UNIVERSITY OF ALBERTA

Synthesis of γ-Hydroxybutenolides Using $NaClO_2$, Total Synthesis of (+)-Benesudon and Synthetic Studies on CP-225,917

by

Minaruzzaman 

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

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To all my teachers

Abstract

The first chapter of this thesis describes the development of a methodology of preparation of γ-hydroxybutenolides from 3,4-disubstituted furans using $NaClO_2$ as an oxidizing agent. This process works well for electron-rich furans in aqueous ethanol containing NaH_2PO_4. Unsymmetrically substituted furans give a mixture of regioisomers. By applying this methodology, a natural product, microperfuranone, was also synthesized in seven steps. This method is general, it requires inexpensive reagents and an aqueous solvent system makes this reaction environmentally acceptable.

The second chapter of this thesis describes the first asymmetric total synthesis of (+)-*ent*-benesudon, the enantiomer of a compactly functionalized natural product. Benesudon is recognized for its strong antifungal and antibacterial activities as well as cytotoxic activities with IC_{90} values of 1-2 μg/mL. The synthesis has corrected the relative stereochemistry and established the absolute stereochemistry of benesudon. During this study, a methodology was developed to construct the hindered ketene acetal using $Cu(OAc)_2$ and $Pb(OAc)_4$.

The final chapter of this thesis describes the synthesis of the core structure of the natural product CP-225,917 with all required functionalities. To this end, a novel

methodology named intramolecular conjugate displacement and a Grob-like fragmentation were applied to build up the core structure. CP-225,917 is an important compound because its biological properties suggest that it inhibits enzymes involved in cholesterol biosynthesis and has anticancer properties. The current synthetic endeavor has developed a short synthetic route to the core structure.

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At first I would like to thank the University of Alberta and Department of Chemistry for giving me this opportunity to accomplish my research in a competitive scientific environment.

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Finally, many thanks to Lijuan Yuan and my family members for their encouragement, help and support.

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List of Abbreviations

Ac	acetyl
acac	acetyl acetonate
AIBN	2,2'-azobisisobutyronitrile
Ar	argon
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bu	butyl
t-Bu	*tert*-butyl
calcd	calculated
CAN	ammonium cerium(IV) nitrate
cat	catalyst
cod	cyclooctadiene
concd	concentrated
Cp	cyclopentadienyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N,N*-dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
Dess-Martin Reagent	1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxo-3(H)-one
DHP	dihydropyran
DIAD	diisopropyl azodicarboxylate
DIBAL	diisobutylaluminum hydride
DMAP	4-(dimethylamino)pyridine
DMF	*N,N*-dimethylformamide
DMP	Dess-Martin periodinane

DMSO	dimethyl sulfoxide
EDCI	*N*-(3-dimethylamino)propyl-*N*-ethylcarbodiimide
Et	ethyl
FTIR	Fourier Transform Infrared
H	hour(s)
HMPA	hexamethylphosphoric triamide
Hz	hertz
IC	inhibitory concentration
ICD	intramolecular conjugate displacement
Im	imidazole
KHMDS	potassium hexamethyldisilazide
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazide
MCPBA	*m*-chloroperoxybenzoic acid
Me	methyl
Min	minute(s)
MOM	methoxymethyl
mp	melting point
Ms	methanesulfonyl
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMO	4-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser enhancement
PCC	pyridinium chlorochromate
Pg	protecting group

Ph	phenyl
PhMe	toluene
Pin	pinacolate (pinacol, 2,3-dimethyl-2,3-butanediol)
PMB	*p*-methoxybenzyl
PMBM	*p*-methoxybenzyloxymethyl
ppm	parts per million
i-Pr	isopropyl
Pr	propyl
pyr	pyridine
rt	room temperature
SM	starting material
TASF	tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBAF	tetrabutylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TEMPO	2,2,6,6-Tetramethylpiperidin-1-oxyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Tol	*p*-toluene-
TPAP	tetra-*n*-propylammonium perruthenate
Ts	*p*-toluenesulfonyl

CHAPTER I

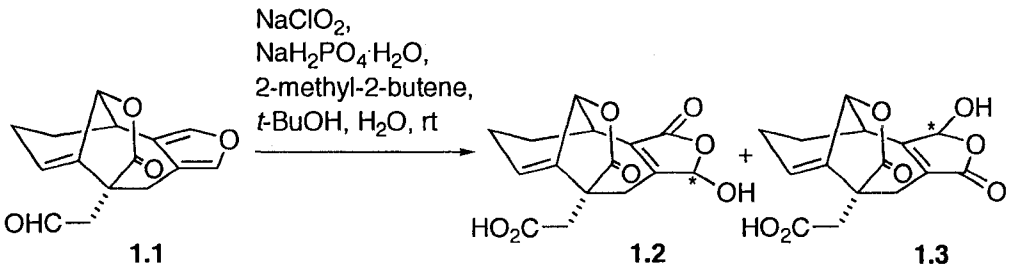
A General Oxidative Method for Conversion of Furans into γ-Hydroxybutenolides: Use of Sodium Chlorite

1. Introduction

1.1 Background

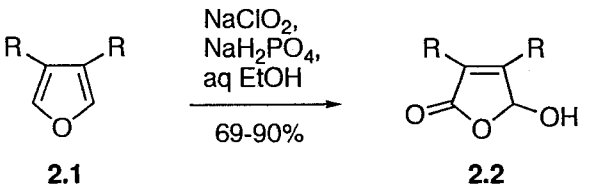
Pinnick oxidation is widely used to oxidize the aldehyde functional group into a carboxylic acid unit. During synthetic studies on CP-225,917, the furan **1.1** was treated with $NaClO_2$ under the standard Pinnick oxidation conditions.[1] The aldehyde group of **1.1** was converted into a carboxylic acid and at the same time the furan subunit was oxidized, so that a mixture of the regioisomeric γ-hydroxybutenolides **1.2** and **1.3** was obtained (Scheme 1).[2,3] The process is general and

SCHEME 1



we find that inexpensive $NaClO_2$ is a general reagent for desymmetrization and oxidation of 3,4-disubstituted furans **2.1** into γ-hydroxybutenolides **2.2** in high yield. The reaction conditions, which are summarized in Scheme 2, were also optimized in my studies.[4]

SCHEME 2



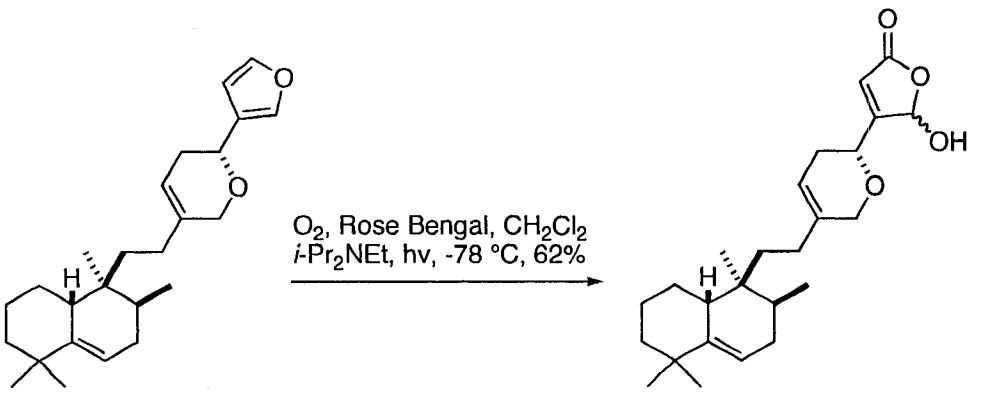
2.1 **2.2**

1.2 Other Methods to Synthesize γ-Hydroxybutenolides

The conversion of furans into γ-hydroxybutenolides is normally done by exposure to singlet oxygen ($^1O_2$), which is generated by bubbling molecular oxygen through the reaction solution containing the sensitizer rose Bengal or methylene blue at -78 °C while irradiating the mixture with visible light. The product is then treated with an organic base.[5] Cacospongionolide F (**3.2**), an anti-inflammatory agent, was synthesized from the advanced intermediate furan **3.1** by using singlet oxygen (Scheme 3) under these photochemical conditions.[6]

Other oxidizing agents such as NBS,[7a,b] MCPBA,[7c,d] chromic acid,[7e,f] and H_2O_2-V(VI)[7g,h] have occasionally been used to convert furans into γ-hydroxybutenolides, but the photochemical method is by far the most common procedure.

SCHEME 3



3.1 **3.2**

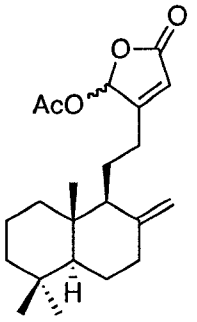
Cacospongionolide F

1.3 γ-Hydroxybutenolide Natural Products

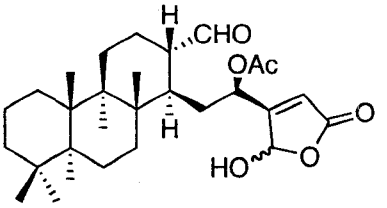
Butenolides, a class of α,β-unsaturated lactones, are substances produced by organisms such as bacteria, fungi and gorgonians.[8a] The subclass of γ-hydroxybutenolides [5-hydroxy-2(*5H*)-furanones] also appears in a number of pharmacologically active natural and unnatural products such as luffolide (**4.2**), which has anti-inflammatory activity,[8b] dysidiolide (**4.3**), which is an inhibitor of the cdc25A protein phosphatase,[8c] and its analogue **4.4**, which has antitumor properties.[8d]

The diverse biological activities of many naturally occurring γ-hydroxybutenolides have prompted numerous synthetic investigations. The γ-hydroxybutenolide moiety has been established as the important pharmacophore for many of the biologically active γ-hydroxybutenolides.[8e]

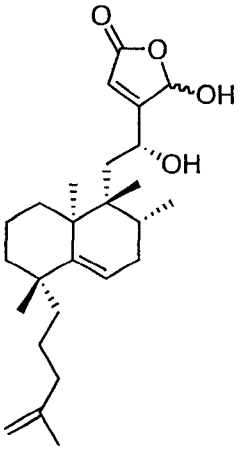
SCHEME 4



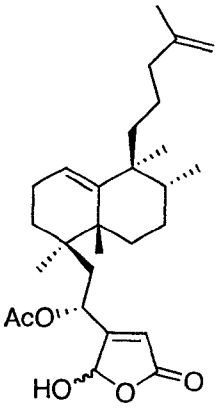
(+) Lagerstronolide
4.1



Luffolide
antiinflamatory activity
4.2



Dysidiolide
antitumoural
4.3



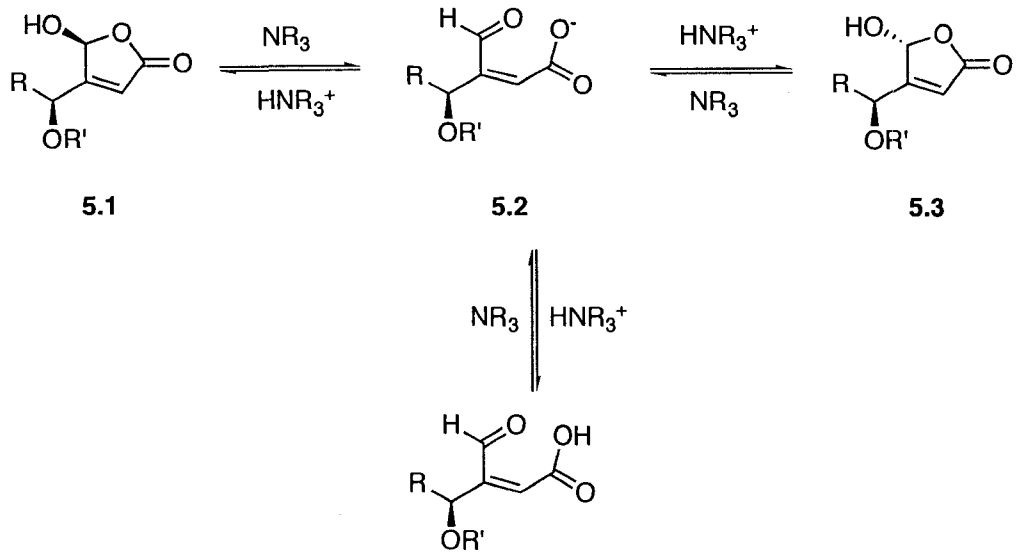
Dysidiolide analogue
antitumoural
4.4

1.4 Epimerization of γ-Hydroxybutenolides

In the literature, it has been documented that γ-hydroxybutenolides are in dynamic equilibrium with the open-chain tautomer, the corresponding 4-oxo-2(*Z*)-alkenoic acid form **5.2**,[9a] although the 4-oxo-2(*E*)-alkenoic acid form (not shown in Scheme 5) is a possibility in some cases. The equilibrium for the ring-chain tautomerism largely favors the ring tautomer. The careful mechanistic studies by

McClelland[9b] and Bowden[9c] provided an excellent starting point for the proposed amine-catalyzed epimerization of γ-hydroxybutenolides presented in Scheme 5. Qualitatively the rate of epimerization appears to be related to the basicity of the amines (pyridine < *N*-methylmorpholine < DBU).[9d]

SCHEME 5

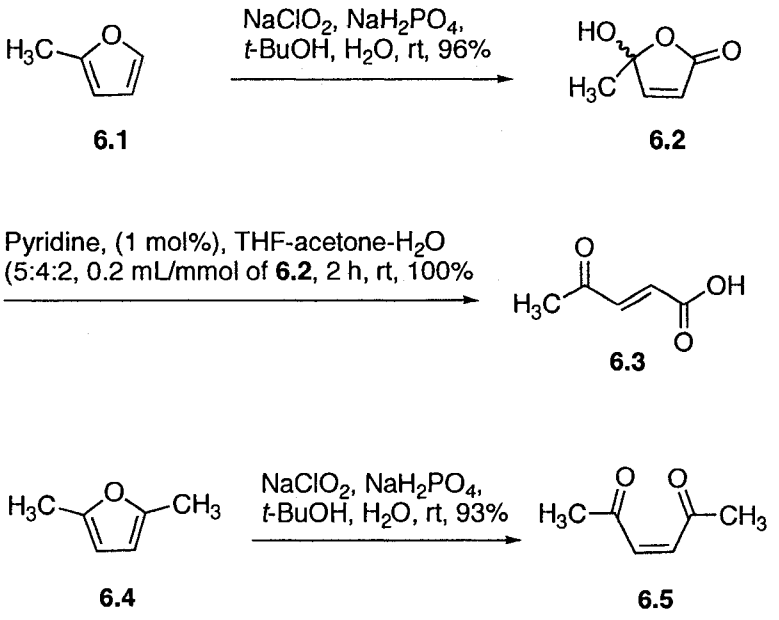


5.1 **5.2** **5.3**

5.4

After our work[2,4] was published, another paper appeared[9e] that described the synthesis of 2-alkyl-2-hydroxybutenolides (**6.2**) by reaction of 2-alkylfurans (**6.1**) with $NaClO_2$ in aqueous acidic solution. The synthesis of 2-ene-1,4-diones (**6.5**) was also presented and these were made from 2,5-dialkylfurans (**6.4**) (Scheme 6).[9e] Stereoselective conversion of the alkyl butenolides (**6,1**) into 4-oxo-2(*E*)-alkenoic acids (**6.3**) has been accomplished by treatment with a catalytic amount of pyridine.[9f]

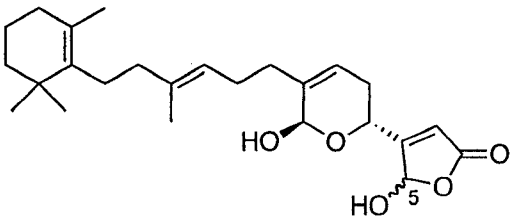
SCHEME 6



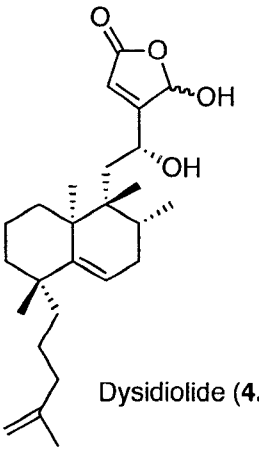
6.1 **6.2** **6.3** **6.4** **6.5**

Some natural products [e.g. manoalide (**7.1**)] have additional chiral centers and they can exist as a pair of epimers at C-5, with a clear set of doubled peaks for the ^{1}H and ^{13}C NMR spectra (indicating slow epimerization) or with broad and poorly defined peaks (indicating an intermediate rate of epimerization). In the case of dysidiolide **4.3**, selective crystallization of one epimer was possible.[9g]

SCHEME 7



Manoalide (**7.1**)



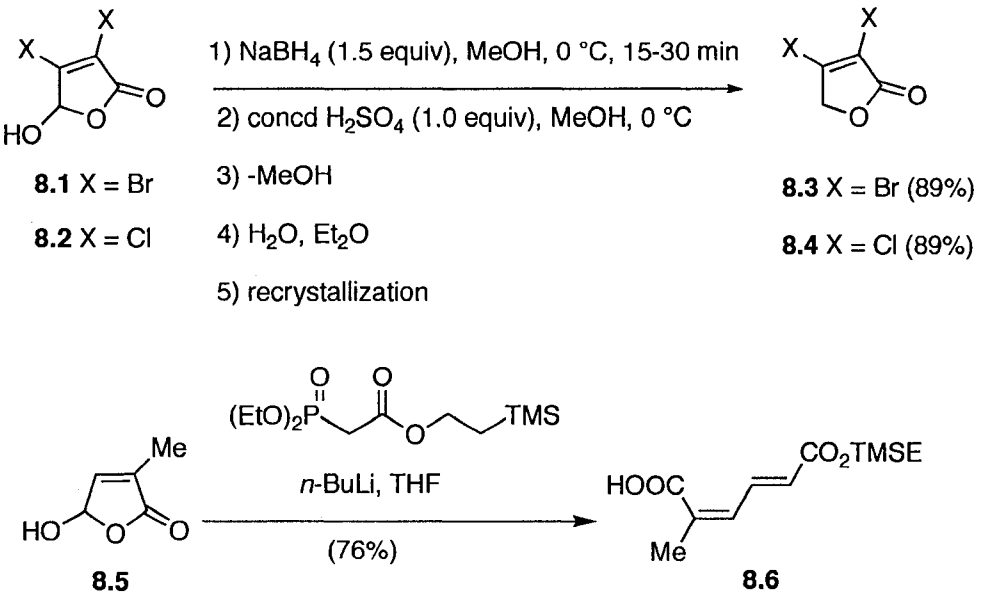
Dysidiolide (**4.3**)

1.5 Synthetic Applications

γ-Hydroxybutenolides are densely functionalized four carbon units containing several groups such as OH, α,β-unsaturated lactone and hemiacetal. These functional groups can be manipulated to build up more complex molecules or other subunits of natural or unnatural products. 3,4-Dibromo- and 3,4-dichlorofuran-2(*5H*)-ones **8.3** and **8.4** were synthesized from 3,4-dihalo substituted γ-hydroxybutenolides **8.1** and **8.2**, respectively by $NaBH_4$ reduction on a multi-gram scale.[10a]

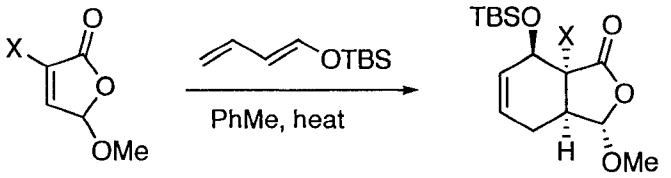
The hemiacetal subunit of hydroxy butenolide **8.5** could be used as a masked aldehyde which was utilized for Wittig olefination to form the acid **8.6** in the total synthesis of (+)-superstolide A by Roush and his group (Scheme 8).[10b]

SCHEME 8



After protecting the alcohol as a methyl ether, the resulting α,β-unsaturated lactones **9.1** and **9.2** can be used as dienophiles for Diels-Alder reactions.[10c]

SCHEME 9

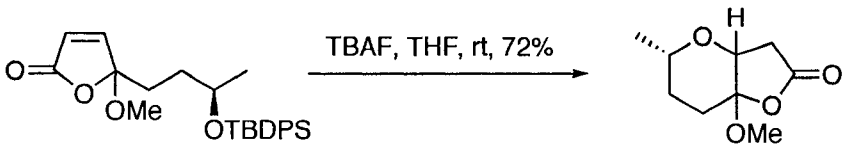


9.1 X = H
9.2 X = Br
9.3 X = H
9.4 X = Br

The -OH protected butenolides **10.1** can act as Michael acceptors. In the following example, the *t*-$BuPh_2Si$ group was

removed with Bu_4NF to gave the bicyclic lactone **10.2** through an intramolecular Michael addition.[10d]

SCHEME 10

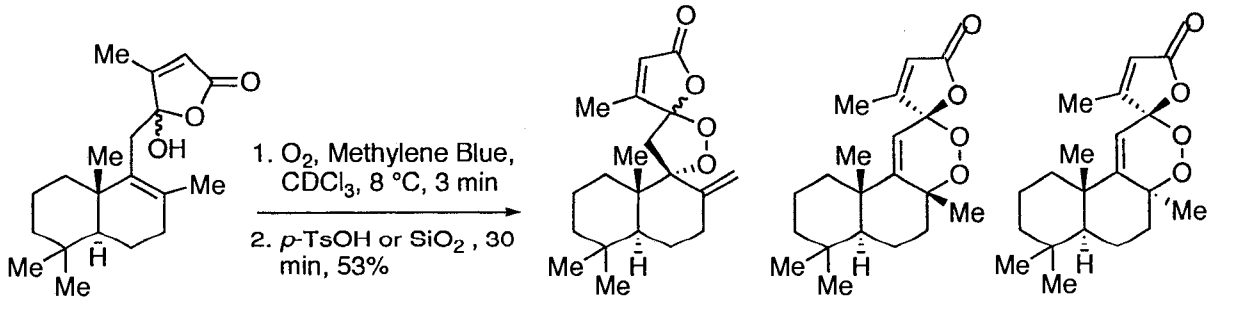


10.1 **10.2**

mixture of two diastereomers

Vassilikogiannakis and his group synthesized[10e] the natural product (+)-premnalane A (**11.4**) from the advanced intermediate 4-hydroxybutenolide **11.1** by using a singlet oxygen mediated ene reaction. The allylic hydroperoxides from the ene reaction were cyclized in the presence of catalytic *p*-TsOH to give rise to the desired (+)-premnalene A (**11.4**), along with the 5-membered γ-spiroperoxy lactones **11.2**.[10e]

SCHEME 11



11.1 **11.2** **11.3** **11.4**

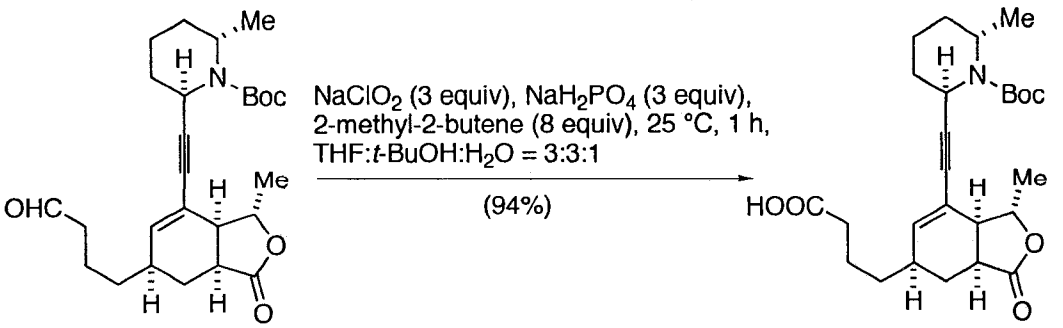
***epi*-Premnalane A** **(+)-Premnalane A**

The above examples show that the γ-hydroxybutenolide unit has some uses in complex molecule synthesis, and presumably, further use of this synthon will be seen in the future.

1.6 Use of $NaClO_2$ in Organic Chemistry

Sodium chlorite ($NaClO_2$), a very cheap oxidizing agent, has been extensively used in water treatment and as a bleaching agent in the paper, pulp, and textiles industries.[11a] It also finds application as a component in therapeutic rinses, mouthwashes, toothpastes and gels, mouth sprays, chewing gums and lozenges, and also in contact lens cleaning solution under the trade name Purite.[11b] However, in the field of synthetic organic chemistry, applications of sodium chlorite are not that broad because of its insolubility in organic solvents. The most impressive use of sodium chlorite is its efficient oxidation of aldehydes to the corresponding carboxylic acids in acidic aqueous media (Scheme 12).[11c]

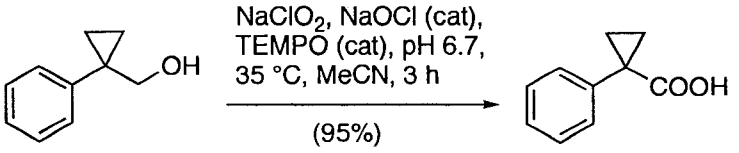
SCHEME 12



12.1 **12.2**

A second use is as the stoichiometric oxidant of a TEMPO-catalyzed oxidation of primary alcohols to carboxylic acids (Scheme 13).[11d]

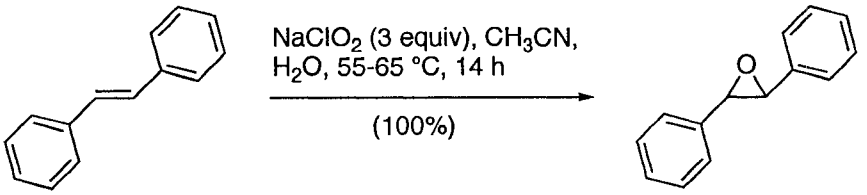
SCHEME 13



13.1 **13.2**

A recently reported application is the epoxidation of a variety of olefins using sodium chlorite as an oxidant without a catalyst at 55-65 °C (Scheme 14).[11d]

SCHEME 14

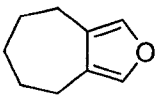


14.1 **14.2**

2. RESULTS AND DISCUSSION

To establish the generality of the use of inexpensive $NaClO_2$ as a potential oxidizing agent for the conversion of 3,4-disubstituted furans into γ-hydroxybutenolides, a total of 8 different types of furan were synthesized. Then, by carrying out a number of control experiments involving the $NaClO_2$-mediated oxidation, optimized conditions were identified so that the process gave high yields.

