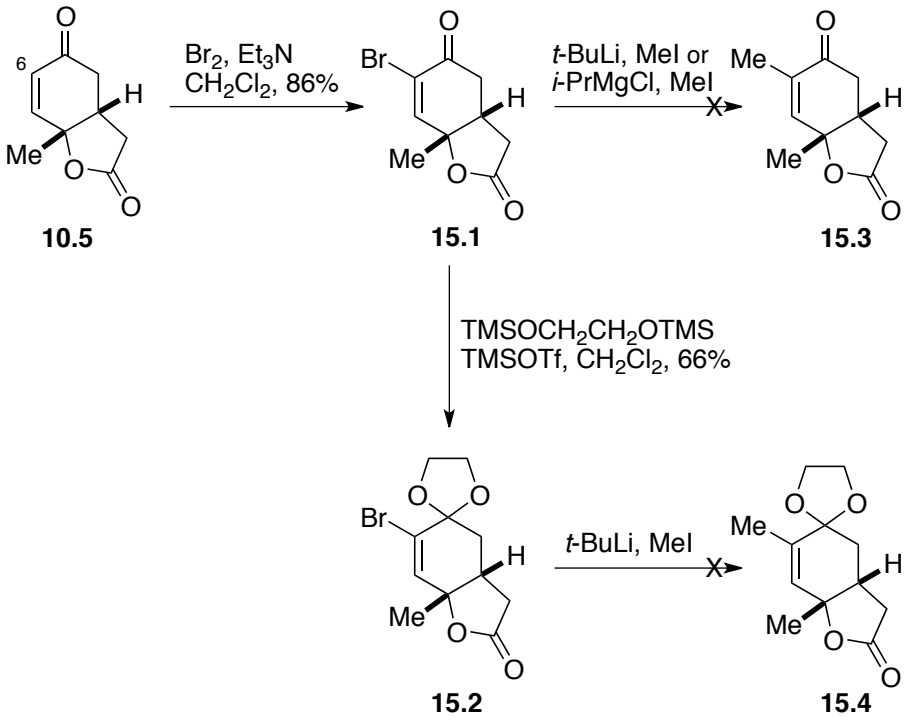
2.2 Synthetic studies towards sorbicillactone A

Our synthetic studies towards sorbicillactone A began with commercially available *p*-cresol (**13.5**). Oxidation with Oxone in the presence of $NaHCO_3$ in MeCN-H_2O, using a procedure developed by Carreño and co-workers,[15] gave cyclohexadienone **10.1** in 64% yield. Acylation of the hydroxyl group of **10.1** with bromoacetyl bromide produced **14.1** in 76% (crude yield), which was then subjected to Finkelstein reaction with NaI to give the iodo-ester **13.4**. This underwent radical cyclization under stannane-mediated conditions, giving the cyclized product **10.5** (racemic) in 84% yield.



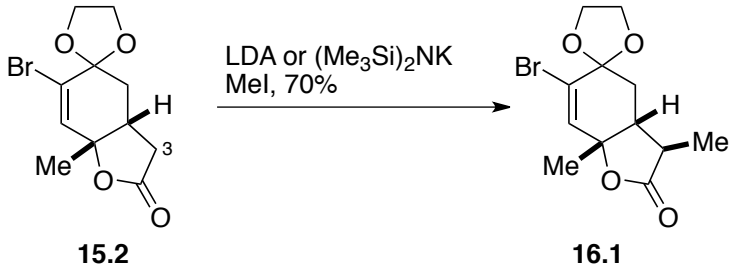
Scheme 14

After the synthesis of the bicyclic core, we studied the installation of the methyl group at C-6. The first approach was to try metal-halogen exchange chemistry. Bromination of **10.5**, using Br_2 and Et_3N, gave the desired bromo compound **15.1** (Scheme 15), but all attempts to replace the halogen by a methyl unit failed to give the desired product **15.3**. As this outcome might be due to the presence of acidic hydrogens in the molecule, we protected the ketone as the cyclic ketal **15.2**, using 1,2-bis(trimethylsiloxy)ethane and $Me_3SiOSO_2CF_3$. However, subsequent attempts at methylation (**15.2→15.4**) again failed.



Scheme 15

At this point, we reacted the bicyclic ketal **15.2** with LDA or KHMDS and MeI to study the stereochemical outcome of alkylation at C-3 (Scheme 16).



Scheme 16

The desired C-3 methylated bicyclic lactone **16.1** was obtained in 70% yield as a single isomer. Moreover, X-ray crystallographic analysis of **16.1**

(Figure 1) showed that the stereochemistry obtained at C-3 was opposite to that observed by Harned and co-workers.[11] In our case the alkylation at C-3 occurs from the more accessible *exo* face. From this experiment, it is clear that in order to get the proper stereochemistry of sorbicillactone A at C-3, the nitrogen unit must be installed before the methyl unit.

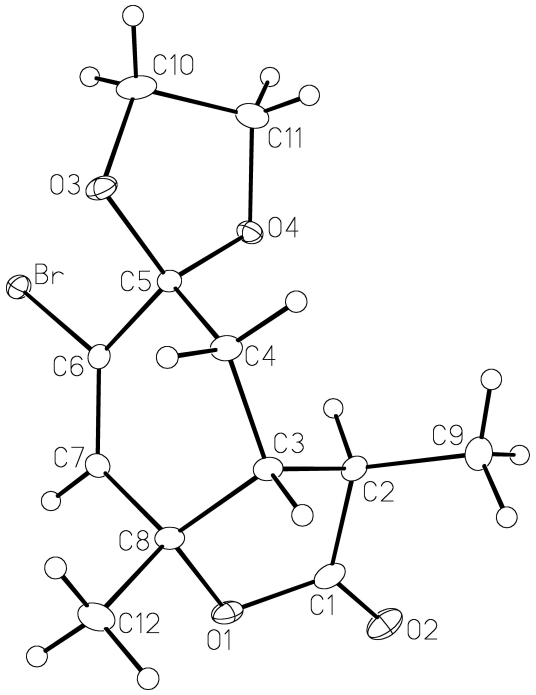
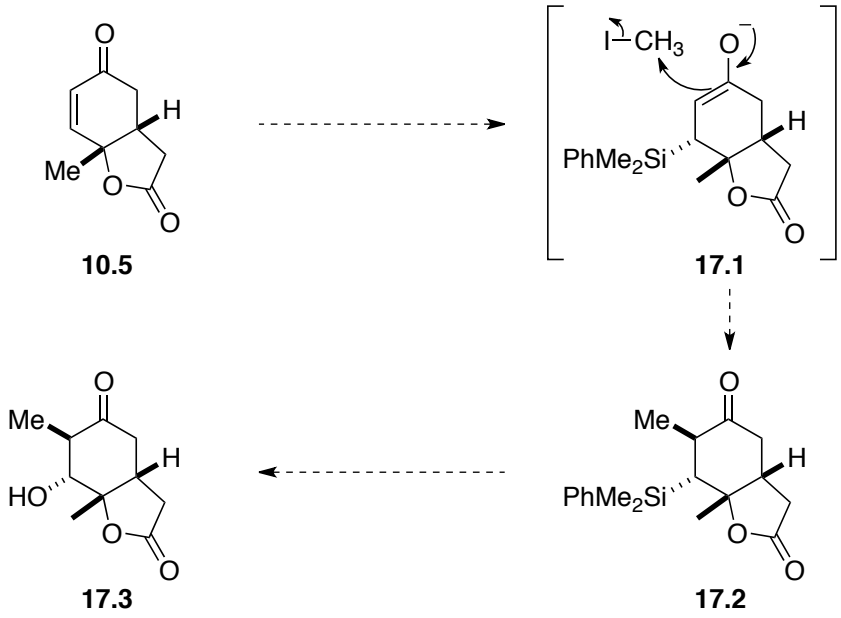


Figure 1. ORTEP diagram of compound 16.1

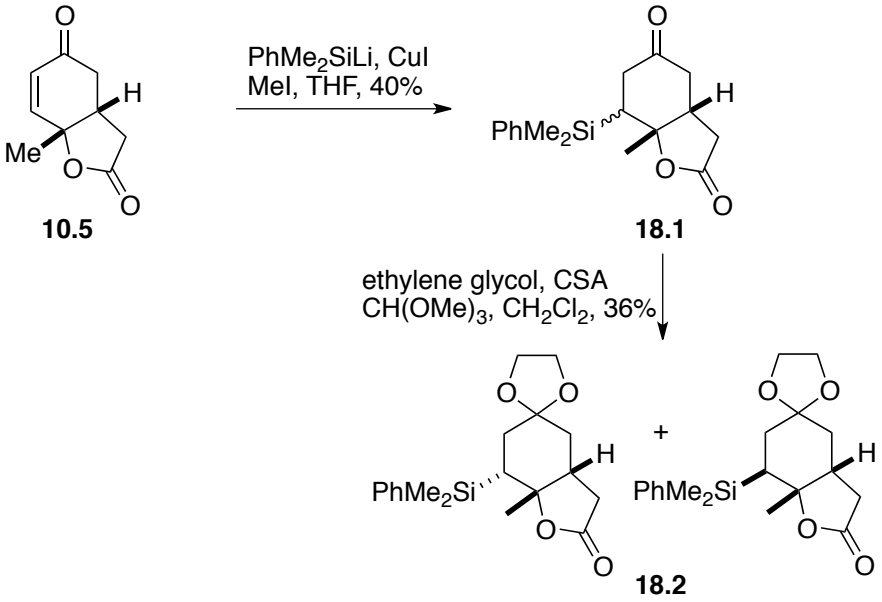
Our second approach was to do a conjugate addition on the bicyclic lactone **10.5**, using a phenyldimethylsilyl cuprate, and then to quench the intermediate **17.1** with methyl iodide so as to form compound **17.2**. The silicon

group would then be replaced by a hydroxyl group via a Fleming-Tamao oxidation[16] to afford **17.3** (Scheme 17).



Scheme 17

In order to achieve the synthesis of compound **17.2**, we first treated the bicyclic lactone **10.5** with $PhMe_2SiLi$ and CuI, followed by MeI. The desired product was obtained in very low yield, but we were able to isolate an inseparable mixture of the two silanes **18.1** in 40% yield. The isomers **18.1** were separable after protecting the ketone as the cyclic ketals **18.2** (Scheme 18).



Scheme 18

Fortunately, by changing the source of copper from CuI to CuCN, we were able to synthesize the desired bicyclic lactone **17.2** in 80% yield as a single isomer (Scheme 19). X-ray crystallographic analysis of **17.2** showed that both substituents at C-6 and C-7 are equatorial (Figure 2).

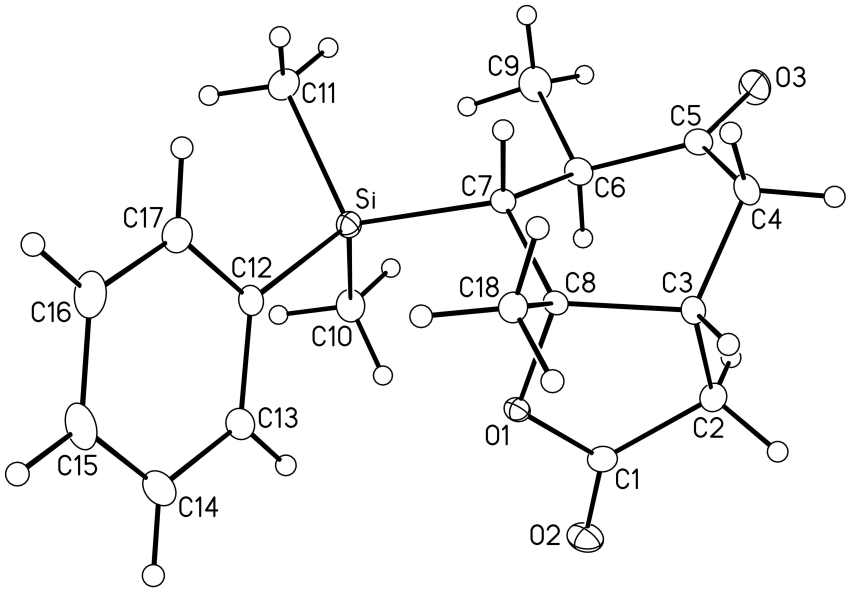
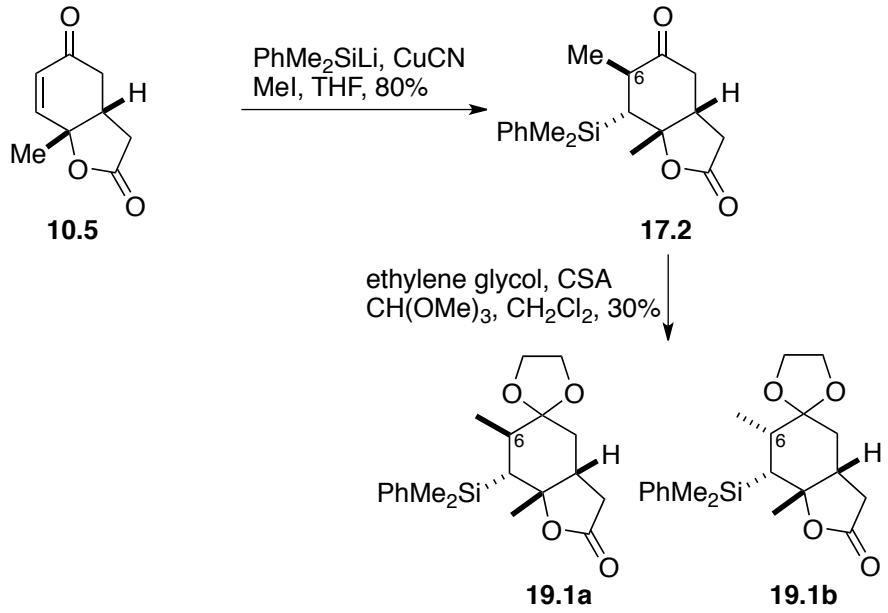


Figure 2. ORTEP diagram of compound 17.2

After the synthesis of silyl bicyclic lactone **17.2**, the next step was to replace the silyl group by a hydroxyl group via a Fleming-Tamao oxidation. Fleming and co-workers reported that the presence of a ketone group can be problematic for this step,[16] and so we first tried to protect the ketone in **17.2** as a cyclic ketal **19.1** (Scheme 19).



Scheme 19

The protected cyclic ketal was isolated in low yield (30%) as a mixture of C-6 isomers (**19.1a** and **19.1b**), because both the ketone **17.2** and the ketal **19.1** can undergo epimerization at position C-6 under the reaction conditions. However, it is not clear whether epimerization occurs before protection or afterwards. The more polar isomer **19.1a** was separated partially from the other isomer and X-ray crystallographic analysis of this compound showed that the C-6 methyl is equatorial (Figure 3).

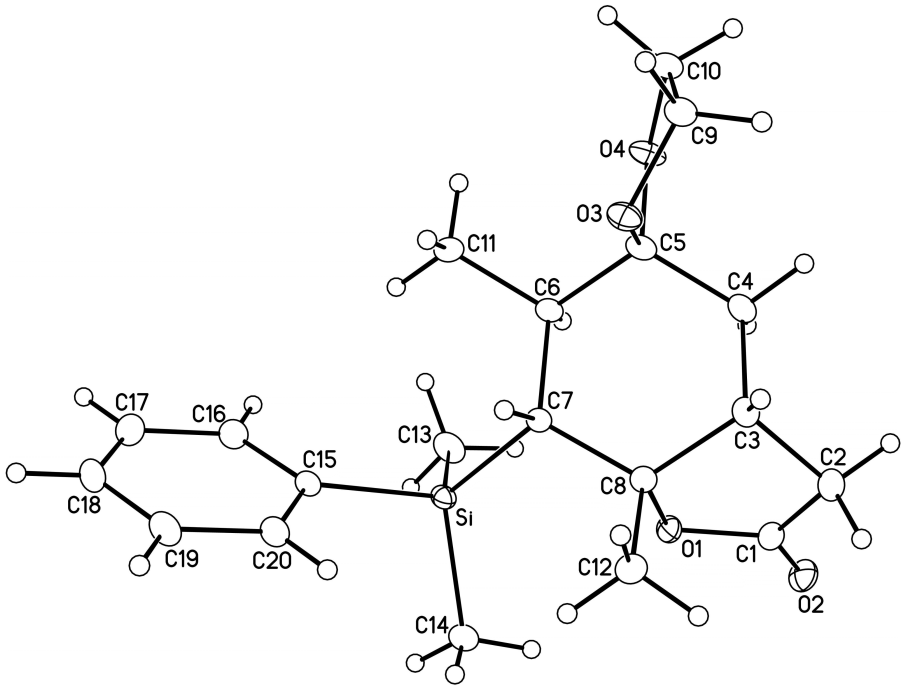
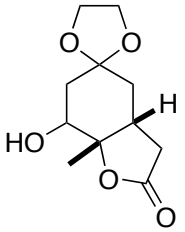
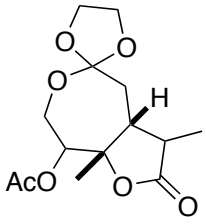


Figure 3. ORTEP diagram of compound 19.1a

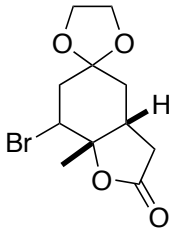
The next step was to replace the silicon group by a hydroxyl. First we tried the oxidation on the model compound **18.2,** using KBr, NaOAc, AcOH and AcOOH, the conditions reported by Fleming and co-workers.[16] During this reaction three different spots were detected on the thin layer chromatograms. HRMS of material extracted from these spots showed masses 251.0889 ($C_{11}H_{16}NaO_5$), 309.0941 ($C_{13}H_{18}NaO_7$) and 313.0046 ($C_{11}H_{15}{}^{79}BrNaO_4$), which could be, respectively, **20.1**, **20.2** and **20.3**.



20.1



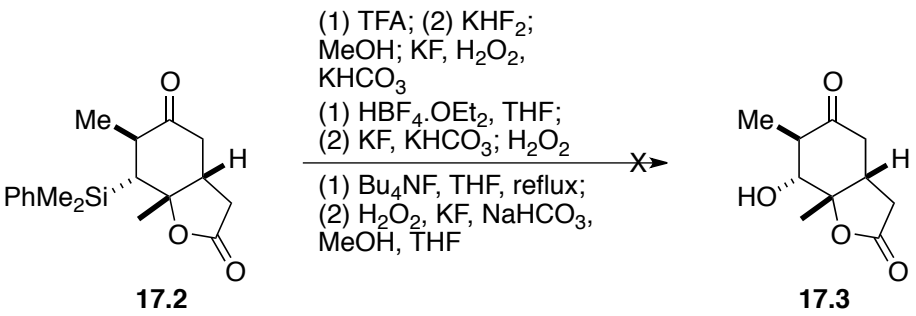
20.2



20.3

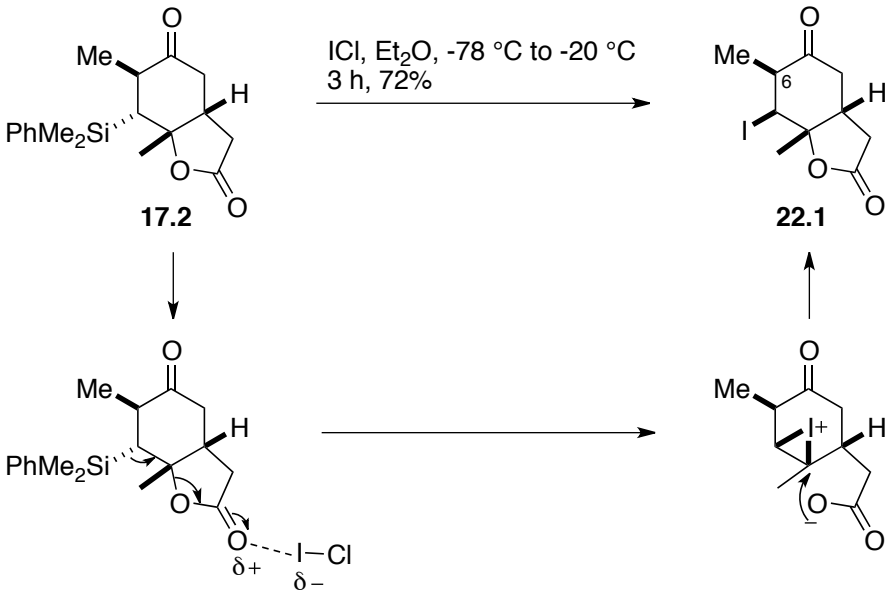
Scheme 20

Later, we tried oxidation of silicon in **17.2** using different procedures (Scheme 21) reported in the literature,[17] but none gave the desired product (**17.3**).