2.1 Synthesis, Control Experiments and Desymmetrization

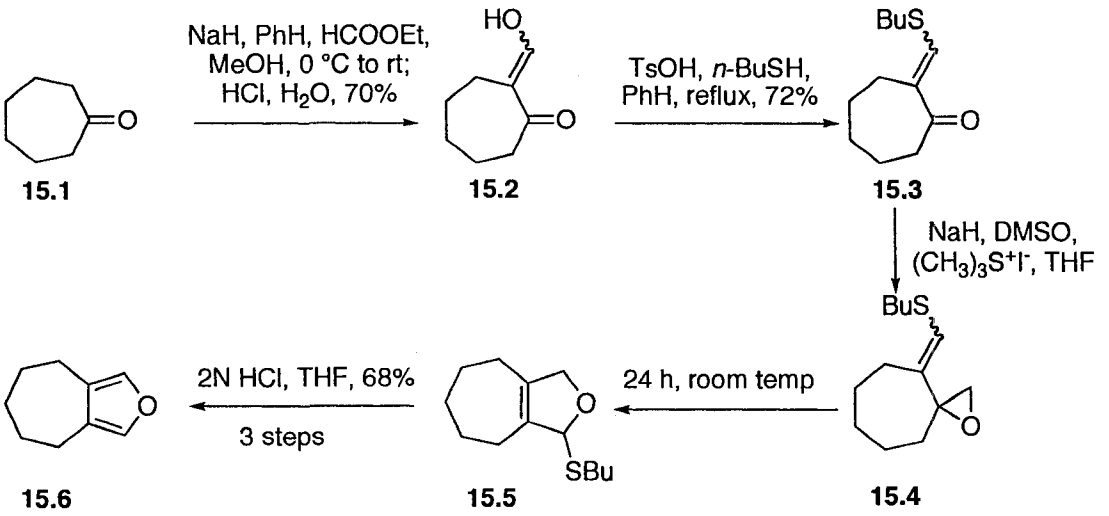


Synthesis and Oxidation

The synthesis of the cycloheptane fused bicyclic furan **15.6** was commenced by α-formylation of cycloheptanone **15.1** using EtOCHO in the presence of NaH in PhH (Scheme 15).[12] Subsequently the *n*-butylthiomethylene derivative **15.3** was obtained according to the method developed by Ireland and Marshall.[13] The vinyl oxirane **15.4** was obtained from the *S*-butyl-α-thiomethylene ketone **15.3** by reaction with a nonstabilized sulfur ylide[14] prepared from trimethylsulfonium iodide and NaH in DMSO-THF. The crude epoxide **15.4** was left under vacuum for 24 h. During this time, the epoxide rearranged to dihydrofuran **15.5**, and this material was treated with dilute hydrochloric acid in THF to induce

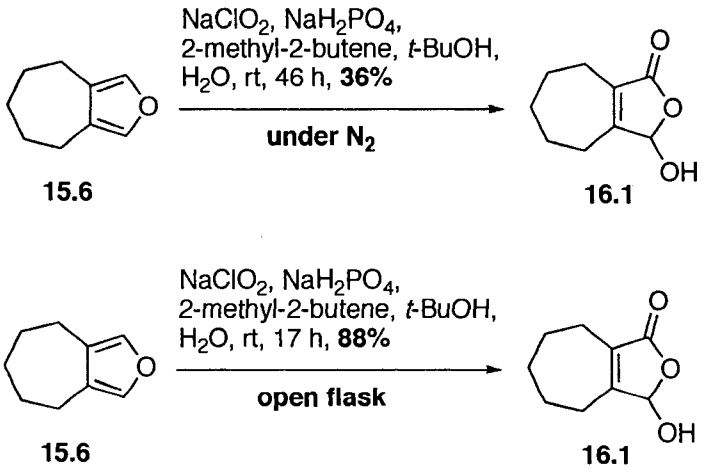
aromatization to the furan **15.6**, which was obtained in 68% yield from **15.3**.[15,16]

SCHEME 15



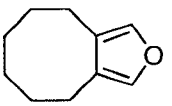
With the furan **15.6** in hand, the original oxidative conditions[1] ($NaClO_2$, $NaH_2PO_4.H_2O$, 2-methyl-2-butene, *t*-BuOH and water) were applied (Scheme 16). The oxidation was carried out under a slight static pressure of nitrogen at room temperature for 46 h with additional portions of an aqueous solution of $NaClO_2$ and $NaH_2PO_4.H_2O$ being added at regular intervals. The reaction mixture was diluted with ethyl acetate and the pH was adjusted to 3 with 1N HCl. The solvent was evaporated and the crude residue was purified over silica to afford **16.1** (36%) together with the unreacted furan. This oxidation can be applied to desymmetrize furans which are symmetrically substituted at the C-3 and C-4 positions.

SCHEME 16



Molar ratio of furan : $NaClO_2$: NaH_2PO_4 : olefin = 1 : 9 : 6 : 9

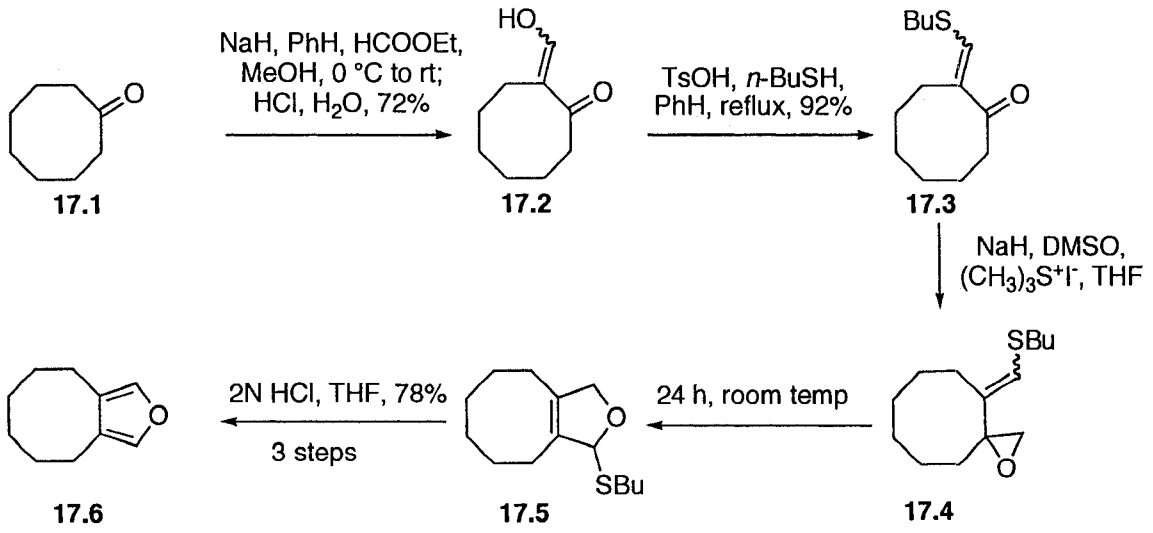
Later, it was found that reaction done in an open flask gave a higher yield, suggesting that evaporation of the 2-methyl-2-butene facilitated the process. Brief optimization studies quickly established that oxidation in the absence of olefin was indeed fast and gave an improved yield (88%).[4]



Synthesis and Oxidation

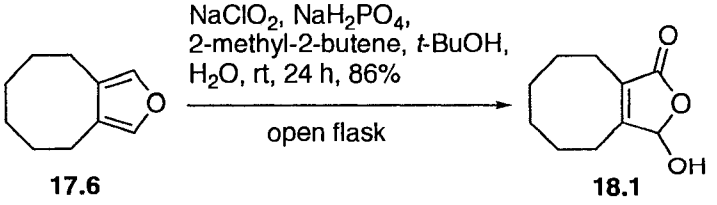
The volatile furan **17.6** was synthesized in five steps from cyclooctanone following the synthetic procedure used for **15.6** (Scheme 17).[12,17]

SCHEME 17

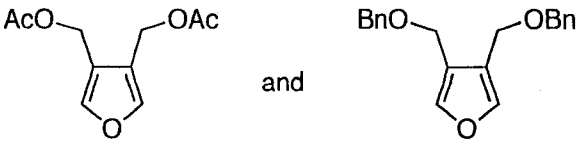


When the furan **17.6** was subjected to the optimized conditions (open flask) established for **16.1**, it gave 4-hydroxy-butenolide **18.1** (86%) within 24 h at room temperature in aqueous *t*-BuOH (Scheme 18). The molar ratio of furan:$NaClO_2$:NaH_2PO_4:olefin was 1:138:88:175. To consume all the starting material **17.6**, additional amounts of $NaClO_2$ and NaH_2PO_4 had to be added after 19 h.

SCHEME 18



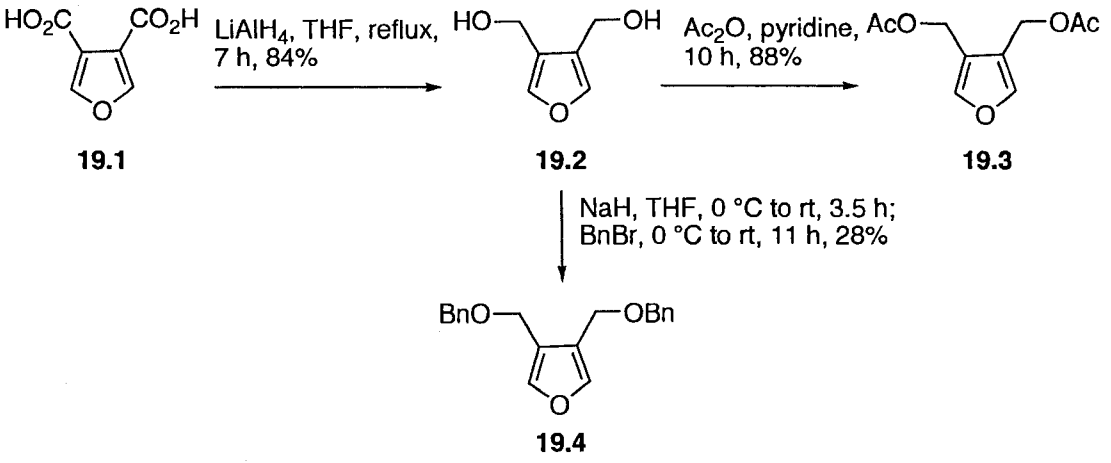
Molar ratio of furan : $NaClO_2$: NaH_2PO_4 : olefin = 1 : 138 : 88 : 175



Synthesis, Oxidation, Optimization and Mechanistic Studies

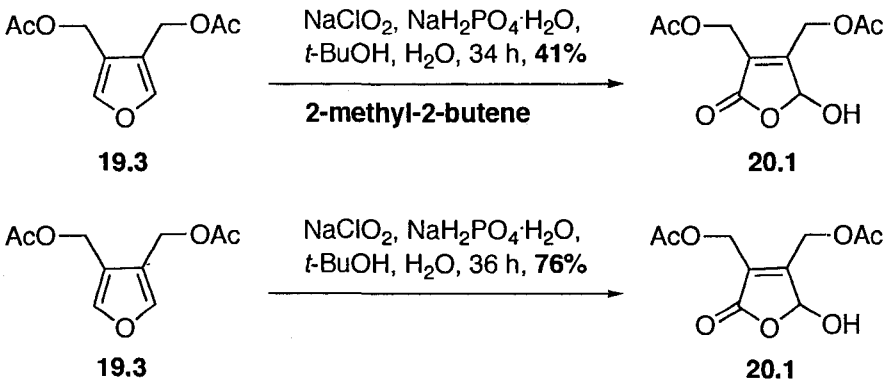
3,4-Furandicarboxylic acid **19.1** was reduced to diol **19.2** by $LiAlH_4$ in THF, followed by acetylation with acetic anhydride to give diacetate **19.3**.[18] When diol **19.2** was treated with BnBr and NaH in THF, then benzyl ether **19.4**[19] was obtained (Scheme 19).

SCHEME 19



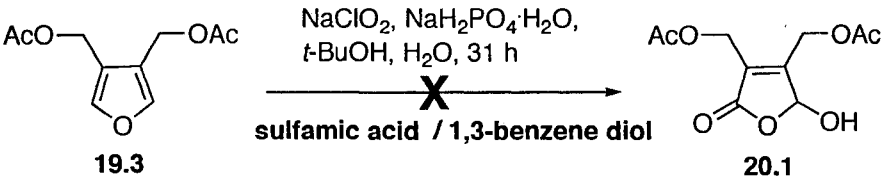
1. Brief optimization studies with **19.3** quickly established that oxidation in the absence of added olefin gave a cleaner reaction with an improved yield (Scheme 20).

SCHEME 20



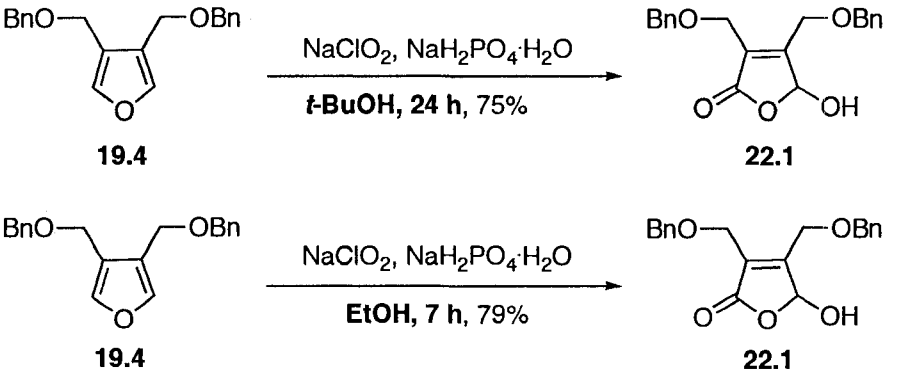
Use of other scavengers instead of 2-methyl-2-butene, such as sulfamic acid (H_2NSO_3H) or 1,3-benzenediol[1,20] also inhibited the oxidation (Scheme 21).

SCHEME 21



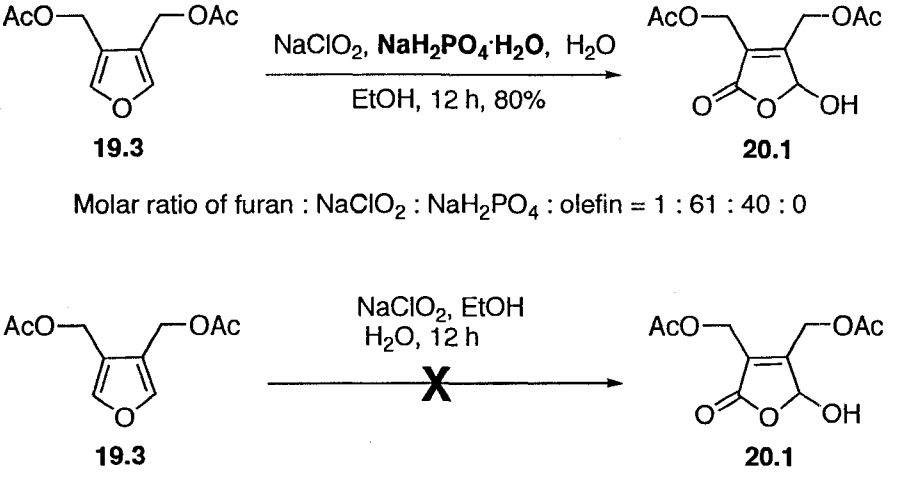
Finally, we decided to use aqueous EtOH as the solvent instead of *t*-BuOH. This modification (with **19.4**) led to an increased yield (**22.1**) and a significantly shorter reaction time (ca. 7 vs 24 h) (Scheme 22). By changing the solvent system from aqueous *t*-BuOH to aqueous EtOH and in the absence of 2-methyl-2-butene, it was found that the oxidation of

SCHEME 22



furan **19.3** went to completion within 12 h (Scheme 23). In the case of *t*-BuOH as the solvent system, the same reaction took almost 36 h (See Scheme 20).

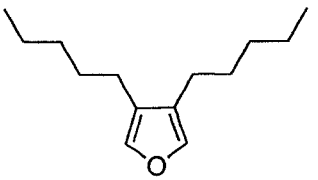
SCHEME 23



An experiment with **19.3** in which $NaH_2PO_4.H_2O$ was omitted gave no oxidation product (Scheme 23). The pH of a mixture of $NaClO_2$ (0.5 g) and $NaH_2PO_4.H_2O$ (0.5 g) in H_2O (5 mL) is 4.5.

This value indicates that an acidic solution is required for the success of the oxidation.

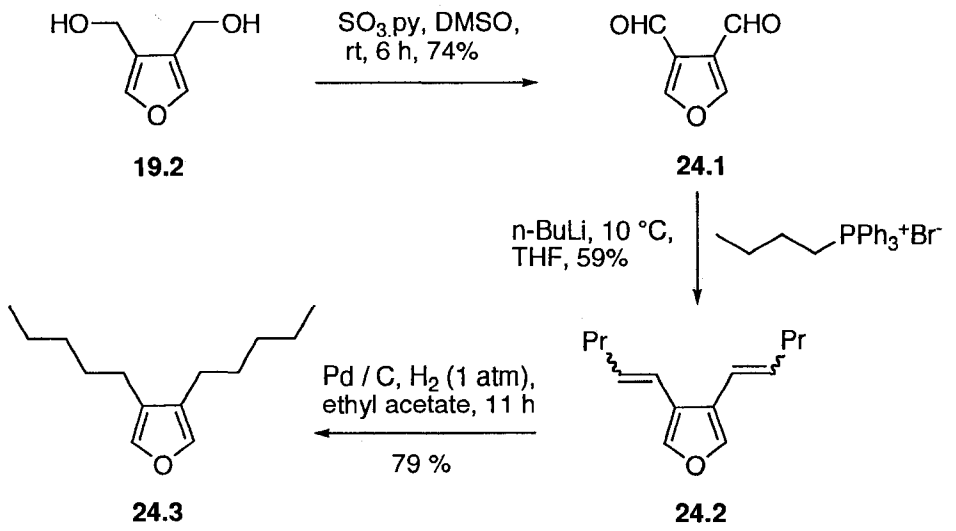
At the end of the oxidation, the color of the reaction mixture became greenish-yellow and the mixture had an irritating unpleasant smell. To avoid exposure to such volatile material, a reductive workup procedure was developed. The reaction mixture was washed with aqueous $NaHSO_3$ solution with the result that the solution became colorless and odorless. Then the aqueous layer was saturated with solid NaCl and extracted with EtOAc.



Synthesis and Oxidation

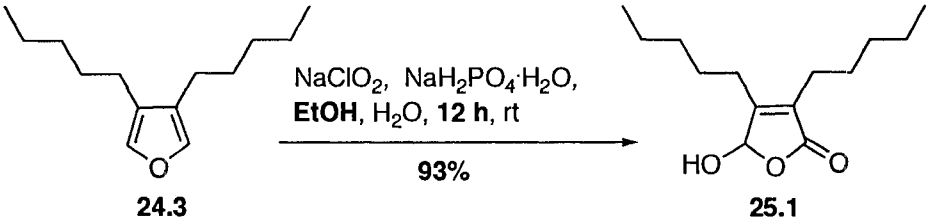
The 3,4–dipentyl substituted symmetrical furan **24.3** was synthesized in five steps from commercially available furan dicarboxylic acid **19.1**. The diol **19.2** was obtained by reduction of dicarboxylic acid **19.1** with $LiAlH_4$ in high yield (Scheme 19). The use of MnO_2 or the Swern oxidation were not successful for oxidizing diol **19.2** into aldehyde **24.1**. However, the pyridine-SO_3 complex in DMSO gave a 74% yield of the required aldehyde. This bis-aldehyde (**24.1**) was homologated by Wittig reaction using *n*-butyltriphenyl-phosphonium bromide in the presence of *n*-BuLi to afford a mixture of inseparable alkenes **24.2** in 59% yield. Pd/C mediated hydrogenation then gave **24.3** (79%) (Scheme 24).

SCHEME 24



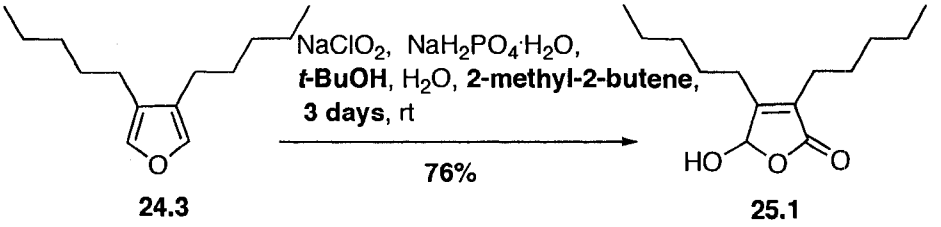
The modified oxidation process with reduced amounts of reagents (the molar ratio of furan:$NaClO_2$:$NaH_2PO_4.H_2O$:olefin = 1:61:40:0 in aqueous EtOH at room temperature) was then applied to oxidize and desymmetrize the furan **24.3.** This experiment gave γ-hydroxybutenolide **25.1** in high yield (93%) within 12 h, after reductive workup with 1M $NaHSO_3$ (Scheme 25). On the other hand, the original conditions with a slight excess of reagents (molar ratio of furan:$NaClO_2$:$NaH_2PO_4.H_2O$:olefin = 1:74:48:107 in aqueous *t*-BuOH) afforded **25.1** in 76% yield after 3 days.

SCHEME 25



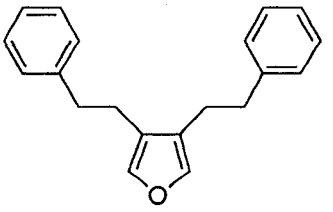
24.3 **25.1**

Molar ratio of furan : $NaClO_2$: NaH_2PO_4 : olefin = 1 : 61 : 40 : 0



24.3 **25.1**

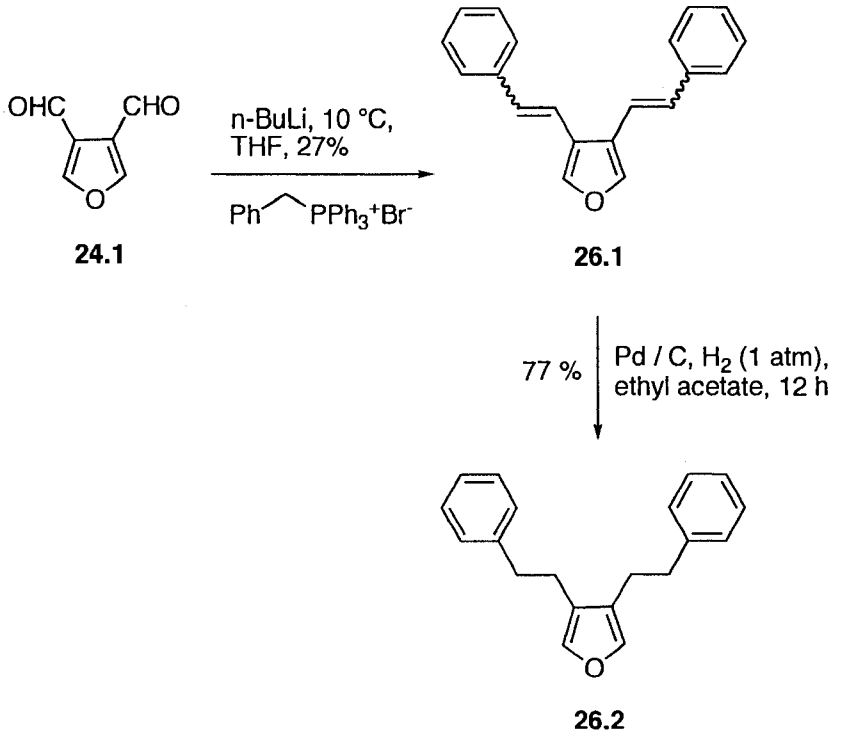
Molar ratio of furan : $NaClO_2$: NaH_2PO_4 : olefin = 1 : 74 : 48 : 107



Synthesis and Oxidation

The symmetrically substituted furan **26.2** was synthesized from **24.1** in three steps using the procedures described in Scheme 26. Subsequent oxidation of **26.2**, applying the

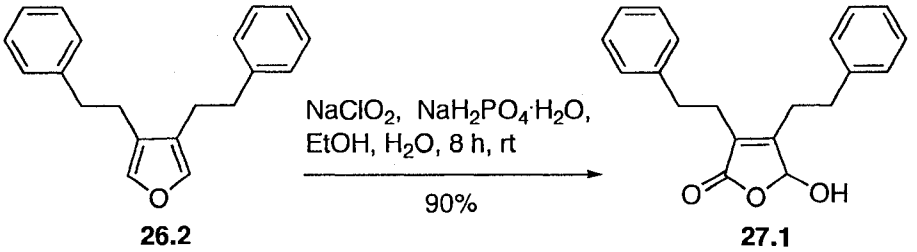
SCHEME 26



24.1 **26.1** **26.2**

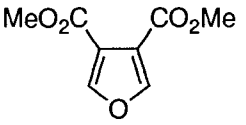
optimized conditions, gave **27.1** in high yield (90%) within a relatively short time (8 h) (Scheme 27).

SCHEME 27



26.2 **27.1**

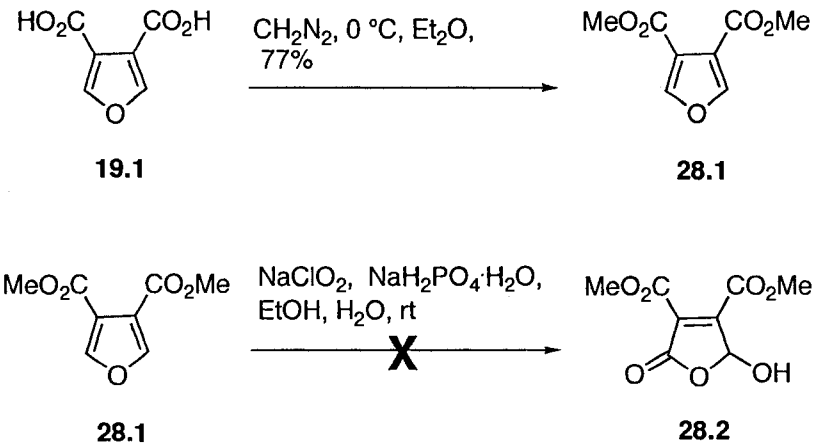
Molar ratio of furan : $NaClO_2$: NaH_2PO_4 : olefin = 1 : 100 : 64 : 0



Synthesis and Oxidation

The diester **28.1** was obtained in 77% yield by quenching the acid **19.1** with freshly prepared CH_2N_2 in Et_2O at 0 °C (Scheme 28). Subsequent oxidation experiments showed that two ester groups attached directly to the furan ring prevent oxidation. Presumably, this is due to the electron deficiency of the furan ring, compared to an alkyl-substituted furan, as the oxidation works with alkyl and substituted alkyl groups.

SCHEME 28

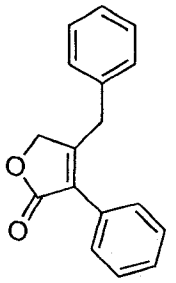


2.2 Synthesis of a Natural Product, Microperfuranone and Use of an Unsymmetrically Substituted Furan for Oxidation

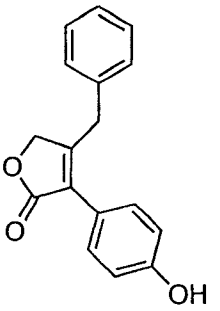
Microperfuranone (**29.5**)[21] was (Scheme 29) synthesized by using our $NaClO_2$-mediated oxidation methodology. The compound

possesses a rare structural motif and only a few other examples are known in the literature, such as eutypoid A, isolated from a South China Sea marine fungus of the genus *Eutypa*, and gymnoascolides A-C, isolated from the Australian soil ascomycete *Gymnoascus reessii and Malbranchea filamentosa* IFM41300.[22] Microperfuranone shows very weak mouse monoamine oxidase inhibitory activity.[23]

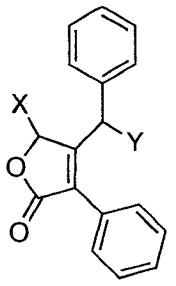
SCHEME 29



gymnoascolide A (**29.1**)

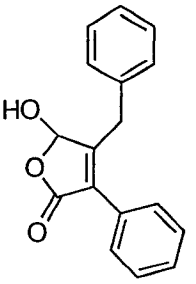


eutypoid (**29.2**)



gymnoascollide B (**29.3**, X = β-OMe, Y = OH)

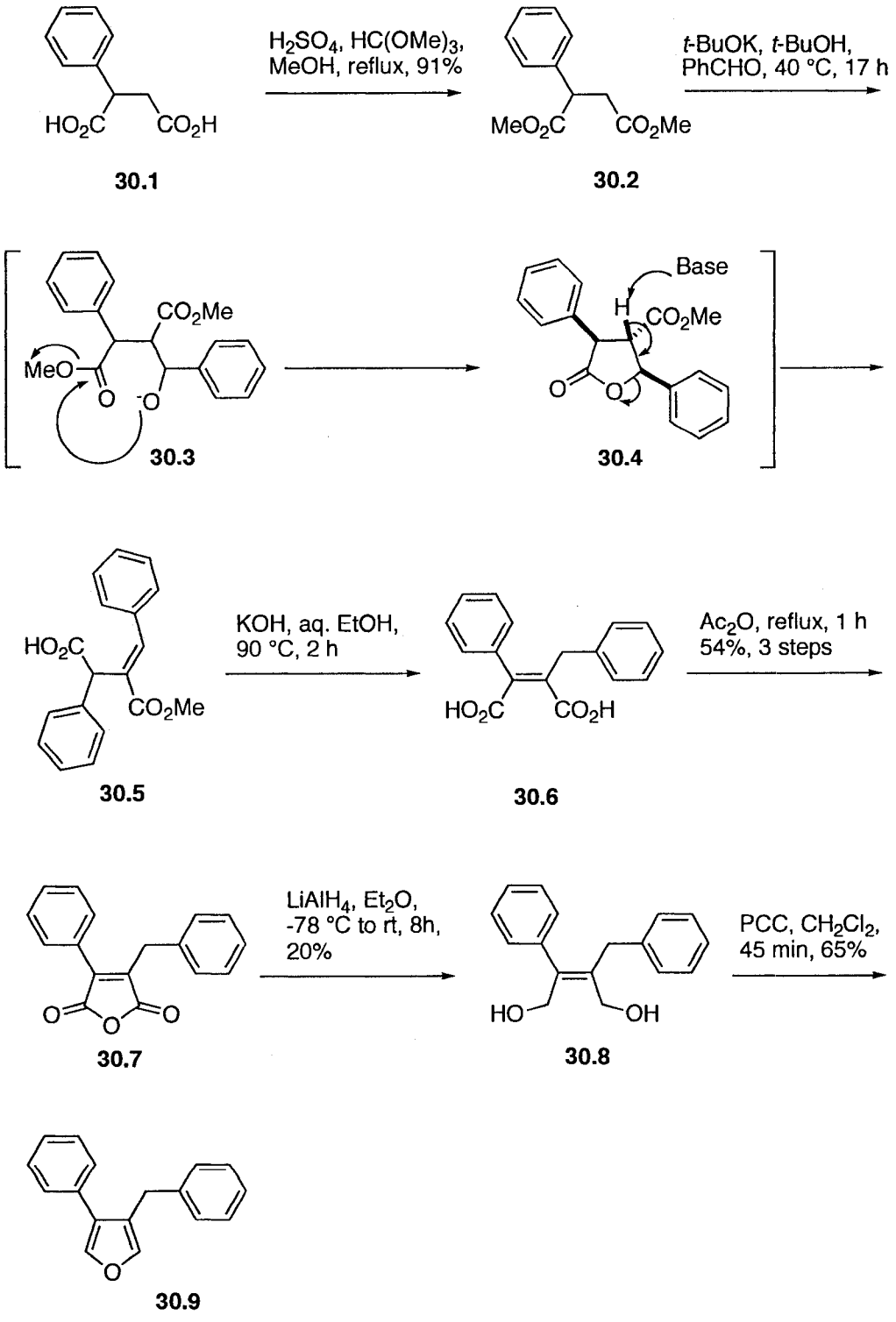
gymnoascollide C (**29.4**, X = α-OMe, Y = OH)



microperfuranone (**29.5**)

All the examples, except those shown in Scheme 29 are 3,4-disubstituted symmetrical furans and the methodology works reproducibly to desymmetrize the furans. The target natural product, microperfuranone, is a 3-phenyl-4-benzyl

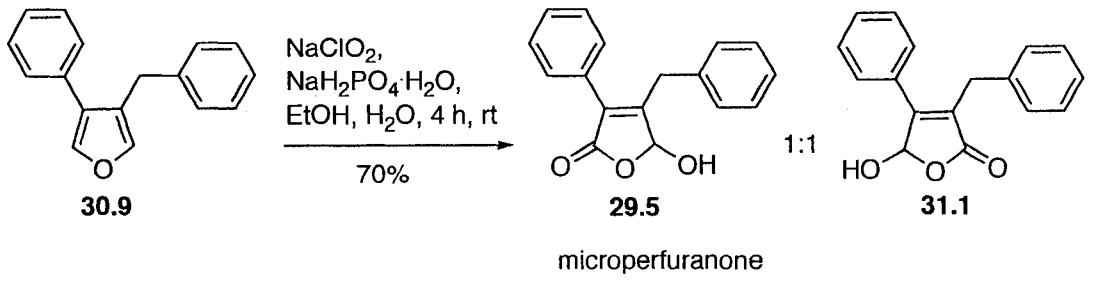
SCHEME 30


H2SO4, HC(OMe)3,
MeOH, reflux, 91%
t-BuOK, t-BuOH,
PhCHO, 40 °C, 17 h
HO2C
CO2H
MeO2C
CO2Me
30.1
30.2
MeO
CO2Me
Base
30.3
30.4
KOH, aq. EtOH,
90 °C, 2 h
Ac2O, reflux, 1 h
54%, 3 steps
30.5
30.6
LiAlH4, Et2O,
-78 °C to rt, 8h,
20%
PCC, CH2Cl2,
45 min, 65%
HO
OH
30.7
30.8
30.9

substituted unsymmetrical furan derivative. The synthesis of 3-phenyl-4-benzyl substituted furan **30.9** was started by Fischer esterification of phenyl succinic acid **30.1.**[24] Stobbe condensation of dimethyl phenylsuccinate ester **30.2** with benzaldehyde, followed by hydrolysis with KOH in aqueous ethanol, gave the corresponding dicarboxylic acid **30.6**, which was refluxed in Ac_2O to give 2-phenyl-3-(phenylmethyl)maleic anhydride **30.7.**[25] Anhydride **30.7** was exposed to the action of $LiAlH_4$ and then PCC oxidation gave furan **30.9**, the precursor of microperfuranone (Scheme 30).

With the unsymmetrically substituted furan **30.9** in hand, the $NaClO_2$ mediated oxidation was attempted (Scheme 31). As expected, it formed both regioisomers **29.5** and **31.1** (1:1, 70%). The ^1H, ^{13}C, IR and mass spectra of the less polar isomer **29.5** were identical with the reported spectra of microperfuranone.[21,23]

SCHEME 31



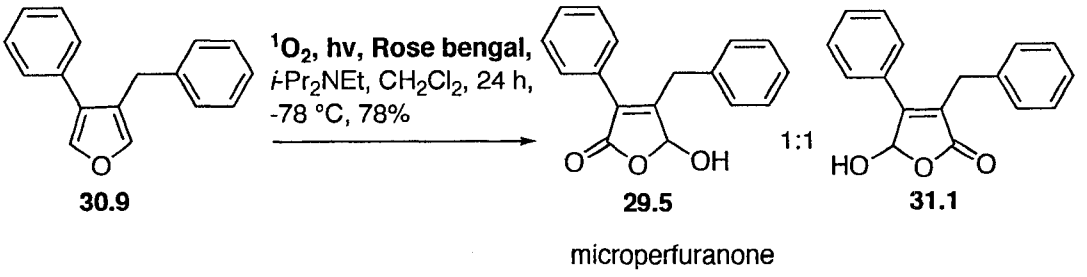
Molar ratio of furan : $NaClO_2$: NaH_2PO_4 : olefin = 1 : 39 : 26 : 0

The total synthesis of the fungal metabolite **29.5** was accomplished in six steps from commercially available phenylsuccinic acid by using our methodology. However this desymmetrization does not provide any control of regioselectivity with 3,4-unsymmetrically substituted furans.

2.3 Oxidation by the Standard Method Using Singlet Oxygen

Furan **30.9** was subjected to the Rose Bengal mediated singlet oxygen method for comparison[26] with our procedure. Dry O_2 gas was continuously bubbled through a solution of furan **30.9**, *i*-Pr_2NEt and Rose Bengal in dry CH_2Cl_2 at -78 °C and at the same time, the pink colored solution was irradiated by a 300 W tungsten filament lamp for 24 h while maintaining the temperature -78 °C (Scheme 32). After standard workup and purification, we again obtained a 1:1 mixture of regioisomers (78% yield).

SCHEME 32



30.9 **29.5** **31.1**

microperfuranone

The standard method requires dry solvent and dry oxygen, and maintenance of the temperature at -78 °C. On the other hand, the $NaClO_2$ mediated oxidation does not require dry

solvents or low temperatures, and the oxidation can be done by simply mixing all of the reagents at room temperature. Both methods give almost the same yield but the $NaClO_2$ procedure is somewhat more convenient.

2.4. Mechanistic Considerations

Chlorine exists in various oxidation states from -1 to +7 in aqueous solution. Chlorite ion/chlorous acid, with chlorine in the +3 oxidation state, is in the middle of this series and can be involved in a redox process as either an oxidizing or a reducing agent. Reactions with strong oxidants produce chlorine dioxide and/or chlorate ion. The reduction of chlorite ion typically produces chloride ion as the reduced product.[27]

Our oxidation was carried out in a weakly acidic medium (pH = 4.5, NaH_2PO_4 buffer). Under these conditions the chlorite ion is in equilibrium with chlorous acid.[28] The acid-catalyzed disproportionation of chlorous acid[29] is sensitive to the conditions and can be summarized by the following equation (Scheme 33).

SCHEME 33

$$H^+ + ClO_2^- \rightleftharpoons HClO_2 \qquad \text{Fast}$$

33.1

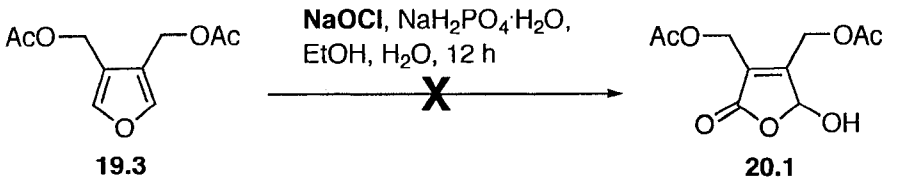
$$5HClO_2 = 4ClO_2 + Cl^- + H^+ + 2H_2O \qquad \text{Slow}$$

33.2

$NaClO_2$ itself is not stable in acidic solution and it produces ClO_2 (aq) as a yellow gas. The color of the reaction mixture became yellow after adding all the reagents. The ClO_2 molecule is contains an odd number of electrons. Odd electron molecules are often highly reactive and ClO_2 is typical in this respect. Odd electron molecules often dimerize in order to pair the electrons, but ClO_2 does not. This is thought to be because the odd electron is delocalized. ClO_2 has an inherent radical property, i.e. a resonance structure with an unpaired electron can be drawn,[30] but we have not established if our oxidation reaction involves ClO_2 and/or another radical species.

It is also known that HOCl can be produced during $NaClO_2$ oxidations.[1] Therefore **19.3** was treated with NaOCl and $NaH_2PO_4.H_2O$, but **20.1** was not formed (Scheme 34). Starting material **19.3** merely decomposed to a complex mixture. Consequently, the side product HOCl cannot be the effective oxidizing agent in this case.

SCHEME 34



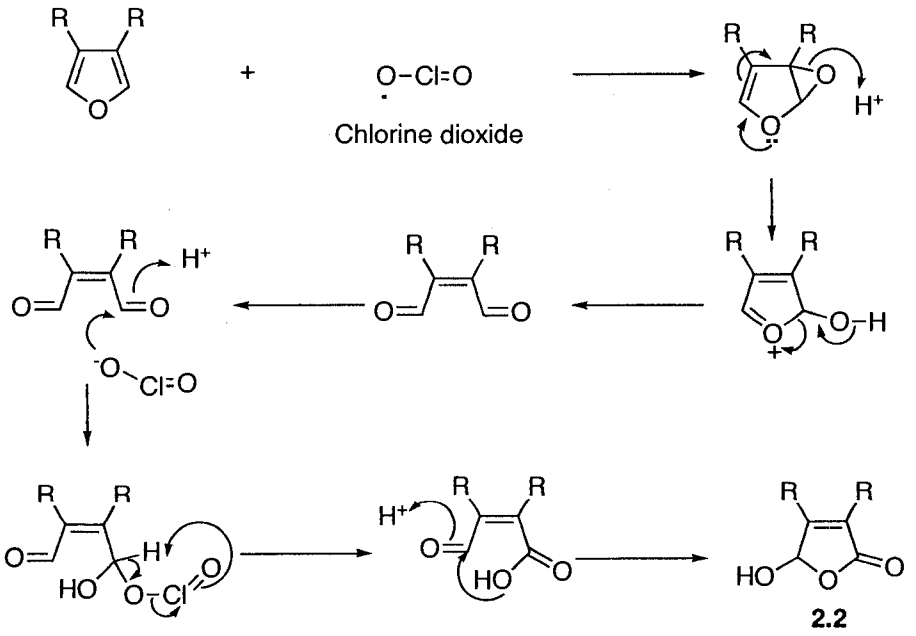
19.3 **20.1**

During the intermediate stages of the reaction, several spots were observed on TLC examination of a drop of the

reaction mixture. But when the reaction was over, then only one spot was observed on TLC and it corresponded to the desired product. Clearly, the reaction involves several intermediates or one intermediate that is unstable on silica gel.

We have not established the mechanism of the oxidations, but a plausible mechanism can be proposed on the basis of the above experimental observations and literature precedent. Initially the furan derivatives can form an epoxide via a free a radical mechanism,[31] and a dialdehyde can be formed after opening of the epoxide. One of the aldehyde groups can be oxidized to a carboxylic acid under Pinnick oxidation conditions and later the cyclic isomer forms under acidic conditions (Scheme 35).[32]

SCHEME 35



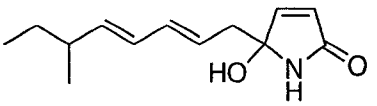
If the effective reagent is ClO_2, these experiments show that $NaClO_2$ is a convenient alternative source. ClO_2 itself has not been tested for oxidation of furans.

3. Future Research

3.1 Synthesis of 5-Hydroxy-3-pyrrolin-2-one

The 5-hydroxy-3-pyrrolin-2-one is a key structural component of a growing number of naturally occurring and biologically important compounds. Our methodology could be applied to synthesize this class of compounds for example axinellamide[33] (Scheme 36).

SCHEME 36



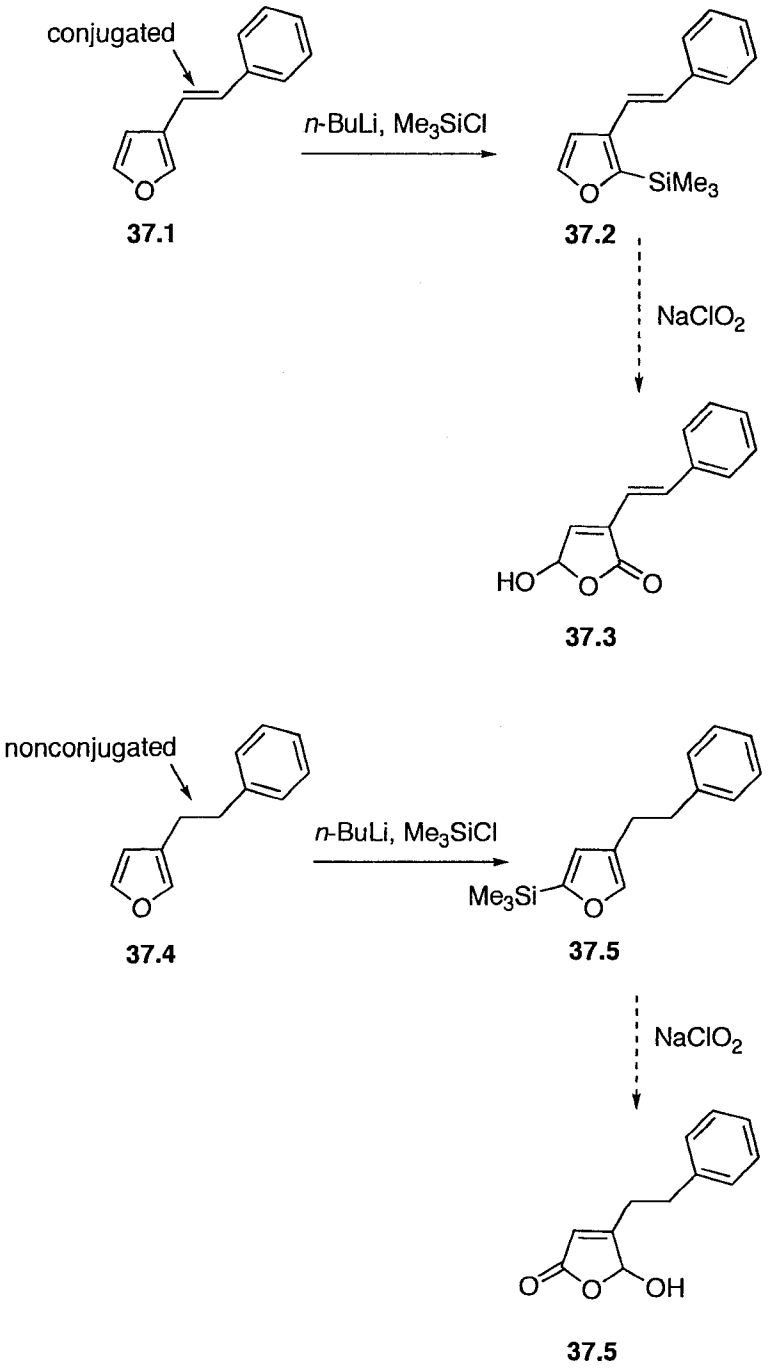
axinellamide

3.2 Traceless Protecting Group Directed Regiocontrolled Oxidation

Careful placement of a silicon group either at C-2 or C-5 of an unsymmetrically substituted furan **37.1** may direct the regioselectivity. Control of regioselectivity has been observed for the ortholithiation of 3-aryl and 3-styryl furans,[34] where lithiation occurs preferentially at the sterically encumbered 2-position. This silicon group may bias the regiochemical outcome in the oxidation of

substituted furans, but we have not yet tested this possibility (Scheme 37).

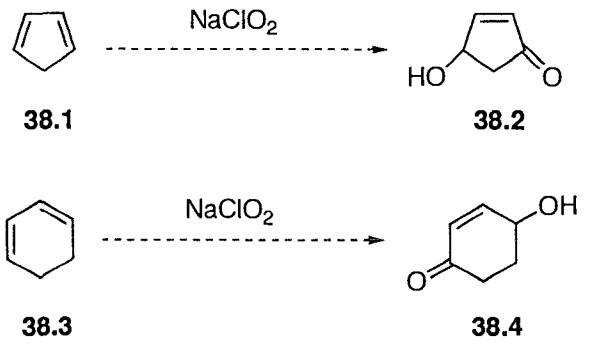
SCHEME 37



3.3 Cyclopentadiene and Cyclohexadiene as Substrates

In our oxidations we ultimately obtain the same products that are available by the action of singlet oxygen and base. By analogy, it may be worth trying the oxidation on cyclopentadiene **38.1** and cyclohexadiene **38.3** in a Kornblum-DeLamare fashion[35] (Scheme 38).

SCHEME 38



4. Conclusion

In summary, a new synthetic method has been developed to oxidize 3,4-disubstituted furans into γ-hydroxybutenolides in high yield by treatment with $NaClO_2$ in aqueous EtOH containing NaH_2PO_4. $NaClO_2$ is inexpensive and this oxidation does not require any dry solvents or special precautions. The limitation of this reaction is that it works well with electron rich furans only. The procedure can be applied to desymmetrize symmetrically substituted furans.

Experimental Section

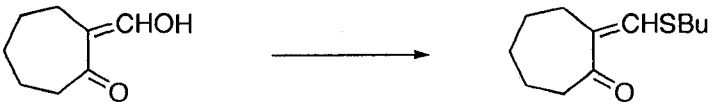
2-(Hydroxymethylene)cycloheptanone (15.2).

15.1 **15.2**

NaH (60% dispersion in oil, 3.63 g, 90.64 mmol) was placed in a three-necked round-bottomed flask equipped with a mechanical stirrer and closed by septa. The system was flushed with N_2 and dry PhH (100 mL) was added from a syringe. The stirrer was started and dry MeOH (89 μL, 2.2 mmol) was injected with a microsyringe. An ice bath was raised into place, and a mixture of cycloheptanone **15.1** (10.52 mL, 89.15 mmol) and EtOCHO (7.2 mL, 89 mmol) was added dropwise over 1.5 h (syringe pump). During the addition there was a visible evolution of gas and a paste-like cream colored precipitate formed. At the end of the addition, the ice bath was removed and stirring was continued for 1 h. The mixture was diluted with Et_2O (50 mL) and the suspension was collected on a sintered filter funnel and washed with Et_2O. The crude sodium salt was dissolved in a minimum amount of water and the stirred solution was acidified to pH 5 by dropwise addition of concentrated hydrochloric acid. The mixture was extracted with Et_2O and the combined organic extracts were dried (Na_2SO_4) and evaporated to afford **15.2**[15,16] (5.61 g, 51%)

as an oil which was an inseparable mixture of isomers: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.56-1.80 (m, 7 H), 2.20-2.50 (m, 2 H), 2.60-2.80 (m, 2 H), 7.63 (d, *J* = 6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.66 (t), 24.68 (t), 28.66 (t), 28.69 (t), 29.84 (t), 29.86 (t), 31.74 (t), 31.83 (t), 42.07 (t), 42.09 (t), 114.7 (s), 170.87 (d), 170.9 (d), 204.3 (s).

2-(Butylsulfanylmethylene)cycloheptanone (15.3).



15.2 **15.3**

$TsOH.H_2O$ (100 mg) and BuSH (4.93 mL, 0.0460 mol) were added to a solution of **15.2** (5.61 g, 0.04 mol) in PhH (200 mL), and the mixture was refluxed for 5 h, using a Dean-Stark apparatus to collect the water (ca 1 mL) (N_2 atmosphere). Much **15.2** remained (TLC, silica, 1:7 EtOAc-hexane) and so more $TsOH.H_2O$ (20.0 mg) was added, and refluxing was continued for 6 h. At this point almost all **15.2** had reacted (TLC control). The deep yellow mixture was cooled and washed with 10% aqueous $KHCO_3$ (50 mL) (the aqueous layer remained basic), and water, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (3.2 x 29 cm) using 1:7 EtOAc-hexane, gave **15.3**[15,16] (5.38 g, 63%) as a mixture of isomers (5.38 g, 63%): ^{1}H NMR (($CDCl_3$, 400 MHz) δ 0.93 (t, *J* = 7.3 Hz, 3 H), 1.38-1.46 (m, 2 H), 1.65-1.76 (m,

8 H), 2.42-2.68 (m, 4 H), 2.83 (t, J = 7.4 Hz, 2 H), 7.43 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.5 (q), 21.6 (t), 25.1 (t), 28.7 (t), 29.2 (t), 31.3 (t), 32.2 (t), 32.6 (t), 43.2 (t), 135.5 (s), 141.2 (d), 200.3 (s).

4-(Butylsulfanylmethylene)-1-oxaspiro[2.6]nonane (15.4).[15,16,36]

15.3 **15.4**

NaH (60% dispersion, 135 mg, 3.38 mmol) was placed in a three-necked flask which was then flushed with N_2 and closed with an air condenser and septa. Dry DMSO (2.5 mL) was added by syringe, and the solution was stirred and heated at 55-60 °C until gas evolution had stopped (ca 30 min). The oil bath was removed, and the resulting cloudy light yellow warm solution was diluted with dry THF (3 mL), and then the mixture was cooled to -1 to -5 °C (bath temperature, ice-salt) (this procedure gives best results). During the following steps the bath temperature was kept in this range. Me_3SI (471 mg, 2.3 mmol) in DMSO (3 mL) was added dropwise from a syringe over 30 min (syringe pump). (This procedure gives better results than addition of the solid reagent.) The reaction mixture was stirred for 1 h at the same temperature after the addition. At this stage the mixture was a light

yellow paste. A solution of **15.3** (391.4 mg, 1.84 mmol) in dry THF (3 mL) was added dropwise over 30 min from a syringe (syringe pump) at -1 to -5 °C. After the addition, stirring at the same temperature was continued for 30 min. The mixture was now a light orange color. The cooling bath was removed and stirring was continued for 4 h. The color of the solution was now deep orange. The mixture was poured onto crushed ice (50 g) and extracted five times with an equal volume of pentane. The combined organic extracts containing **15.4**[15,16,36] were dried (Na_2SO_4) and stored over the drying agent in a refrigerator overnight.

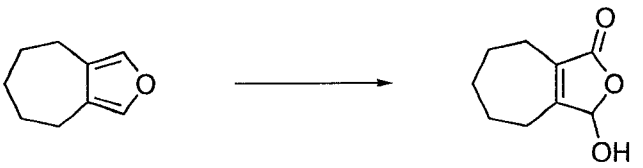
5,6,7,8-Tetrahydro-4*H*-cyclohepta[*c*]furan (15.6).

15.4 **15.6**

The following day, the drying agent in the above mixture was filtered off and the solvent was evaporated (water pump). The residual oil was dissolved in THF (4 mL) and hydrochloric acid (2 N, 1 mL) was added. The mixture was stirred vigorously for 4 h at room temperature, and the aqueous phase was extracted twice with Et_2O. Solid anhydrous K_2CO_3 was added to the combined organic extracts to dry and neutralize the solution. The mixture was filtered and evaporated (water pump). Flash chromatography of the residue over silica gel

(3 x 23 cm), using hexane, gave **15.6**[15,16] (140 mg, 56%) as a volatile oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.12 (s, 2 H), 2.51 (t, *J* = 5.6 Hz, 4 H), 1.75-1.85 (m, 2 H), 1.60-1.67 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.8 (t), 29.8 (t), 32.7 (t), 127.5 (s), 138.3 (d).

3-Hydroxy-3,4,5,6,7,8-hexahydrocyclohepta[*c*]furan-1-one (12.1).



15.6 **16.1**

In the following experiment a cold container of 2-methyl-2-butene (just removed from the refrigerator) was opened, and a portion was taken up into a syringe.