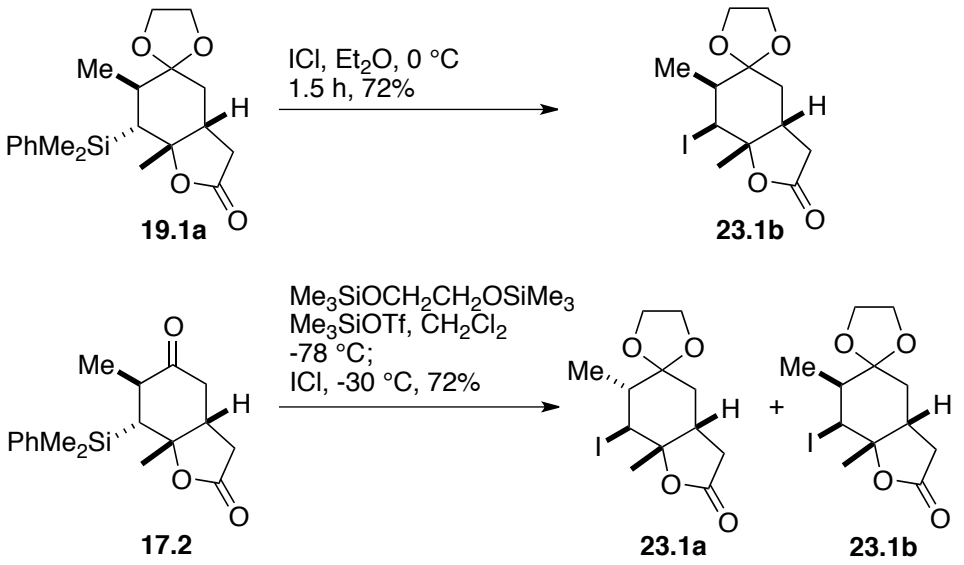
Scheme 21

At this stage, an extensive literature survey showed that aryltrimethylsilanes can be iodinated using a silver salt and a source of iodine (either ICl or I_2).[18] Encouraged by these reports, we tried the iodination of **17.2** using ICl (Scheme 22), and the product **22.1** was isolated in 72% yield. The product contains a minor amount of another compound that has the same mass as **22.1**; it might be the other isomer at C-6.



Scheme 22

Encouraged by this result, we next tried the same chemistry on protected ketal **19.1a**, and were able to isolate the product **23.1b** in 82% yield. The stereochemistry of the product was later confirmed by combining the results of NMR and by X-ray analysis. From these results, a new one-pot procedure was developed for the protection of the ketone carbonyl and for the desilylative iodination of bicyclic lactone **17.2** (Scheme 23) to give the isomers **23.1a** and **23.1b**.



Scheme 23

Reaction of **17.2** with 1,2-bis(trimethylsilyloxy)ethane and $Me_3SiOSO_2CF_3$ at -78 °C for 4 h resulted in protection of the ketone as well as opening of the bicyclic lactone, which, on subsequent reaction with ICl at -30 °C for 15 min (monitoring by low resolution mass spectrometry) gave the desired products **23.1a** and **23.1b**, epimeric at C-6. X-ray crystallographic structures were obtained for both isomers, establishing that iodine is equatorial whereas the methyl is equatorial in the more polar isomer **23.1a** and axial in less polar isomer **23.1b** (Figures 4 and 5).

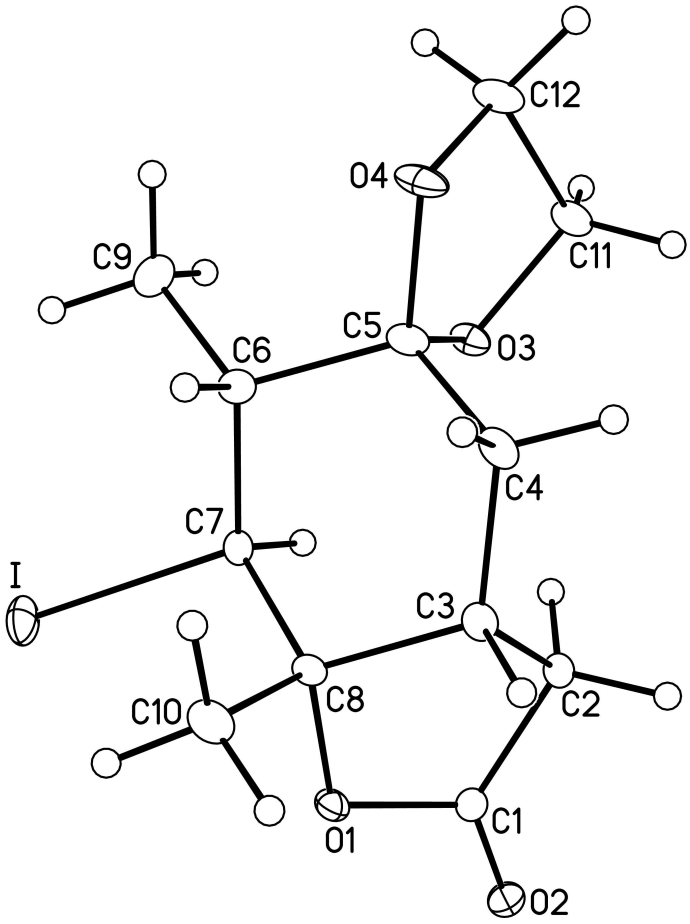


Figure 4. ORTEP diagram of compound 23.1a

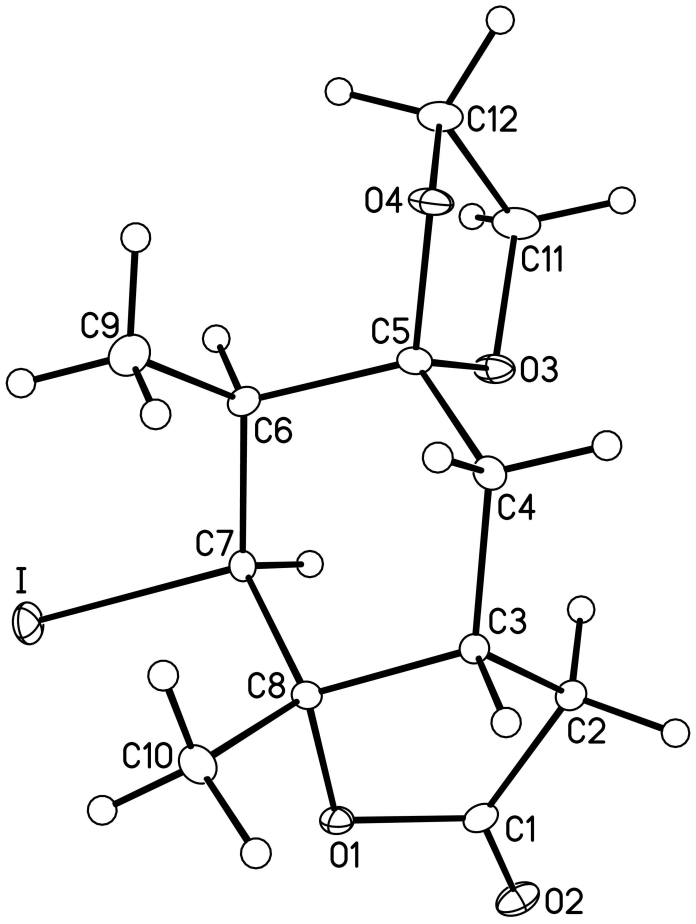
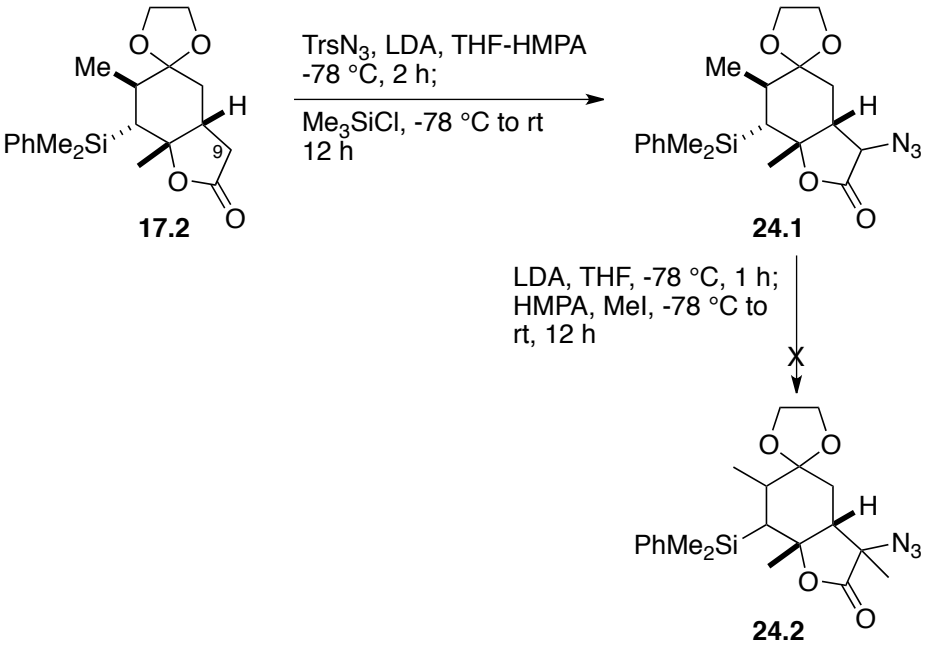


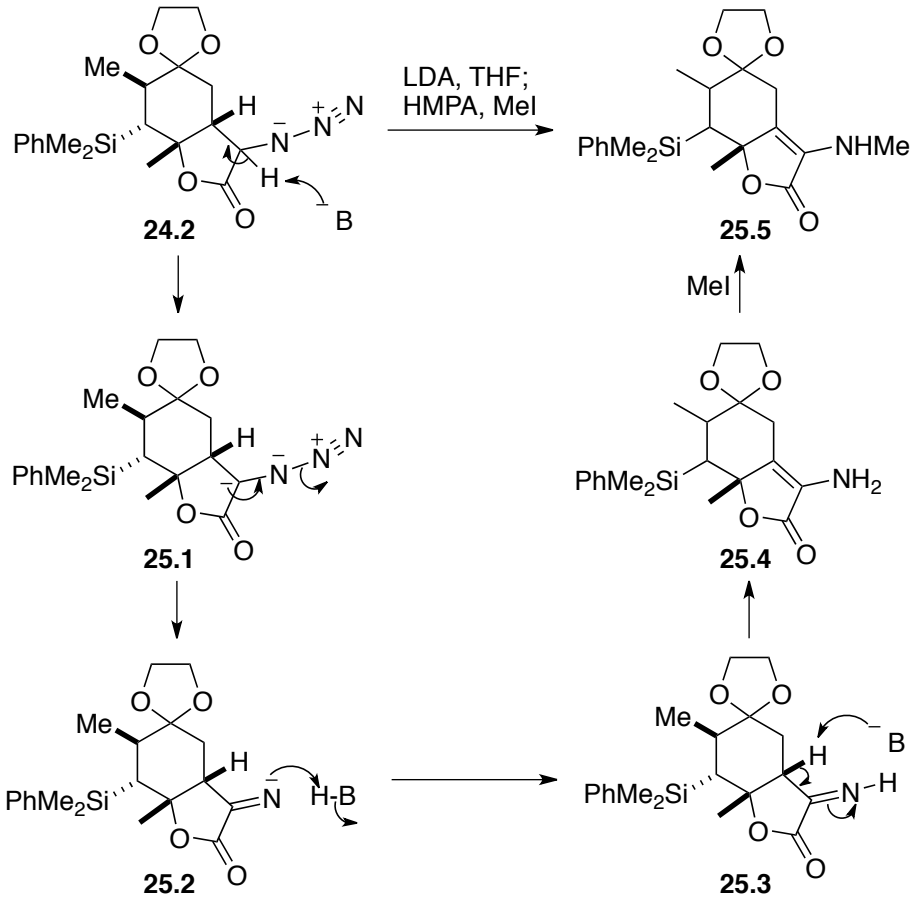
Figure 5. ORTEP diagram of compound 23.1b

In the meantime, we also studied the installation of the side chains at C-3 of **17.2**. Reaction of **17.2** with LDA, followed by addition of 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$SO$_2$N$_3$ (trisyl azide) and then quenching with Me$_3$SiCl,[19] gave the desired isomer **24.1**, the presence of which was confirmed by high resolution mass spectrometry. Compound **24.1** was then subjected to alkylation using LDA and MeI, but unfortunately no desired product **24.2** was obtained (Scheme 24).



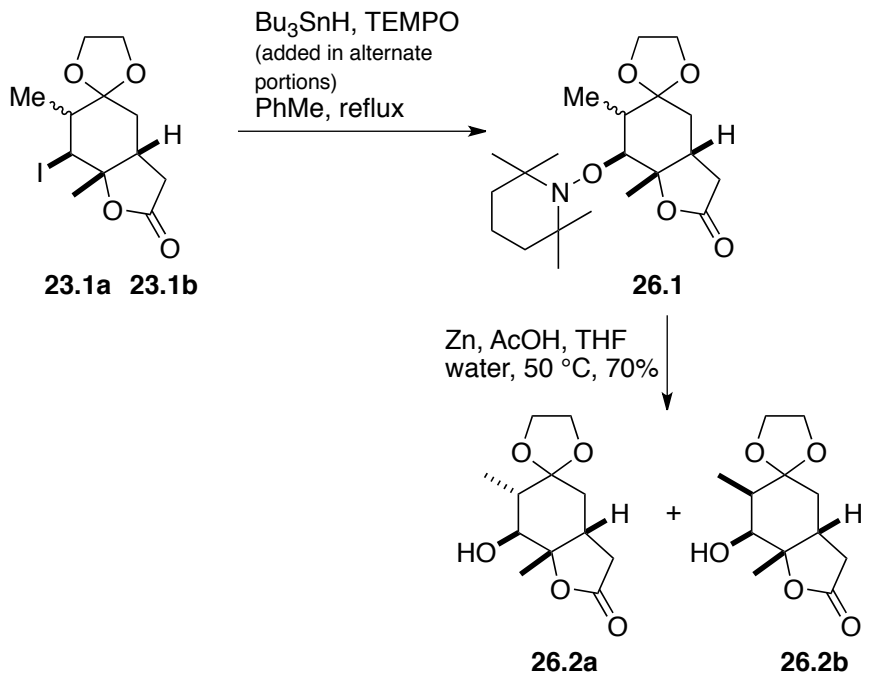
Scheme 24

One product from this reaction was isolated. It had a mass of 410.1751 corresponding to the formula $C_{21}H_{29}NNaO_4Si$. The infrared spectrum showed a broad band at 3373 cm^{-1}, which might indicate the presence of an N-H bond. By comparing these observations with literature observations on the behavior of azido lactones,[20] the structure **25.5** was assigned for this compound (Scheme 25).



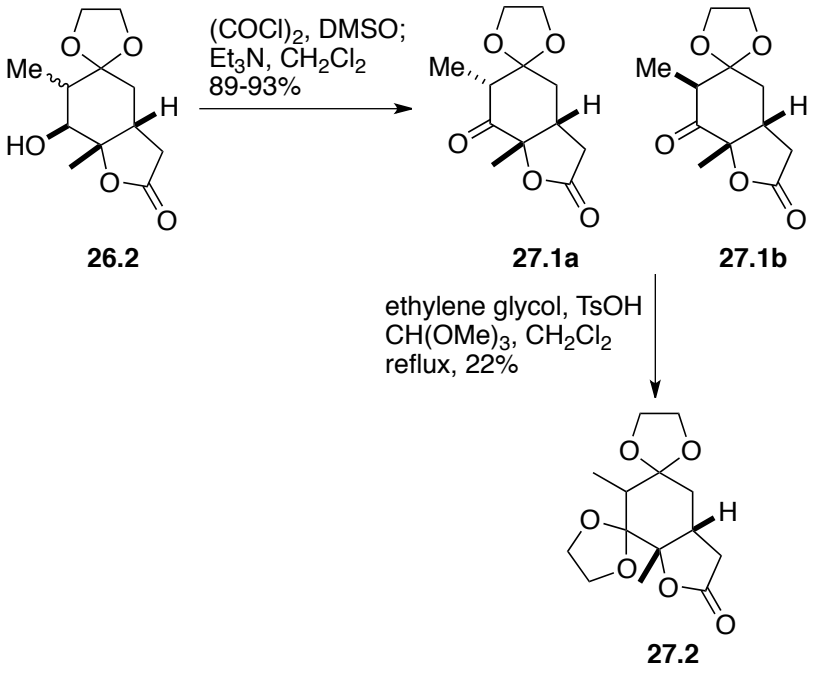
Scheme 25

After the successful synthesis of iodo-lactone **23.1**, our next objective was to replace the iodine moiety by a hydroxyl group. This was done by using a standard two-step free radical method where Bu_3SnH and AIBN were added in portions alternating with portions of TEMPO.[21] The labile N-O bond of the TEMPO adduct **26.1**, was then cleaved with Zn in AcOH to give the hydroxy-lactones **26.2a** (less polar alcohol) and **26.2b** (more polar alcohol), which were separated.



Scheme 26

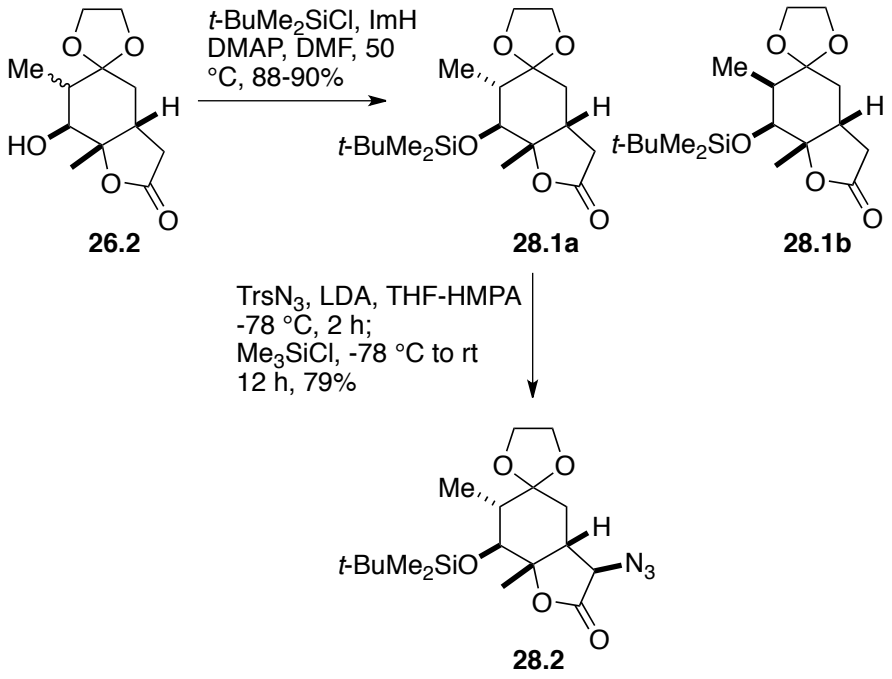
Next, we decided to oxidize the hydroxyl group to a ketone and protect it as a ketal, so that the global deprotection of both ketals at a later stage could give the core bicyclic structure of sorbicillactone A. The oxidation of both alcohols **26.2a** and **26.2b** under Swern conditions proceeded smoothly to give the desired ketones **27.1a** (from less polar alcohol) and **27.1b** (from more polar alcohol). Unfortunately, attempts to protect the ketone did not give an acceptable yield (under various conditions) of the desired product **27.2** (Scheme 27).



Scheme 27

Therefore, we decided to continue the synthesis with hydroxy-lactone **26.2**. To this end, the hydroxyl group was first protected as a TBDMS-ether **28.1a** (less polar isomer) and **28.1b** (more polar isomer), and the subsequent experiments were done using the less polar isomer **28.1a**.

Treatment of **28.1a** with LDA, trisyl azide and subsequent quenching with Me_3SiCl gave the desired azide **28.2** (Scheme 28).[19] The stereochemistry of **28.2** was confirmed by single crystal X-ray analysis (Figure 6) which indicated that the azide approached the substrate from the more accessible *exo* face, as expected.