$NaClO_2$ (1.00 g, 11.1 mmol) and $NaH_2PO_4.H_2O$ (1.00 g, 7.25 mmol) were dissolved in water (10 mL) and an aliquot (3 mL) of this freshly-made solution was added to a stirred solution of **15.6** (176.50 mg, 1.30 mmol) and 2-methyl-2-butene (0.9 mL) in *t*-BuOH (4 mL). Stirring at room temperature was continued overnight (mixture open to the air), by which stage the color of solution had become yellow. Some **15.6** remained (TLC, silica, 3:7 EtOAc-hexane). $NaClO_2$ (0.50 g, 5.53 mmol) and $NaH_2PO_4.H_2O$ (0.500 g, 3.62 mmol) were dissolved in water (5 mL) and an aliquot (3 mL) of this freshly-made solution was added to the reaction mixture. Stirring was continued for 18

h. EtOAc (20 mL) was added and the pH was adjusted to 3 (pH paper) by addition of 1 N hydrochloric acid. The aqueous layer was saturated with NaCl and extracted with EtOAc (4 x 15 mL). The combined organic extracts (yellow) were dried (Na_2SO_4) and evaporated. During the evaporation the residue became colorless but the distillate was yellow. Flash chromatography of the residue over silica gel (2 x 21 cm), using 3:7 EtOAc-hexane, gave **16.1** (191.3 mg, 88%) as a colorless oil: FTIR (CH_2Cl_2 cast) 3351, 1736 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.61-1.80 (m, 6 H), 2.36-2.59 (m, 4 H), 4.59 (br s, 1 H), 5.87 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.80 (t), 26.72 (t), 26.79 (t), 27.60 (t), 30.07 (t), 97.64 (d), 131.71 (s), 161.35 (s), 172.42 (s), exact mass *m/z* calcd for $C_9H_{12}O_3$ 168.07864, found 168.07885.

2-(Hydroxymethylene)cyclooctanone (17.2).[12,17]

17.1 **17.2**

NaH (60% dispersion in oil, 3.22 g, 80.56 mmol) was placed in a three-necked round-bottomed flask equipped with a mechanical stirrer and closed by septa. The system was flushed with N_2 and dry PhH (74 mL) was added from a syringe. The stirrer was started and dry MeOH (79 μL, 2.0 mmol) was injected by microsyringe. An ice bath was raised into place,

and a mixture of cyclooctanone **17.1** (10.44 mL, 79.24 mmol) and EtOCHO (6.37 mL, 79.24 mmol) was added dropwise by syringe over 1.5 h (syringe pump). During the addition there was a visible evolution of gas, and a paste-like pale yellow mixture formed. At the end of the addition, the ice bath was removed and stirring was continued for 1 h. The mixture was diluted with Et_2O (40 mL) and the suspension was collected on a sintered filter funnel and washed with Et_2O. The crude sodium salt was dissolved in a minimum amount of water and the stirred solution was acidified to pH 5 by dropwise addition of concentrated hydrochloric acid. The mixture was extracted with Et_2O and the combined extracts were dried (Na_2SO_4) and evaporated to afford **17.2** (7.23 g, 59%) as a yellow oil.

2-(Butylsulfanylmethylene)cyclooctanone (17.3).

17.2 **17.3**

$TsOH.H_2O$ (100 mg) and BuSH (5.61 mL, 0.052 mol) were added to a solution of **17.2** (7.0 g, 0.045 mol) in PhH (260 mL), and the mixture was refluxed for 12 h, using a Dean-Stark apparatus to collect the water (ca 1 mL) (N_2 atmosphere). The deep brown mixture was cooled and washed with 10% aqueous $KHCO_3$ (50 mL) (the aqueous layer remained

basic), and water, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (5.5 x 21 cm) (20 g silica per g crude mixture), using 1:10 EtOAc-hexane, gave **17.3**[12,17] (6.00 g, 58%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.93 (t, *J* = 7.3 Hz, 3 H), 1.40-1.49 (m, 4 H), 1.50-1.69 (m, 6 H), 1.74-1.79 (m, 2 H), 2.60-2.65 (m, 4 H), 2.84 (t, *J* = 7.4 Hz, 2 H), 7.47 (s, 1 H).

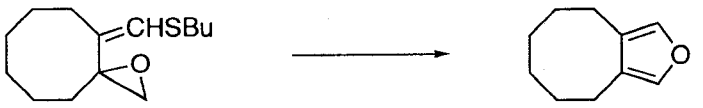
4-(Butylsulfanylmethylene)-1-oxaspiro[2.6]decane (17.4).

17.3 **17.4**

NaH (60% in oil, 0.264 g, 6.40 mmol) was placed in a 100-mL three-necked flask, carrying an air condenser. The flask was quickly closed with septa and flushed with N_2. Dry DMSO (4 mL) was added and the mixture was stirred magnetically. An oil bath was then raised into place, and the stirred mixture was heated at 55-60 °C until gas evolution stopped (ca 40 min). The resulting cloudy, light yellow solution was diluted with dry THF (2 mL), and the mixture was cooled to -1 to -3 °C (external bath temperature) (this procedure gives best results). During the following steps the bath temperature was kept in this range. Me_3SI (1.02 g, 5.00 mmol) in DMSO (3 mL) was added dropwise from a syringe

over 30 min (syringe pump). (This procedure gives better results than addition of the solid reagent.) The reaction mixture was stirred at the same temperature for 1 h after the addition. A solution of **17.3** (0.906 g, 4.00 mmol) in dry THF (3 mL) was added dropwise over 30 min from a syringe (syringe pump) at -1 to -3 °C. After the addition, stirring at the same temperature was continued for 30 min. The cooling bath was removed and stirring was continued for 4 h. The color of the solution was then orange. The mixture was poured onto crushed ice (50 g) and extracted five times with an equal volume of petroleum ether. The combined organic extracts were dried (Na_2SO_4) and stored over the drying agent in a refrigerator overnight.

4,5,6,7,8,9-Hexahydrocycloocta[*c*]furan (17.6).



17.4 **17.6**

The following day, the drying agent in the above mixture was filtered off and the solvent was evaporated (water pump). The residual oil was dissolved in THF (8 mL), 2 N hydrochloric acid (2 mL) was added, and the mixture was stirred vigorously for 4 h at room temperature. The aqueous phase was extracted twice with Et_2O. Solid anhydrous K_2CO_3 was added to the combined organic extracts to dry and neutralize

the solution, and the mixture was filtered and evaporated. Flash chromatography of the residue over silica gel (4 x 18 cm), using 1:10 EtOAc-hexane, gave **17.6** (212.0 mg, 35%) as a volatile oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.44-1.47 (m, 4 H), 1.56-1.61 (m, 4 H), 7.14 (s, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.6 (t), 25.4 (t), 31.3 (t), 125.6 (s), 138.5 (d).

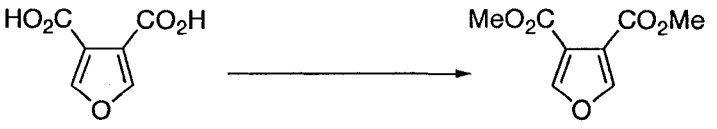
3-Hydroxy-3,4,5,6,7,8-hexahydrocycloocta[*c*]furan-1-one (18.1).

17.6 **18.1**

A freshly-made solution of $NaClO_2$ (1.00 g, 11.1 mmol) and NaH_2PO_4 (1.0 g, 7.0 mmol) in water (10 mL) was added to a stirred solution of **17.6** (320 mg, 2.14 mmol) and 2-methyl-2-butene (1.0 mL) in *t*-BuOH (10 mL). Stirring was continued for 19 h (mixture open to air). At this stage some **17.6** remained (TLC, silica, 3:7 EtOAc-hexane). More *t*-BuOH (2 mL) and 2-methyl-2-butene (0.5 mL) were added. $NaClO_2$ (0.500 g, 5.53 mmol) and NaH_2PO_4 (0.50 g, 3.5 mmol) were dissolved in water (5 mL) and a portion (3 mL) of this freshly made solution was added to the reaction mixture. Stirring was continued for 24 h, by which time no **17.6** remained (TLC, silica, 3:7 EtOAc-hexane), and the mixture had become yellow.

EtOAc (20 mL) was added and the pH was adjusted to 3 (pH paper) by addition of dilute hydrochloric acid (1 M). The aqueous phase was extracted with EtOAc (4 x 15 mL) and the combined organic extracts (yellow) were dried (Na_2SO_4) and evaporated. During the evaporation, the residue became colorless but the distillate was yellow. Flash chromatography of the residue over silica gel (2 x 23 cm), using 3:7 EtOAc-hexane, gave **18.1** (332.5 mg, 86%) as a colorless oil: FTIR 3369, 1732 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.53-1.88 (m, 8 H), 2.46-2.58 (m, 4 H), 3.42 (d, *J* = 2 Hz, 1 H), 5.89 (d, *J* = 4.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.8 (t), 25.0 (t), 25.4 (t), 25.9 (t), 26.1 (t), 97.8 (d), 129.6 (s), 160.3 (s), 172.5 (s); exact mass (electrospray) *m/z* calcd for $C_{10}H_{14}NaO_3$ (M + Na) 205.08352, found 205.08369.

3,4-Furandicarboxylic Acid Dimethyl Ester (28.1).

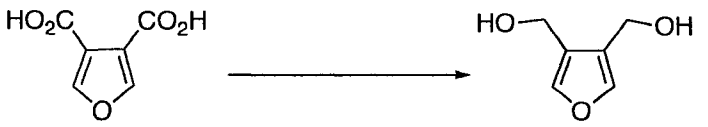


19.1 **28.1**

Ethereal CH_2N_2 was added dropwise to a stirred and cooled (0 °C) solution of furan-3,4-dicarboxylic acid **19.1** (332 mg, 2.13 mmol) in a mixture of Et_2O (25 mL) and MeOH (6 mL) until the color of the solution became yellow. Stirring was continued for another 30 min, and the solution was evaporated. Flash chromatography of the residue over silica

gel (3 x 9 cm), using 1:2 EtOAc-hexane, gave **28.1**[37] (300 mg, 77%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.84 (s, 6 H), 7.98 (s, 2 H).

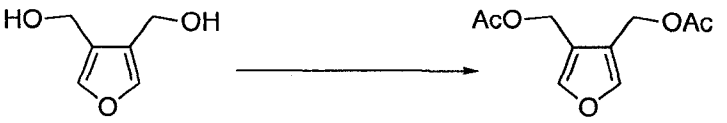
[4-(Hydroxymethyl)furan-3-yl]methanol.



19.1 **19.2**

$LiAlH_4$ (383.5 mg, 9.600 mmol) was added portionwise to s stirred solution of 3,4-furandicarboxylic acid **19.1** (500 mg, 3.20 mmol) in dry THF (50 mL). The mixture was refluxed for 7 h, and then cooled to 0 °C. The mixture was quenched with MeOH (5 mL), followed by addition of saturated aqueous Na_2SO_4 (10 mL) solution. The mixture was stirred for 30 min at room temperature, Et_2O (25 mL) was added, and the mixture was filtered. The insoluble material was washed with Et_2O (3 x 25 mL), and the combined organic extracts were dried (Na_2SO_4) and evaporated (water pump). Flash chromatography of the residue over silica gel (3 x 10 cm), using 1:1 EtOAc-hexane, gave [4-(hydroxymethyl)furan-3-yl]methanol **19.2**[37] (362.4 mg, 88%) as a syrup: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.98 (br s, 2 H), 4.60 (s, 4 H), 7.40 (s, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 55.4 (t), 124.4 (s), 141.0 (d).

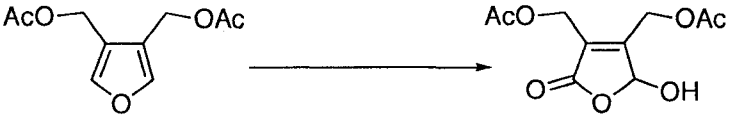
Acetic Acid [4-(Acetoxymethyl)furan-3-yl]methyl Ester (19.3).



19.2 **19.3**

Ac_2O (0.2 mL, 2.0 mmol) was added to a stirred solution of [4-(hydroxymethyl)furan-3-yl]methanol **19.2** (100.0 mg, 0.78 mmol) in dry pyridine (2 mL). Stirring was continued for 10 h. The mixture was diluted with EtOAc (24 mL) and washed with 2 N HCl (3 x 5 mL), aqueous $KHCO_3$ (3 x 5 mL) and brine (3 x 5 mL). The organic phase was dried (Na_2SO_4) and evaporated (water pump). Flash chromatography of the residue over silica gel (1.6 x 22 cm), using 1:1 EtOAc-hexane, gave **19.3**[38] (145.4 mg, 88%): ^1H NMR ($CDCl_3$, 300 MHz) δ 2.04 (s, 6 H), 5.01 (s, 4 H), 7.43 (s, 2 H).

Acetic Acid 4-Acetoxymethyl-5-hydroxy-2-oxo-2,5-dihydro-furan-3-ylmethyl Ester (20.1).



19.3 **20.1**

A freshly-made solution of $NaClO_2$ (0.50 g, 5.5 mmol) and $NaH_2PO_4.H_2O$ (0.50 g, 3.6 mmol) in water (5 mL) was added to a stirred solution of **19.3** (17.8 mg, 0.083 mmol) in EtOH (5 mL). Stirring was continued for 12 h (mixture open to the

air), and the yellow mixture was diluted with EtOAc (15 mL). Aqueous $NaHSO_3$ (1 M, 6 mL) was added, and the solution became colorless. The aqueous layer was saturated with NaCl and extracted with EtOAc (4 x 20 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (3 x 6 cm), using 5:7 EtOAc-hexane, gave **20.1** (16.4 mg, 80%): FTIR ($CHCl_3$ cast) 3369, 1748 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.11 (s, 3 H), 2.14 (s, 3 H), 4.07 (d, J = 8 Hz, 1 H), 4.90-5.14 (m, 4 H), 6.09 (d, J = 8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.52 (q), 20.61 (q), 55.35 (t), 57.42 (t), 96.88 (d), 127.28 (s), 157.10 (s), 169.66 (s), 170.64 (s), 170.68 (s); exact mass m/z calcd for $C_{10}H_{12}O_7$ 244.05830, found 244.05817.

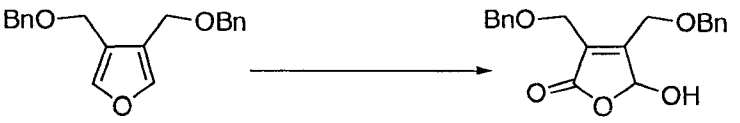
3,4-Bis(benzyloxymethyl)furan (19.4).

19.2 **19.4**

A solution of the [4-(hydroxymethyl)furan-3-yl]methanol **19.2** (260 mg, 2.03 mmol) in dry THF (10 mL) was added dropwise over 10 min to a stirred and cooled (0 °C) slurry of NaH (60% in oil, 162 mg, 4.06 mmol) in dry THF (12 mL). After the addition the ice-bath was removed and stirring was continued for 3.5 h. The mixture was cooled to 0 °C (ice bath), BnBr (0.48 mL, 4.06 mmol) was added dropwise over 2

min and stirring was continued for 11 h. The reaction was quenched by adding brine (10 mL) and the mixture was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were dried over Na_2SO_4 and evaporated. Flash chromatography of the residue over silica gel (2 x 19 cm), using 1:1 EtOAc-hexane gave **19.4**[37] (159.8 mg, 26%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.44 (s, 4 H), 4.47 (s, 4 H), 7.23-7.43 (m, 12 H).

3,4-Bis(benzyloxymethyl)-5-hydroxy-5*H*-furan-2-one (22.1).

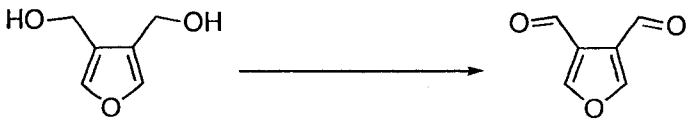


19.4 **22.1**

A freshly-made solution of $NaClO_2$ (0.50 g, 5.53 mmol) and $NaH_2PO_4.H_2O$ (0.50 g, 3.6 mmol) in water (5 ml) was added to a stirred solution of **19.4** (39.0 mg, 0.126 mmol) in EtOH (5 mL). Stirring was continued for 7.5 h (mixture open to the air). EtOAc (20 mL) was added to the yellow reaction mixture, and the aqueous layer was saturated with NaCl, and extracted with EtOAc (4 x 20 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (3 x 10 cm), using 3:7 EtOAc-hexane, gave **22.1** (34.0 mg, 79%): FTIR ($CDCl_3$ cast) 3354, 1766 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.43 (d, J =

7.5 Hz, 1 H), 4.33-4.64 (m, 8 H), 6.10 (d, J = 7.5 Hz, 1 H), 7.26-7.39 (m, 10 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 62.33 (t), 63.41 (t), 73.48 (t), 73.64 (t), 96.54 (d), 127.84 (d), 127.86 (d), 127.91 (d), 127.96 (d), 128.16 (d), 128.18 (d), 128.51 (d), 128.58 (d), 137.05 (d), 137.50 (d), 127.96 (s), 137.05 (s), 137.50 (s), 157.75 (s), 170.03 (s); exact mass m/z calcd for $C_{20}H_{20}O_5$ 340.13107, found 340.13090.

[4-(Hydroxymethyl)furan-3-yl]methanol (24.1).



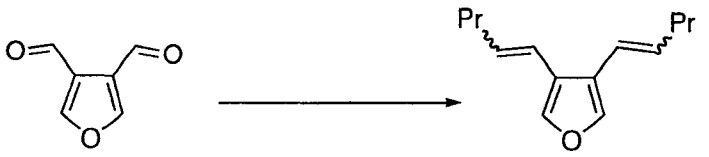
19.2 **24.1**

A solution of pyridine-SO_3 complex (0.414 g, 2.60 mmol) in DMSO (3 mL) was added to a stirred solution of [4-(hydroxymethyl)furan-3-yl]methanol **19.2** (110 mg, 0.78 mmol) in DMSO (2 mL), the temperature being maintained at room temperature during the addition and subsequent reaction period. Stirring was continued for 6 h, and the mixture was acidified to pH 4.5-5 (pH paper) by addition of 1 N hydrochloric acid. Water (25 mL) was added and the mixture was extracted with CH_2Cl_2 (4 x 25 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated (water pump). Flash chromatography of the residue over silica gel (2.4 x 16 cm), using 3:7 EtOAc-hexane, gave furan-3,4-dicarbaldehyde **24.1**[38] (78.8 mg, 74%) as a white solid: ^1H NMR ($CDCl_3$, 400

MHz) δ 8.17 (s, 2 H), 10.30 (s, 2 H).

3,4-Dipentylfuran (24.2).

(a) 3,4-Dipent-1-enylfuran.

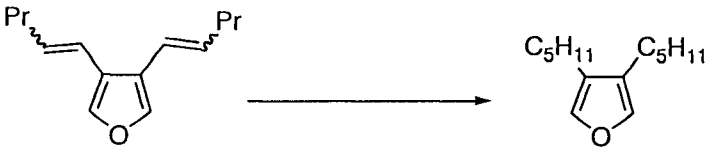


24.1 **24.2**

n-BuLi (1.67 M in hexane, 0.87 mL, 1.45 mmol) was added dropwise to a stirred solution of *n*-butyltriphenylphosphonium bromide (0.369 g, 0.92 mmol) in dry THF (10 mL) at room temperature. The resulting deep-red solution was then cooled to 10 °C (dry ice-acetone bath) and stirred for 10 min. A solution of furan-3,4-dicarbaldehyde **24.1** (50.0 mg, 0.403 mmol) in dry THF (3 mL) was added over 2 min and stirring at 10 °C was continued for 30 min. Water (30 mL) was added and the aqueous layer was extracted with Et_2O (2 x 25 mL). The combined organic extracts were evaporated, and flash chromatography of the residue over silica gel (2.4 x 16 cm), using hexane, gave 3,4-dipent-1-enylfuran **24.2** (48.4 mg, 59%): FTIR (CH_2Cl_2 cast) 3017, 2958, 2871 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.95 (t, J = 7.6 Hz, 6 H), 1.45-1.54 (m, 4 H), 2.15-2.21 (m, 4 H), 5.68-5.74 (m, 2 H), 6.08 (dt, J = 11.2, 2 Hz, 2 H), 7.40 (s, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.87 (q), 22.67 (t), 31.50 (t), 117.44 (d), 121.67 (s), 133.46 (d),

139.81 (d); exact mass (EI) *m/z* calcd for $C_{14}H_{20}O$ 204.15141, found 204.15125.

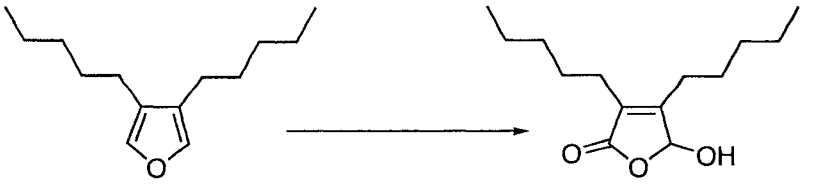
(b) 3,4-Dipentylfuran (24.3).



24.2 **24.3**

Pd-C (9.00 mg) was added to a N_2-flushed flask containing a solution of 3,4-dipent-1-enylfuran **24.2** (130 mg, 0.636 mmol) in EtOAc (10 mL). The flask was flushed with H_2 and the mixture was stirred under H_2 for 11 h. The mixture was filtered through a small pad of Celite and the filtrate was evaporated. Flash chromatography of the residue over silica gel (2.4 x 15 cm), using hexane, gave **24.3** (104.0 mg, 78%): FTIR (CH_2Cl_2 cast) 2957, 2858 cm cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.91 (t, *J* = 6.8 Hz, 6 H), 1.34-1.36 (m, 8 H), 1.51-1.60 (m, 4 H), 2.34 (t, *J* = 7.6 Hz, 4 H), 7.27 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.02 (q), 22.48 (t), 23.53 (t), 29.03 (t), 31.72 (t), 125.22 (s), 138.90 (d); exact mass *m/z* calcd for $C_{14}H_{24}O$ 208.18271, found 208.18238.

5-Hydroxy-3,4-dipentyl-5*H*-furan-2-one (25.1).

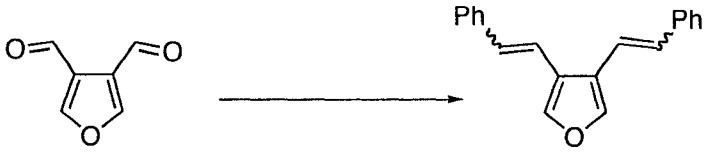


24.3 **25.1**

A freshly-made solution of $NaClO_2$ (0.500 g, 5.53 mmol) and $NaH_2PO_4.H_2O$ (0.50 g, 3.6 mmol) in water (5 mL) was added to a stirred solution of **24.3** (19.5 mg, 0.094 mmol) in EtOH (5 mL). Stirring was continued for 12 h (mixture open to the air) and the mixture was diluted with EtOAc (15 mL). Aqueous $NaHSO_3$ (1 M, 11 mL) was added, and the solution became colorless. The aqueous layer was saturated with NaCl and extracted with EtOAc (4 x 20 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2.4 x 25 cm), using 1:4 EtOAc-hexane, gave **25.1** (21 mg, 93%): FTIR (CH_2Cl_2 cast) 3377, 1742 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.88-0.93 (m, 6 H), 1.30-1.70 (m, 12 H), 2.24 (t, *J* = 8 Hz, 2 H), 2.38-2.44 (m, 2 H), 3.43 (d, *J* = 8 Hz, 1 H), 5.95 (d, *J* = 7.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.9 (q), 13.9 (q), 22.3 (t), 22.4 (t), 23.5 (t), 27.0 (t), 27.2 (t), 27.8 (t), 31.6 (t), 31.8 (t), 97.0 (d), 130.3 (s), 159.4 (s), 172.0 (s); exact mass *m/z* calcd for $C_{14}H_{24}O_3$ 240.17255, found 240.17325.

3,4-Di(phenethyl)furan (26.2).

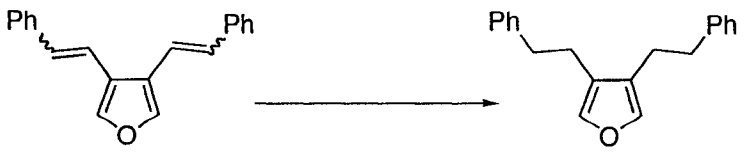
(a) 3,4-Distyrylfuran.



24.1 **26.1**

n-BuLi (1.67 M in hexane, 3.25 mL, 5.43 mmol) was added dropwise to a stirred solution of benzyltriphenylphosphonium bromide (2.3 g, 5.3 mmol) in dry THF (21 mL) at room temperature. The resulting deep-red solution was then cooled to 10 °C (dry ice-acetone bath) and stirred for 10 min. A solution of furan-3,4-dicarbaldehyde **24.1** (300.0 mg, 2.417 mmol) in dry THF (3 mL) was added over 2 min and stirring at 10 °C was continued for 1 h. Water (30 mL) was added and the aqueous layer was extracted with Et_2O (25 x 3 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (3 x 15 cm), using hexane, gave 3,4-distyrylfuran **26.1** (180 mg, 27%) as a colorless liquid, which was used directly in the next step.

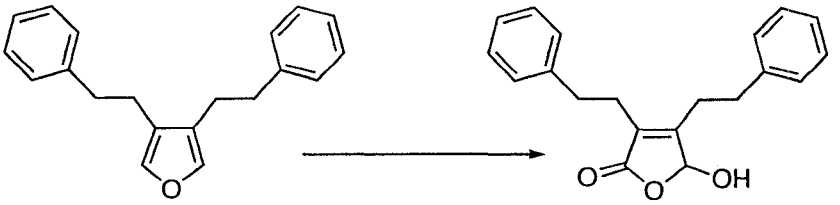
(b) 3,4-Di(phenethyl)furan (26.2).



26.1 **26.2**

Pd-C (9.0 mg) was added to a solution of 3,4-distyrylfuran **26.1** (108 mg, 0.396 mmol) in EtOAc (6 mL) under N_2. The flask was then flushed with H_2, and the mixture was stirred overnight under H_2 (balloon). The mixture was filtered through a small pad of Celite, using EtOAc (30 mL) as a rinse. Evaporation of the filtrate and flash chromatography of the residue over silica gel (2 x 14 cm), using 1:15 EtOAc-hexane, gave **26.2** (84.7 mg, 77%) as a colorless liquid: FTIR (CH_2Cl_2 cast) 3084, 3061, 3025, 2925, 2857 cm cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.64 (t, *J* = 8.4 Hz, 4 H), 2.86 (t, *J* = 7.2 Hz, 1 H), 7.14-7.30 (m, 12 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.58 (t), 35.81 (t), 124.36 (s), 126.12 (d), 128.35 (d), 141.98 (d); exact mass *m/z* calcd for $C_{20}H_{20}O$ 276.15143, found 276.15169.

5-Hydroxy-3,4-diphenethyl-5*H*-furan-2-one (27.1).