Scheme 28

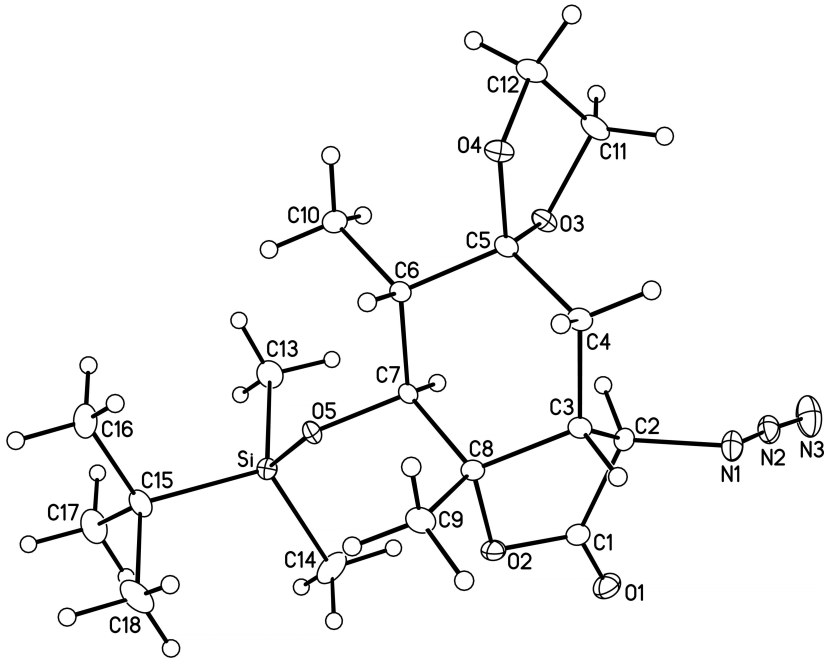
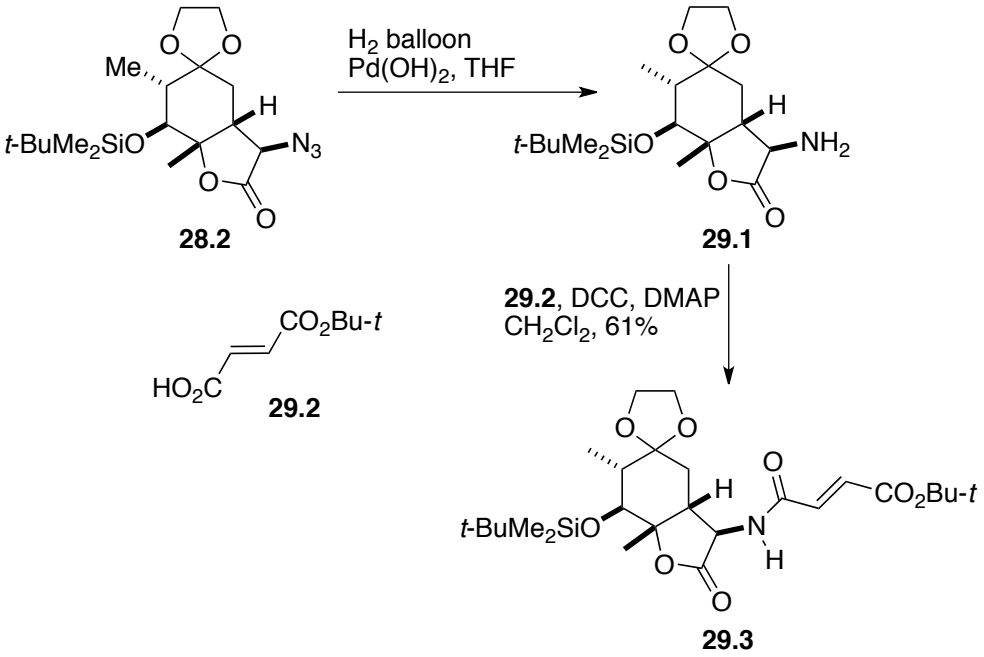


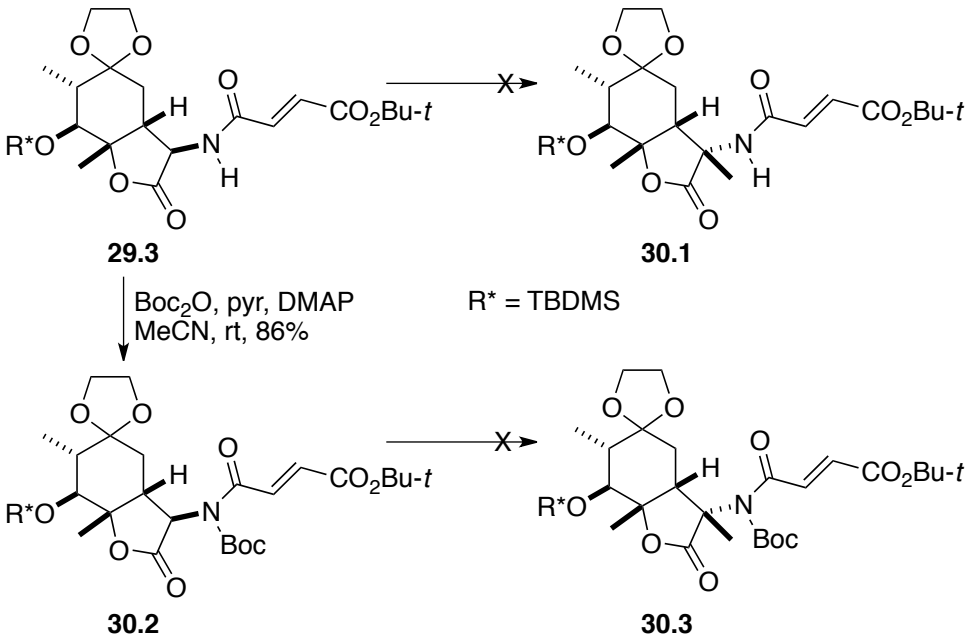
Figure 6. ORTEP diagram of compound 28.2

Our next plan was to install the fumaryl unit present on the nitrogen and then carry out the alkylation at C-3. To do this, the azide **28.2** was first reduced to amine **29.1** by hydrogenation using Pearlman's catalyst and hydrogen. Coupling of the crude amine with acid **29.2**[22] using DCC and DMAP gave the desired product **29.3** in 61% yield.



Scheme 29

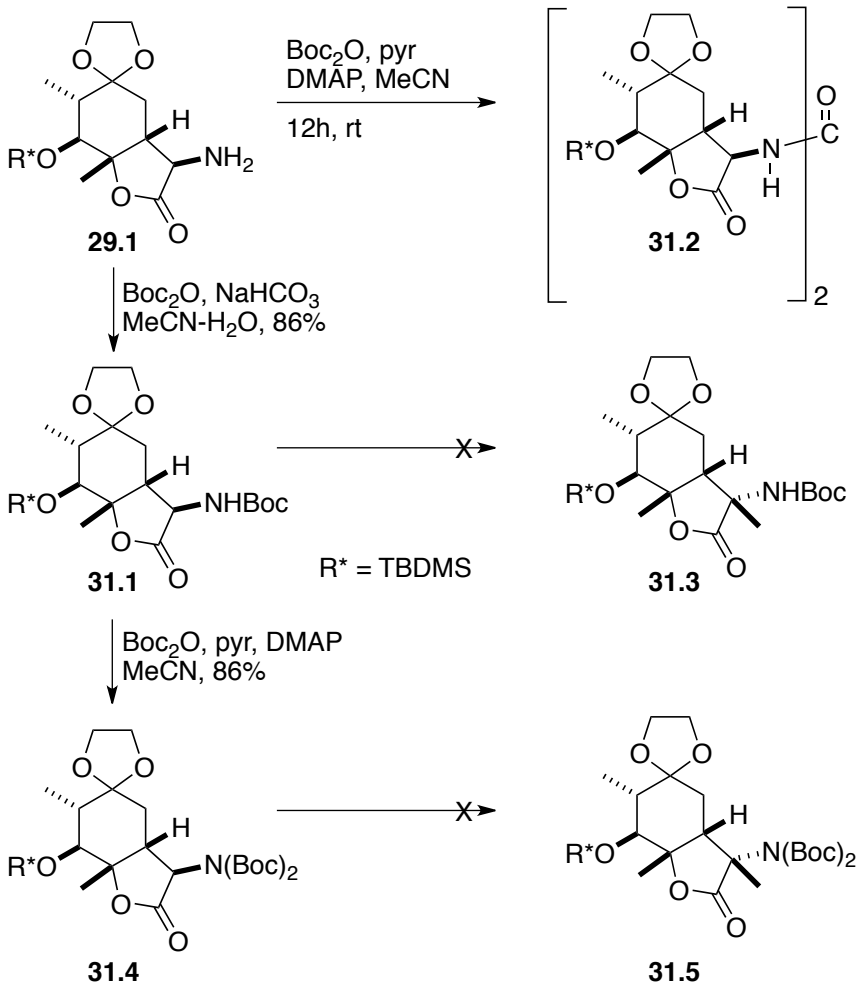
However, attempted alkylation of **29.3** (LDA, MeI or LiHMDS, MeI) met with no success. Protection of the nitrogen with Boc_2O and pyridine gave **30.2** (Scheme 30), but subsequent alkylation (LiHMDS, MeI) also did not work (no starting material was recovered, and only a complex mixture formed). We suspected that the unsaturated ester moiety should not be present for this alkylation reaction.



Scheme 30

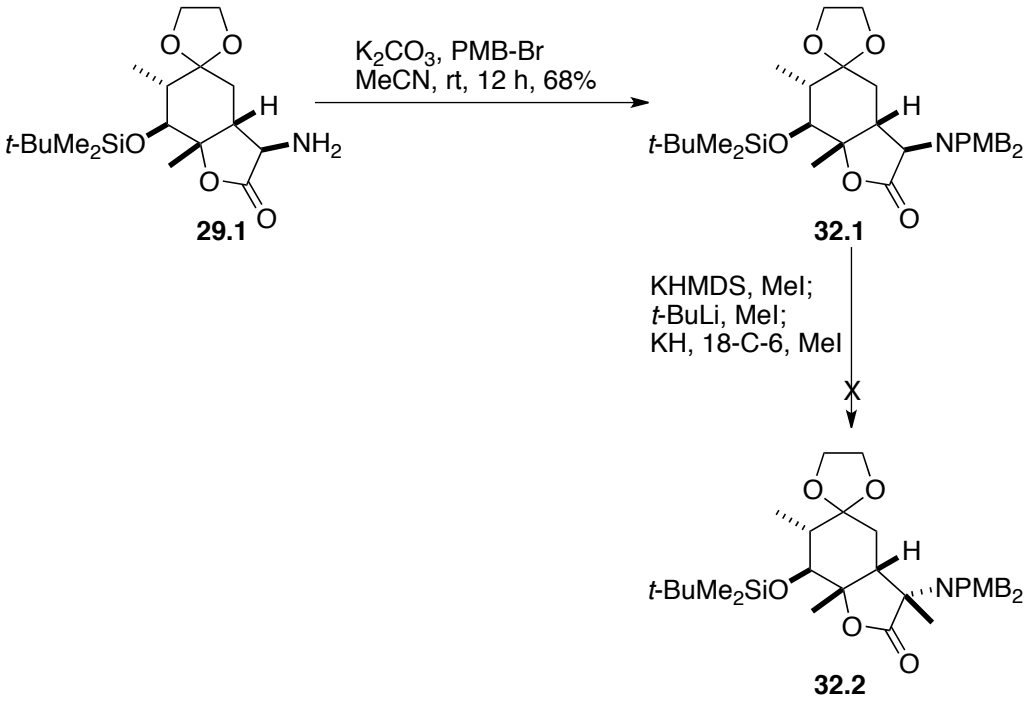
Therefore, we next protected the amine **29.1**, using Boc_2O and $NaHCO_3$ to give mono nitrogen-protected amide **31.1** (when we used Boc_2O and *pyridine* to carry out the mono protection, we did not get any of the desired product **31.1**, and obtained instead **31.2** as the main product). Attempted alkylation of **31.1** (LDA, MeI or KHMDS, MeI or LDA, BuLi, MeI[23]) also did not give any desired product **31.3**, the starting material being partially recovered.

Amine **29.1** was then doubly protected using Boc_2O and pyridine to obtain compound **31.4**, which also failed to undergo alkylation (LDA, MeI or or LDA, BuLi, MeI, LiCl[23]).



Scheme 31

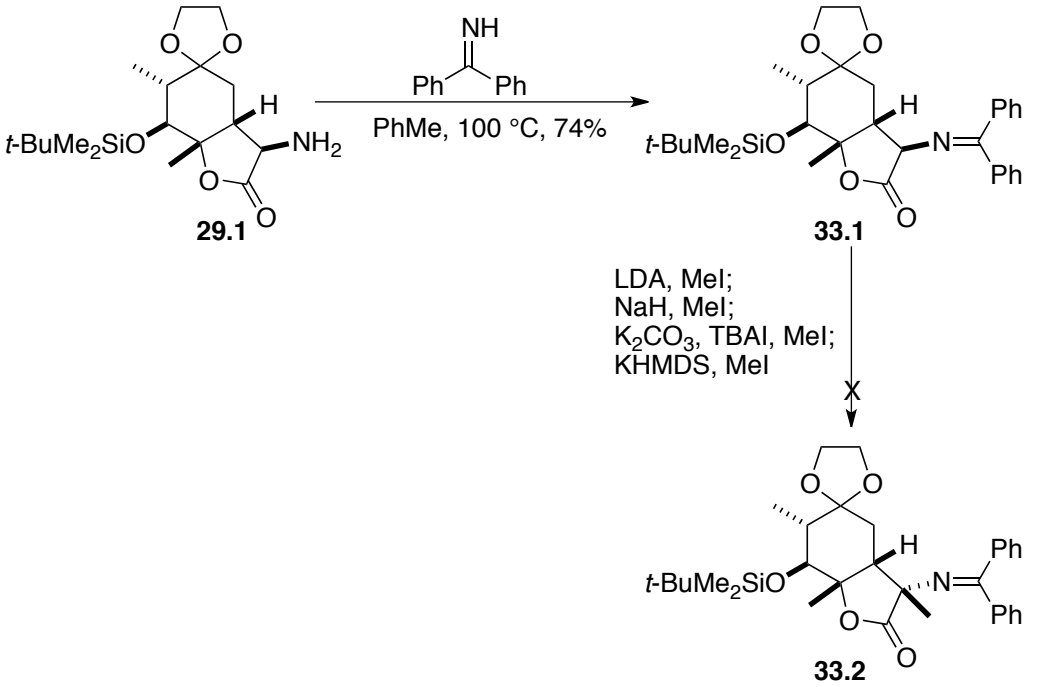
Next, the amine was protected as its bis-PMB derivative, using K_2CO_3 and PMB-Br in MeCN. The desired product (**32.1**) was isolated in 68% yield, but all attempted alkylation conditions we applied to **32.1** (Scheme 32) failed to give the desired product (**32.2**) and only a complex mixture was formed.



Scheme 32

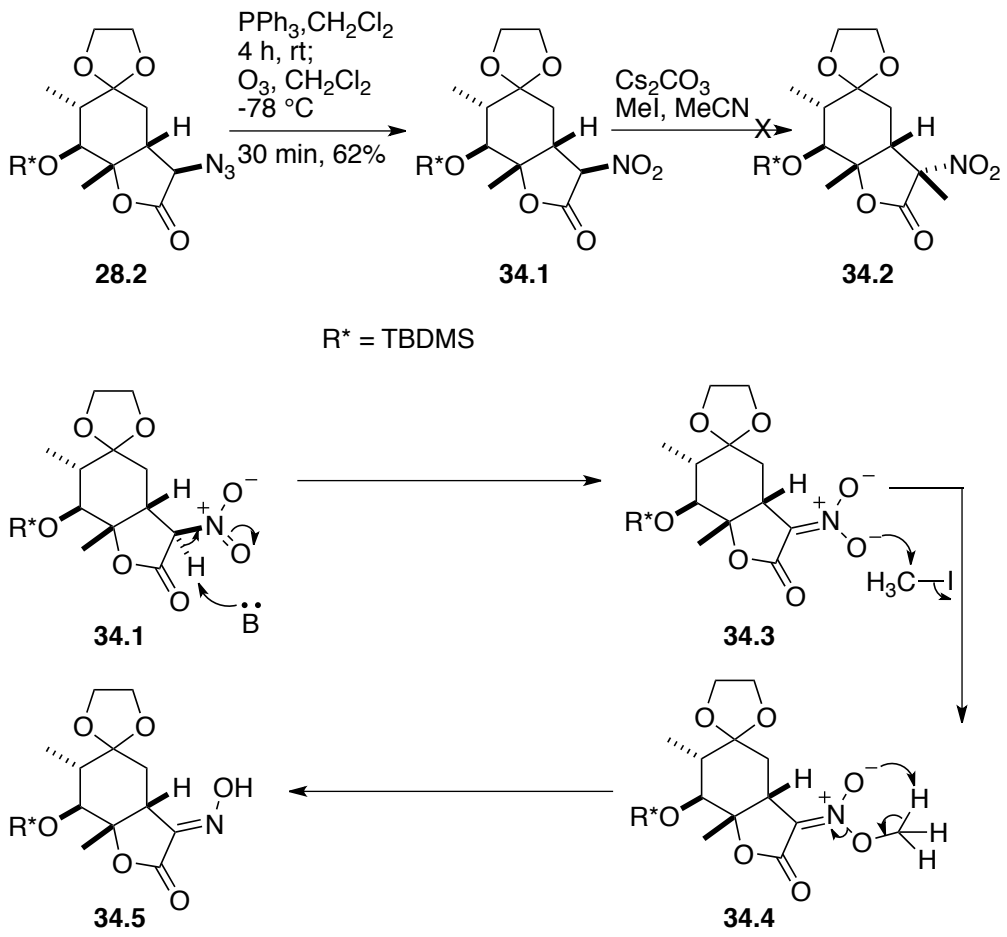
Amine **29.1** was then converted to the imine **33.1** by heating with benzophenone imine in PhMe at 100 °C. Various alkylation conditions (see Scheme 33) were tried in order to alkylate imine **33.1**, but none of them was successful and the product **33.2** was not detected (by low resolution mass spectral measurements).

From all these experiments, we concluded that the α-hydrogen in these substrates may not be easily accessible under normal deprotonation conditions.



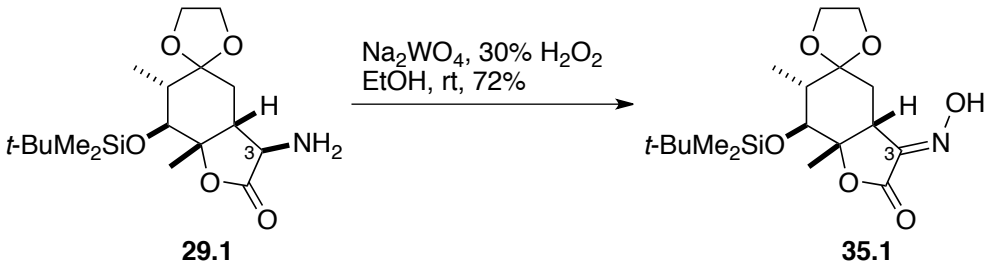
Scheme 33

By increasing the acidity of the α-hydrogen, it might be possible to effect deprotonation and, in order to increase the acidity, we converted the azide **28.2** into the corresponding nitro compound by a procedure reported by Corey and co-workers.[24] Treatment of the azide with Ph_3P, followed by ozone, gave the desired nitro compound **34.1** in 62% yield. Alkylation of **34.1** using Cs_2CO_3 and MeI in MeCN did not give any of the desired product **34.2**, but two products were isolated which, according to high resolution mass spectrometry, had masses of 408.1813 ($C_{18}H_{31}NNaO_6Si$) and 438.1919 ($C_{19}H_{33}NNaO_7Si$). By comparing this observation with a literature report[25] on the behavior of nitro lactones we suspect that **34.5** and **34.4** are possible structures for these compounds.



Scheme 34

Because of the failure to install the methyl unit via an electrophilic route, our next attempt was to examine nucleophilic addition at C-3 for installing the methyl unit. For this purpose the amine **29.1** was first converted to the corresponding oxime **35.1** by reaction with Na_2WO_4, 30% H_2O_2 in EtOH.[26] The desired product **35.1** was isolated in 72% yield (Scheme 35). The stereochemistry of the oxime was confirmed by single crystal X-ray analysis (Figure 7).



Scheme 35

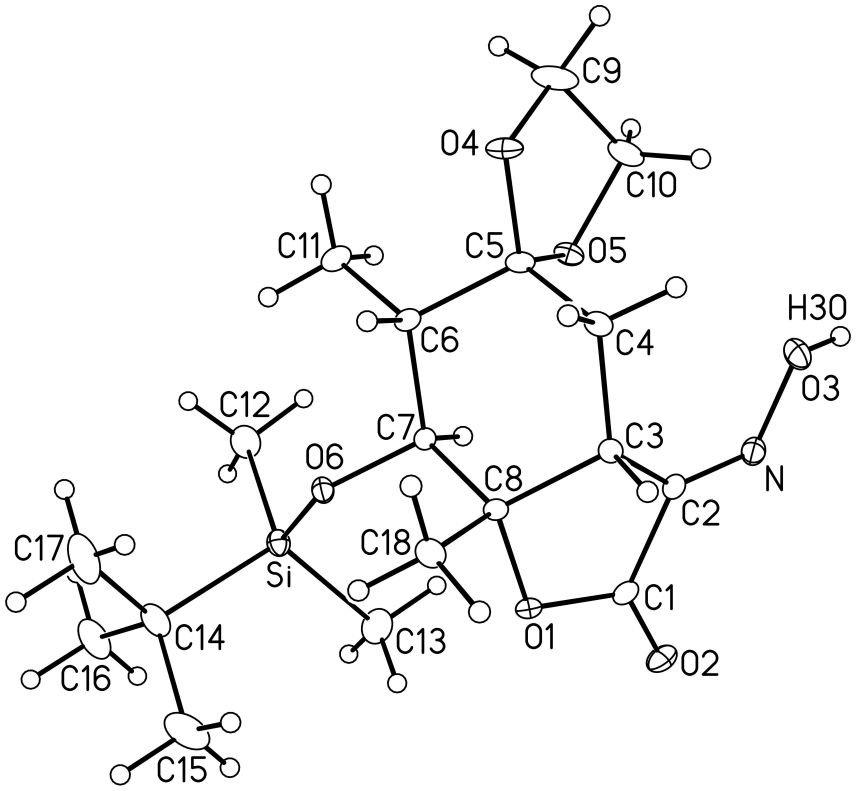
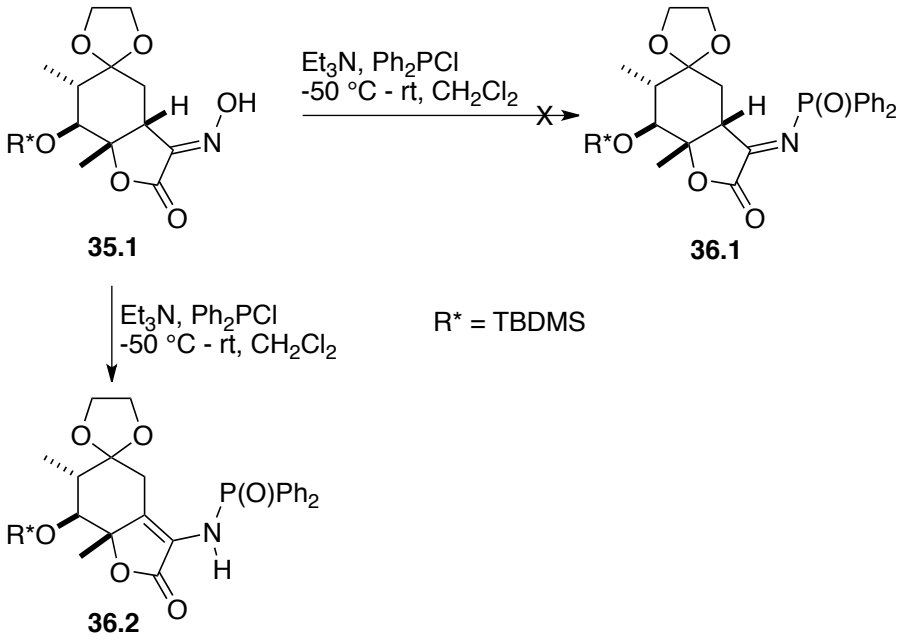


Figure 7. ORTEP diagram of compound 35.1

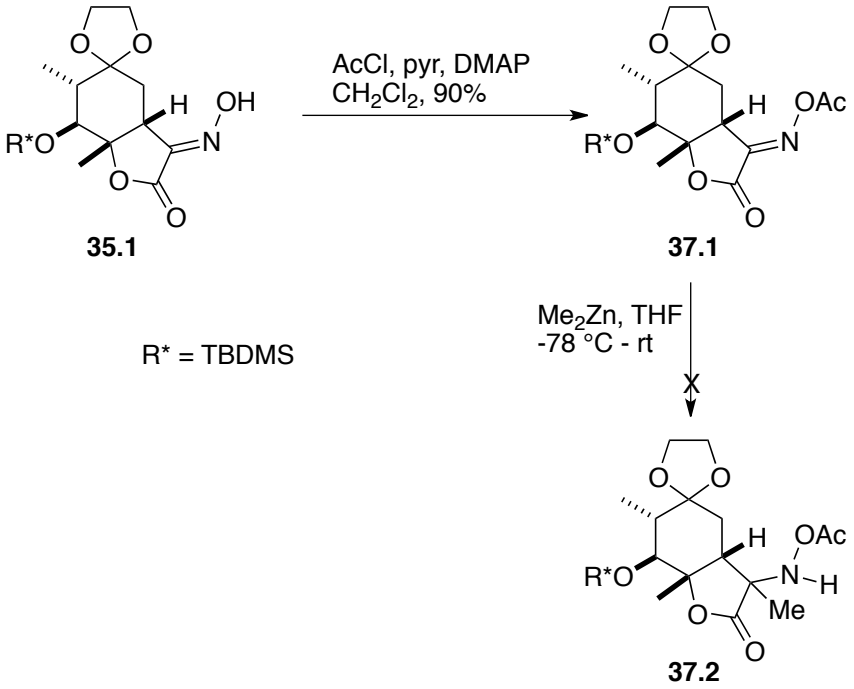
To improve the reactivity of oxime **35.1** towards nucleophilic addition, an electron withdrawing group needs to be installed at nitrogen.[14] To do this, we tried to convert the oxime **35.1** into the phosphinic amide **36.1** using Ph_2PCl and

Et_3N.[14] But none of the desired product was isolated and, instead, we got product **36.2** (Scheme 36).



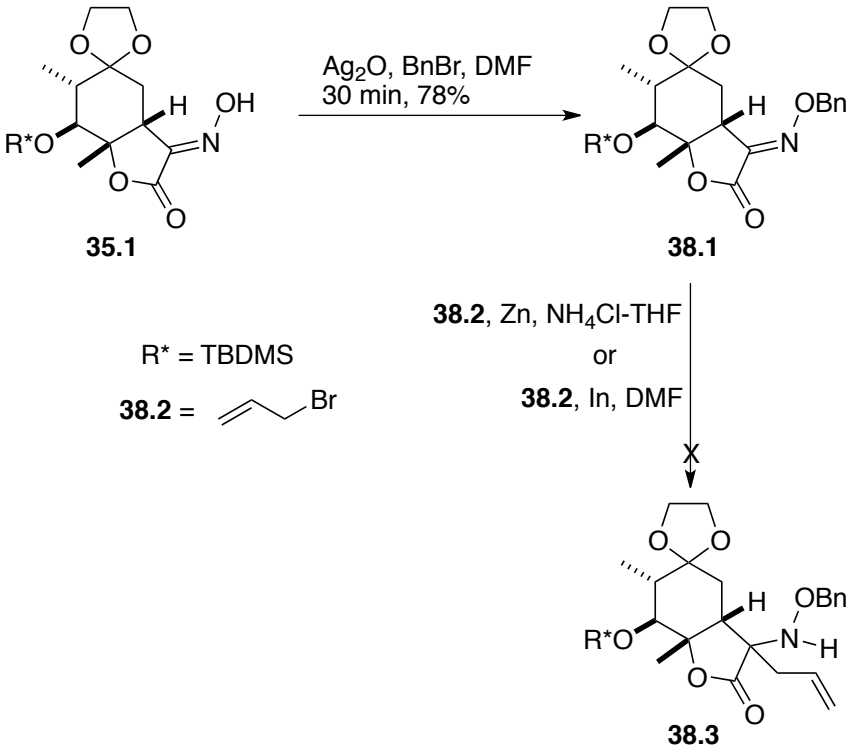
Scheme 36

Therefore, we decided to protect the oxime as its *O*-acetate and then try the nucleophilic addition. With this idea in mind, we made the protected oxime **37.1** by treating **35.1** with AcCl, DMAP and pyridine. Unfortunately, attempted addition of Me_2Zn to **37.1** also did not give any of the expected product **37.2** (Scheme 37). Low-resolution mass spectrometric analysis showed that the OAc group was attacked by the nucleophile instead of the ketimine moiety.



Scheme 37

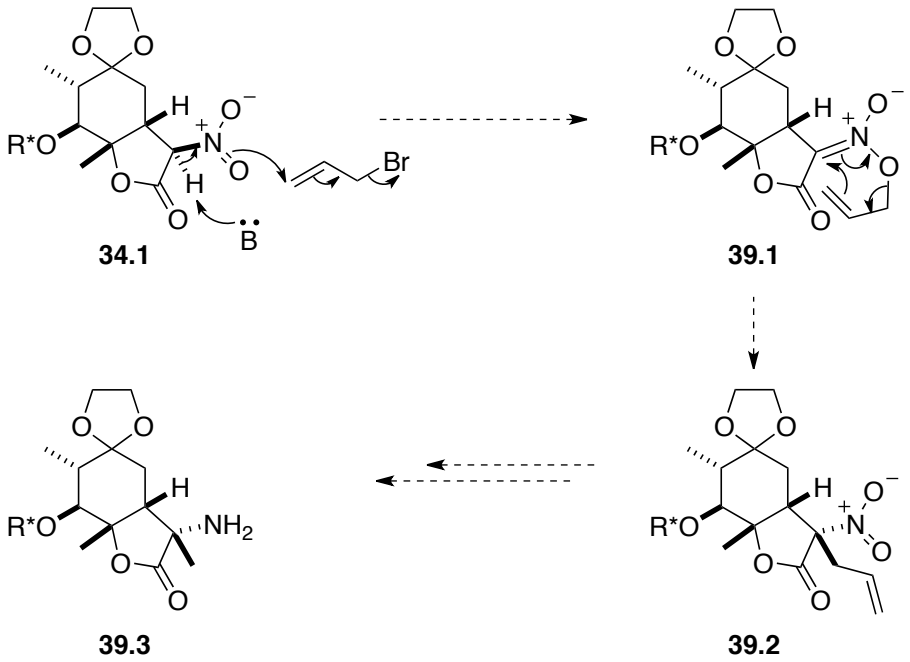
Our next plan was to add an allyl group to the oxime and later convert this group into the required methyl unit. In 1996, Hanessian and co-workers reported a zinc-mediated allylation of oximes in aqueous media.[27] Ritson and co-workers in 2004, reported an indium mediated allylation of oxime ethers as well.[28] In order to try these two procedures in our synthesis, we made the benzyl oxime ether **38.1** by reacting oxime **35.1** with BnBr and Ag_2O in DMF. But, we were not able to isolate any of the desired allylated product **38.3**, under the Hanessian or Ritson conditions.



Scheme 38

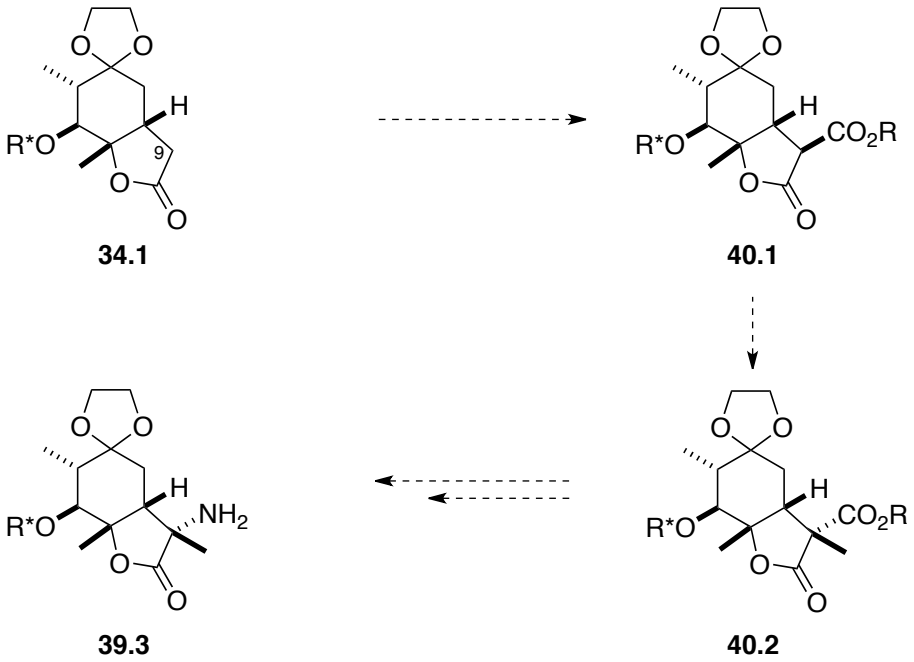
2.2.1 Further plans for the installation of methyl unit

When we tried the alkylation on the nitro compound (**34.1**) using MeI (see Scheme 34), the methyl unit went onto the oxygen instead of the α-position (C-3). Therefore, if we use use allyl bromide instead of methyl iodide we may be able to get the *O*-allylated compound **39.1**, which on heating may undergo a rearrangement to give the desired *C*-allylated product **39.2** (see Scheme 39).



Scheme 39

We may also try to follow the same principle that Harned and co-workers used:[11] Install an electron-withdrawing group such as an ester at C-3 and do the alkylation at this position. The ester group can then be converted to an amine by a Curtius rearrangement (Scheme 40). In our series, unlike the system used by Harned, alkylation occurs from the *exo* face.



Scheme 40

3. CONCLUSION

During this project, most of the carbon skeleton present in sorbicillactone A was assembled. The core bicyclic unit was generated through a stannane-mediated radical cyclization. A new one-pot approach for protection and iodolactonization was developed that allowed us to protect the ketone carbonyl and install the required C-7 hydroxyl. The stereochemistry of key compounds was confirmed by X-ray analysis. A number of different alkylation procedures were tried to install the methyl unit at C-3, but further work on this step is required and is now in progress.

4. Experimental

General Procedures. Unless stated to the contrary, the following conditions apply: 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 x 42 cm) of R3-11 catalyst[29] and then through a similar column of Drierite. All solvents for reactions were dried, as described below. Glassware was dried in an oven for at least 3 h before use (120 °C) and either cooled in desiccators over Drierite, or assembled quickly, sealed with rubber septa, and allowed to cool under a slight static pressure of Ar. Reaction mixtures were stirred with Teflon-coated magnetic stirring bars.

Hexane used for chromatography was distilled before use.

Products were isolated from solution by evaporation under water aspirator vacuum at room temperature, using a rotary evaporator.

Microliter syringes were washed with water and acetone using a suction device to draw the solvents through. Then air was sucked through for 1 min. The solution to be dispensed was drawn up and expelled, and this operation was repeated several times before drawing up the sample to be used. Cannula transfers were always done under slight pressure (Ar or N_2), not by suction.

Commercial thin layer chromatography (TLC) plates (silica gel, Merck 60F-254) were used. Spots were detected by spraying the plate with a solution of phosphomolybdic acid,[30] followed by charring on a hot plate, or by examination under UV light. Silica gel for flash chromatography was Merck type 60 (230-400 mesh).

Dry solvents were prepared under an inert atmosphere and transferred by dry syringes fitted with oven-dried needles, or by cannula. Dry THF was distilled from sodium benzophenone ketyl. Dry Et_3N, *i*-Pr_2NH, CH_2Cl_2, and pyridine were distilled from CaH_2. All other solvents were used as purchased. Commercial (Aldrich) solutions of *n*-BuLi (in hexanes) were titrated and found to have the stated molarity.

FTIR measurements were recorded on a Nicolet 7000 FTIR instrument. Measurements were made as casts from specified solvent.

^1H nuclear magnetic resonance spectra were recorded with Varian INOVA-300 (at 300 MHz), Varian INOVA-400 (at 400 MHz), or Varian INOVA-500 (at 500 MHz) spectrometers in the specified deuterated solvent. ^{13}C spectra were recorded with Varian INOVA-400 (at 100 MHz) or Varian INOVA-500 (at 125 MHz) spectrometers. The symbols s, d, t, and q used for ^{13}C NMR signals indicate 0, 1, 2, or 3 attached hydrogens, respectively, which are assigned based on APT experiments.

Mass spectra were recorded with Agilent Technologies 6220 oaTOF, Agilent technologies 5975C MSD single quadrupole mass spectrometers. Low resolution LC-mass spectra were measured with an Agilent 1100MSD single quadrupole mass spectrometer with electrospray ionization.

Solvent mixtures specified as x% A-B indicate that X mL of A were mixed with (100-X) mL of B.

Compounds isolated by flash chromatography were pure by TLC and, unless otherwise stated, also as judged by high field ^1H and ^{13}C NMR spectra.

4-Hydroxy-4-methylcyclohexa-2,5-dien-1-one (10.1).

13.5 **10.1**

An intimate mixture of Oxone (284.5 g, corresponding to 1.87 mol of $KHSO_5$) and $NaHCO_3$ (116.5 g, 1.39 mol) was added in portions over 30 min to a vigorously stirred solution of *p*-cresol (10 g, 92.47 mmol) in a mixture of MeCN (100 mL) and water (400 mL) contained in a 1-L three-necked flask. Two necks of the flask were fitted with septa, each pierced by a needle attached to a cut-off plastic syringe attached to a balloon. Once the addition was over the third neck was also fitted with a balloon in the same way. The progress of the reaction was monitored by TLC (silica, 50% EtOAc-hexane) and, when the reaction was over (usually 1 h), the mixture was diluted with water. Then $Na_2S_2O_3$ (73.05 g, 924.7 mmol) was added with stirring, and stirring was continued overnight. The mixture was extracted with EtOAc and the combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (6 x 15 cm), using 50% EtOAc-hexane, gave **10.1** (7.34 g, 64%) as a solid: FTIR (microscope) 3389, 3044, 2979, 2931, 1667, 1637, 1622 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.43 (s, 3 H), 3.33 (s, 1 H), 6.15 (d, J = 10.2 Hz, 2 H), 6.88 (d, J = 10.1 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.7 (q), 67.1

(s), 126.8 (d), 152.8 (d), 185.8 (s); exact mass (electrospray) *m/z* calcd for $C_7H_8NaO_2$ (M + Na) 147.0412, found 147.0417.

1-Methyl-4-oxocyclohexa-2,5-dien-1-yl 2-bromoacetate (14.1).

10.1 **14.1**

DMAP (974 mg, 7.98 mmol) and then pyridine (16.13 mL, 199.9 mmol) were added to a stirred and cooled (0 °C) solution of **10.1** (4.95 g, 39.9 mmol) in CH_2Cl_2. Neat $BrCH_2COBr$ (10.4 mL, 119.7 mmol) was added by syringe pump over 15 min. The ice bath was removed and stirring was continued for 1 h. The mixture was quenched with saturated aqueous $CuSO_4$ and extracted with CH_2Cl_2. The combined organic extracts were washed with water and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (5 x 15 cm), using 40% EtOAc-hexane, gave crude **14.1** (7.42 g, ca 76%) as a solid, which was used directly without characterization.

1-Methyl-4-oxocyclohexa-2,5-dien-1-yl 2-iodoacetate (13.4).

14.1 **13.4**

NaI (15.1 g, 100.86 mmol) was added to a solution of **14.1** (6.18 g, 25.22 mmol) in reagent grade acetone (150 mL). The mixture was stirred and refluxed for 6 h, cooled to room temperature and evaporated. The residue was filtered through a pad of Celite, using EtOAc, and the filtrate was washed with water and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (5 x 15 cm), using 20% EtOAc-hexane, gave **13.4** (5.44 g, 74%) as a solid: FTIR (microscope) 3048, 2984, 2933, 2869, 1736, 1666, 1630, 1609 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.58 (s, 3 H), 3.66 (s, 2 H), 6.26 (d, J = 10.2 Hz, 2 H), 6.88 (d, J = 10.2 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.0 (q), 75.5 (t), 128.7 (d), 147.8 (d), 167.3 (s), 184.7 (s); exact mass (electrospray) m/z calcd for $C_9H_9INaO_3$ (M + Na) 314.948, found 314.9489.

(3a*R*,7a*S*)-*rel*-7a-Methyl-2,3,3a,4,5,7a-hexahydro-1-benzofuran-2,5-dione (10.5).

13.4 **10.5**

A solution of Bu_3SnH (3.23 mL, 12.18 mmol) and AIBN (181 mg, 1.11 mmol) in dry PhH (80 mL) was added by syringe pump over 8 h to a refluxing solution of **13.4** (3.23 g, 11.07 mmol) in PhH (553 mL) contained in a 1-L round-bottomed flask (N_2 atmosphere). After the addition refluxing was continued overnight. The solution was cooled and evaporated and the residue was taken up in the minimum amount of CH_2Cl_2 and applied to the top of a chromatography column (3 x 15 cm) made up with flash chromatography silica gel-10% KF and 40% EtOAc-hexane. Development of the column with 40% EtOAc-hexane gave **10.5** (1.54 g, 84%) as a solid: FTIR (microscope) 3039, 2979, 2932, 2869, 1790, 1684, 1627, 1419 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.67 (s, 3 H), 2.40 (dd, *J* = 17.5, 11.7 Hz, 1 H), 2.59 (ddd, *J* = 17.3, 3.1, 0.9 Hz, 1 H), 2.69 (ddd, *J* = 17.4, 10.6, 6.9 Hz, 2 H), 2.88-2.94 (m, 1 H), 6.06 (d, *J* = 10.3 Hz, 1 H), 6.63 (dd, *J* = 10.3, 1.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 24.2 (q), 34.7 (t), 36.8 (t), 40.9 (d), 81.5 (s), 129.2 (d), 146.5 (d), 173.7 (s), 195.0 (s); exact mass (electrospray) *m*/*z* calcd for $C_9H_{10}NaO_3$ (M + Na) 189.0522, found 189.0518.

(3a*R*,7a*S*)-*rel*-6-Bromo-7a-methyl-2,3,3a,4,5,7a-hexahydro-1-benzofuran-2,5-dione (15.1).

10.5 **15.1**

A solution of Br_2 (41 μL, 0.80 mmol) in CH_2Cl_2 (2 mL) was added dropwise over 5 min to a stirred and cooled (0 °C) solution of **10.5** (121 mg, 0.73 mmol) in CH_2Cl_2 (8 mL). Stirring at 0 °C was continued for 30 min and then Et_3N (0.51 mL, 3.64 mmol) was added at a fast dropwise rate, the ice bath was removed and stirring was continued for 1 h. The mixture was quenched with dilute hydrochloric acid (1 M, 10 mL) and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 40% Et_2O-hexane, gave **15.1** (153.4 mg, 86%) as a solid: FTIR (cast film) 3041, 2980, 2931, 2869, 1781, 1700, 1611, 1417 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.70 (s, 3 H), 2.43 (dd, *J* = 17.5, 11.4 Hz, 1 H), 2.72-2.85 (m, 3 H), 2.89-3.01 (m, 1 H), 7.11 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 24.2 (q), 34.5 (t), 36.8 (t), 40.9 (d), 83.2 (s), 125.2 (s), 146.9 (d), 173.1 (s), 187.3 (s); exact mass (electrospray) *m*/*z* calcd for $C_9H_9{}^{79}BrNaO_3$ (M + Na) 266.9627, found 266.9625.