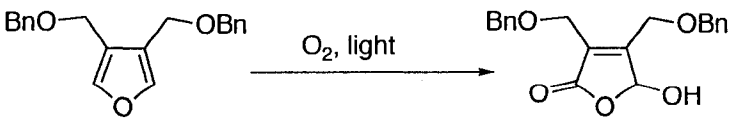


26.2 **27.1**

A freshly-made solution of $NaClO_2$ (0.60 g, 6.6 mmol) and $NaH_2PO_4.H_2O$ (0.60 g, 4.4 mmol) in water (6 mL) was added to a stirred solution of **26.2** (34.0 mg, 0.123 mmol) in EtOH (6 mL). Stirring was continued for 4 h (mixture open to the

air). At this stage some **26.2** remained (TLC, silica, 3:7 EtOAc-hexane). $NaClO_2$ (0.500 g, 5.53 mmol) and $NaH_2PO_4.H_2O$ (0.500 g, 3.62 mmol) were dissolved in H_2O (5 mL) and an aliquot (1 mL) of the freshly-made solution was added to the reaction mixture. Stirring was continued for another 4 h. The yellow-colored solution was diluted with EtOAc (25 mL) and the aqueous layer was saturated with NaCl and extracted with EtOAc (4 x 15 m L). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (10 x 3 cm), using 3:7 EtOAc-hexane gave **27.1** (34.3 mg, 90%): FTIR (CH_2Cl_2 cast) 3353, 1738 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.44-2.75 (m, 8 H), 3.26 (d, J = 8.4 Hz, 1 H), 5.79 (d, 8 Hz, 1 H), 7.07-7.31 (m, 10 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.7 (t), 27.7 (t), 33.3 (t), 33.5 (t), 97.2 (d), 126.3 (d), 126.6 (d), 128.2 (d), 128.5 (d), 128.6 (d), 128.7 (d), 129.7 (s), 140.1 (s), 140.8 (s), 159.2 (s), 171.9 (s); exact mass calcd for $C_{20}H_{20}O_3$ *m/z* 308.14124, found 308.14054.

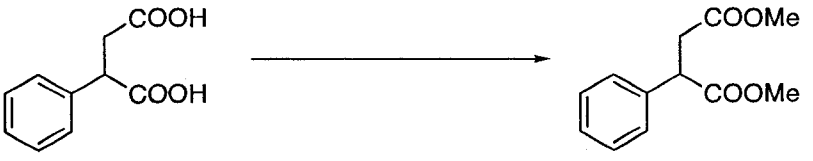
3,4-Bis(benzyloxymethyl)-5-hydroxy-5*H*-furan-2-one (22.1).



19.4 **22.1**

Rose Bengal (1.82 mg) was added to a solution of **19.4** (36.0 mg, 0.117 mmol) and *i*-Pr_2NEt (0.22 mL, 1.3 mmol) in CH_2Cl_2 (6 mL). The solution was cooled to -78 °C and anhydrous O_2 (dried by passage through Drierite) was bubbled through it for 10 min, after which the mixture was irradiated with a 200 W tungsten filament lamp (placed about 9 inches away) with continued passage of O_2. After 20 h, the pink solution was diluted with Et_2O (20 mL) and washed with hydrochloric acid (1 N, 25 mL) and brine (20 mL), dried (Na_2SO_4), and directly filtered through a pad of silica gel (1.5 x 30 cm), using Et_2O (50 mL) as a rinse. Evaporation of the filtrate, and flash chromatography of the residue over silica gel (2.2 x 23 cm), using 3:7 EtOAc-hexane, gave **22.1** (38.0 mg, 96%): ^1H NMR ($CDCl_3$, 300 MHz) δ 3.49 (d, *J* = 7.5 Hz, 1 H), 4.32-4.64 (m, 8 H), 6.10 (d, *J* = 7.5 Hz, 1 H), 7.26-7.37 (m, 10 H).

Dimethyl 2-phenylsuccinate (30.2).

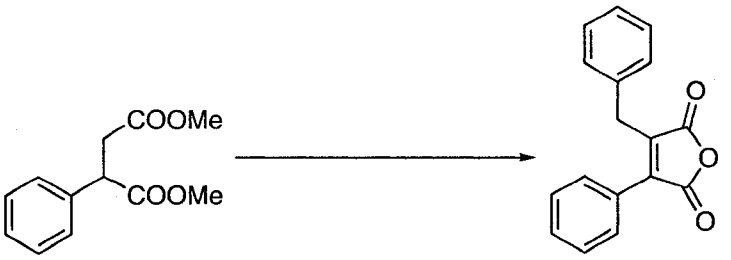


30.1 **30.2**

Concentrated H_2SO_4 (1 mL) followed by trimethyl orthoformate **30.1** (1.4 mL, 12.8 mmol) were added to a solution of phenyl succinic acid (2.5 g, 12.9 mmol) in MeOH

(100 mL). The solution was refluxed for 28 h and then cooled, washed sequentially with H_2O (50 mL), 10% $KHCO_3$ (50 mL) and H_2O (50 mL). The organic layer was evaporated and the residue was purified by flash chromatography over silica gel (4.5 x 12 cm), using 1:3 EtOAc-hexane, to afford **30.2**[24] (2.64 g, 91%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.68 (dd, *J* = 16.9, 5.3 Hz, 1 H), 3.22 (dd, *J* = 17.0, 10.1 Hz, 1 H), 3.68 (s, 3 H), 3.69 (s, 3 H), 4.10 (dd, *J* = 10.1, 5.3 Hz, 1 H), 7.27-7.36 (m, 5 H).

3-Benzyl-4-phenyl-furan-2,5-dione (30.7).



30.2 **30.7**

A mixture of dimethyl phenylsuccinate **30.2** (5.12 g, 23.0 mmol), benzaldehyde (3.20 g, 30.2 mmol) and dry *t*-BuOH (50 mL) was added to a stirred solution of potassium *t*-butoxide (5.2 g, 46 mmol) in *t*-BuOH (50 mL) at room temperature. After being stirred at 40 °C for 43 h, the solution was cooled and poured into ice-water (200 mL) and the separated oil was taken up in Et_2O. The aqueous layer was acidified with 10% H_2SO_4 to pH 1 and then extracted with EtOAc (4 x 75 mL). The

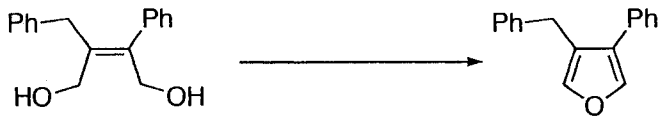
combined organic extracts were washed with brine, and evaporated to give a brown oil (8.3 g) which was dissolved in a mixture of KOH (3.35 g, 58.9 mmol), EtOH (70 mL) and H_2O (35 mL). The resulting mixture was refluxed for 2 h. The solvent was evaporated and the residue was diluted with water (35 mL), and washed with Et_2O (1 x 20 mL). The aqueous layer was acidified with 10% H_2SO_4 to pH 1 and extracted with EtOAc (4 x 30 mL). The combined organic extracts were washed with brine and evaporated to give a brown oil (8 g), which was heated under reflux in Ac_2O (40 mL) for 1 h. Removal of the solvent left a brown oil (6.4 g), which was purified by flash chromatography over silica gel (4.5 x 21 cm), using 1:9 EtOAc-hexane, to give **30.7**[25] (5.07 g, 54%): ^1H NMR ($CDCl_3$, 500 MHz) δ 4.03 (s, 2 H), 7.18-7.21 (m, 2 H), 7.25-7.27 (m, 1 H), 7.30-7.34 (m, 2 H), 7.48-7.53 (m, 3 H), 7.60-7.62 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 30.5 (t), 127.1 (s), 127.4 (d), 128.4 (d), 129.0 (d), 129.1 (d), 129.4 (d), 131.2 (d), 135.4 (s), 140.7 (d), 141.1 (s), 164.8 (s), 165.8 (s).

3-Benzyl-4-phenylfuran (30.8). (a) (*Z*)-3-Benzyl-2-phenyl-2-butene-1,4-diol.

30.7 **30.8**

$LiAlH_4$ (783.0 mg, 19.6 mmol) was added to a stirred and cooled (-78 °C) solution of 3-benzyl-4-phenylfuran-2,5-dione **30.7** (2.07 g, 7.83 mmol) in dry Et_2O (30 mL). After 30 min, the cooling bath was removed and stirring was continued for 8 h. Et_2O (35 mL) was added, followed by saturated aqueous NH_4Cl. The aqueous layer was extracted with Et_2O (2 x 30 mL), and the combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 1:1 EtOAc-hexane, gave (*Z*)-2-benzyl-3-phenyl-2-butene-1,4-diol (**30.8**) (386 mg, 20%): FTIR ($CHCl_3$ cast) 3334 cm cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.94 (br s, 2 H), 3.49 (s, 2 H), 4.27 (s, 2 H), 4.51 (s, 2 H), 7.12-7.39 (m, 10 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 38.58 (t), 61.38 (t), 63.98 (t), 126.30 (d), 127.16 (d), 128.38 (d), 128.49 (d), 128.56 (d), 128.70 (d), 138.31 (s), 139.44 (s), 140.89 (s), 141.58 (s); exact mass *m/z* calcd for $C_{17}H_{18}O_2$ 254.13068, found 254.13017.

(b) 3-Benzyl-4-phenylfuran (30.9).

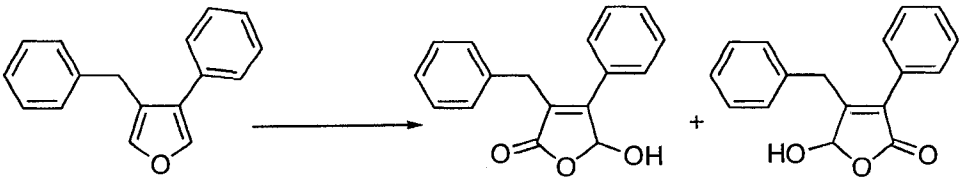


30.8 **30.9**

PCC (777 mg, 2.24 mmol) was added to a stirred solution of (*Z*)-2-benzyl-3-phenyl-2-butene-1,4-diol **30.8** (335 mg, 1.32 mmol) in dry CH_2Cl_2 (7.2 mL) (N_2 atmosphere). Stirring was continued for 45 min, and the mixture was diluted with CH_2Cl_2

(20 mL) and filtered through a pad of silica gel (6 x 25 cm). The flask residue was washed with CH_2Cl_2 (25 mL), which was also filtered through the silica gel pad. The combined organic solutions were evaporated, and flash chromatography of the residue over silica gel (3 x 10 cm), using hexane, gave **30.9** (200.0 mg, 65%): FTIR (CH_2Cl_2 cast) 3026, 1494 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.87 (s, 2 H), 7.11-7.12 (m, 1 H), 7.20-7.36 (m, 10 H), 7.52 (d, *J* = 2 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 30.31 (t), 123.55 (s), 126.14 (d), 127.00 (d), 127.05 (s), 128.18 (d), 128.39 (d), 128.44 (d), 128.46 (d), 128.52 (d), 128.63 (d), 128.67 (d), 128.68 (d), 132.55 (s), 140.01 (d), 140.01 (s), 141.53 (d); exact mass *m/z* calcd for $C_{17}H_{14}O$ 234.10446, found 234.10459.

3-Benzyl-5-hydroxy-4-phenyl-5*H*-furan-2-one (31.1) and 4-Benzyl-5-hydroxy-3-phenyl-5*H*-furan-2-one (29.5).



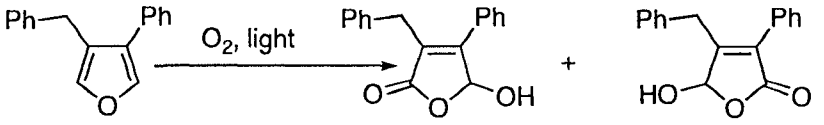
30.9 **31.1** **29.5**

A freshly-made solution of $NaClO_2$ (0.20 g, 2.2 mmol) and $NaH_2PO_4.H_2O$ (0.20 g, 1.45 mmol) in water (2 mL) was added to a stirred solution of **30.9** (30.3 mg, 0.129 mmol) in EtOH (2 mL). Stirring was continued for 4.5 h (mixture open to the air). EtOAc (20 mL) was added, and the aqueous layer was

saturated with NaCl and extracted with EtOAc (4 x 15 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 46 cm), using 3:7 EtOAc-hexane, gave **31.1** and **29.5** (ca 1:1, 24 mg, 69%). The more polar compound, 3-benzyl-5-hydroxy-4-phenyl-5*H*-furan-2-one (**31.1**), had: FTIR (CH_2Cl_2 cast) 3358, 1738 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.67 (d, J = 8.5 Hz, 1 H), 3.88 (AB q, $\Delta\nu_{AB}$ = 39.6 Hz, J = 15.5 Hz), 6.45 (d, J = 8 Hz, 1 H), 7.22-7.55 (m, 10 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 30.1 (t), 97.2 (d), 126.7 (d), 128.3 (d), 128.3 (d), 128.7 (s), 128.8 (d), 129.0 (d), 130.3 (s), 130.4 (d), 137.1 (s), 156.0 (s), 171.8 (s); exact mass m/z calcd for $C_{17}H_{14}O_3$ 266.09430, found 266.09464.

The less polar isomer, 4-benzyl-5-hydroxy-3-phenyl-5*H*-furan-2-one (**29.5**) (microperfuranone), had: FTIR ($CHCl_3$ cast) 3373, 1736 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.94 (AB q, $\Delta\nu_{AB}$ = 119.7 Hz, J = 15.2 Hz), 4.27 (br s, 1 H), 5.90 (d, J = 4.8 Hz, 1 H), 7.17-7.52 (m, 10 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 32.4 (t), 96.5 (d), 127.2 (d), 128.7 (d), 128.8 (d), 128.9 (s), 129.0 (d), 129.0 (d), 129.2 (d), 129.9 (s), 136.0 (s), 158.4 (s), 170.96 (s); exact mass m/z calcd for $C_{17}H_{14}O_3$ 266.09430, found 266.09445.

3-Benzyl-5-hydroxy-4-phenyl-5*H*-furan-2-one (31.1) and 4-Benzyl-5-hydroxy-3-phenyl-5*H*-furan-2-one (29.5).



30.9 **31.1** **29.5**

Rose Bengal (4.80 mg) was added to a solution of **30.9** (49 mg, 0.21 mmol) and *i*-Pr_2NEt (0.38 mL, 2.18 mmol) in CH_2Cl_2 (7 mL). The solution was cooled to -78 °C and anhydrous O_2 (dried by passage through Drierite) was bubbled through for it 10 min, after which the mixture was irradiated with a 200 W tungsten filament lamp (placed about 9 inches away) with continued passage of O_2. After 20 h, the pink solution was diluted with Et_2O (20 mL) and washed with hydrochloric acid (1 N, 10 mL) and brine (20 mL), dried (Na_2SO_4), and filtered through a pad of silica gel (2 x 3 cm), using Et_2O (50 mL) as a rinse. Evaporation of the filtrate at room temperature, and flash chromatography of the residue over silica gel (2 x 23 cm), using 3:7 EtOAc-hexane, gave a mixture of **31.1** and **29.5** (43.5 mg, 78%) as an oil: FTIR (CH_2Cl_2 cast) 3362, 1736 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) (mixture of both isomers) δ 3.78-4.14 (m, 3 H), 5.91 (d, *J* = 7.5 Hz, 1 H), 6.45 (d, *J* = 8.1 Hz, 1 H), 7.18-7.55 (m, 10 H); ^{13}C NMR ($CDCl_3$, 100 MHz) (mixture of both isomers) δ 29.97 (t), 32.41 (t), 96.78 (d), 97.68 (d), 126.68 (d), 127.16 (d), 128.23 (s), 128.26 (d), 128.36 (d), 128.68 (d), 128.72 (d), 128.83 (d), 128.94 (d), 129.00 (d), 129.02 (d), 129.13 (d), 129.73 (s), 130.37 (s), 130.37 (d), 136.00 (s), 137.09 (s), 156.72 (s), 158.76 (s),

171.38 (s), 172.72 (s); exact mass *m/z* calcd for $C_{17}H_{14}O_3$ 266.09430, found 266.09426.

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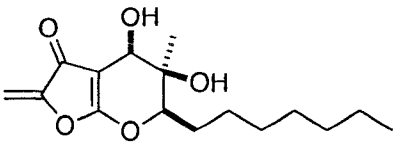
CHAPTER II

Oxidative Decarboxylation as a Route to ketene Acetals: Assignment of Relative and Absolute Stereochemistry to the Fungal Metabolite Benesudon by Total Synthesis

1. INTRODUCTION

Benesudon, originally assigned the structure and relative stereochemistry shown in **1**, is a metabolite isolated from an uncommon type of fungus.[1] The substance shows antibacterial and antifungal activity and has a cytotoxic effect with IC_{90} values of 1-2 μg/mL.[1] So far, no synthetic work on benesudon has been reported apart from that done in this laboratory as part of my research program. Although structure **1** is compact, it still

SCHEME 1

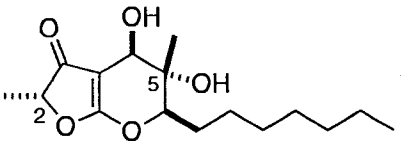


benesudon **1**

incorporates several features within its small framework – ketene acetal, α-methylene ketone, enol ether, and vinylogous ester subunits that are readily discernable and are also interrelated. Assignment of the gross structure of benesudon was made by application of appropriate spectroscopic techniques, especially ^{1}H and ^{13}C NMR measurements, and the relative stereochemistry shown was supported by the observed nuclear Overhauser effects. However, during our synthetic work, the isolation and structure determination of a related compound – aigialone **2**

– was reported.[2] This substance, which is a metabolite of a marine fungus, is crystalline and its relative stereochemistry was established by X-ray analysis. Apart from the presence of a methyl group at C(2) instead of the methylene of benesudon, the noteworthy feature of aigialone is the relative stereochemistry, which differs at C(5) from that suggested for benesudon. The X-ray data also showed that in the solid state the new metabolite has the two hydroxyl groups and the heptyl chain pseudoaxial, and nuclear Overhauser data for deuterochloroform solutions could be rationalized on the basis of this unusual conformation. The two compounds **1** and **2** were obtained from different organisms and, while the X-ray data for **2** suggested the need for stereochemical revision of structure **1**, we did not regard the evidence as compelling and so we continued with our route to **1**; however, in the event, we eventually found that revision is indeed required.

SCHEME 2

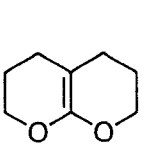


2

The structure type represented by benesudon is rare, not only among natural products but also in its own right,

and an examination of both the Beilstein and SciFinder Scholar databases for ketene acetals embedded within bicyclic systems retrieves very few examples besides benzo-fused compounds (i.e. chromones) and γ-pyranones. The only relevant substances we have been able to locate, apart from model compounds made in our own studies, are those shown in Scheme 3. The ketene acetals **3.1**,[3] **3.2**,[4] **3.3**[4] and **3.4**[5] are totally synthetic products, while **3.5**[6] (trichodion) and **3.6**[7] (cyclogregatin) were isolated from fungi. The former natural product is an inhibitor of inflammatory signal transduction pathways,[6b] and the latter has weak antimicrobial, antifungal and cytotoxic activity.[7] Compounds **3.1-3.3**, **3.5** and **3.6** were known before we started our synthetic work, while **3.4**, which is formed by a complicated rearrangement, was reported after[8] we had begun. Where the carbonyl group resides within a six-membered ring, as in the relatively simple structures **3.2** and **3.3**, synthetic access by Diels-Alder cycloaddition is straightforward,[4] but the presence of a carbonyl group in the five-membered ring makes the identification of potential synthetic routes more complicated; no general approaches were available when we started and, as far as we are aware, the only method is that resulting from the present investigation.

SCHEME 3. Bicyclic Ketene Acetals



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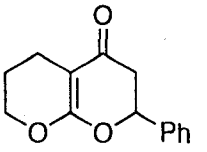

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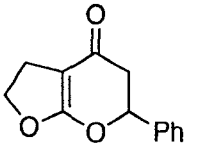

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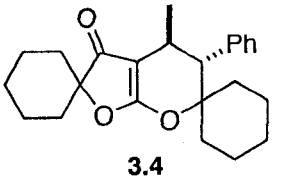

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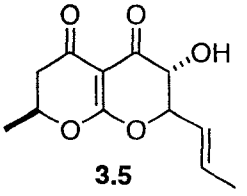
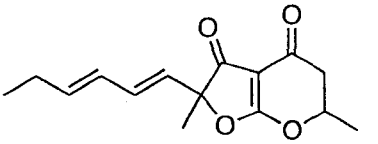


3.5



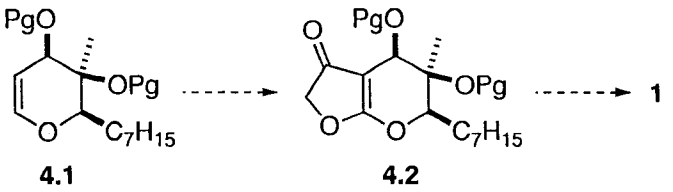
3.6

2. RESULTS AND DISCUSSION

2.1 Initial Approaches

In our initial studies we underestimated the difficulties we would encounter in trying to introduce the central double bond that is characteristic of benesudon. Our first approach was based on a compound of type **4.1** onto which we hoped to build a five-membered ring (**4.1**→**4.2**). From that point, methylenation and deprotection would generate the target. In order to simplify our work we decided to use methyl α-D-glucopyranoside as the source of the six-membered ring **4.1** (Scheme 4). This decision implies an arbitrary assumption that benesudon has the same absolute configuration as D-glucose at the corresponding asymmetric centers.

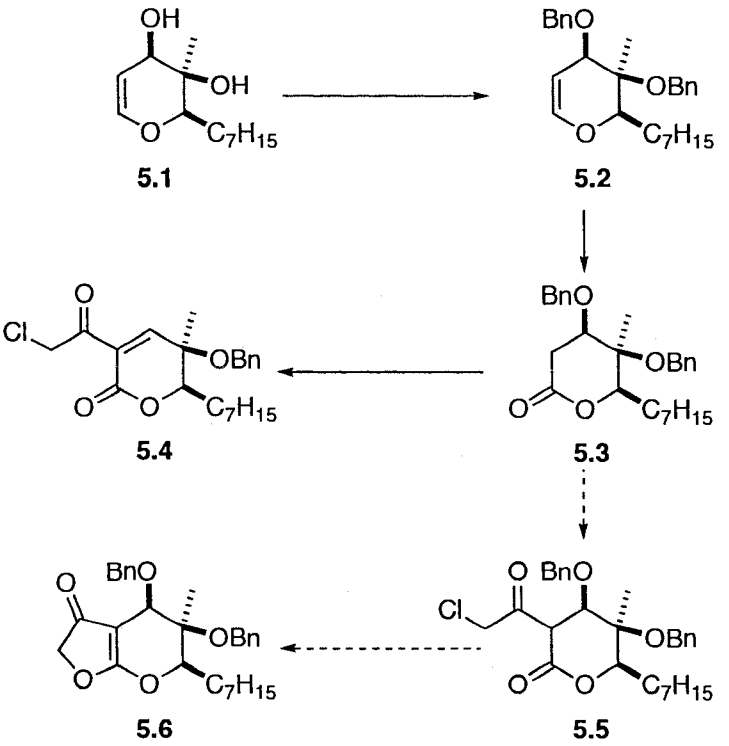
SCHEME 4. Initial Plan



With this plan in mind, the diol **5.1**, whose synthesis from D-glucose is described later, was protected by benzylation[9] and then oxidized to the lactone **5.3**. Deprotonation with LDA at -78 °C[9] and treatment with $ClCH_2COCl$ did effect acylation but we were unable to prevent

loss of the secondary benzyloxy group so that the product we isolated[9] was the enone **5.4.** The intention had been to explore the pathway **5.3→5.5→5.6,** but access to this route was blocked by the ready expulsion of the benzyloxy group.

SCHEME 5. Attempted Acylation of a δ-Lactone

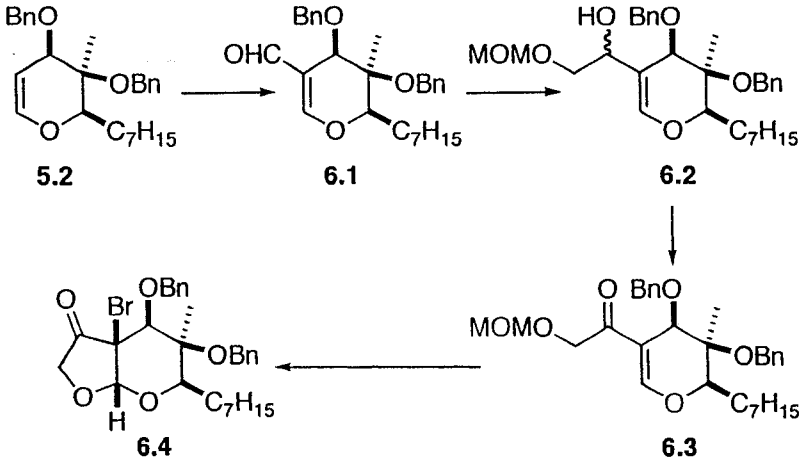


5.1 **5.2** **5.3** **5.4** **5.5** **5.6**

Our next approach[9b] was again based on **5.2,** but this time the compound was subjected to Vilsmeier-Haack formylation (Scheme 6, **5.2→6.1**), and the product was exposed to the action of $MeOCH_2OCH_2Li$, generated in situ from $MeOCH_2OCH_2SnBu_3$[10] and BuLi. Oxidation of the resulting alcohols with TPAP/NMO produced the ketone **6.3,** and

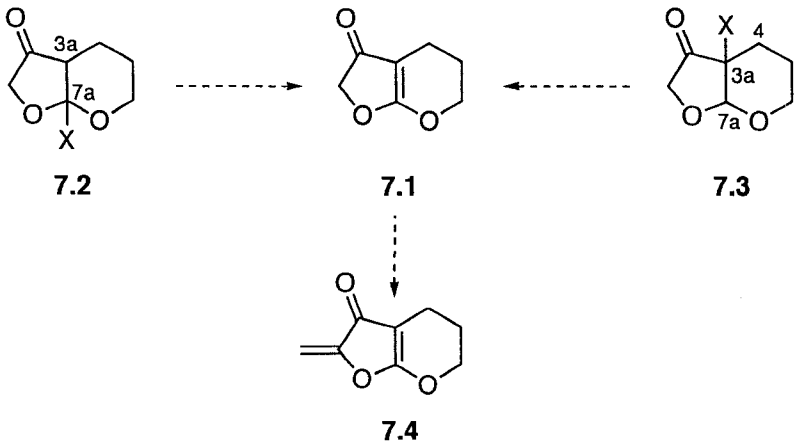
treatment with NBS and CF_3CO_2H generated the cyclized product **6.4** in 53% yield. While the gross structure of **6.4** is clear from its NMR spectra, the ring fusion stereochemistry is a tentative assignment; cis ring fusion would be expected, but whether the bromine is cis or trans to the adjacent benzyloxy group was not established.[9b,11] With the bicyclic skeleton in hand attempts were made to introduce the central double bond, but all experiments to this end were unsuccessful,[9b,12] and we were eventually forced to adopt the conservative approach of studying a simple model compound in the hope of being able to devise a robust route to the ketene acetal core structure characteristic of benesudon. Accordingly, our target became[9b] the model **7.1** (Scheme 7) which we expected would be easily convertible into the α-methylene compound **7.4**.