(3a*R*,7a*S*)-*rel*-6-Bromo-7a-methyl-3,3a,4,7a-tetrahydro-2*H*-spiro[1-benzofuran-5,2'-[1,3]dioxolan]-2-one (15.2).

15.1 **15.2**

$Me_3SiOSO_2CF_3$ (20.37 μL, 0.1125 mmol) and 1,2-bis(trimethylsiloxy)ethane (0.18 mL, 0.75 mmol) were added dropwise in that order to a stirred and cooled (-78 °C) solution of **15.1** (23 mg, 0.09 mmol) in CH_2Cl_2 (1 mL). The cold bath was left in place but not recharged and stirring was continued for 5 h. At this point the ^1H NMR spectrum of a worked-up sample showed that the reaction was complete. The solvent was evaporated and the residue in a little CH_2Cl_2 was applied directly to the top of a flash chromatography silica gel column made up in a Pasteur pipette (0.6 x 7 cm) with hexane. Development of the column with 40% EtOAc-hexane gave **15.2** (18 mg, 66%) as a solid: FTIR (cast film) 2975, 2895, 1774, 1701, 1642, 1474, 1429 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.51 (s, 3 H), 2.03-2.13 (m, 2 H), 2.61-2.71 (m, 2 H), 2.85-2.91 (m, 1 H), 3.98-4.04 (m, 2 H), 4.17-4.27 (m, 2 H), 6.22 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 25.2 (q), 33.7 (t), 34.9 (t), 38.7 (d), 66.0 (t), 66.3 (t), 83.45 (s), 103.7 (s), 129.2 (s), 134.5 (d), 174.9 (s); exact mass (electrospray) *m/z* calcd for $C_{11}H_{13}{}^{79}BrNaO_4$ (M + Na) 310.9889, found 310.9884.

(3*R*,3a*R*,7a*S*)-*rel*-6-Bromo-3,7a-dimethyl-3,3a,4,7a-tetrahydro-2*H*-spiro[1-benzofuran-5,2'-[1,3]dioxolan]-2-one (16.1).

15.2 **16.1**

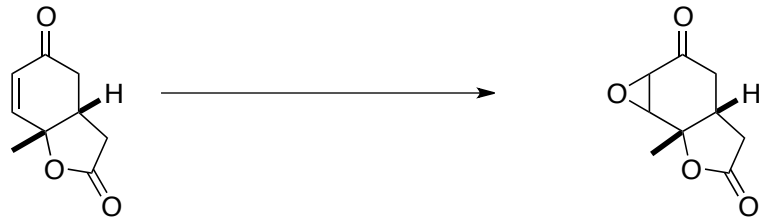
Use of $(Me_3Si)_3NK$

$(Me_3Si)_3NK$ (0.5 M in PhMe, 0.12 mL, 0.06 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of **15.2** (15 mg, 0.05 mmol) in THF (1 mL). Stirring was continued for 50 min and then MeI (4.84 μL, 0.08 mmol) was added and stirring at -78 °C was continued for 20 min. The reaction flask was then transferred to an ice bath, stirring was continued for 10 min, the mixture was quenched with saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The combined organic extracts were washed with water and brine, dried ($MgSO_4$) and evaporated. The residue, in a little CH_2Cl_2, was applied directly to the top of a flash chromatography silica gel column made up in a Pasteur pipette (0.6 x 7 cm) with hexane. Development of the column with 20% EtOAc-hexane gave **16.1** (11 mg, 70%) as a solid:

Use of LDA

A stock solution of LDA was prepared by addition of BuLi (2.5 M in hexane, 0.27 mL, 0.67 mmol) to a stirred and cooled (-78 °C) solution of *i*-Pr_2NH (78.8 μL, 0.78 mmol) in THF (5 mL). Stirring was continued for 30 min. A portion (0.53 mL, 0.12 mmol LDA) of this stock solution was taken up into a syringe and added dropwise to a stirred and cooled (-78 °C) solution of **15.2** (15 mg, 0.05 mmol) in THF (1 mL). Stirring was continued for 50 min and then MeI (6.46 μL, 0.01 mmol) was added and stirring at -78 °C was continued for 30 min. The reaction flask was then transferred to an ice bath, stirring was continued for 15 min, the mixture was quenched with saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The combined organic extracts were washed with water and brine, dried ($MgSO_4$) and evaporated. The residue, in the minimum amount of CH_2Cl_2, was applied directly to the top of a flash chromatography silica gel column made up in a Pasteur pipette (0.6 x 7 cm) with hexane. Development of the column with 20% EtOAc-hexane gave **16.1** (11 mg, 70%) as a solid: FTIR (cast film) 2977, 2932, 2895, 1777, 1641, 1456, 1434 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.23 (d, *J* = 7.0 Hz, 3 H), 1.51 (s, 3 H), 2.12-2.21 (m, 3 H), 3.08-3.15 (m, 1 H), 3.97 (td, *J* = 7.5, 6.3 Hz, 1 H), 4.06 (ddd, *J* = 7.3, 6.3, 4.4 Hz, 1 H), 4.19 (td, *J* = 7.4, 6.4 Hz, 1 H), 4.27 (ddd, *J* = 7.6, 6.4, 4.4 Hz, 1 H), 6.20 (d, *J* = 1.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.2 (q), 24.6 (q), 32.8 (t), 37.8 (d), 47.6 (d), 66.2 (t), 66.2 (t), 81.8 (s), 103.5 (s), 128.0 (s), 135.3 (d), 177.8 (s); exact mass (electrospray) *m/z* calcd for $C_{12}H_{15}{}^{79}BrNaO_4$ (M + Na) 325.0046, found 325.0041.

(1*S*,7*R*)-*rel*-1-Methyl-3,10-dioxatricyclo[5.3.0.0^{2,4}]decane-5,9-dione (i).



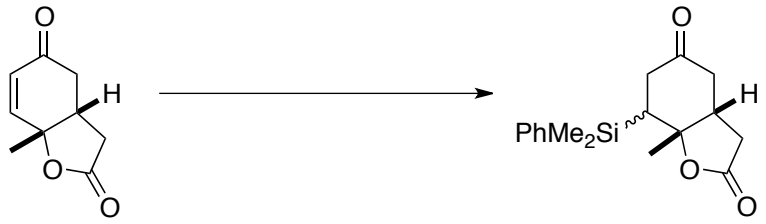
10.5 **i**

Aqueous KOH (1 M, 92 μL, 0.092 mmol) and H_2O_2 (30%, 0.26 mL, 2.3 mmol) were added in that order to a stirred and cooled (-10 °C, Haake immersion cooler in a bath of aqueous ethylene glycol) solution of **10.5** (83 mg, 0.50 mmol) in MeOH (3 mL). Stirring at -10 °C was continued overnight and then the MeOH was evaporated at room temperature. The residue was extracted with CH_2Cl_2 and the combined organic extracts were washed with water and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (0.8 x 15 cm), using 40% EtOAc-hexane, gave epoxide **i** as two separable diastereomers. The less polar isomer (32 mg, 35%) had: FTIR (cast film) 3479, 2979, 2954, 2932, 1772, 1731, 1682, 1419, 1379 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.80 (s, 3 H), 2.21 (ddd, *J* = 14.3, 3.1, 0.9 Hz, 1 H), 2.29 (dd, *J* = 17.9, 10.9 Hz, 1 H), 2.74 (dd, *J* = 17.9, 9.4 Hz, 1 H), 2.79-2.85 (m, 1 H), 3.05 (dd, *J* = 14.3, 4.8 Hz, 1 H), 3.41 (dd, *J* = 3.6, 0.8 Hz, 1 H), 3.58 (dd, *J* = 3.6, 1.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 23.9 (s), 33.4 (t), 34.4 (t), 43.1 (d), 55.3 (d), 62.0 (d), 80.0 (s), 173.3

(s), 204.0 (s); exact mass (electrospray) *m/z* calcd for $C_9H_{10}NaO_4$ (M + Na) 205.0471, found 205.0466.

The more polar isomer (34 mg, 37%) had: FTIR (cast film) 3421, 2984, 2936, 1780, 1724 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.55 (s, 3 H), 2.45 (dd, *J* = 16.0, 8.3 Hz, 1 H), 2.62-2.68 (m, 1 H), 2.71-2.87 (m, 3 H), 3.48 (dd, *J* = 4.3, 0.5 Hz, 1 H), 3.66 (dd, *J* = 4.3, 1.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 23.9 (q), 37.1 (t), 37.4 (t), 39.4 (d), 56.2 (d), 62.4 (d), 81.9 (s), 174.1 (s), 203.4 (s); exact mass (electrospray) *m/z* calcd for $C_9H_{10}NaO_4$ (M + Na) 205.0471, found 205.0466.

(3a*R*,7a*S*)-*rel*-7-[Dimethyl(phenyl)silyl]-7a-methyloctahydro-1-benzofuran-2,5-dione (18.1).



10.5 **18.1**

A solution of $PhMe_2SiCuLi$ was prepared as follows:[16]

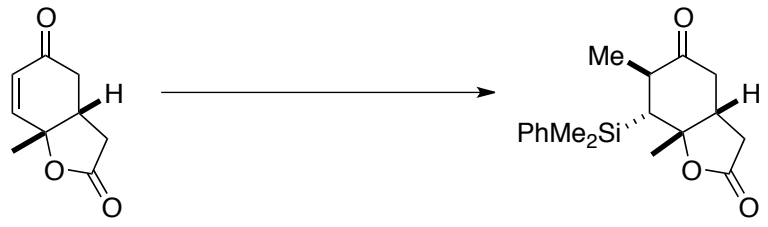
Lithium wire (97 mg, 13.92 mmol) was cut into small pieces (1-2 mm long) that were allowed to drop into a beaker of dry hexane. The pieces were removed with tweezers, blotted with filter paper and transferred to a pear-shaped flask containing THF (4 mL) (Ar atmosphere). The contents of the flask were

cooled (0 °C) and stirred while $PhMe_2SiCl$ (1 mL, 5.95 mmol) was added dropwise. Stirring was continued for 4 h, by which time a deep red color had formed, to give a 1 M solution of $PhMe_2SiLi$.

In another flask dry HMPA (0.98 mL) was added to a stirred mixture of CuI (295 mg, 1.54 mmol) and THF (8 mL) and the mixture was cooled (-78 °C). The solution of $PhMe_2SiLi$ (3.1 mL, 3.1 mmol) was taken up into a syringe and added dropwise with stirring to the CuI mixture. After the addition, stirring at -78 °C was continued for 10 min, and at 0 °C (ice bath) for 1 h. The mixture was then recooled to -78 °C, and a solution of **10.5** (234 mg, 1.41 mmol) in THF (3 mL) was added dropwise over 5 min. The cold bath was left in place but not recharged and stirring was continued for 50 min. The mixture was recooled to -78 °C and MeI (0.44 mL, 7.04 mmol) was added. Stirring was continued at -78 °C for 20 min and at 0 °C (ice bath) for 2 h. The mixture was filtered through a pad of Celite using Et_2O as a rinse. The filtrate was washed with dilute hydrochloric acid (1 M), water and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 40% EtOAc-hexane, gave an inseparable mixture of the two silanes **18.1** (171 mg, 40%). Only a trace of the *C*-methylated silane was isolated, but this compound could be made as described below. Compounds **18.1** had: FTIR (cast film) 2963, 1770, 1717, 1427 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.43-0.49 (m, 6 H), 1.49-1.46 (m, 3 H), 2.10-2.21 (m, 2 H), 2.26-2.58 (m, 5 H), 2.72-2.91 (m, 2 H), 7.35-7.39 (m, 3 H), 7.49-7.51 (m, 1 H), 7.54-7.56 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ -3.8 (q), -3.4 (q), -2.3 (q), -2.2 (q), 24.8 (q), 29.5 (q), 31.6 (t), 32.5 (t), 34.9 (t), 35.4 (t), 37.1 (t), 37.5 (t),

39.8 (t), 41.1 (d), 41.4 (t), 41.5 (d), 86.9 (s), 87.7 (s), 128.1 (d), 128.1 (d), 129.6 (d), 129.6 (d), 134.0 (d), 134.1 (d), 136.5 (s), 136.9 (s), 174.6 (s), 174.7 (s), 209.6 (s), 210.1 (s); exact mass (electrospray) *m/z* calcd for $C_{17}H_{22}NaO_3Si$ (M + Na) 325.123, found 325.1225.

(3a*R*,6*S*,7*R*,7a*S*)-*rel*-7-[Dimethyl(phenyl)silyl]-6,7a-dimethyloctahydro-1-benzofuran-2,5-dione (17.2).



10.5 **17.2**

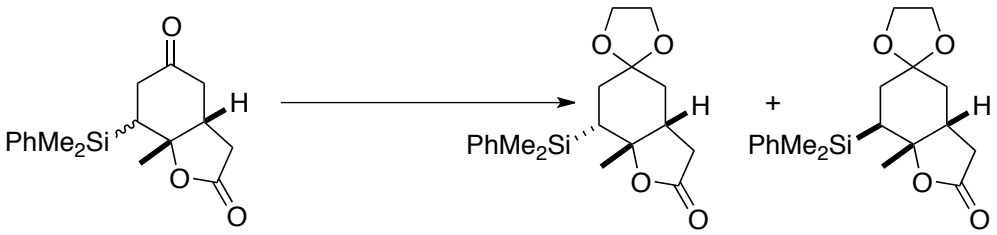
A solution of $PhMe_2SiCuLi$ was prepared as follows:[16]

Lithium wire (387 mg, 55.76 mmol) was cut into small pieces (1-2 mm long) that were allowed to drop into a beaker of dry hexane. The pieces were removed with tweezers, blotted with filter paper and transferred to a pear-shaped flask containing THF (16 mL) (Ar atmosphere). The contents of the flask were cooled (0 °C) and stirred while $PhMe_2SiCl$ (4 mL, 23.82 mmol) was added dropwise. Stirring was continued for 4 h, by which time a deep red color had formed, to give a 1 M solution of $PhMe_2SiLi$.

In another flask dry HMPA (3.6 mL) was added to a stirred mixture of CuCN (808.4 mg, 9.02 mmol) and THF (36 mL) and the mixture was cooled (0

°C). The solution of $PhMe_2SiLi$ (18.1 mL, 18.1 mmol) was taken up into a syringe and added dropwise over ca 5 min to the CuCN mixture. After the addition, stirring at 0 °C was continued for 1 h, and the mixture was then cooled to -78 °C. A solution of **10.5** (1.5 g, 9.03 mmol) in THF (5 mL) was added dropwise over 5 min. After this addition the temperature was allowed to rise over ca 2 h to -20 °C (by not recharging the cold bath). At this point, examination of the mixture by TLC (silica, 40% EtOAc-hexane, developed three times) showed that all **10.5** had reacted. The mixture was cooled to -50 °C and HMPA (5 mL) was added, followed by MeI (5.6 mL, 90.26 mmol). Stirring was continued without recharging the cold bath so that the temperature rose to 0 °C over 2 h. The mixture was quenched with saturated aqueous NH_4Cl and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 15 cm), using 40% EtOAc-hexane, gave **17.2** (2.26 g, 80%) as a solid: FTIR (cast film) 2973, 1771, 1714, 1488, 1458, 1427 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.47 (s, 3 H), 0.51 (s, 3 H), 1.03 (d, *J* = 7.2 Hz, 3 H), 1.56 (s, 3 H), 2.08 (dd, *J* = 16.5, 8.3 Hz, 1 H), 2.17 (dd, *J* = 18.0, 4.9 Hz, 1 H), 2.38-2.47 (m, 3 H), 2.68-2.74 (m, 1 H), 2.84 (dd, *J* = 18.0, 8.9 Hz, 1 H), 7.33-7.37 (m, 1 H), 7.54-7.56 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ -1.9 (q), -0.1 (q), 18.4 (q), 30.7 (q), 35.6 (t), 40.0 (t), 40.7 (d), 41.0 (d), 42.1 (d), 87.9 (s), 128.0 (d), 129.3 (d), 134.1 (d), 138.1 (s), 174.7 (s), 212.2 (s); exact mass (electrospray) *m/z* calcd for $C_{18}H_{24}NaO_3Si$ (M + Na) 339.1387, found 339.1378.

(3a*R*,7*R*,7a*S*)-*rel*-7-[Dimethyl(phenyl)silyl]-7a-methylhexahydro-2*H*-spiro[1-benzofuran-5,2'-[1,3]dioxolan]-2-one (18.2a) and (3a*R*,7*S*,7a*S*)-*rel*-7-[Dimethyl(phenyl)silyl]-7a-methylhexahydro-2*H*-spiro[1-benzofuran-5,2'-[1,3]dioxolan]-2-one (18.2b).



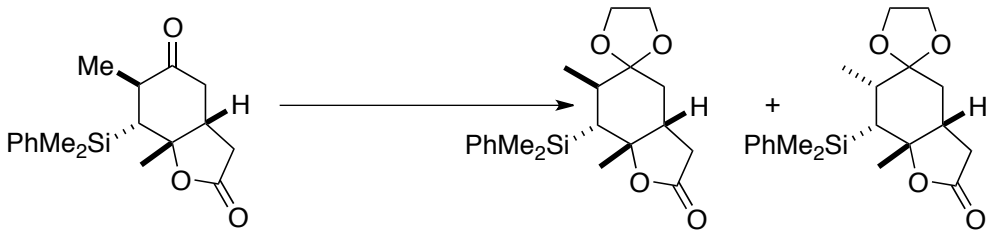
18.1 **18.2a,b**

Ethylene glycol (0.63 mL, 11.32 mmol), camphorsulfonic acid (26 mg, 0.11 mmol) and $MeC(OMe)_3$ (0.62 mL, 5.66 mmol) were added in that order to a stirred solution of **18.1** (171 mg, 0.57 mmol) in CH_2Cl_2 (3 mL). Stirring was continued for 4 h (TLC monitoring, silica, 40% EtOAc-hexane), at which point the reaction was complete. The mixture was quenched with saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The combined organic extracts were washed with water and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (0.8 x 15 cm), using 40% EtOAc-hexane, gave **18.2-more polar** (39 mg, 20%) and **18.2-less polar** (31 mg, 16%), both as oils. We did not assign stereochemistry to the individual isomers. The less polar isomer had: FTIR (cast film) 2954, 2892, 1769, 1447, 1428 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.40 (s, 3 H), 0.44 (s, 3 H), 1.46-1.49 (m, 4 H), 1.64-

1.69 (m, 2 H), 1.79-1.88 (m, 2 H), 2.38-2.46 (m, 2 H), 3.12-3.11 (m, 1 H), 3.68-3.73 (m, 1 H), 3.81-3.92 (m, 3 H), 7.34-7.36 (m, 3 H), 7.49-7.51 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ -3.5 (q), -1.8 (q), 23.3 (q), 29.4 (d), 32.9 (t), 32.9 (t), 33.9 (t), 43.8 (d), 63.9 (t), 64.4 (t), 86.9 (s), 107.5 (s), 127.8 (d), 129.1 (d), 133.9 (d), 137.8 (s), 176.2 (s); exact mass (electrospray) *m*/*z* calcd for $C_{19}H_{26}NaO_4Si$ (M + Na) 369.1493, found 369.1487.

The more polar isomer: FTIR (cast film) 2956, 2887, 1770, 1452, 1428 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.39 (s, 3 H), 0.47 (s, 3 H), 1.24 (s, 3 H), 1.43-1.48 (m, 1 H), 1.53-1.62 (m, 3 H), 1.80 (ddd, *J* = 13.8, 6.4, 2.4 Hz, 1 H), 2.18 (dd, *J* = 17.6, 1.8 Hz, 1 H), 2.42 (dddd, *J* = 11.0, 7.7, 6.3, 1.6 Hz, 1 H), 2.83 (dd, *J* = 17.6, 7.7 Hz, 1 H), 3.80-3.82 (m, 1 H), 3.87-3.92 (m, 3 H), 7.34-7.36 (m, 3 H), 7.55-7.57 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ -2.7 (q), -1.6 (q), 27.7 (q), 31.3 (d), 32.0 (t), 36.9 (t), 36.9 (t), 41.6 (d), 64.3 (t), 64.3 (t), 86.9 (s), 107.5 (s), 127.9 (d), 129.1 (d), 134.0 (d), 138.7 (s), 176.4 (s); exact mass (electrospray) *m*/*z* calcd for $C_{19}H_{26}NaO_4Si$ (M + Na) 369.1493, found 369.1488.

(3a*R*,6*S*,7*R*,7a*S*)-*rel*-7-[Dimethyl(phenyl)silyl]-6,7a-dimethylhexahydro-2*H*-spiro[1-benzofuran-5,2'-[1,3]dioxolan]-2-one (19.1a) and (3a*R*,6*R*,7*R*,7a*S*)-*rel*-7-[Dimethyl-(phenyl)silyl]-6,7a-dimethylhexahydro-2*H*-spiro[1-benzofuran-5,2'-[1,3]dioxolan]-2-one (19.1b).



17.2 **19.1a** **19.1b**

Ethylene glycol (0.22 mL, 4.01 mmol), camphorsulfonic acid (9.3 mg, 0.04 mmol) and $HC(OMe)_3$ (0.22 mL, 2.01 mmol) were added to a stirred solution of **17.2** (single isomer, 63 mg, 0.21 mmol) in CH_2Cl_2 (1 mL) and stirring was continued for 24 h, by which time all **17.2** had reacted (TLC monitoring, silica, 15% EtOAc-hexane). The mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$. The organic phase was washed with water and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (0.6 x 7 cm), using 15% EtOAc-hexane, gave the more polar isomer (**19.1a**) (13 mg, 18%) and the less polar isomer (**19.1b**) (9 mg, 12%), as solids. The more polar isomer was pure and the stereochemistry was established by single crystal X-ray analysis. The less polar isomer was contaminated by some of the more polar and its ^1H NMR spectrum was too complicated to be informative. The more polar isomer had: FTIR (cast film) 2975, 2882, 1771, 1462, 1427 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.42 (s, 3 H), 0.50 (s, 3 H), 0.90 (d, J = 6.5 Hz, 3 H), 1.27 (s, 3 H), 1.55-1.70 (m, 4 H), 2.03 (dd, J = 11.3, 7.4 Hz, 1 H), 2.29 (d, J = 17.6 Hz, 1 H), 2.90 (dd, J = 17.6, 7.4 Hz, 1 H), 3.80-3.84 (m, 1 H), 3.90-3.97 (m, 4 H), 7.38-7.39 (m, 3 H), 7.59-7.61 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ -2.8 (q), -1.3

(q), 11.7 (q), 27.9 (q), 31.3 (d), 32.0 (t), 36.4 (t), 40.8 (d), 49.7 (d), 64.8 (t), 65.3 (t), 87.5 (s), 108.8 (s), 127.9 (d), 129.0 (d), 133.9 (d), 138.9 (s), 176.6 (s); exact mass (electrospray) *m*/*z* calcd for $C_{20}H_{28}NaO_4Si$ (M + Na) 383.1649, found 383.1644.

(3*R*,3a*R*,7*R*,7a*S*)-*rel*-3-Azido-7-[dimethyl(phenyl)silyl]-6,7a-dimethyl-hexahydro-2*H*-spiro[1-benzofuran-5,2'-[1,3]dioxolan]-2-one (24.1).

17.2 **24.1**

A stock solution of LDA was prepared by addition of BuLi (2.5 M in hexane, 0.45 mL, 1.13 mmol) to a stirred and cooled (-78 °C) solution of *i*-Pr_2NH (0.18 mL, 1.23 mmol) in THF (2 mL). Stirring was continued for 30 min. A portion (0.263 mL, 0.43 mmol LDA) of this stock solution was taken up into a syringe and added dropwise to a stirred and cooled (-78 °C) solution of **17.2** (C-6 isomer mixture, 37 mg, 0.10 mmol) in THF (1 mL). Stirring was continued for 50 min and HMPA (0.1 mL), followed by a solution of 2,4,6-(*i*-$Pr)_3C_6H_2SO_2N_3$ (38.1 mg, 1.12 mmol) in THF (1 mL), was added dropwise and stirring at -78 °C was continued for 2 h. Me_3SiCl (65.17 μL, 0.51 mmol) was added and stirring was

continued overnight, the cold bath being left in place but not recharged. The mixture was quenched with pH 7 buffer and the organic phase was extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (0.8 x 15 cm), using 10% EtOAc-hexane), gave **24.1** (27 mg, 66%) as a mixture of isomers: exact mass (electrospray) *m/z* calcd for $C_{20}H_{27}N_3NaO_4Si$ (M + Na) 424.1663, found 424.1655.

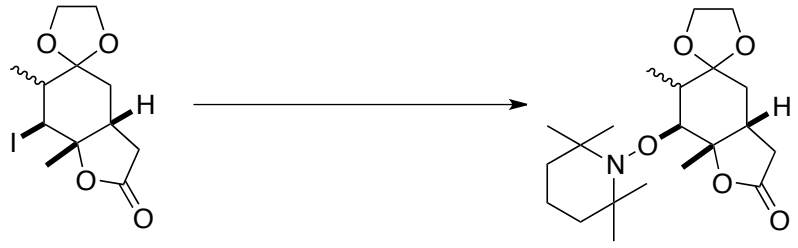
(3a*R*,6*S*,7a*S*)-*rel*-7-Iodo-6,7a-dimethylhexahydro-2*H*-spiro[1-benzo-furan-5,2'-[1,3]dioxolan]-2-one (23.1b).

19.1a **23.1b**

ICl (1 M in CH_2Cl_2, 27 μL, 0.027 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **19.1a** (10 mg, 0.027 mmol) in Et_2O (1 mL). After 1 h, examination of the mixture by TLC (silica, 30% EtOAc-hexane) showed that some **19.1a** remained and so more ICl (1 M in CH_2Cl_2, 14 μL, 0.014 mmol)) was added. Stirring was continued at 0 °C for 30 min, by which time reaction was complete, and the mixture was then filtered through a pad of Celite, using Et_2O as

a rinse. Evaporation of the filtrate and flash chromatography of the residue over silica gel (0.6 x 7 cm), using 60% Et_2O-hexane, gave **23.1b** (8 mg, 82%) as an oil: FTIR (cast film) 2983, 2943, 2893, 1778, 1721, 1682 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.26 (d, *J* = 7.5 Hz, 3 H), 1.71 (s, 3 H), 1.78-1.81 (m, 1 H), 2.19 (dd, *J* = 15.0, 6.4 Hz, 1 H), 2.24-2.30 (m, 1 H), 2.50 (dd, *J* = 17.8, 8.8 Hz, 1 H), 2.82 (dddd, *J* = 12.7, 8.6, 6.4, 2.2 Hz, 1 H), 3.33 (dd, *J* = 17.8, 12.6 Hz, 1 H), 3.91-4.03 (m, 1 H), 4.84 (d, *J* = 4.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.7 (q), 28.2 (t), 28.7 (q), 33.9 (t), 39.5 (d), 40.5 (d), 46.3 (d), 64.2 (t), 64.7 (t), 84.6 (s), 109.1 (s), 174.8 (s); exact mass (electrospray) *m/z* calcd for $C_{12}H_{17}INaO_4$ (M + Na) 375.0064, found 375.0057.

(3a*R*,7*S*,7a*S*)-*rel*-6,7a-Dimethyl-7-[(2,2,6,6-tetramethylpiperidin-1-yl)oxy]hexahydro-2*H*-spiro[1-benzofuran-5,2'-[1,3]dioxolan]-2-one (26.1).



23.1a, 23.1b **26.1**

Solutions of Bu_3SnH (4.68 mL, 17.66 mmol) in PhMe (10 mL) and of TEMPO (4.13 g, 26.49 mmol in PhMe (10 mL) were prepared. An aliquot (3.3 mL) of the stannane solution was added by syringe over 2 min to a refluxing

solution of **23.1a** and **23.1b** (mixture of C-6 isomers) (1.55 g, 4.41 mmol) in PhMe (26.4 mL) and then an aliquot (6.7 mL) of the TEMPO solution was added over 2 min. The remaining stannane and TEMPO solutions were then added sequentially, each in three equal portions, over the next 60 min, i.e. 20 min, 40 min and 60 min after the first addition of TEMPO. Refluxing was continued for an additional 30 min and the solvent was then evaporated. Flash chromatography of the residue over flash chromatography silica gel-10% KF (2 x 15 cm), using 40% EtOAc-hexane, gave **26.1** as a mixture of isomers (1.17 g, 70%) as a solid, which was used for the next step without separation.

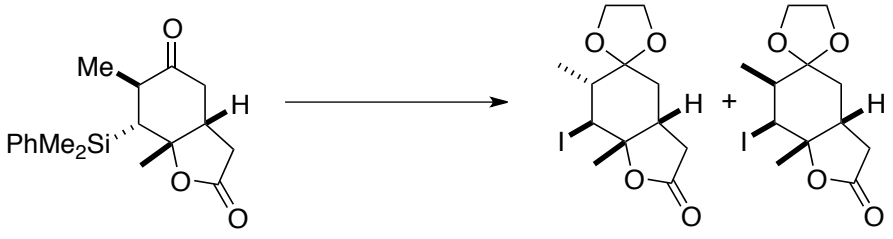
(3a*R*,6*S*,7*S*,7a*S*)-*rel*-7-Iodo-6,7a-dimethyloctahydro-1-benzofuran-2,5-dione (22.1).

17.2 **22.1**

ICl (1 M in CH_2Cl_2, 63.2 μL, 0.06 mmol) was added to a stirred and cooled (-78 °C) solution of **17.2** (10 mg, 0.03 mmol) in Et_2O (1 mL). No reaction was observed (TLC) after 1 h and so the mixture was allowed to warm to -20 °C over ca 30 min, at which point some reaction occurred (TLC). The mixture was

allowed to warm to 0 °C. More ICl (1 M in CH_2Cl_2, 31 μL, 0.031 mmol) was added and the mixture was maintained at 0 °C for 15 min. The mixture was quenched with saturated aqueous $Na_2S_2O_3$ and extracted with Et_2O. The combined organic extracts were washed with water and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (0.6 x 7 cm), using 60% Et_2O-hexane, gave **22.1** (7 mg, 72%) as a single isomer: FTIR (cast film) 2978, 2932, 2893, 1773, 1721, 1682, 1454, 1426 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.39 (d, *J* = 6.9 Hz, 3 H), 1.80 (s, 3 H), 2.48-2.67 (m, 3 H), 2.72-2.77 (m, 1 H), 2.89-3.00 (m, 2 H), 4.37 (d, *J* = 12.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 18.3 (q), 26.8 (q), 35.6 (t), 38.8 (d), 39.3 (d), 40.5 (t), 49.8 (d), 85.0 (s), 172.8 (s), 205.3 (s); exact mass (electrospray) *m/z* calcd for $C_{10}H_{13}INaO_3$ (M + Na) 330.9802, found 330.9795.

(3a*R*,6*R*,7*S*,7a*S*)-*rel*-7-Iodo-6,7a-dimethylhexahydro-2*H*-spiro[1-benzofuran-5,2'-[1,3]dioxolan]-2-one (23.1a) and (3a*R*,6*S*,7*S*,7a*S*)-*rel*-7-Iodo-6,7a-dimethylhexahydro-2*H*-spiro[1-benzofuran-5,2'-[1,3]dioxolan]-2-one (23.1b).

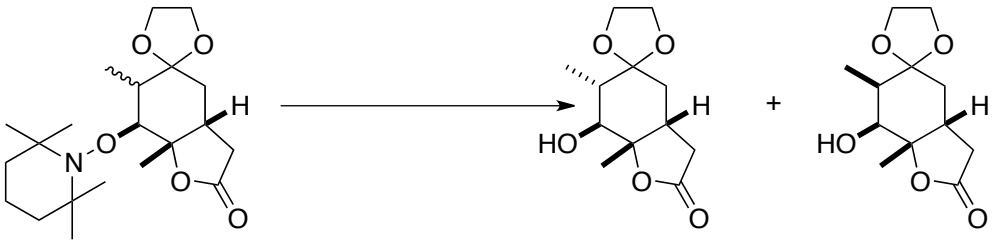


17.2 **23.1a** **23.1b**

1,2-Bis(trimethylsilyloxy)ethane (4.5 mL, 18.56 mmol) and $Me_3SiOSO_2CF_3$ (1.12 mL, 6.19 mmol) were added dropwise to a stirred and cooled (-78 °C) solution of **17.2** (1.96 g, 6.19 mmol) in CH_2Cl_2 (37 mL). The cold bath was left in place but not recharged and stirring was continued for 4 h, by which time the temperature had risen to room temperature and all of **17.2** had reacted (monitoring by low resolution mass spectrometry). The mixture was then cooled to -30 °C and ICl (1 M solution in CH_2Cl_2, 12.3 mL, 12.38 mmol) was added at a fast dropwise rate. Stirring was continued for 10 min (monitoring by low resolution mass spectrometry) and the mixture was quenched with saturated aqueous $Na_2S_2O_3$ and extracted with CH_2Cl_2. The combined organic extracts were washed with water and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 80% Et_2O-hexane, gave **23.1a** and **23.1b** which were separated into three fractions: the less polar isomer **23.1b** (348 mg, 16%), the more polar isomer **23.1a** (305 mg, 14%) and a mixture of the two (915 mg, 42%), all as solids: The more polar isomer **23.1a** had: FTIR (cast film) 2983, 2937, 2898 1782, 1766, 1458, 1435 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.17 (d, *J* = 6.6 Hz, 3 H), 1.75 (s, 3 H), 1.82 (dd, *J* = 14.9, 6.3 Hz, 1 H), 1.94 (dd, *J* = 14.9, 2.0 Hz, 1 H), 2.10 (dd, *J* = 12.9, 6.6 Hz, 1 H), 2.43 (dd, *J* = 17.5, 8.4 Hz, 1 H), 2.79 (dddd, *J* = 13.3, 8.4, 6.4, 1.9 Hz, 1 H), 3.20 (dd, *J* = 17.6, 13.4 Hz, 1 H), 3.94-4.05 (m, 4 H), 4.40 (d, *J* = 12.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 17.6 (q), 25.6 (q), 32.1 (t), 33.2 (t), 40.3 (d), 44.7 (d), 44.9 (d), 65.0 (t), 65.6 (t), 85.6 (s), 108.1 (s), 174.8 (s); exact mass (electrospray) *m/z* calcd for $C_{12}H_{17}INaO_4$ (M + Na) 375.0064, found 375.0057.

The less polar isomer **23.1b** had: FTIR (cast film) 2983, 2943, 2893, 1778, 1721, 1682 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.26 (d, *J* = 7.5 Hz, 3 H), 1.71 (s, 3 H), 1.78-1.81 (m, 1 H), 2.19 (dd, *J* = 15.0, 6.4 Hz, 1 H), 2.24-2.30 (m, 1 H), 2.50 (dd, *J* = 17.8, 8.8 Hz, 1 H), 2.82 (dddd, *J* = 12.7, 8.6, 6.4, 2.2 Hz, 1 H), 3.33 (dd, *J* = 17.8, 12.6 Hz, 1 H), 3.91-4.03 (m, 1 H), 4.84 (d, *J* = 4.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.7 (q), 28.2 (t), 28.7 (q), 33.9 (t), 39.5 (d), 40.5 (d), 46.3 (d), 64.2 (t), 64.7 (t), 84.6 (s), 109.1 (s), 174.8 (s); exact mass (electrospray) *m*/*z* calcd for $C_{12}H_{17}INaO_4$ (M + Na) 375.0064, found 375.0054.

(3a*R*,6*S*,7*S*,7a*S*)-*rel*-7-Hydroxy-6,7a-dimethylhexahydro-2*H*-spiro[1-benzofuran-5,2'-[1,3]dioxolan]-2-one (26.2a) and 3a*R*,6*R*,7*S*,7a*S*)-*rel*-7-Hydroxy-6,7a-dimethyl-hexahydro-2*H*-spiro[1-benzofuran-5,2'-[1,3]dioxo-lan]-2-one (26.2b).



26.1 **26.2a** **26.2b**

Water (50 mL), AcOH (41.5 mL) and Zn powder (60.1 g, 921.2 mmol) were added to a stirred solution of **26.1** (1.75 g, 4.60 mmol) in THF (100 mL). The mixture was stirred and heated at 50 °C in a flask fitted with a reflux

condenser. Heating was continued for 6 h and the mixture was cooled and filtered through a pad of Celite, using EtOAc as a rinse. The filtrate was washed with saturated aqueous $NaHCO_3$, water and brine. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 60% EtOAc-hexane, gave **26.2b** (more polar) (423 mg, 38%) and **26.1a** (less polar) (356 mg, 32%) as solids. The more polar isomer (**26.2b**) had: FTIR (cast film) 3466, 2980, 2941, 2893, 1765, 1458, 1437 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.05 (d, *J* = 6.6 Hz, 3 H), 1.51 (s, 3 H), 1.75-1.80 (m, 1 H), 1.89-1.95 (m, 2 H), 2.12 (d, *J* = 4.0 Hz, 1 H), 2.50 (dd, *J* = 17.2, 8.7 Hz, 1 H), 2.56-2.62 (m, 1 H), 3.09 (t, *J* = 8.6 Hz, 1 H), 3.78 (dd, *J* = 11.4, 4.0 Hz, 1 H), 3.97-4.05 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 9.2 (q), 18.0 (q), 32.2 (t), 34.2 (t), 40.6 (d), 42.4 (d), 65.0 (t), 65.5 (t), 75.5 (d), 88.2 (s), 110.1 (s), 176.0 (s); exact mass (electrospray) *m/z* calcd for $C_{12}H_{18}NaO_5$ (M + Na) 265.1046, found 265.1043.

The less polar isomer (**26.2a**) had: FTIR (cast film) 3465, 2976, 2938, 2888, 1776, 1458, 1430 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.09 (d, *J* = 6.5 Hz, 3 H), 1.26-1.34 (m, 1 H), 1.57 (s, 3 H), 1.67 (d, *J* = 11.7 Hz, 1 H), 1.93 (ddd, *J* = 12.6, 9.7, 6.7 Hz, 2 H), 2.25 (d, *J* = 17.3 Hz, 1 H), 2.45 (dt, *J* = 11.9, 6.6 Hz, 1 H), 3.00 (dd, *J* = 17.3, 6.7 Hz, 1 H), 3.45 (t, *J* = 11.5 Hz, 1 H), 3.94-4.03 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 9.5 (q), 23.1 (q), 37.4 (t), 37.6 (t), 37.7 (d), 42.4 (d), 65.1 (t), 65.5 (t), 77.5 (d), 86.0 (s), 108.4 (s), 175.2 (s); exact mass (electrospray) *m/z* calcd for $C_{12}H_{18}NaO_5$ (M + Na) 265.1046, found 265.1042.

(3a*R*,6*R*,7a*S*)-*rel*-6,7a-Dimethylhexahydro-2*H*-spiro[1-benzofuran-5,2'-[1,3]dioxolan]-2,7-dione (27.1b).

26.2b **27.1b**

DMSO (0.11 mL, 1.54 mmol) was added to a stirred and cooled (-78 °C) solution of $(COCl)_2$ (0.11 mL, 1.25 mmol) in CH_2Cl_2 (2 mL). The mixture was stirred for 30 min and then a solution of **26.2b** (69 mg, 0.28 mmol) in CH_2Cl_2 (2 mL) was added dropwise over ca 2 min. Stirring at -78 °C was continued for 45 min and then Et_3N (0.32 mL, 2.26 mmol) was added dropwise. The cold bath was left in place but not recharged and stirring was continued for 4 h, during which time the mixture attained room temperature. The mixture was quenched with saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The combined organic extracts were washed with water and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (0.8 x 15 cm), using 60% EtOAc-hexane, gave **27.1b** (64 mg, 93%) as an oil: FTIR (cast film) 2986, 2943, 2894, 1787, 1729, 1453 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.13 (d, *J* = 6.6 Hz, 3 H), 1.51 (s, 3 H), 1.76 (dd, *J* = 14.1, 11.3 Hz, 1 H), 2.18 (dd, *J* = 14.1, 7.0 Hz, 1 H), 2.40 (dd, *J* = 17.4, 0.9 Hz, 1 H), 2.57-2.62 (m, 1 H), 2.97 (dd, *J* = 17.4, 7.1 Hz, 1

H), 3.17 (q, *J* = 6.6 Hz, 1 H), 3.93-4.07 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 6.7 (q), 20.2 (q), 36.0 (t), 38.2 (t), 38.4 (d), 50.4 (d), 65.7 (t), 65.8 (t), 84.5 (s), 109.2 (s), 175.2 (s), 202.1 (s); exact mass (electrospray) *m/z* calcd for $C_{12}H_{16}NaO_5$ (M + Na) 263.089, found 263.0885.

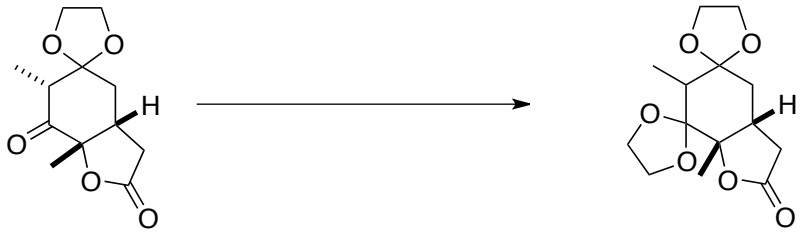
(3a*R*,6*S*,7a*S*)-*rel*-6,7a-Dimethylhexahydro-2*H*-spiro[1-benzofuran-5,2'-[1,3]dioxolan]-2,7-dione (27.1a).