SCHEME 6. Formation of Five-Membered Ring without Central Double Bond



2.2 Synthesis of the Core Structure

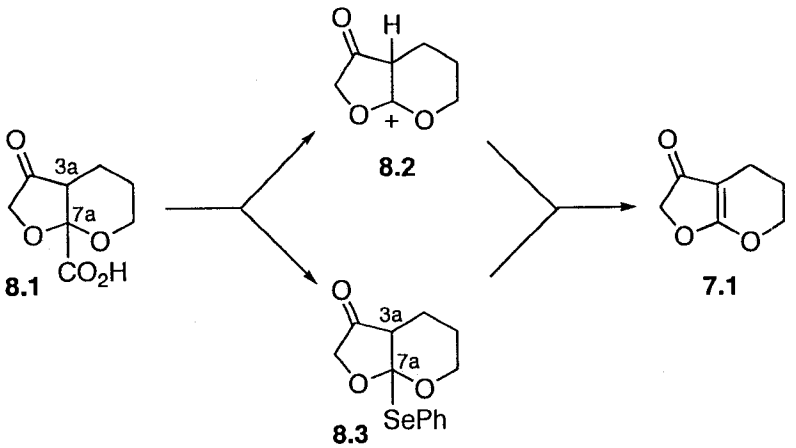
SCHEME 7. Potential Routes to the Core Structure 7.1.



In principle, **7.1** should be accessible from compounds of type **7.2** or **7.3** by a proper choice of X. The stereochemical requirements of the two routes depend on the nature of X. If this substituent is PhSe, then X and the adjacent ring fusion hydrogen must be cis, while if X is a halogen then the ring fusion stereochemistry should be trans so as to allow for an anti elimination pathway. However, there is an additional factor in that for intermediate **7.3** the group X should preferably also have a relative stereochemistry with respect to the C(4) substituent such that elimination towards C(4) is mechanistically blocked. If X is a heteroatom (e.g. as in SePh) then compounds of type **7.2** might be difficult to handle because of their inherent lability. This disadvantage for routes via **7.2** is offset, however, by the

fact that **7.2** requires only one stereochemical restriction – the relationship of X to the adjacent ring fusion hydrogen, while for **7.3** the stereochemical relationship to two hydrogens – those at both C(4) and C(7a) – must be considered. In the event, our experimental work related to the model compound **7.1** was based exclusively on the approach via **7.2** and we decided to set X = CO_2H. This choice would offer the possibility of replacing the carboxyl group by a halogen or by PhSe (Scheme 8, **8.1→8.3**), using the derived Barton ester, and might also serve directly for introduction of the C(3a)-C(7a) double bond by oxidative decarboxylation (Scheme 8, **8.1→8.2→7.1**). This plan was first studied by H. Yang,[9b] but was taken over and completed by me.

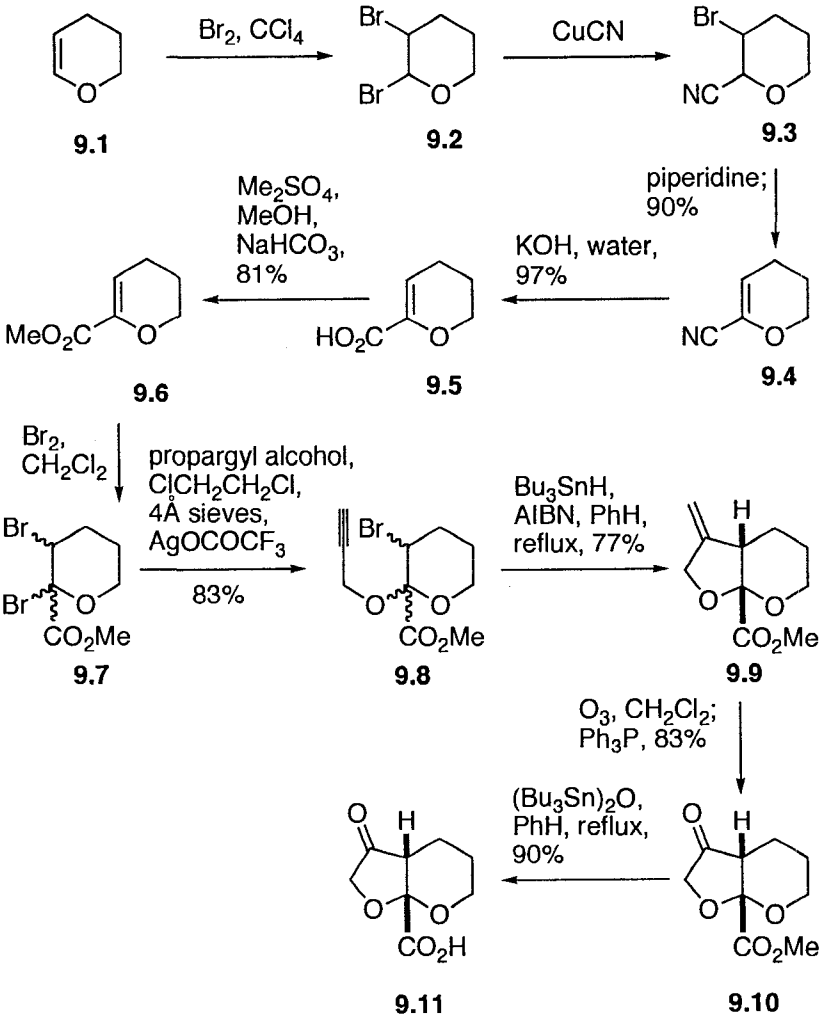
SCHEME 8. Potential Methods for Generating the Ketene Acetal System



Our route to **8.1** began with dihydropyran, which was converted, following a published method,[14] into the unsaturated nitrile **9.4** (Scheme 9). Base hydrolysis and esterification[15a] then gave ester **9.6**. Reaction with Br_2 formed the dibromides **9.7** and addition to a mixture of propargyl alcohol, 4Å molecular sieves and $AgOCOCF_3$[15b] provided the bromoethers **9.8**. These are correctly constituted for radical cyclization, and reaction with Bu_3SnH in the presence of an initiator brought about the desired 5-*exo digonal* closure (**9.8**→**9.9**), and ozonolysis then gave ketone **9.10**. In order to try the oxidative decarboxylation, we had only to hydrolyze the ester group in **9.10**, but this initially proved to be troublesome,[9b] and experiments using LiOH in aqueous MeOH were unsuccessful. However, when $(Bu_3Sn)_2O$[16] was eventually tried the reaction worked smoothly (90%), although the product **9.11** was not very stable and was best used within an hour of its isolation.

Having obtained the acid **9.11** we were now in a position to try to replace the carboxyl group by PhSe, PhS, or a 2-pyridylthio group,[17] so that oxidation via a selenoxide or sulfoxide would generate the crucial C(3a)-C(7a) double bond. Surprisingly, experiments directed to this end were unpromising[9b] and so we had to investigate the remaining pathway of oxidative decarboxylation, using

SCHEME 9. Preparation of Acid 9.11 for Oxidative Decarboxylation

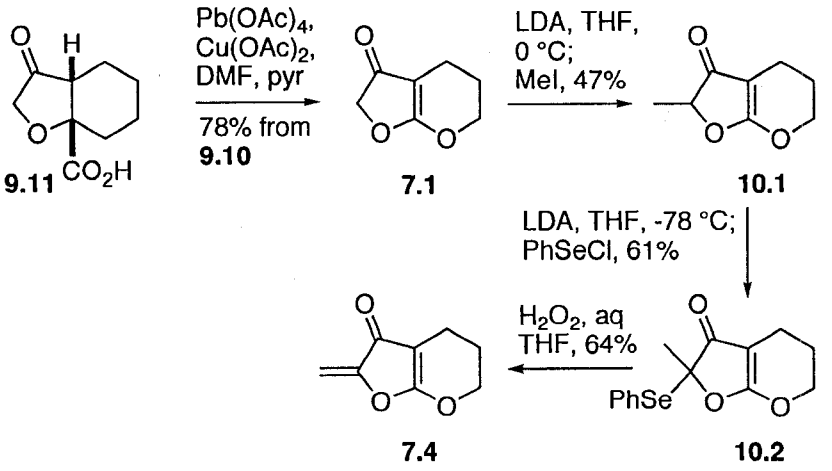


$Pb(OAc)_4$ in the presence of a cupric salt.[18] Although such experiments were first attempted by H. Yang,[9b] it was decided that I should make a more extensive investigation and, in the event, this further work led to a solution to the problem.

Our first experiment involved treating the acid **9.11** with $Pb(OAc)_4$ and $Cu(OAc)_2.H_2O$ in the presence of pyridine under conditions close to those reported in the literature for oxidative decarboxylation[18a] and, although the yield was very low, a small amount of **7.1** was indeed isolated. We then repeated the experiment a number of times, varying the conditions slightly each time, until we found a reliable procedure that gave the desired product in satisfactory yield (78% from ester **9.10**). In this optimized method, $Cu(OAc)_2.H_2O$ is added to a solution of freshly-prepared carboxylic acid **8.1** in dry PhH, followed after a few minutes by addition at 30-min intervals and in the dark, of several portions of $Pb(OAc)_4$.

Initially standard methods for the α-methylenation of ketones[19] were applied to **7.1**, but these experiments were unsuccessful. Consequently, the ketene acetal **7.1** was first methylated in the standard way (Scheme 10, LDA, THF, MeI). The yield in this step was poor because of extensive bis-methylation, but little effort was made to improve the reaction because this was only a model study. Phenylselenation of **10.1** and selenoxide fragmentation then gave **7.4**, the core structure of benesudon, as a sharp-melting solid. Unlike its parent acid **9.11**, the complete core structure **7.4** was easily handled and did not seem to be noticeably sensitive.

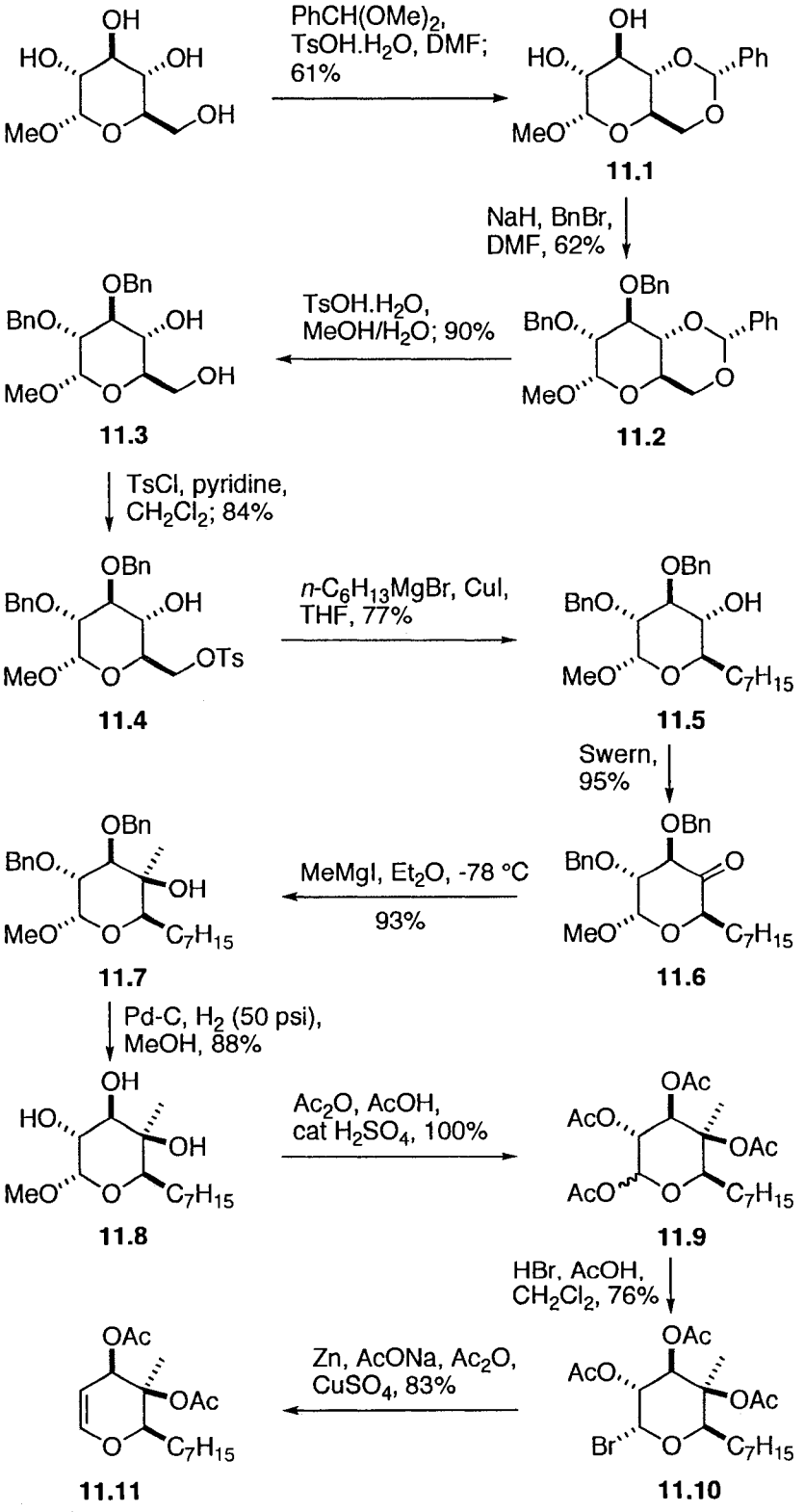
SCHEME 10. Formation of the Core Structure of Benesudon.



2.3 Synthesis of benesudon – original stereochemistry

Once we had established a method for constructing the ketene acetal subunit we returned to the task of making the natural product and, as stated above, based our approach on the use of D-glucose. This was converted in four simple steps by known procedures into the tosylate **11.4**.[20] Homologation with the organocuprate made from *n*-$C_6H_{13}MgBr$ gave alcohol **11.5**,[20] which was then oxidized under Swern conditions (**11.5**→**11.6**). All the substituents of the ketone are equatorial and there was no danger of epimerization adjacent to the carbonyl group. Reaction with MeMgI in Et_2O afforded tertiary alcohol **11.7** with little of the epimeric alcohol, the ratio of the two being 24:1 in favor of **11.7**. Later, in this work we would need the isomeric tertiary alcohol and it is fortunate that the stereochemical outcome of this reaction can be controlled by a proper choice of

SCHEME 11. Preparation of the Key Glycal.

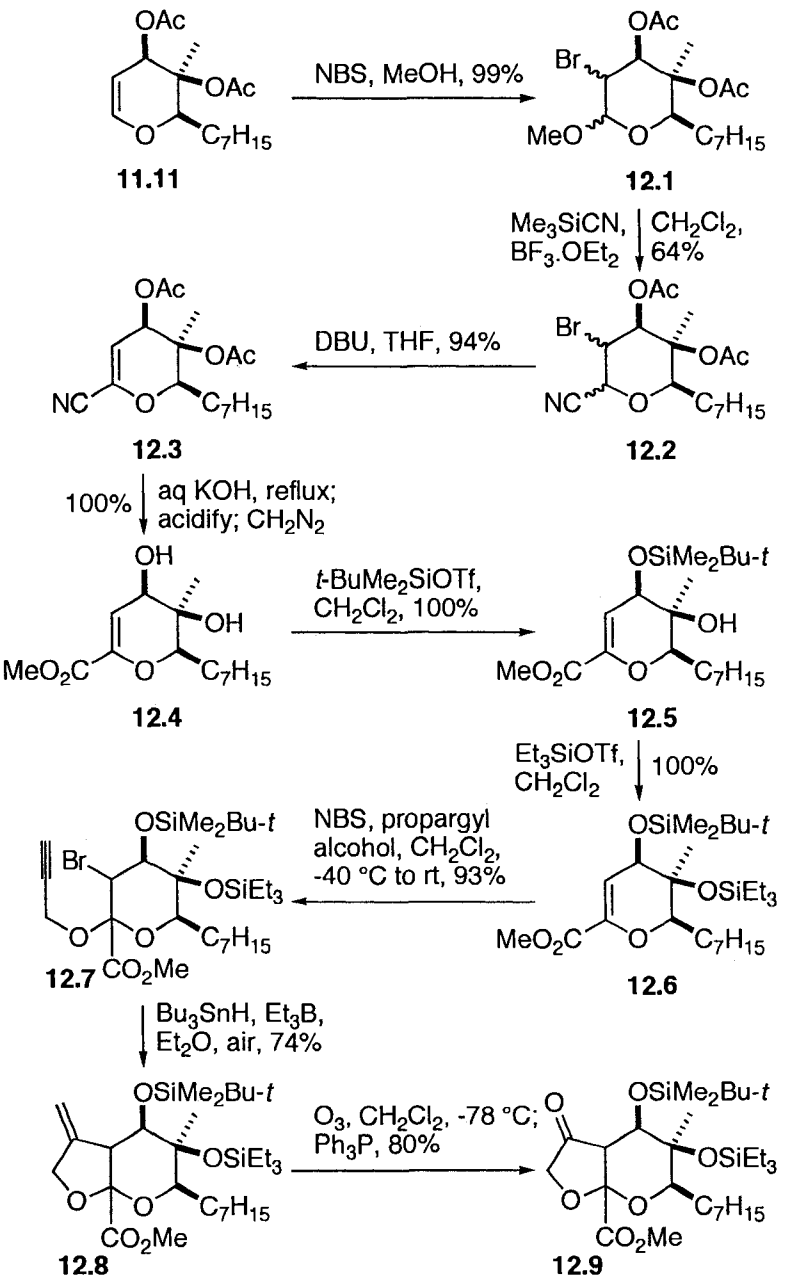


reagent (organolithium or Grignard reagent), solvent and temperature.[21,22] In the present case, the choice of ethereal MeMgI was made by analogy with the stereochemistry reported[21] for reaction of a related ketone differing only in the nature of the C(6) substituent (OCH_2OCPh_3 instead of C_7H_{15}). The correctness of the stereochemical assignment was established by X-ray analysis of a compound made from **11.7** during H. Yang's initial studies.[9b,23]

Debenzylation by hydrogenolysis, and acetylation led to the tetraacetates **11.9**, and at this stage the anomeric acetoxy group was replaced by bromine in the standard way. Finally, Zn reduction produced glycal **11.11**. This compound represents the portion of our target (**1**) onto which we planned to build the remainder of the ketene acetal, using methods developed in making the unsubstituted core structure.

In our model study (Scheme 9, **9.1**→**9.5**), simple bromine addition and reaction with CuCN had served to introduce the nitrile group, but this method did not work when applied to **11.11** (or to the corresponding bis-*O*-benzyl analog), and so a different approach was needed. Reaction of the glycal **11.11** with NBS in MeOH gave the expected 2-bromoglycosides **12.1**, and the anomeric methoxy group was then replaced by reaction with Me_3SiCN in the presence of $BF_3.OEt_2$.[24] Base treatment now caused elimination to the unsaturated nitrile

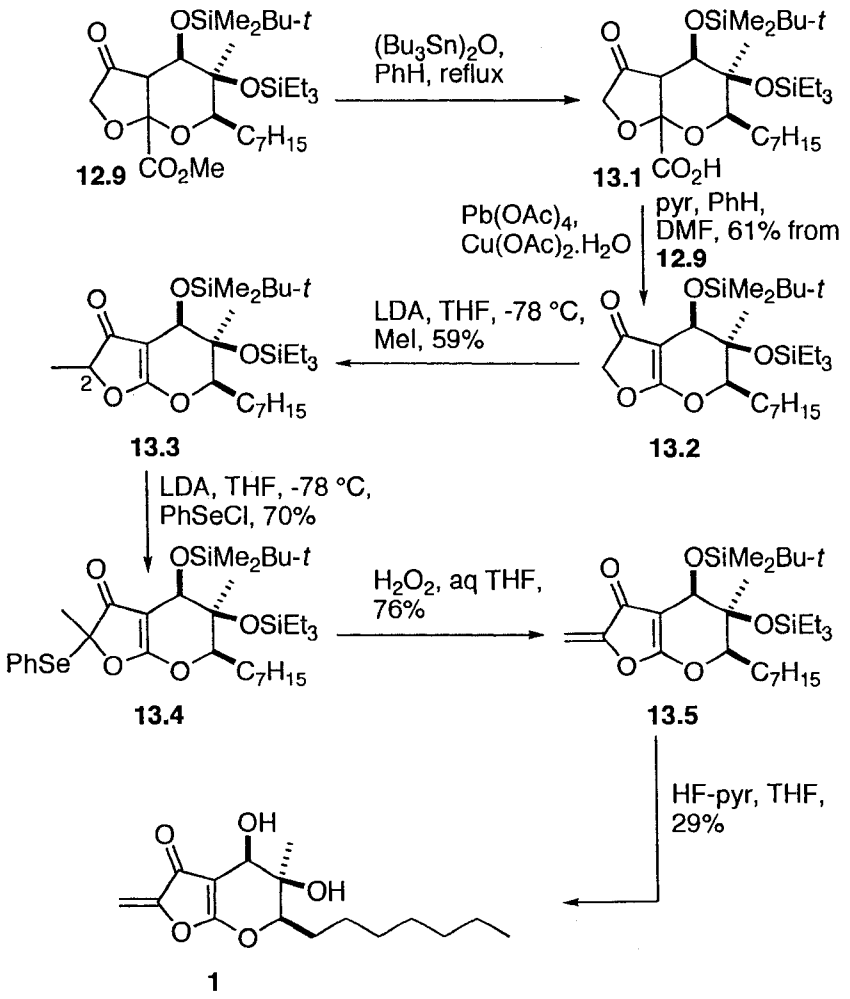
SCHEME 12. Elaboration of Glycal 11.11.



12.3. As in the model study, the nitrile was hydrolyzed with aqueous KOH and the resulting acid was methylated.

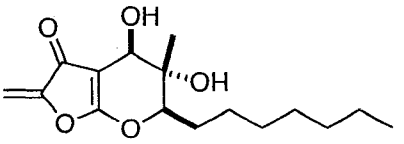
We initially intended to protect both hydroxyls of **12.4** as their *tert*-butyldimethylsilyl ethers, but only the secondary hydroxyl could be so protected, and therefore the remaining tertiary hydroxyl was masked as its triethylsilyl ether (**12.4→12.5→12.6**). Next, in order to attach the acetylenic side chain, we tried the method that had been successful in the preparation of the core structure, but this procedure did not work in the present case. However, after several trial experiments we were able to find conditions that did allow conversion of **12.6** into **12.7**; these involved use of a large excess of propargyl alcohol in the presence of NBS. Likewise, the conditions previously used for the radical cyclization in making the core structure were also unsuccessful, but when we tried Bu_3SnH and Et_3B in the presence of air,[25] cyclization occurred satisfactorily (74%). Finally, ozonolysis took us to the point where the next step was introduction of the critical central double bond and, for this reaction (Scheme 13) both the tin oxide-mediated ester hydrolysis and the oxidative decarboxylation occurred under the conditions established in our route to the core structure. Methylation of the ketone under standard conditions provided compound **13.3** as a single isomer whose stereochemistry at C(2) was not established.

SCHEME 13. Formation of Originally Proposed Structure of Benesudon.



Phenylselenation in the usual way proceeded without incident, as did the subsequent oxidation and fragmentation of the selenoxide, bringing the route to **13.5**, a protected version of the target. Removing the silicon protecting groups was troublesome, and use of Bu_4NF in THF with or without AcOH was unsuccessful; it appears that the desired

product **1** is sensitive to fluoride ion. Use of HF-pyridine was the most promising method and gave **1** in 29% yield. We did not try to optimize these conditions mainly because the NMR spectra, especially the ^{13}C NMR spectrum, of **1** differed significantly from those reported for natural benesudon. There was no doubt about the gross structure assigned to benesudon, and so only a stereochemical alteration was necessary, and the most likely candidate was **3** with a stereochemistry analogous to aigialone (**2**).

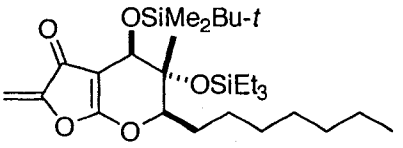


3

2.4 Synthesis of benesudon

In principle, the route we had used to make **1** should be applicable to **3** because, as mentioned earlier, the stereochemical outcome of the addition of organometallic reagents to ketone **11.6** can be controlled, and this should be the only step that requires alteration. In the event, matters were not nearly so simple; conversion of ketone **11.6** to the tertiary alcohol with stereochemistry corresponding to **3** was readily achieved, but this stereochemical alteration exerted a profound influence on other reactions so that appreciable modification was necessary. Moreover, the structure **3** appeared to be even

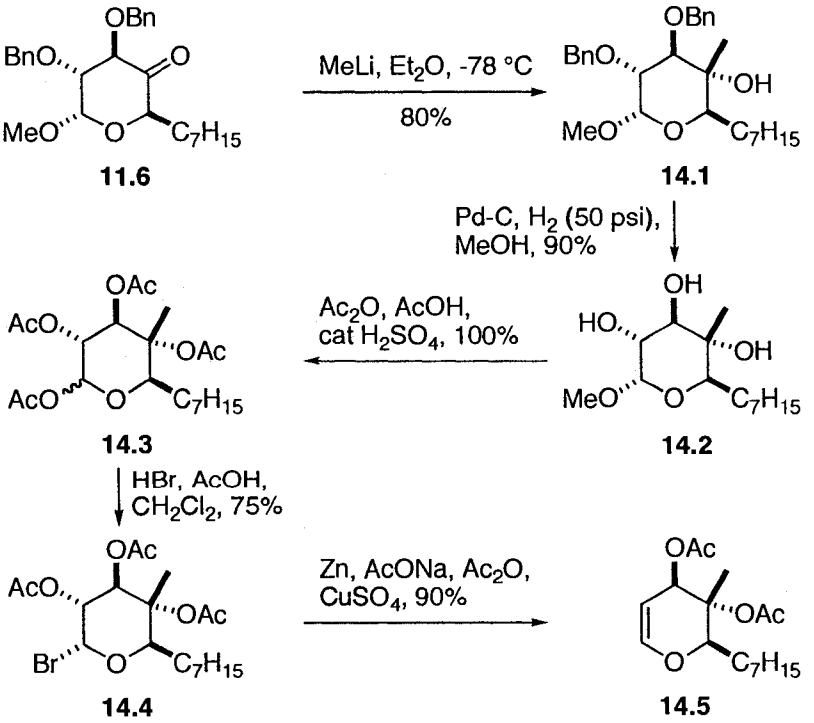
more sensitive to fluoride ion than **1** and, although we were able to reach **4** (as described below), it was impossible to



4

remove the *t*-BuMe$_2$Si group without destroying the material. Consequently, we had to repeat the whole sequence with a more labile protecting group for the secondary hydroxyl group and we selected Et$_3$Si – a choice that proved

SCHEME 14. Preparation of the Glycal with Inverted Quaternary Center.