26.2a **27.1a**

DMSO (52.8 μL, 0.74 mmol) was added to a stirred and cooled (-78 °C) solution of $(COCl)_2$ (57 μL, 0.65 mmol) in CH_2Cl_2 (1 mL). The mixture was stirred for 30 min and then a solution of **26.2a** (36 mg, 0.15 mmol) in CH_2Cl_2 (1 mL) was added dropwise over ca 1 min. Stirring at -78 °C was continued for 45 min and then Et_3N (0.16 mL, 1.17 mmol) was added dropwise. The cold bath was left in place but not recharged and stirring was continued for 4 h, during which time the mixture attained room temperature. The mixture was quenched with saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The combined organic extracts were washed with water and brine, dried ($MgSO_4$) and evaporated. Flash

chromatography of the residue over silica gel (0.8 x 15 cm), using 60% EtOAc-hexane, gave **27.1a** (32 mg, 89%) as an oil: FTIR (cast film) 2987, 2941, 2897, 1784, 1731, 1455 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.12 (d, *J* = 6.5 Hz, 3 H), 1.69 (s, 3 H), 2.12 (dd, *J* = 15.0, 2.2 Hz, 1 H), 2.21 (dd, *J* = 14.9, 6.0 Hz, 1 H), 2.47 (dd, *J* = 17.2, 8.0 Hz, 1 H), 2.77 (dddd, *J* = 12.6, 8.1, 5.9, 2.2 Hz, 1 H), 2.93 (dd, *J* = 17.2, 12.7 Hz, 1 H), 3.10 (q, *J* = 6.5 Hz, 1 H), 3.98-4.08 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 6.5 (q), 22.4 (q), 32.8 (t), 32.9 (t), 41.5 (d), 51.2 (d), 65.3 (t), 66.1 (t), 87.3 (s), 111.5 (s), 174.3 (s), 204.1 (s); exact mass (electrospray) *m/z* calcd for $C_{12}H_{16}NaO_5$ (M + Na) 263.089, found 263.0885.

(3'a*R*,7'a*S*)-*rel*-6',7'a-Dimethylhexahydrodispiro[1,3-dioxolan-2,5'-[1]benzofuran-7',2''-[1,3]dioxolan]-2'-one (27.2).



27.1a **27.2**

$HC(OMe)_3$ (0.27 mL, 2.5 mmol), ethylene glycol (0.14 mL, 2.5 mmol) and $TsOH.H_2O$ (2 mg) were added to a stirred solution of **27.1a** (20 mg, 0.08 mmol) in CH_2Cl_2 (1 mL). Stirring was continued for 2 h, at which point analysis of a sample by LC-MS showed only a weak signal for **27.2**. The mixture was refluxed

overnight, cooled, quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic extracts were washed with water and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (0.6 x 7 cm), using 50% Et_2O-hexane, gave **27.2** (5 mg, 22%) as an oil, which was a single isomer (^1H and ^{13}C NMR). We did not establish the stereochemistry of the C-6 methyl group: FTIR (cast film) 2985, 2949, 2895, 1776 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.98 (d, *J* = 6.7 Hz, 3 H), 1.56 (s, 3 H), 1.82 (dd, *J* = 14.8, 6.3 Hz, 1 H), 2.05 (dd, *J* = 14.9, 2.8 Hz, 1 H), 2.26 (q, *J* = 6.7 Hz, 1 H), 2.38 (dd, *J* = 17.1, 9.4 Hz, 1 H), 2.57 (dddd, *J* = 12.5, 9.4, 6.4, 3.0 Hz, 1 H), 3.25-3.15 (m, 1 H), 3.84-4.20 (m, 8 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 5.8 (q), 21.3 (q), 32.3 (t), 33.4 (t), 41.5 (d), 44.1 (d), 64.1 (t), 65.6 (t), 66.0 (t), 68.0 (t), 87.6 (s), 109.7 (s), 111.3 (s), 176.5 (s); exact mass (electrospray) *m/z* calcd for $C_{14}H_{20}NaO_6$ (M + Na) 307.1152, found 307.1146.

(3a*R*,6*S*,7*S*,7a*S*)-*rel*-7-[(*tert*-Butyldimethylsilyl)oxy]-6,7a-dimethyl-hexahydro-2*H*-spiro[1-benzofuran-5,2'-[1,3]dioxolan]-2-one (28.1a)

26.2a **28.1a**

t-$BuMe_2SiCl$ (1.52 g, 10.08 mmol), imidazole (1.03 g, 15.12 mmol) and DMAP (15 mg, 0.13 mmol) were added in that order to a stirred solution of **26.2a** (305 mg, 1.26 mmol) in DMF (5 mL). The mixture was heated at 50 °C for 16 h (N_2 atmosphere), at which point not all **26.2a** had reacted (TLC, silica, 80% Et_2O-hexane). *t*-$BuMe_2SiCl$ (569 mg, 3.78 mmol) and imidazole (428 mg, 6.3 mmol) were added and stirring at 70 °C was continued for 1 h, by which time reaction was complete (TLC). The mixture was cooled and diluted with Et_2O. The organic phase was washed with saturated aqueous NH_4Cl, water and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 60% Et_2O-hexane, gave **28.1a** (403 mg, 90%) as a solid: FTIR (cast film) 2936, 2954, 2887, 2857, 1772, 1473, 1463 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.07 (s, 3 H), 0.16 (s, 3 H), 0.91-0.94 (m, 12 H), 1.43 (s, 1 H), 1.71 (dd, *J* = 14.7, 6.3 Hz, 1 H), 1.80-1.89 (m, 2 H), 2.41 (dd, *J* = 17.2, 8.7 Hz, 1 H), 2.51 (dddd, *J* = 12.8, 8.6, 6.3, 2.2 Hz, 1 H), 3.05 (dd, *J* = 17.2, 12.8 Hz, 1 H), 3.68 (d, *J* = 11.4 Hz, 1 H), 3.90-4.00 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ -4.7 (q), -4.1 (q), 9.9 (q), 18.3 (q), 18.5 (s), 26.1 (q), 32.1 (t), 34.1 (t), 41.0 (d), 43.9 (d), 64.8 (t), 65.5 (t), 76.5 (d), 88.3 (s), 110.3 (s), 176.0 (s); exact mass (electrospray) *m*/*z* calcd for $C_{18}H_{32}NaO_5Si$ (M + Na) 379.1911, found 379.1903.

(3a*R*,6*R*,7*S*,7a*S*)-*rel*-7-[(*tert*-Butyldimethylsilyl)oxy]-6,7a-dimethyl-hexahydro-2*H*-spiro[1-benzofuran-5,2'-[1,3]dioxolan]-2-one (28.1b).

26.2b **28.1b**

t-$BuMe_2SiCl$ (2.95 g, 19.58 mmol), imidazole (1.33 g, 19.58 mmol) and DMAP (20 mg, 0.16 mmol) were added in that order to a stirred solution of **26.2b** (316 mg, 1.31 mmol) in DMF (2 mL). The mixture was heated at 70 °C for 48 h (N_2 atmosphere), cooled and diluted with Et_2O. The organic phase was washed with saturated aqueous NH_4Cl, water and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 60% Et_2O-hexane, gave **28.1b** (429 mg, 92%) as a solid: FTIR (cast film) 2956, 2933, 2886, 2858, 1777 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.10 (s, 6 H), 0.90 (s, 9 H), 0.98 (d, *J* = 7.3 Hz, 3 H), 1.48 (s, 3 H), 1.67 (dd, *J* = 13.4, 10.9 Hz, 1 H), 2.00 (dd, *J* = 13.4, 7.2 Hz, 1 H), 2.21-2.16 (m, 1 H), 2.29 (dd, *J* = 17.3, 5.5 Hz, 1 H), 2.39-2.34 (m, 1 H), 2.82 (dd, *J* = 17.3, 8.7 Hz, 1 H), 3.62 (d, *J* = 5.2 Hz, 1 H), 3.96-3.91 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ -4.3 (q), -4.1 (q), 12.0 (q), 18.2 (s), 24.8 (q), 26.0 (q), 37.2 (t), 37.4 (d), 38.1 (t), 44.5 (d), 64.4 (t), 65.6 (t), 79.4 (d), 86.1 (s), 109.0 (s), 176.4 (s); exact mass (electrospray) *m/z* calcd for $C_{18}H_{32}NaO_5Si$ (M + Na) 379.1911, found 379.1914.

(3*R*,3a*R*,6*S*,7*S*,7a*S*)-*rel*-3-Azido-7-[(*tert*-Butyldimethylsilyl)oxy]-6,7a-dimethylhexa-hydro-2*H*-spiro[1-benzofuran-5,2'-[1,3]dioxolan]-2-one (28.2).

28.1a **28.2**

BuLi (2.5 M in hexane, 0.61 mL, 1.53 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of *i*-Pr_2NH (0.25 mL, 1.79 mmol) in THF (4 mL). Stirring was continued for 30 min and the resulting solution was taken up into a syringe and added dropwise over ca 5 min to a stirred and cooled (-78 °C) solution of **28.1a** (455 mg, 1.28 mmol) in THF (6 mL). Stirring was continued for 1 h at -78 °C and then HMPA (0.6 mL) was added, followed by solid trisyl azide (791 mg, 2.56 mmol). Stirring was continued for 30 min at -78 °C and then neat Me_3SiCl (0.65 mL, 5.11 mmol) was injected. Stirring was continued for 4 h, the cold bath being left in place but not recharged, so that the mixture attained room temperature. The mixture was quenched with pH 7 buffer and extracted with Et_2O. The combined organic extracts were washed with water and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 15 cm), using 30% Et_2O-hexane, gave **28.2** (398 mg, 79%) as a solid: FTIR (cast film) 2956, 2931, 2888, 2858, 2113, 1785, 1473, 1463 cm^{-1}; ^1H NMR

($CDCl_3$, 500 MHz) δ 0.06 (s, 3 H), 0.14 (s, 3 H), 0.89-0.94 (m, 12 H), 1.45 (s, 3 H), 1.72 (dd, *J* = 15.0, 6.0 Hz, 1 H), 1.80-1.86 (m, 1 H), 2.00 (d, *J* = 14.8 Hz, 1 H), 2.28 (dd, *J* = 12.3, 5.6 Hz, 1 H), 3.57 (d, *J* = 11.3 Hz, 1 H), 3.91-4.04 (m, 4 H), 4.77 (d, *J* = 12.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ -4.6 (q), -4.1 (q), 9.8 (q), 18.3 (q), 18.5 (s), 26.1 (q), 30.6 (t), 44.0 (d), 47.4 (d), 60.8 (d), 65.0 (t), 65.5 (t), 77.1 (d), 86.2 (s), 109.9 (s), 172.3 (s); exact mass (electrospray) *m/z* calcd for $C_{18}H_{31}N_3NaO_5Si$ (M + Na) 420.1925, found 420.1923. Recrystallization of a sample from Et_2O-hexane by diffusion of hexane into an ether solution gave crystals suitable for X-ray analysis.

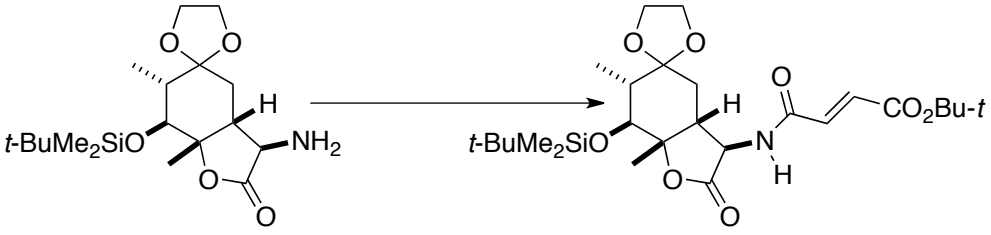
(3*R*,3a*R*,6*S*,7*S*,7a*S*)-*rel*-3-Amino-7-[(*tert*-Butyldimethylsilyl)oxy]-6,7a-dimethylhexa-hydro-2*H*-spiro[1-benzofuran-5,2'-[1,3]dioxolan]-2-one (29.1).

28.2 **29.1**

Pearlman's reagent [$Pd(OH)_2$, 4 mg] was added to a solution of **28.2** (40 mg, 0.10 mmol) in THF (1 mL) and the mixture was stirred under an atmosphere of H_2 (balloon). Stirring was continued for 1.5 h, by which time all **28.2** had reacted (TLC, silica, 50% EtOAc-hexane). The mixture was filtered through a

pad of Celite, using EtOAc as a rinse. Evaporation of the filtrate gave **29.1**, which was kept under oil pump vacuum and used directly in the next step.

***tert*-Butyl (2*E*)-3-{[(3*R*,3a*R*,6*S*,7*S*,7a*S*)-*rel*-7-[(*tert*-butyldimethylsilyl)-oxy]-6,7a-dimethyl-2-oxohexahydro-2*H*-spiro[1-benzofuran-5,2'-[1,3]dioxo-lane]-3-yl]carbamoyl}prop-2-enoate (29.3).**

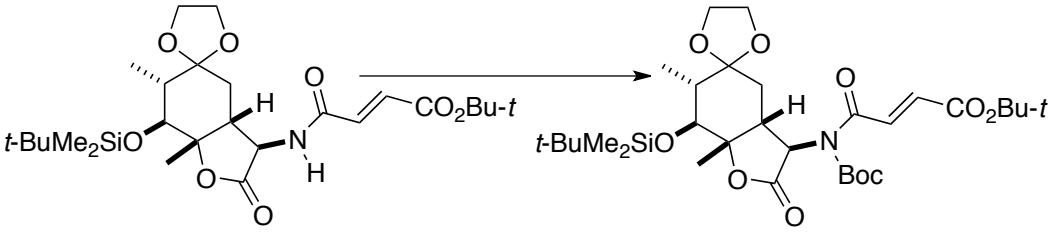


29.1 **29.3**

DCC (101.3 mg, 0.45 mmol) and DMAP (19.9 mg, 0.16 mmol) were added to a stirred and cooled solution of crude **29.1** (from 0.16 mmol azide **28.2**) and acid **29.2**[22] (56.3 mg, 0.33 mmol) in CH_2Cl_2 (2 mL). After 5 min the ice bath was removed and stirring was continued for 3 h, by which time all the amine had reacted (TLC, silica, 50% Et_2O-hexane). The mixture was diluted with Et_2O and washed with saturated aqueous $NaHCO_3$, water and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (0.8 x 15 cm), using 30% Et_2O-hexane, gave **29.3** (52 mg, 61%) as a solid: FTIR (cast film) 3368, 2979, 2956, 2932, 2888, 2858, 1763, 1719, 1684, 1528, 1473, 1462 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.07 (s, 3 H), 0.14 (s, 3 H), 0.92-0.97 (m, 12 H), 1.47-

1.51 (m, 12 H), 1.61-1.65 (m, 1 H), 1.84 (dd, *J* = 11.3, 6.6 Hz, 1 H), 2.15 (d, *J* = 14.9 Hz, 1 H), 2.40 (dd, *J* = 12.3, 6.3 Hz, 1 H), 3.71 (d, *J* = 11.3 Hz, 1 H), 3.85 (q, *J* = 7.2 Hz, 1 H), 3.98-4.2 (m, 1 H), 4.06-4.10 (m, 1 H), 4.16-4.20 (m, 1 H), 5.43 (dd, *J* = 12.4, 7.9 Hz, 1 H), 6.05-6.11 (m, 1 H), 6.78 (q, *J* = 16.6 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ -4.6 (q), -4.1 (q), 9.7 (q), 18.5 (s), 18.7 (q), 26.1 (q), 28.0 (q), 30.1 (t), 43.9 (d), 48.8 (d), 53.0 (d), 65.0 (t), 65.2 (t), 77.3 (d), 81.8 (s), 86.6 (s), 109.5 (s), 133.4 (d), 134.2 (d), 164.3 (s), 164.3 (s), 174.0 (s); exact mass (electrospray) *m*/*z* calcd for $C_{26}H_{43}NNaO_8Si$ (M + Na) 548.3, found 548.3.

***tert*-Butyl (2*E*)-4-{[(3*R*,3a*R*,6*S*,7*S*,7a*S*)-*rel*-7-[(*tert*-butyldimethylsilyl)oxy]-6,7a-dimethyl-2-oxohexahydro-2*H*-spiro[1-benzofuran-5,2'-[1,3]dioxolane]-3-yl][(*tert*-butoxy)carbonyl]amino}-4-oxobut-2-enoate (30.2).**



29.3 **30.2**

Pyridine (33.8 μL, 0.42 mmol), DMAP (ca 1 mg) and Boc_2O (96.2 μL, 0.42 mmol) were added in that order to a stirred and cooled (0 °C) solution of **29.3** (22 mg, 0.042 mmol) in MeCN (1 mL). After the addition the cold bath was removed and stirring was continued overnight. The mixture was quenched with

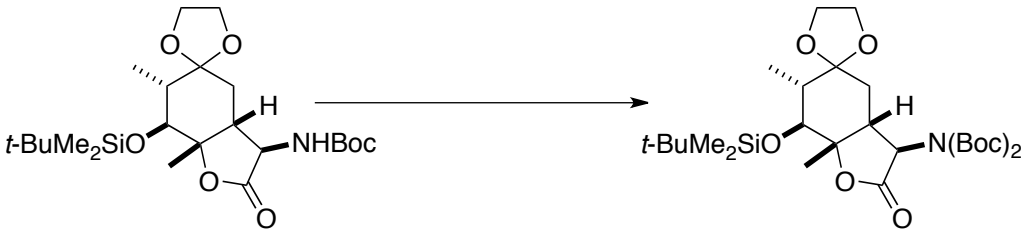
saturated aqueous $CuSO_4$ and extracted with CH_2Cl_2. The combined organic extracts were washed with water and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (0.6 x 7 cm), using 20% Et_2O-hexane, gave **30.2** (22 mg, 86%) as a solid: FTIR (cast film) 2980, 2936, 2888, 2858, 1784, 1742, 1720, 1687, 1473, 1461 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.08 (s, 3 H), 0.16 (s, 3 H), 0.90-0.95 (m, 12 H), 1.49-1.55 (m, 22 H), 1.80-1.84 (m, 2 H), 2.84-2.95 (m, 1 H), 3.69 (d, *J* = 11.4 Hz, 1 H), 3.83 (q, *J* = 7.2 Hz, 1 H), 3.94-4.10 (m, 3 H), 5.95-6.03 (m, 1 H), 6.59-6.64 (m, 1 H), 7.50-7.56 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ -4.6 (q), -4.0 (q), 9.7 (q), 18.5 (s), 18.8 (q), 26.1 (q), 27.9 (q), 28.0 (q), 30.1 (t), 43.8 (d), 65.0 (t), 65.2 (t), 77.5 (d), 81.7 (s), 85.8 (s), 86.3 (s), 109.4 (s), 132.2 (d), 136.1 (d), 164.4 (d); exact mass (electrospray) *m*/*z* calcd for $C_{31}H_{51}NNaO_{10}Si$ (M + Na) 648.3174, found 648.3178.

***tert*-Butyl *N*-[(3*R*,3a*R*,6*S*,7*S*,7a*S*)-*rel*-7-[(*tert*-butyldimethylsilyl)oxy]-6,7a-dimethyl-2-oxohexahydro-2*H*-spiro[1-benzofuran-5,2'-[1,3]dioxolan]-3-yl]carbamate (31.1).**

29.1 **31.1**

Boc_2O (58.8 mg, 0.27 mmol) and solid $NaHCO_3$ (18.1 mg, 0.21 mmol) were added to a stirred and cooled (0 °C) solution of **29.1** [from azide **28.2** (43 mg, 0.108 mmol)] in a mixture of MeCN (1.2 mL) and water (0.4 mL). The cooling bath was left in place but not recharged and stirring was continued for 3 h, by which time the mixture had reached room temperature. The mixture was quenched with saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The combined organic extracts were washed with water and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (0.8 x 15 cm), using 20% EtOAc-hexane, gave **31.1** (43.6 mg, 86% over two steps) as a solid: FTIR (cast film) 3352, 2979, 2954, 2931, 2888, 2858, 1783, 1718, 1520, 1473, 1462 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.05 (s, 3 H), 0.13 (s, 3 H), 0.92-0.94 (m, 12 H), 1.45 (s, 12 H), 1.57-1.65 (m, 1 H), 1.83 (dq, *J* = 11.4, 6.5 Hz, 1 H), 2.10 (d, *J* = 14.4 Hz, 1 H), 2.33-2.38 (m, 1 H), 3.67 (d, *J* = 10.7 Hz, 1 H), 3.85 (q, *J* = 7.1 Hz, 1 H), 3.97-4.12 (m, 3 H), 4.80 (d, *J* = 8.0 Hz, 1 H), 4.99 (t, *J* = 8.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ -4.6 (q), -4.1 (q), 9.7 (q), 18.5 (s), 18.7 (q), 26.1 (q), 28.2 (q), 30.0 (t), 43.9 (d), 48.3 (d), 53.8 (d), 64.9 (t), 65.1 (t), 80.2 (s), 77.3 (d), 85.8 (d), 109.6 (s), 155.4 (s), 174.3 (s); exact mass (electrospray) *m*/*z* calcd for $C_{23}H_{41}NNaO_7Si$ (M + Na) 494.2545, found 494.2543.

***tert*-Butyl *N*-[(3*R*,3a*R*,6*S*,7*S*,7a*S*)-*rel*-7-[(*tert*-butyldimethylsilyl)oxy]-6,7a-dimethyl-2-oxohexahydro-2*H*-spiro[1-benzofuran-5,2'-[1,3]dioxolan]-3-yl]-*N*-[(*tert*-butoxy)carbonyl]carbamate (31.4).**



31.1 **31.4**

DMAP (1 mg), pyridine (8.5 μL, 0.11 mmol) and Boc_2O (23.1 mg, 0.11 mmol) were added to a stirred and cooled (0 °C) solution of **31.1** (10 mg, 0.02 mmol) in MeCN (0.5 mL). After 5 min, the ice bath was removed and stirring was continued for 1 h. The mixture was quenched with saturated aqueous $CuSO_4$ and extracted with CH_2Cl_2. The combined organic extracts were washed with water and brine, dried ($MgSO_4$) and evaporated. The residue, in a little CH_2Cl_2, was applied directly to the top of a flash chromatography silica gel column made up in a Pasteur pipette (0.6 x 7 cm) with CH_2Cl_2. Development of the column with 20% Et_2O-hexane gave **31.4** (10.5 mg, 86%) as a solid: FTIR (cast film) 2980, 2937, 2888, 2858, 1787, 1759, 1740, 1705, 1473, 1461 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.06 (s, 3 H), 0.16 (s, 3 H), 0.91-0.94 (m, 12 H), 1.48-1.55 (m, 21 H), 1.61 (dd, *J* = 14.9, 6.8 Hz, 1 H), 1.79-1.90 (m, 2 H), 2.92-2.96 (m, 1 H), 3.67 (d, *J* = 11.4 Hz, 1 H), 3.81-3.86 (m, 1 H), 3.93-4.00 (m, 1 H), 4.04-4.08 (m, 1 H), 5.64 (d, *J* = 12.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ -4.7 (q), -4.0 (q), 9.7 (q), 18.5 (s), 18.7 (q), 26.2 (q), 28.0 (q), 30.2 (t), 43.8 (d), 44.2 (d), 58.3 (t), 64.9 (t), 65.1 (t), 77.4 (d), 83.7 (s), 85.5 (s), 109.6 (s), 172.3 (s); exact mass (electrospray) *m/z* calcd for $C_{28}H_{49}NNaO_9Si$ (M + Na) 594.3069, found 594.3091.

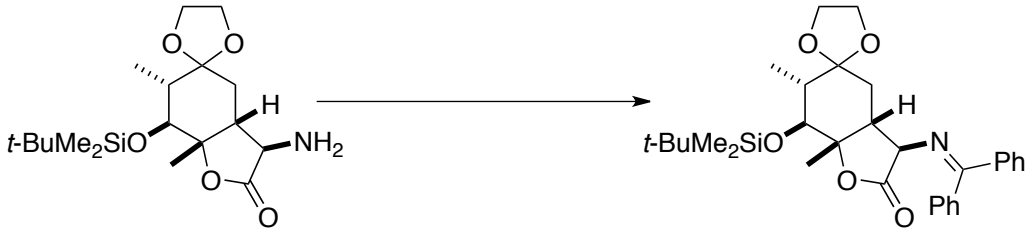
(3*R*,3a*R*,6*S*,7*S*,7a*S*)-*rel*-3-{Bis[(4-methoxyphenyl)methyl]amino}-7-[(*tert*-butyldimethylsilyl)oxy]-6,7a-dimethylhexahydro-2*H*-spiro[1-benzofuran-5,2'-[1,3]dioxolan]-2-one (32.1).

29.1 **32.1**

K_2CO_3 (35.5 mg, 0.26 mmol) and PmbBr (18.5 μL, 0.13 mmol) were added to a stirred solution of **29.1** [from azide **28.2** (17 mg, 0.048 mmol)] in MeCN (0.5 mL), and stirring was continued overnight. The mixture was quenched with water and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. The residue, in a little CH_2Cl_2, was applied directly to the top of a flash chromatography silica gel column made up in a Pasteur pipette (0.6 x 7 cm) with CH_2Cl_2. Development of the column with 20% EtOAc-hexane gave **32.1** (17.7 mg, 68%) as a solid: FTIR (cast film) 2953, 2933, 2901, 2856, 1763, 1612, 1586, 1512, 1463, 1442 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.08 (s, 3 H), 0.19 (s, 3 H), 0.83 (d, *J* = 6.6 Hz, 3 H), 0.93 (s, 9 H), 1.40 (s, 3 H), 1.56 (dd, *J* = 14.5, 6.9 Hz, 1 H), 1.74 (dq, *J* = 11.8, 6.1 Hz, 1 H), 1.88 (dd, *J* = 14.5, 1.1 Hz, 1 H), 2.34-2.37 (m, 1 H), 2.86 (q, *J* = 7.3 Hz, 1 H), 3.40 (dt, *J* = 7.9, 5.8 Hz, 1 H), 3.47 (d, *J* = 11.4 Hz, 1 H), 3.68-3.75 (m, 3

H), 3.81-3.88 (m, 9 H), 4.13 (d, *J* = 12.2 Hz, 1 H), 6.86-6.88 (m, 4 H), 7.27 (dd, *J* = 10.8, 2.2 Hz, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ -4.6 (q), -4.0 (q), 9.7 (q), 18.51 (s), 19.1 (q), 26.1 (q), 30.5 (t), 43.9 (d), 44.6 (d), 54.1 (t), 55.3 (d), 61.4 (d), 64.8 (t), 64.8 (t), 77.6 (d), 85.3 (s), 109.8 (s), 113.7 (d), 130.1 (d), 131.9 (s), 158.8 (s), 175.1 (s); exact mass (electrospray) *m/z* calcd for $C_{34}H_{49}NNaO_7Si$ (M + Na) 634.3171, found 634.3171.

(3*R*,3a*R*,6*S*,7*S*,7a*S*)-*rel*-7-[(*tert*-Butyldimethylsilyl)oxy]-3-[(diphenylmethylidene)amino]-6,7a-dimethylhexahydro-2*H*-spiro[1-benzofuran-5,2'-[1,3]dioxolan]-2-one (33.1).

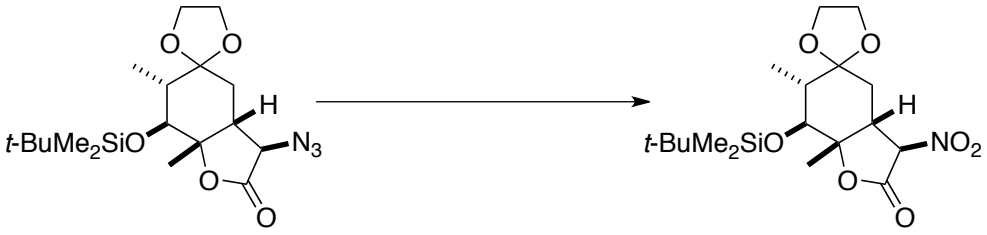


29.1 **33.1**

Benzophenone imine (12.6 μL, 0.076 mmol) was added to a solution of **29.1** [from azide **28.2** (20 mg, 0.05 mmol)] in PhMe (0.5 mL) and the mixture was heated at 100 °C for 6 h (TLC monitoring, silica, 50% EtOAc-hexane), by which time all **29.1** had reacted. The solvent was evaporated and the residue, in a little CH_2Cl_2, was applied directly to the top of a flash chromatography silica gel column made up in a Pasteur pipette (0.6 x 7 cm) with CH_2Cl_2. Development of

the column with 50% EtOAc-hexane gave **33.1** (19.9 mg, 74%) as a solid: FTIR (cast film) 2954, 2930, 2888, 2857, 1776, 1622, 1598, 1576, 1472, 1446, 1463 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ -0.00 (s, 3 H), 0.12 (s, 3 H), 0.79 (d, *J* = 6.6 Hz, 3 H), 0.89-0.92 (m, 9 H), 1.51 (s, 3 H), 1.67-1.68 (m, 2 H), 1.76 (dd, *J* = 11.4, 6.6 Hz, 1 H), 3.00 (ddd, *J* = 11.5, 4.8, 3.3 Hz, 1 H), 3.36-3.42 (m, 2 H), 3.45-3.55 (m, 1 H), 3.71 (td, *J* = 7.4, 6.3 Hz, 1 H), 3.79 (ddd, *J* = 7.5, 6.5, 5.0 Hz, 1 H), 4.79 (d, *J* = 11.5 Hz, 1 H), 7.31-7.36 (m, 2 H), 7.38-7.42 (m, 3 H), 7.45-7.48 (m, 3 H), 7.62-7.64 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ -4.8 (q), -4.1 (q), 9.7 (q), 18.5 (q), 28.2 (q), 30.9 (t), 43.9 (d), 49.6 (d), 64.8 (d), 64.8 (t), 65.3 (t), 77.2 (d), 86.2 (s), 109.8 (s), 128.1 (d), 128.2 (d), 128.6 (d), 129.1 (d), 129.2 (d), 130.5 (d), 135.9 (s), 139.5 (s), 173.7 (s), 174.0 (s); exact mass (electrospray) *m*/*z* calcd for $C_{31}H_{41}NNaO_5Si$ (M + Na) 558.2646, found 558.2643.

(3*R*,3a*R*,6*S*,7*S*,7a*S*)-*rel*-7-[(*tert*-butyldimethylsilyl)oxy]-6,7a-dimethyl-3-nitrohexahydro-2*H*-spiro[1-benzofuran-5,2'-[1,3]dioxolan]-2-one (34.1).



28.2 **34.1**

Ozonized oxygen was passed into cooled (-78 °C) CH_2Cl_2 (3.4 mL) until the solution became blue.

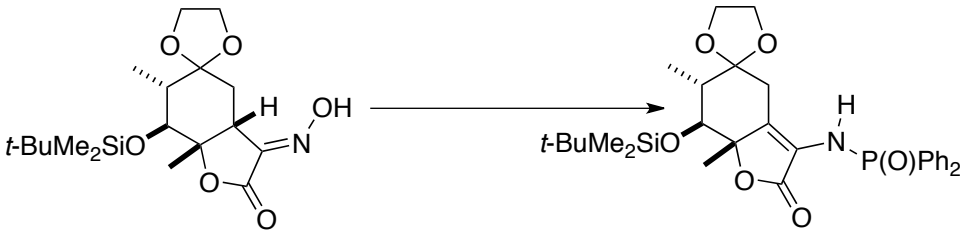
Ph_3P (9 mg, 0.03 mmol) was added to a stirred solution of **28.2** (10 mg, 0.025 mmol) and stirring was continued for 4 h. The resulting mixture was then transferred by syringe to the above stirred and cooled (-78 °C) saturated solution of O_3 in CH_2Cl_2. Stirring at -78 °C was continued for 30 min and then Ar was bubbled through the solution until the blue color was discharged. Evaporation of the solvent and flash chromatography of the residue over silica gel (0.6 x 7 cm), using 30% EtOAc-hexane, gave **34.1** (6.2 mg, 62%) as an oil: FTIR (cast film) 2982, 2956, 2931, 2889, 2858, 1794, 1564 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.07 (s, 3 H), 0.14 (s, 3 H), 0.95-0.92 (m, 12 H), 1.57 (s, 3 H), 1.88-1.77 (m, 2 H), 1.96 (dd, *J* = 15.2, 1.8 Hz, 1 H), 3.28 (ddd, *J* = 12.6, 5.9, 1.8 Hz, 1 H), 3.47 (d, *J* = 11.3 Hz, 1 H), 4.06-3.94 (m, 4 H), 6.02 (d, *J* = 12.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ -4.6 (q), -4.2 (q), 9.7 (q), 18.0 (q), 18.4 (s), 26.0 (q), 30.4 (t), 43.9 (d), 46.8 (d), 65.1 (t), 65.6 (t), 77.6 (d), 85.8 (d), 86.9 (s), 109.3 (s), 164.9 (s); exact mass (electrospray) *m/z* calcd for $C_{18}H_{31}NNaO_7Si$ (M + Na) 424.1762, found 424.1755.

(3*E*,3a*R*,6*S*,7*S*,7a*S*)-*rel*-7-[(*tert*-butyldimethylsilyl)oxy]-3-(hydroxy-imino)-6,7a-dimethylhexahydro-2*H*-spiro[1-benzofuran-5,2'-[1,3]dioxolan]-2-one (35.1).

29.1 **35.1**

$Na_2WO_4.2H_2O$ (24 mg, 0.072 mmol) and then H_2O_2 (30%, 0.5 mL, 5.8 mmol) were added to a stirred solution of **29.1** [from azide **28.2** (20 mg, 0.050 mmol)] in absolute EtOH (0.5 mL). Stirring was continued for 4 h, by which time all **29.1** had reacted (TLC monitoring, silica, 1:1 EtOAc-hexane). The mixture was quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The combined organic extracts were washed with saturated aqueous $NaHSO_3$ and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (0.6 x 7 cm), using 30% EtOAc-hexane, gave **35.1** (15 mg, 72%) as a solid: FTIR (cast film) 3298, 2955, 2931, 2887, 2858, 1777 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.09 (s, 3 H), 0.17 (s, 3 H), 0.96-0.92 (m, 12 H), 1.45 (s, 3 H), 1.97-1.87 (m, 2 H), 2.60 (dd, *J* = 14.3, 4.3 Hz, 1 H), 3.21 (dd, *J* = 6.7, 4.4 Hz, 1 H), 3.61 (d, *J* = 8.8 Hz, 1 H), 3.96-3.87 (m, 4 H), 9.17 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ -4.6 (q), -4.2 (q), 10.9 (q), 18.3 (s), 20.8 (q), 26.0 (q), 30.4 (t), 43.2 (d), 44.0 (d), 64.6 (t), 65.5 (t), 78.1 (d), 85.9 (s), 108.8 (s), 150.2 (s), 164.9 (s); exact mass (electrospray) *m/z* calcd for $C_{18}H_{31}NNaO_6Si$ (M + Na) 408.1813, found 408.1808. Recrystallization of a sample from Et_2O-hexane by diffusion of hexane into an ether solution gave crystals suitable for X-ray analysis.

(6*S*,7*S*,7a*S*)-*rel*-7-[(*tert*-butyldimethylsilyl)oxy]-3-[(diphenylphosphoryl)amino]-6,7a-dimethyl-4,6,7,7a-tetrahydro-2*H*-spiro[1-benzofuran-5,2'-[1,3]dioxolan]-2-one (36.2).



35.1 **36.2**

Et_3N (5.2 μL, 0.037 mmol) was added dropwise to a stirred and cooled (-50 °C) solution of **35.1** (12 mg, 0.0312 mmol) in CH_2Cl_2 (0.5 mL). After 5 min neat Ph_2PCl (6.7 μL, 0.037 mmol) was added dropwise. The cold bath was left in place but not recharged and stirring was continued for 4 h, by which time the mixture had reached room temperature. The mixture was quenched with water and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (0.6 x 7 cm), using 40% EtOAc-hexane, gave **36.2** (12 mg, 67%) as an oil: FTIR (cast film) 3240, 3060, 2981, 2956, 2930, 2886, 2857, 1759, 1694, 1471, 1462, 1439 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.05 (s, 3 H), 0.17 (s, 3 H), 0.92-0.88 (m, 12 H), 1.23 (s, 3 H), 1.75 (d, *J* = 14.3 Hz, 1 H), 1.81 (dd, *J* = 10.8, 6.6 Hz, 1 H), 3.34 (d, *J* = 10.8 Hz, 1 H), 3.51 (d, *J* = 14.3 Hz, 1 H), 3.86-3.80 (m, 2 H), 3.98-3.89 (m, 2 H), 5.37 (d, *J* = 10.4 Hz, 1 H), 7.51-7.45 (m, 4 H), 7.58-7.53

(m, 2 H), 7.81-7.76 (m, 2 H), 7.90-7.85 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ -4.6 (q), -3.9 (q), 9.9 (q), 17.8 (q), 18.4 (s), 26.1 (q), 34.4 (t), 44.1 (d), 65.3 (t), 65.3 (t), 78.4 (d), 88.1 (s), 109.3 (s), 122.9 (s), 128.9 (s), 128.9 (s), 128.9 (s), 129.0 (s), 130.1 (s), 131.0 (s), 131.2 (s), 131.5 (d), 131.6 (d), 132.1 (d), 132.2 (d), 132.6 (d), 132.7 (d), 137.6 (s), 169.9 (s), 170.0 (s); exact mass (electrospray) *m/z* calcd for $C_{30}H_{40}NNaO_6PSi$ (M + Na) 592.2255, found 592.2255.

[(3*E*,3a*R*,6*S*,7*S*,7a*S*)-7-[(*tert*-butyldimethylsilyl)oxy]-6,7a-dimethyl-2-oxohexahydro-2*H*-spiro[1-benzofuran-5,2'-[1,3]dioxolan]-3-ylidene]amino acetate (37.1).

35.1 **37.1**

DMAP (1 mg), pyridine (10 μL, 0.0124 mmol) and AcCl (14.8 μL, 0.207 mmol) were added in that order to a stirred and cooled (0 °C) solution of **35.1** (16 mg, 0.0415 mmol) in CH_2Cl_2 (1 mL), and stirring was continued for 20 min. The cold bath was removed and stirring was continued for 1. 5 h. The mixture was quenched with saturated aqueous $CuSO_4$ and extracted with CH_2Cl_2 and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash

chromatography of the residue over silica gel (0.6 x 7 cm), using 30% EtOAc-hexane, gave **37.1** (16 mg, 90%) as oil: FTIR (cast film) 2955, 2933, 2887, 2858, 1797 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.10 (s, 3 H), 0.16 (s, 3 H), 0.96-0.88 (m, 12 H), 1.47 (s, 3 H), 1.95-1.90 (m, 1 H), 2.02 (dd, *J* = 13.8, 6.4 Hz, 1 H), 2.35 (s, 3 H), 2.54 (dd, *J* = 14.2, 2.5 Hz, 1 H), 3.26 (dd, *J* = 5.9, 2.9 Hz, 1 H), 3.61 (d, *J* = 7.6 Hz, 1 H), 3.97-3.83 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ -4.6 (q), -4.3 (q), 11.2 (q), 18.2 (s), 19.5 (q), 21.4 (q), 25.9 (q), 31.5 (t), 44.5 (d), 44.6 (d), 64.9 (t), 65.6 (t), 78.1 (d), 85.5 (s), 108.6 (s), 155.7 (s), 162.9 (s), 169.2 (s); exact mass (electrospray) *m/z* calcd for $C_{20}H_{33}NNaO_7Si$ (M + Na) 450.1918, found 450.1916.

(3*E*,3a*R*,6*S*,7*S*,7a*S*)-3-[(Benzyloxy)imino]-7-[(*tert*-butyldimethylsilyl)-oxy]-6,7a-dimethylhexahydro-2*H*-spiro[1-benzofuran-5,2'-[1,3]dioxolan]-2-one (38.1).

35.1 **38.1**

Bu_4NI (9.5 mg, 0.026 mmol), BnBr (4.6 μL, 0.039 mmol) and Ag_2O (Aldrich, 12 mg, 0.052 mmol) were added in that order to a stirred and cooled (0 °C) solution of **35.1** (10 mg, 0.026 mmol) in dry DMF (0.4 mL). Stirring was

continued for 10 min, the cold bath was removed and stirring was continued for 20 min. At this point, examination by TLC (silica, 40% EtOAc-hexane) showed that all **35.1** had reacted. The mixture was filtered through a plug of Celite in a Pasteur pipette, using Et_2O as a rinse. The ether phase was washed with saturated aqueous $Na_2S_2O_3$ and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (0.6 x 7 cm), using 10% Et_2O-hexane, gave **38.1** (9.5 mg, 78%) as a solid: FTIR (cast film) 2955, 2931, 2885, 2858, 1779, 1642, 1472, 1456 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.09 (s, 3 H), 0.16 (s, 3 H), 0.94-0.90 (m, 12 H), 1.42 (s, 3 H), 1.90-1.85 (m, 2 H), 2.40 (dd, *J* = 14.1, 4.3 Hz, 1 H), 3.16 (dd, *J* = 6.7, 4.2 Hz, 1 H), 3.62-3.55 (m, 2 H), 3.81-3.71 (m, 3 H), 5.31 (s, 1 H), 7.39-7.34 (m, 5 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ -4.6 (q), -4.2 (q), 11.2 (q), 18.3 (s), 21.5 (q), 26.0 (s), 30.6 (t), 43.2 (d), 44.2 (d), 64.5 (t), 65.3 (t), 78.0 (d), 78.7 (t), 85.1 (s), 108.8 (s), 128.6 (d), 128.6 (d), 128.7 (d), 136.2 (s), 149.6 (s), 164.6 (s); exact mass (electrospray) *m/z* calcd for $C_{25}H_{37}NNaO_6Si$ (M + Na) 498.2282, found 498.2283.

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(30) Phosphomolybdic acid (15 g) and ceric ammonium sulfate (2.5 g) dissolved in a mixture of water (985 mL) and concentrated sulfuric acid (15 mL).