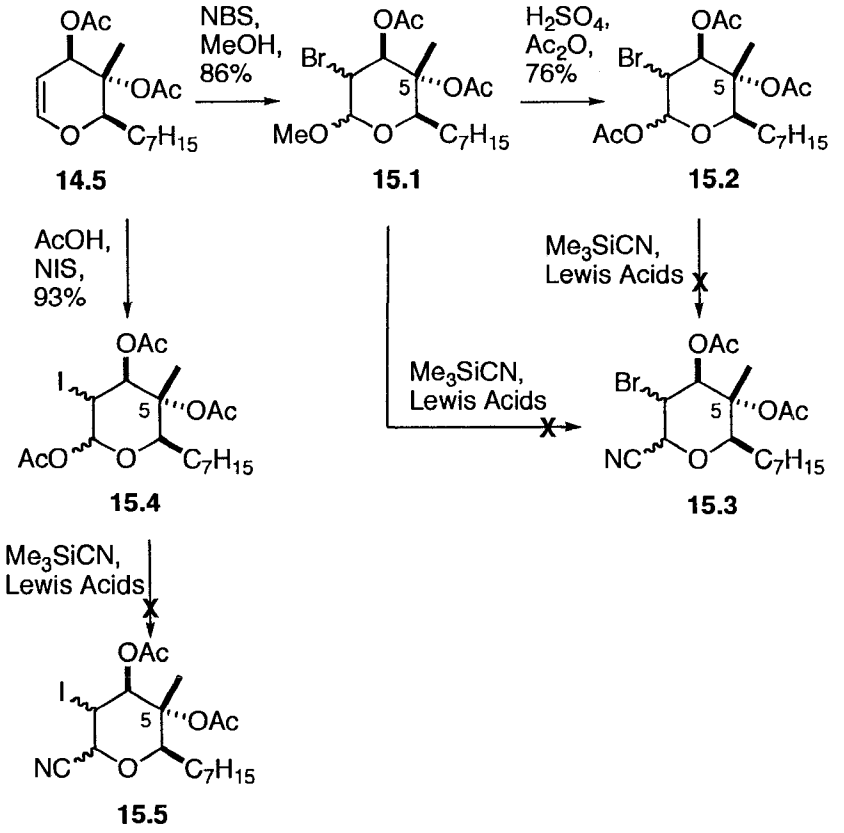


satisfactory, but only just.

We began our approach to **4** by treating ketone **11.6** with MeLi in Et_2O (Scheme 14) and obtained **14.1** with opposite stereochemistry[21,22] to that produced earlier (Scheme 11) by the action of MeMgI in the same solvent. As before, the benzyl groups were removed by hydrogenolysis, and peracetylation, followed by treatment with HBr-AcOH, gave the bromide **14.4.** This was converted into the glycal **14.5** by reaction with Zn.

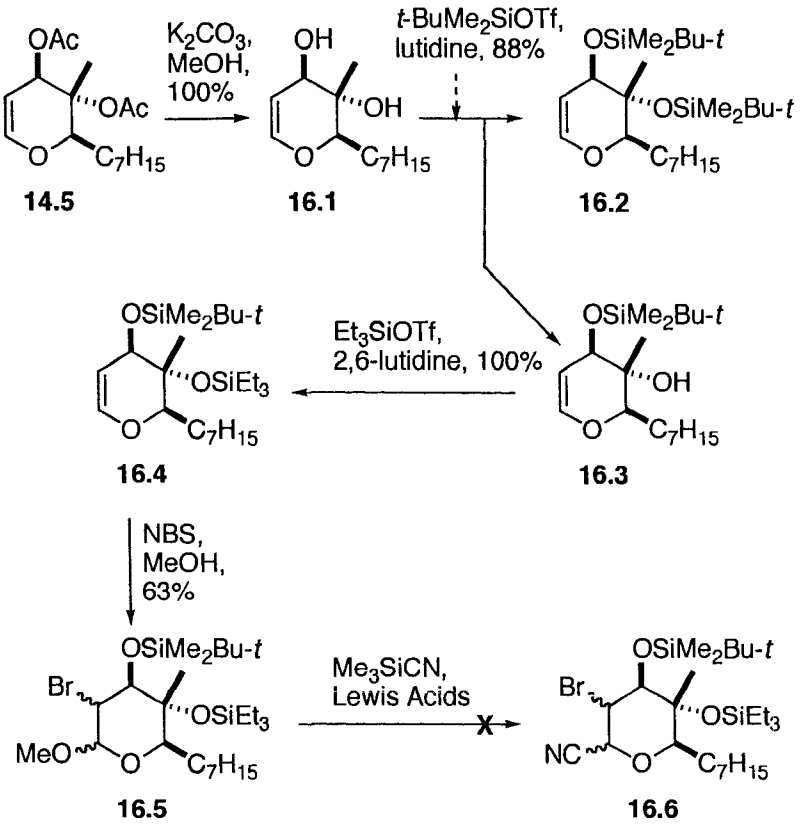
At this point our expectations that the route would follow closely what we had done before were quickly dispelled. Compound **14.5** was converted into methoxy bromides **15.1**[26] (corresponding to what we had done in the earlier series of Scheme 11) and into the acetoxy iodides **15.4** (Scheme 15), but we were unable to replace the anomeric methoxy group by cyanide, using Me_3SiCN in the presence of Lewis acids. It could be replaced by an acetoxy group (to form **15.2**[26]) but even an acetoxy substituent at the anomeric position could not be replaced by cyanide[24a] in acceptable yield. We assume that there is a stereoelectronic effect exerted by the C(5) oxygen function that deactivates the anomeric position. Such effects have been observed before and studied extensively.[27] The magnitude of the effect is strongest when the C(5) oxygen substituent is equatorial, which we assume to be the case with **15.1, 15.2** and **15.4.** Our earlier system (**12.1**)

SCHEME 15. Attempts to Replace the Anomeric Methoxy Group



presumably has this oxygen axial, and so is free from a large deactivating effect at C(1). In the present case the deactivation was sufficiently strong to thwart further progress in our intended route. We wondered if replacement of the acetyl group on the C(4) oxygen by a siloxy unit would result in a smaller degree of deactivation; accordingly, diacetate **14.5** was hydrolyzed and we tried to prepare **16.2** (Scheme 16), but obtained mainly **16.3**. The tertiary hydroxyl was therefore protected as its triethylsilyl ether (**16.4**), but with this compound also we

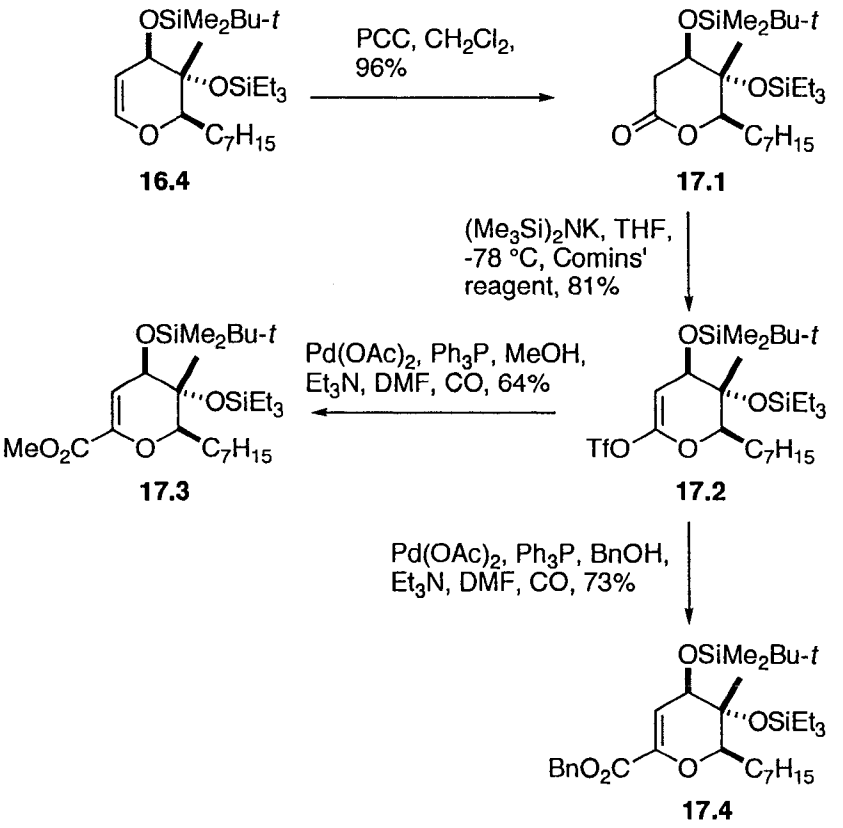
SCHEME 16. Silyl Ether Protected Diol 16.4 Formation



could not introduce a nitrile group at C(2), using methods we had tried with the acetylated analog **14.5**.

It was clear that a different procedure had to be developed in order to ultimately introduce an ester group at C(2). This was eventually achieved, starting from **16.4**, and we were then able to reach **4** which, as mentioned earlier, could not be deprotected without destroying the compound.

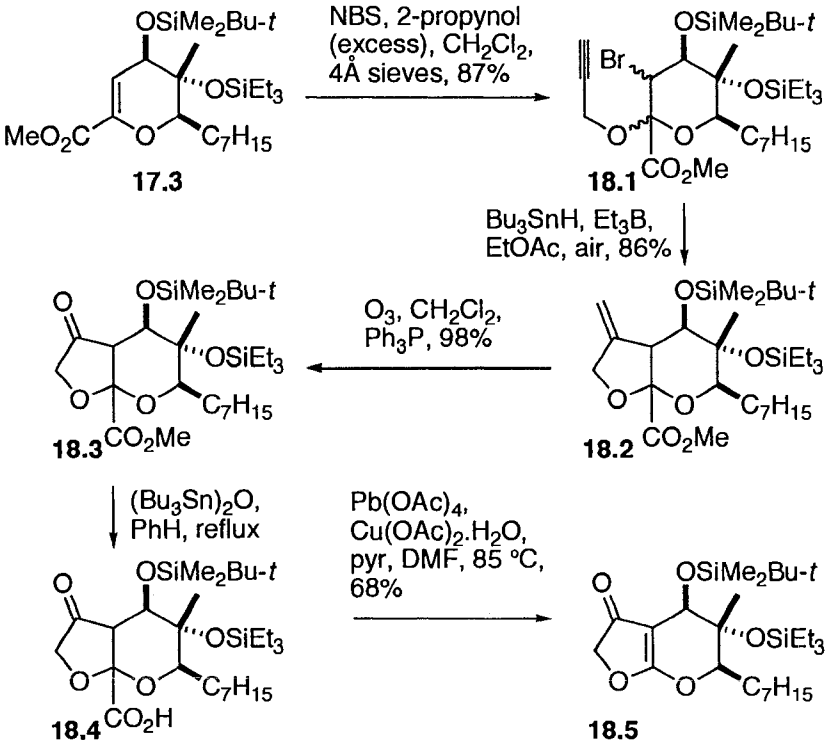
SCHEME 17. Formation of Unsaturated Ester



In order to make **4**, glycal **16.4** was oxidized to lactone **17.1** by PCC[28] and subsequent Pd(0) mediated carbonylation[29] gave unsaturated esters **17.3** and **17.4**. Later, the methyl ester **17.3** was elaborated to **4**, but **17.4** proved unsuitable.

In the presence of a very large excess of propargyl alcohol (propargyl alcohol:CH_2Cl_2 = 1:1) and powdered activated 4Å molecular sieves, bromoetherification of **17.3** was accomplished in high yield (Scheme 18, **17.3→18.1**). The

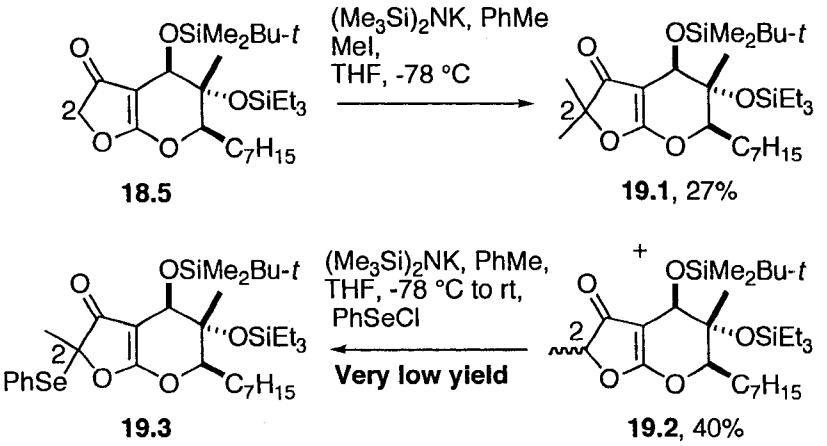
SCHEME 18. Formation of Ketene Acetal



corresponding reaction with the benzyl ester **17.4** did not work. The ketene acetal **18.5** was obtained without incident in five steps from **17.3** (Scheme 18).

Initially, we attempted to introduce a methyl group first at C(2) of **18.5**, but extensive bis-methylation occurred and a mixture of **19.1** and the mono methylated product **19.2** was obtained (Scheme 19). The mono methylated product resisted our attempts at phenylselenation at C(2) (Scheme 19).

SCHEME 19. Unsuccessful Attempts to Construct the α-Methylene Unit.

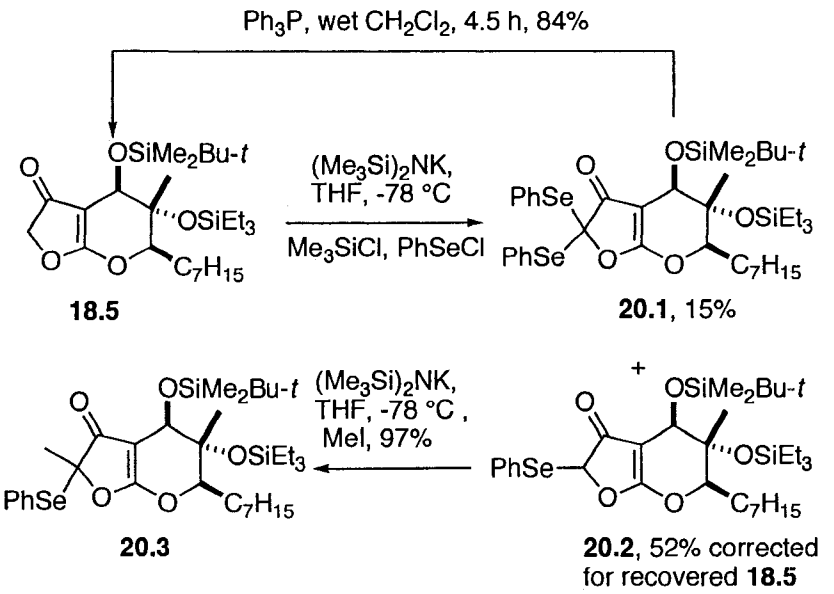


Because of this obstacle, we decided to reverse the order of reactions at C(2); fortunately, this approach worked. The new sequence (Scheme 20) also gave a significant amount of bis-selenated product **20.1** (15%), but this could be reduced by Ph_3P to ketene acetal **18.5** in high yield (84%).

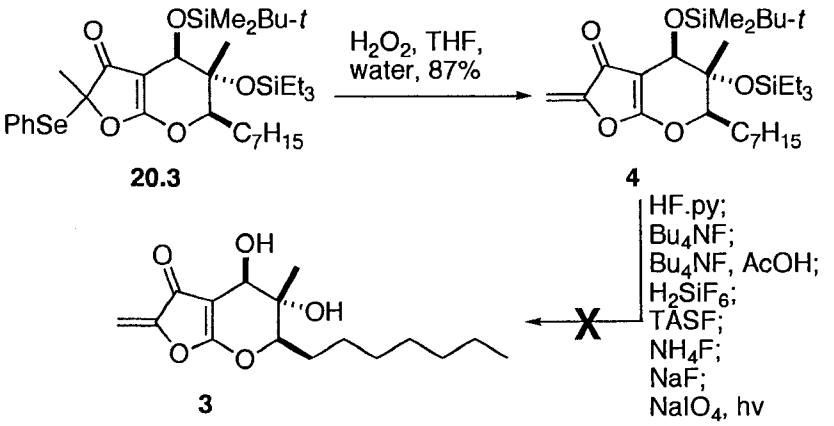
Oxidation of **20.3** with H_2O_2 gave the α,β-unsaturated ketone **4** (Scheme 21) which we were unable to deprotect. In every attempt, either the starting material was recovered or a complex mixture was produced.

This experience caused us to select Et_3Si as the protecting group for *both* hydroxyls of **16.1**. The bis-silylation was easily achieved with $Et_3SiOSO_2CF_3$ (**16.1→22.1**) and we then subjected **22.1** to the same procedures we had developed in making **4** (see Scheme 22).

SCHEME 20. Successful Attempts to Construct the α-Methylene Unit.



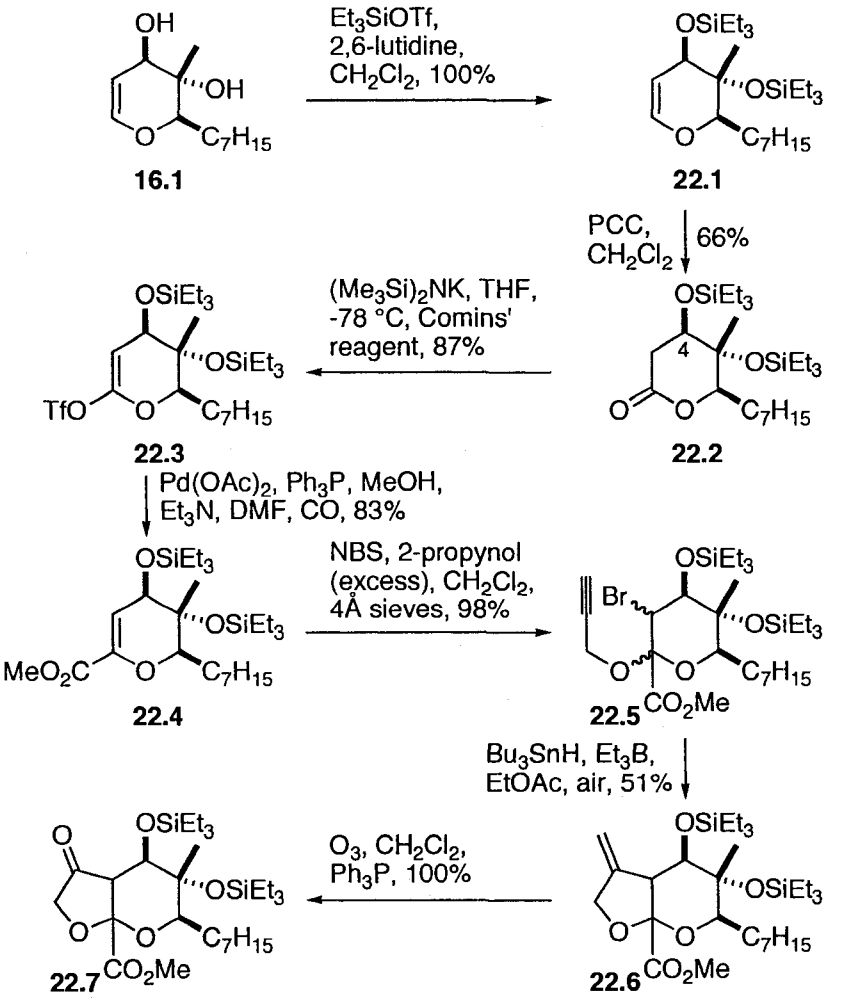
SCHEME 21. Unsuccessful Attempts at Deprotection.



Protection of the hydroxyl groups of **16.1** as triethylsilyl ethers has the added advantage that both hydroxyls are protected at the same time. Oxidation with

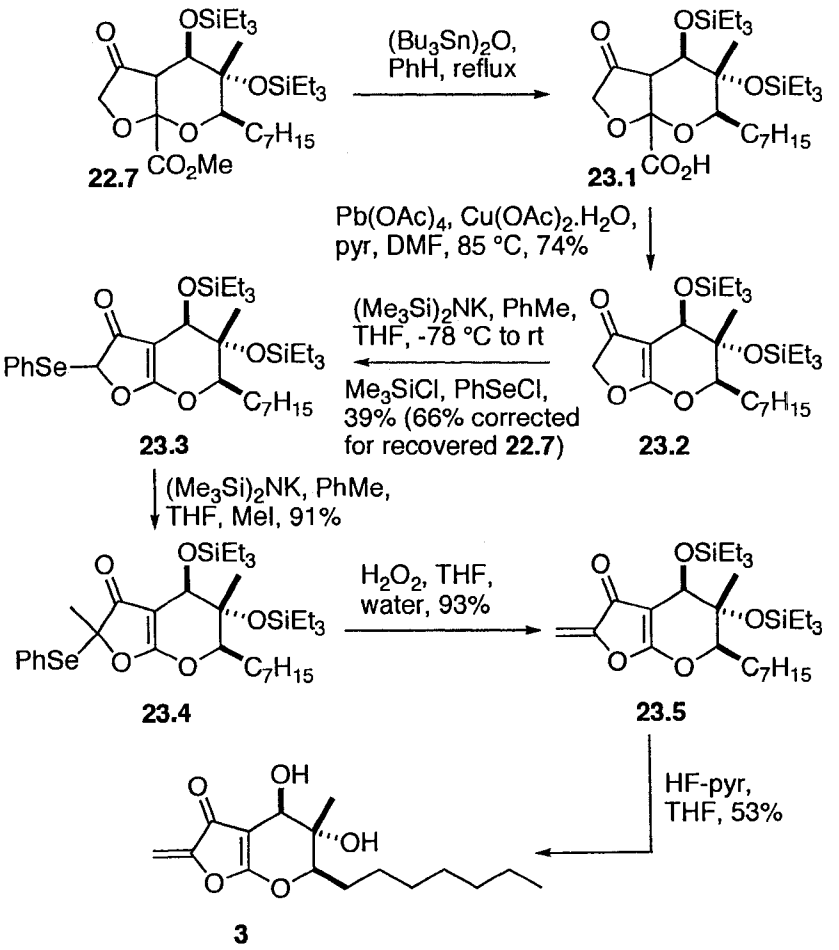
PCC then produced lactone **22.2**[28] in acceptable yield. We did not detect, but did not specifically look for, the product arising by elimination[9a,30] of the C(4) $OSiEt_3$ group and, in fact, lactone **22.2** was a stable and well-behaved compound. When the lactone was treated at a low temperature with $(Me_3Si)_2NK$ and then with Comins' reagent[29] it was possible to isolate the desired enol triflate **22.3**

SCHEME 22. Elaboration of Glycal 16.1.



in good yield. Formation of an enolate from a β-oxygenated δ-lactone without loss of the oxygen substituent is unusual, and only a few cases appear to have been reported.[30,31] Palladium-mediated carbonylation in the presence of MeOH then served to introduce the ester group, bringing the synthesis to **22.4**, which corresponds to **12.6** (Scheme 12), but has different forms of hydroxyl protection and the opposite stereochemistry at C(5). Introducing the

SCHEME 23. Formation of *ent*-Benesudon.



propargyl unit at C(2) by bromoetherification, as had been done earlier in our route to **12.5** (Scheme 12), was achieved efficiently (**22.4**→**22.5**, 98%) by the optimized conditions used for making **18.1**. Radical cyclization of **22.5** to **22.6**, under the same conditions used to make **12.8** (Bu_3SnH, Et_3B, air, EtOAc, room temperature), followed by ozonolysis, gave the keto ester **22.7**.

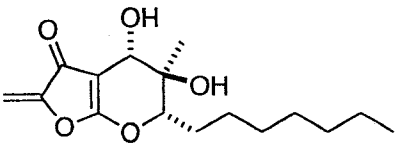
Next, the ester group was hydrolyzed, using $(Bu_3Sn)_2O$, and the central double bond was formed by the oxidative decarboxylation that had been optimized for this task. In the present case, the yield from **22.7** was very satisfactory (74%).

With ketene acetal **23.2** in hand, we had only to attach the exo methylene group and remove the silyl ethers. The first of these tasks proved more difficult than we had anticipated, because attempts to methylate **23.2** led to extensive bis-methylation, and attempts to phenylselenate the monomethylated product that we were able to separate, gave very low yields (<20%). Therefore we again reversed the order of these two steps, but found initially that phenylselenation of **23.2** resulted in extensive bis-phenylselenation. This outcome is understandable by virtue of the fact that the first phenylseleno group facilitates carbanion formation by proton exchange. Fortunately, this difficulty could be largely suppressed by quenching the enolate derived from **23.2** with Me_3SiCl, followed by addition

of PhSeCl. By this means it was possible to convert **23.2** back into **23.3** in 39% yield together with what we assume to be the corresponding bis-phenylselenated product. The latter was converted into **23.2** by treatment with Ph_3P in wet CH_2Cl_2, the overall yield of **23.3** then being 66% after correction for recovered **23.2**.

Once the phenylseleno group was in place, methylation worked well, as did the selenoxide elimination (**23.4**→**23.5**). Finally, application of the HF-pyridine method for desilylation gave the target structure **3**.

The ^1H and ^{13}C NMR spectra of **3** showed slight differences from the reported[1] data. Fortunately, the original sample of the natural product had been preserved at a low temperature and we were able to obtain this material. When we measured the spectra on our own instruments the results were identical to those obtained with synthetic **3**. However, the optical rotation of the two samples was different, the synthetic material being dextrorotatory with $[\alpha]_D$ +124.2 (*c* 0.11, $CHCl_3$) and the natural compound being levorotatory with $[\alpha]_D$ -120.5 (*c* 0.1, $CHCl_3$). Accordingly, natural benesudon has the 4*S*,5*R*,6*S* configuration shown in **5**, and the compound we had made is *ent*-benesudon.

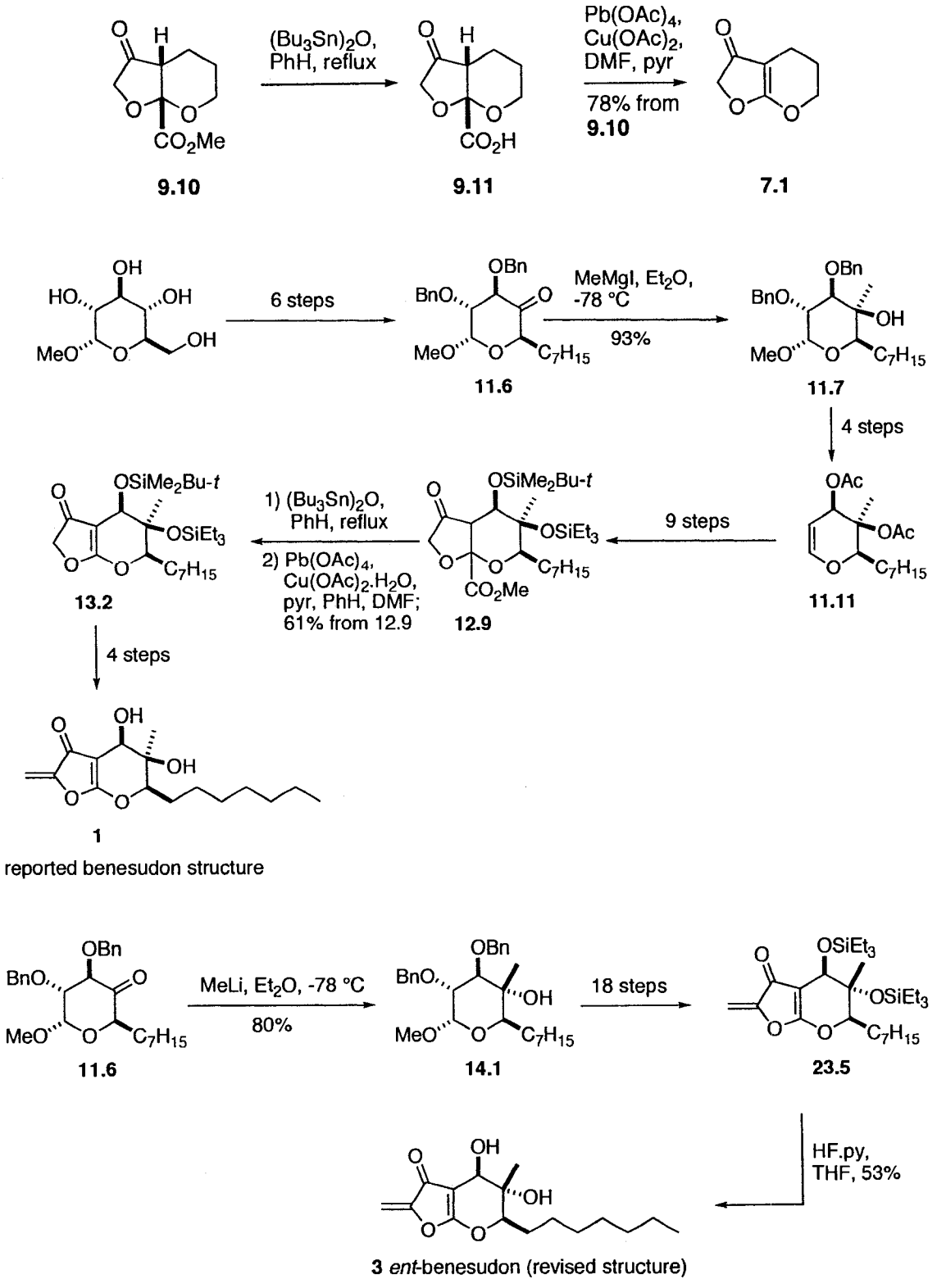


5 (natural benesudon)

3. CONCLUSION

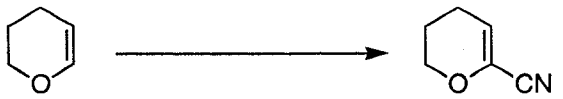
Our synthesis of *ent*-benesudon establishes the relative and absolute stereochemistry of the natural product, and the method we have developed for constructing the unusual ketene acetal subunit is probably general. Our research is summarized in Scheme 24, which shows construction of the core (**9.10→7.1**), formation of the originally reported structure (**1**) of benesudon (**11.6→1**), and, finally, a route to the revised structure (**11.6→3**).

SCHEME 24. Synthetic Studies on Benesudon.



4. EXPERIMENTAL

6-Cyano-3,4-dihydro-2*H*-pyran (9.4).

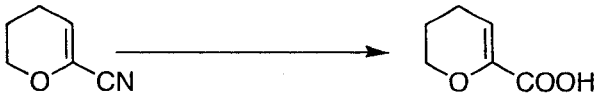


9.1 **9.4**

A solution of Br_2 (95.8 g, 30.0 mL, 0.60 mol) in CCl_4 (11 mL) was added dropwise over 1 h to a stirred and cooled (-6 °C to -20 °C, internal temperature) solution of 3,4-dihydro-2*H*-pyran (50 g, 0.60 mol) in CCl_4 (300 mL). The cold bath was removed and stirring was continued for 3 h. CuCN (56.87 g, 0.64 mol) was added to the resulting solution and the stirred mixture was refluxed for 25 h. The solid was filtered off from the hot mixture as quickly as possible, and the filtrate was cooled to 0 °C. Piperidine (51.9 g, 0.61 mol) was added, the ice bath was left in place, but not recharged, and stirring was continued overnight. The precipitate of piperidine hydrobromide stopped the stirrer, and so the mixture was diluted with CCl_4 (140 mL) and stirring at room temperature was continued for 96 h. The precipitated piperidine hydrobromide was filtered off, and the filtrate was washed with water (4 x 100 mL) and brine, dried (Na_2SO_4) and evaporated. The residue was purified by distillation to give crude **9.4** (31.0 g, bp 52.5 °C/0.15 mmHg) which was

further purified by flash chromatography over silica gel (5 x 18 cm), using 1:4 EtOAc-hexane, to afford pure **9.4**[14] (22.0 mg, 40%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.56-1.94 (m, 2 H), 2.14-2.20 (m, 2 H), 4.07 (t, *J* = 5.4 Hz, 2 H), 5.66 (t, *J* = 4.2 Hz, 1 H); exact mass *m/z* calcd for C_6H_7NO 109.05276, found 109.05271.

5,6-Dihydro-4*H*-pyran-2-carboxylic Acid (9.5).



9.4 **9.5**

A mixture of unsaturated nitrile **9.4** (1.25 g, 0.01 mol) was added to a solution of KOH (1.35 g, 0.03 mol) in water (7 mL) and the mixture was refluxed for 24 h. The solution was cooled, acidified to pH 1, using 1 N HCl, and extracted with Et_2O (3 x 20 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. The crude residue was purified by distillation (Kugelrohr) to give **9.5**[14] (1.26 g, 73%): bp <150 °C, 0.1 mmHg; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.25-1.81 (br s, 1 H), 1.85-1.94 (m, 2 H), 2.20-2.26 (m, 2 H), 4.15 (dt, *J* = 5.1, 0.6 Hz, 2 H), 6.21 (dt, *J* = 4.2, 0.3 Hz, 1 H).

5,6-Dihydro-4*H*-pyran-2-carboxylic Acid Methyl Ester (9.6).

9.5 **9.6**

$NaHCO_3$ (92.5 mg, 1.65 mmol) was added to a stirred solution of **9.5** (136 mg, 1.10 mmol) in MeOH (20 mL). After 30 min Me_2SO_4 (0.19 mL, 1.80 mmol) was added and the mixture was refluxed overnight. The mixture was cooled to room temperature, diluted with EtOAc (20 mL) and washed with water (20 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2.5 x 20 cm), using 1:4 EtOAc-hexane, gave **9.6** (111.70 mg, 79%): FTIR (CH_2Cl_2, cast) 2952, 2877, 1732, 1648, 1437, 1391, 1355, 1340, 1302, 1266, 1222, 1191, 1156, 1113, 1083, 1070, 1056 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.81-1.91 (m, 2 H), 2.15-2.22 (m, 2 H), 3.79 (s, 3 H), 4.11 (t, J = 4.8 Hz, 2 H), 6.07 (dt, J = 4.2, 0.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.6 (t), 21.5 (t), 66.7 (t), 111.4 (d), 144.2 (s), 163.5 (s); exact mass *m/z* calcd for $C_7H_{10}O_3$ 142.06299, found 142.06312.

3-Bromo-2-(prop-2-ynyloxy)tetrahydropyran-2-carboxylic Acid Methyl Ester (9.8).

9.6 **9.8**

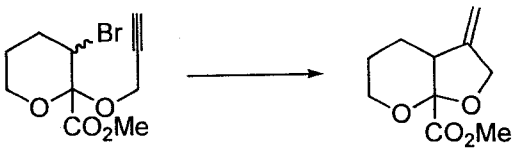
A solution of Br_2 (3.78 mL, 73.7 mmol) in CH_2Cl_2 (60 mL) was added dropwise to a stirred solution of **9.6** (9.45 g, 67.1 mmol) in CH_2Cl_2 (300 mL) and stirring was continued for 6 h. The mixture was washed with 10% aqueous $Na_2S_2O_3$ (200 mL), water (300 mL) and brine (200 mL), dried (Na_2SO_4) and evaporated.

A solution of the resulting crude dibromide in $ClCH_2CH_2Cl$ (30 mL) was added to a stirred mixture of propargyl alcohol (12 mL, 0.21 mol), $AgOCOCF_3$ (12.0 g, 46.1 mmol) and 4Å molecular sieves (45.0 g) in $ClCH_2CH_2Cl$ (150 mL), and stirring was continued for 33 h. The resulting mixture was diluted with CH_2Cl_2 (100 mL) and filtered. The filtrate was washed with saturated aqueous $NaHCO_3$ (200 mL), water (200 mL) and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (5 x 25 cm), using 1:4 EtOAc-hexane, gave **9.8** (15.35 g, 83%) as a mixture of two isomers. The more polar isomer had: FTIR (CH_2Cl_2, cast) 3478, 2955, 2888, 1749, 1438, 1386, 1318, 1269, 1211, 1182, 1150, 1121, 1070, 1047, 1014 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.38-1.44 (m, 1 H), 1.97-2.05 (m, 1 H), 2.15-2.26 (m, 1 H), 2.44 (t, J = 2.4 Hz, 1 H), 2.45-2.54

(m, 1 H), 3.75-3.83 [m, including a singlet (3 H) at δ 3.80, 4 H in all], 3.89-3.96 (m, 1 H), 4.13 (d of AB q, J = 2.5 Hz, J = 15.4 Hz, $\Delta\nu_{AB}$ = 91.5 Hz, 2 H), 4.38 (t, J = 3.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 18.9 (t), 26.9 (t), 48.9 (d), 52.1 (t), 52.7 (q), 62.2 (t), 74.8 (d), 98.0 (s), 167.3 (s); exact mass (electrospray) m/z calcd for $C_{10}H_{13}{}^{79}BrNaO_4$ (M + Na) 298.98894, found 298.98870.

The less polar isomer had: FTIR (CH_2Cl_2, cast) 3286, 2954, 2879, 2126, 1755, 1234 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.68-1.76 (m, 1 H), 2.36 (dq, J = 12.8, 4.1 Hz, 1 H), 2.45 (t, J = 1.5 Hz, 1 H), 2.36 (dq, J = 12.8, 4.1 Hz, 1 H), 2.45 (t, J = 2.5 Hz, 1 H), 3.76-3.83 [m, including a singlet (3 H) at δ 3.80, 4 H in all], 3.87 (dq, J = 12.4, 3.7 Hz, 1 H), 4.26 (dd, J = 12.4, 3.4 Hz, 1 H), 4.45 (AB q, J = 15.6, 2.5 Hz, $\Delta\nu_{AB}$ = 108.4 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 26.9 (t), 29.2 (t), 48.4 (d), 52.2 (t), 52.9 (q), 61.9 (t), 74.3 (d), 79.6 (s), 98.9 (s), 167.3 (s); exact mass (electrospray) m/z calcd for $C_{10}H_{13}{}^{79}BrNaO_4$ (M + Na) 298.9889, found 298.9886.

(3a*R*,7a*R*)-rel-Hexahydro-3-methylene-7a*H*-furo[2,3-b]-pyran-7a-carboxylic Acid Methyl Ester (9.9).



9.8 **9.9**

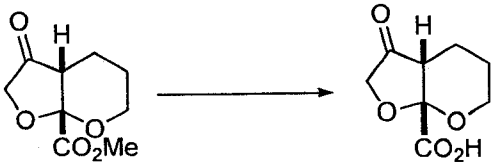
A mixture of Bu_3SnH (3.84 mL, 13.8 mmol) and AIBN (42 mg, 0.25 mmol) in PhH (50 mL) was added by syringe pump over 20 h to a stirred and heated (85-90 °C) solution of **9.8** (2.0 g, 7.2 mmol) in dry PhH (150 mL). After the addition heating was continued for 2 h, and the mixture was then allowed to cool to room temperature. Evaporation of solvent and flash chromatography of the residue over silica gel (3 x 26 cm), using 1:4 EtOAc-hexane, gave **9.9** (1.05 g, 75%) as a single isomer: FTIR (CH_2Cl_2, cast) 2953, 2874, 1742, 1213 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.29-1.41 (m, 1 H), 1.63-1.76 (m, 1 H), 1.93-2.07 (m, 2 H), 3.03-3.08 (m, 1 H), 3.59-3.66 (m, 1 H), 3.80 (s, 3 H), 3.84-3.90 (m, 1 H), 4.55-4.65 (m, 2 H), 4.97 (q, *J* = 2.6 Hz, 1 H), 5.04 (q, *J* = 2.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.7 (t), 22.2 (t), 43.0 (d), 52.6 (q), 64.5 (t), 71.3 (t), 103.3 (s), 104.6 (t), 146.4 (s), 168.7 (s); exact mass *m/z* calcd for $C_{10}H_{14}O_4$ 198.08920, found 198.08899.

(3a*R*,7a*R*)-rel-Hexahydro-3-oxo-7a*H*-furo[2,3-b]pyran-7a-carboxylic Acid Methyl Ester (9.10).

9.9 **9.10**

An O_3-O_2 stream was passed through a stirred and cooled (-78 °C) solution of **9.9** (0.74 g, 3.64 mmol) in CH_2Cl_2 (31 mL) for 15 min, and the solution was then purged with O_2 for 15 min. The cold bath was removed and Ph_3P (1.25 g, 4.73 mmol) was added. Stirring was continued for 4.5 h and the solvent was evaporated. Flash chromatography of the residue over silica gel (3.5 x 17 cm), 1:2 using EtOAc-hexane, gave **9.10** (0.62 g, 83%): FTIR (CH_2Cl_2, cast) 2955, 1765, 1742, 1201 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.40-1.50 (m, 2 H), 1.86-1.98 (m, 1 H), 2.19-2.28 (m, 1 H), 2.91 (dd, J = 6.1, 2.7 Hz, 1 H), 1 H), 3.54-3.65 (m, 1 H), 3.87 (s, 3 H), 3.90-3.98 (m, 1 H), 4.26 (AB q, J = 16.6 Hz, $\Delta\nu_{AB}$ = 19.8 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 19.9 (t), 21.0 (t), 47.6 (d), 53.0 (q), 64.9 (t), 70.4 (t), 102.4 (s), 167.6 (s), 211.1 (s); exact mass (electrospray) *m/z* calcd for $C_9H_{12}NaO_5$ (M + Na) 223.05770, found 223.05808.

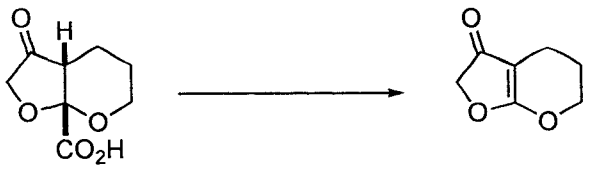
(3a*R*,7a*R*)-rel-Hexahydro-3-oxo-7a*H*-furo[2,3-b]pyran-7a-carboxylic Acid (9.11).



9.10 **9.11**

$(Bu_3Sn)_2O$ (0.97 mL, 1.9 mmol) was added to a solution of **9.10** (96 mg, 0.48 mmol) in dry PhH (7.5 mL), and the solution was refluxed under N_2 for 5 h. The solvent was evaporated and EtOAc (10 mL) was added to the residue. The EtOAc solution was extracted with saturated aqueous $NaHCO_3$ (2 x 10 mL), and the aqueous extract was acidified to pH 1 (pH paper) with ice-cold 2N hydrochloric acid and extracted with EtOAc (4 x 5 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated at room temperature. The crude acid **9.11** was used immediately, without further purification: FTIR (CH_2Cl_2, cast) 3500-2500, 1766 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.43-1.54 (m, 2 H), 1.90-2.01 (m, 1 H), 2.16-2.26 (m, 1 H), 2.89 (dd, *J* = 6.3, 3.4 Hz, 1 H), 1 H), 3.70-3.77 (m, 1 H), 3.94-4.02 (m, 1 H), 4.27 (AB q, *J* = 16.6 Hz, $\Delta\nu_{AB}$ = 25.2 Hz, 2 H), 5.75 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 19.9 (t), 21.0 (t), 47.0 (d), 65.0 (t), 70.5 (t), 101.8 (s), 169.5 (s), 210.5 (s); exact mass (electrospray) *m/z* calcd for $C_8H_{11}O_5$ (M + H) 187.0601, found 187.0603.

5,6-Dihydro-4*H*-furo[2,3-b]pyran-3(2*H*)-one (7.1).



9.11 **7.1**

$Cu(OAc)_2.H_2O$ (56 mg, 0.28 mmol) was added to a stirred solution of the above crude acid **9.11** in dry PhH (2.5 mL) (N_2 atmosphere), and stirring was continued for 5 min. The flask was then wrapped in aluminum foil and $Pb(OAc)_4$ (118 mg, 0.27 mmol) was tipped in. Stirring was continued for 30 min, and another portion of $Pb(OAc)_4$ (55 mg, 0.13 mmol) was added, followed by PhH (1.5 mL). Stirring was again continued for 30 min and a further portion of $Pb(OAc)_4$ (88 mg, 0.20 mmol) was then added, followed by PhH (1 mL) and dry DMF (0.4 mL). The flask was fitted with a reflux condenser and flushed well with N_2 for 30 min (in some experiments, the apparatus was evacuated with the house vacuum and then filled with N_2, and the process was repeated twice more). The mixture was refluxed for 11 h (oil bath at 84 °C). The aluminum foil was removed, and refluxing was continued for 1 h. The resulting green solution was cooled to room temperature and evaporated to a thick oil, which was applied directly to a flash chromatography column made up with silica gel (1.5 x 26 cm). Flash chromatography, using 1:1 EtOAc-hexane, and then pure EtOAc, gave **7.1** (52 mg, 78% over two steps) as a white solid: mp 60-62 °C; FTIR (CH_2Cl_2, cast) 1705, 1600 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.91-1.99 (m, 2 H), 2.33 (t, J = 6.2 Hz, 2 H), 4.47 (apparent t, J = 5.1 Hz, 2 H), 4.52 (s, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.5 (t), 21.2 (t), 71.5 (t), 74.2 (t), 88.9 (s),

182.8 (s), 194.1 (s); exact mass *m/z* calcd for $C_7H_8O_3$ 140.0474, found 140.0473.

5,6-Dihydro-2-methyl-4*H*-furo[2,3-b]pyran-3(2*H*)-one (10.1).

7.1 **10.1**

BuLi (2.5 M in hexanes, 0.16 mL. 0.40 mmol) was added to a stirred and cooled (0 °C) solution of *i*-Pr_2NH (0.043 g, 0.400 mmol) in dry THF (0.8 mL) (N_2 atmosphere), and stirring was continued for 15 min. A solution of **7.1** (45 mg, 0.33 mmol) in THF (0.7 mL) was added dropwise, and stirring at 0 °C was continued for 30 min. Dry HMPA (56 mL, 0.32 mmol) was injected rapidly, followed by MeI (32.25 mL, 0.52 mmol), and stirring was continued at 0 °C for 2.5 h. The reaction was quenched by addition of hydrochloric acid (0.3 M, 3 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (4 x 10 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (1.5 x 29 cm), using 1:1 EtOAc-hexane, gave **10.1** (17.2 mg, 40%) as an oil: FTIR (CH_2Cl_2, cast) 1699, 1598 cm^-

[1]; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.49 (d, *J* = 7.1 Hz, 3 H), 1.94 (apparent pentet, *J* = 6.3 Hz, 2 H), 2.32 (dt, *J* = 6.3, 3.2 Hz, 2 H), 4.45 (dt, *J* = 5.2, 1.0 Hz, 2 H), 4.59 (q, *J* = 7.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.6 (t), 16.3 (q), 21.3 (t), 71.4 (t), 82.5 (d), 87.5 (s), 181.4 (s), 196.9 (s); exact mass *m/z* calcd for $C_8H_{10}O_3$ 154.06298, found 154.06299.

In another experiment, carried out in the same way, some of what we take to be the product of dimethylation was isolated (48 mg, 42%) along with **10.1** (50 mg, 47%). The dimethtylated compound had: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.45 (s, 6 H), 1.91-1.98 (m, 2 H), 2.27-2.32 (m, 2 H), 4.41-4.47 (m, 2 H). No further characterization data were obtained.

5,6-Dihydro-2-methyl-2-(phenylseleno)-4*H*-furo[2,3-b]-pyran-3(2*H*)-one (10.2).

10.1 **10.2**

BuLi (2.5 M in hexanes, 0.03 mL. 0.08 mmol) was added to a stirred and cooled (0 °C) solution of *i*-Pr_2NH (0.010 g, 0.080 mmol) in dry THF (0.2 mL) (N_2 atmosphere), and stirring was continued for 20 min. A solution of **10.1** (9.8 mg, 0.06 mmol) in THF (0.2 mL) was added dropwise, and stirring was continued at 0 °C for 15 min. The mixture was

then cooled to -78 °C, and PhSeCl (freshly sublimed under water pump vacuum, with protection from moisture, 15.3 mg, 0.08 mmol) in THF (0.1 mL) was added rapidly. Stirring was continued for 15 min at -78 °C. The reaction was quenched by addition of saturated aqueous NH_4Cl (2 mL) and diluted with Et_2O (5 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 x 5 mL). The combined organic extracts were washed with water (2 x 10 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (1.5 x 29 cm), using 1:1 EtOAc-hexane, gave **10.2** (11.9 mg, 61%): FTIR (CH_2Cl_2, cast) 1706, 1601 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.40-1.51 (m, 1 H), 1.69-1.84 (m containing a singlet, 5 H in all), 2.06-2.14 (m, 1 H), 4.06-4.12 (m, 1 H), 4.24-4.20 (m, 1 H), 7.28 (t, J = 7.5 Hz, 2 H), 7.37 (tt, J = 5.1, 1.2 Hz, 1 H), 7.63-7.68 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.3 (t), 21.1 (t), 21.9 (q), 71.4 (t), 88.0 (s), 91.9 (s), 125.4 (s), 128.7 (d), 129.4 (d), 137.5 (d), 179.0 (s), 194.1 (s); exact mass m/z calcd for $C_{14}H_{14}O_3{}^{80}Se$ 310.01080, found 310.01091.

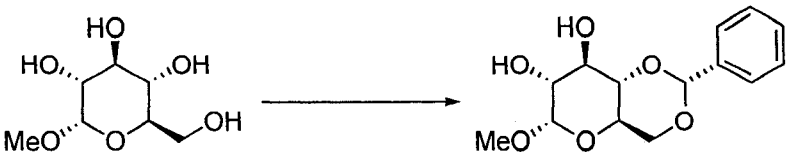
5,6-Dihydro-2-methylene-4*H*-furo[2,3-b]pyran-3(2*H*)-one (7.4).

10.2 **7.4**

H_2O_2 (30%, 0.03 mL) was added to a stirred solution of **10.2** (8 mg, 0.03 mmol) in a mixture of THF (0.9 mL) and water (0.3 mL). Stirring at room temperature was continued for 2.5 h, and the solution was diluted with Et_2O (3 mL) and water (2 mL). The aqueous layer was extracted with Et_2O (3 x 3 mL) and the combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 24 cm), using EtOAc, gave **7.4** (2.5 mg, 64%) as a white solid: mp 63-64 °C; FTIR (CH_2Cl_2, cast) 1595 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.97-2.02 (m, 2 H), 2.37 (t, J = 6.3 Hz, 2 H), 4.53 (t, J = 5.8 Hz, 2 H), 5.12 (d, J = 2.8 Hz, 1 H), 5.53 (d, J = 2.8 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.4 (t), 21.5 (t), 72.0 (t), 90.4 (s), 95.8 (t), 152.8 (s), 178.4 (s), 180.7 (s); exact mass m/z calcd for $C_8H_8O_3$ 152.04735, found 152.04742.

Synthesis of original structure proposed for benesudon.

Methyl 4,6-*O*-[(*R*)-Phenylmethylene]-α-D-glucopyranoside (11.1).

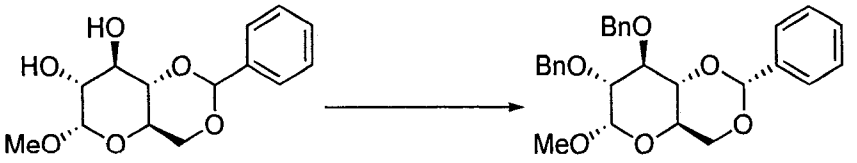


11.1

Methyl α-D-glucopyranoside

$PhCH(OMe)_2$ (42 mL, 0.28 mol), followed by $TsOH.H_2O$ (0.49 g, 2.8 mmol) in DMF (6 mL) was added to a solution of methyl α-D-glucopyranoside (50 g, 0.26 mol) in DMF (96 mL) and the mixture was heated at 70 °C for 1 h. The solution was cooled and poured into a mixture of ice-water (350 mL), saturated aqueous $NaHCO_3$ (50 mL) and Et_2O (100 mL). The resulting mixture was stirred for 20 min and filtered. The resulting white solid was collected and washed with ice cold water and dried under vacuum to afford **11.1**[32] (44.69 g, 61%): ^1H NMR ($CDCl_3$, 300 MHz) δ 2.21 (d, *J* = 9.6 Hz, 1 H), 2.62 (d, *J* = 2.0 Hz, 1 H), 3.51 (s, 3 H), 3.53 (d, *J* = 9.2 Hz, 1 H), 3.62-3.87 (m, 3 H), 3.95 (dt, *J* = 9.2, 2.0 Hz, 1 H), 4.31 (dd, *J* = 9.2, 3.8 Hz, 1 H), 4.82 (d, *J* = 4.0 Hz, 1 H), 5.55 (s, 1 H), 7.49-7.35 (m, 3 H), 7.49-7.52 (m, 2 H); ^{13}C NMR (CD_3OD, 100 MHz) δ 55.8 (q), 63.9 (d), 70.1 (t), 72.0 (d), 74.1 (d), 82.9 (d), 102.1 (d), 103.1 (d), 127.6 (d), 129.1 (d), 129.9 (d), 139.2 (s).

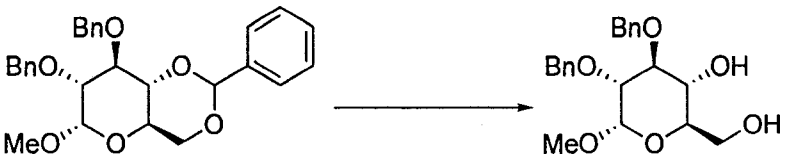
Methyl 2,3-Di-*O*-Benzyl-4,6-*O*-[(*R*)-phenylmethylene]-α-D-glucopyranoside (11.2).



11.1 **11.2**

NaH (80% w/w, 13.3 g, 0.44 mol) was added carefully in portions to a stirred solution of **11.1** (41.8 g, 0.15 mol) in DMF (45 mL). Then BnBr (43 mL, 0.36 mol) was added over 20 min. The solution became hot and was placed in a cold water bath. After 2.5 h, the solution was diluted with EtOAc (400 mL), washed with water (2 x 200 mL), dried ($MgSO_4$) and evaporated. The crude residue was purified by recrystallization from 95% EtOH to give **11.2**[32] (42.30 g, 62%) as a white solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.41 (s, 3 H), 3.54-3.74 (m, 3 H), 3.82 (q, *J* = 7.3 Hz, 1 H), 4.05 (t, *J* = 9.2 Hz, 1 H), 4.27 (q, *J* = 4.6 Hz, 1 H), 4.60 (d, *J* = 3.7 Hz, 1 H), 4.68-4.94 (m, 4 H), 5.55 (s, 1 H), 7.27-7.40 (m, 13 H), 7.48-7.51 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 55.3 (q), 62.3 (d), 69.1 (t), 73.8 (t), 75.3 (t), 78.6 (d), 79.2 (d), 82.2 (d), 99.2 (d), 101.3 (d), 126.0 (d), 127.5 (d), 127.9 (d), 128.0 (d), 128.09 (d), 128.14 (d), 128.2 (d), 128.3 (d), 128.4 (d), 128.9 (d), 137.4 (s), 138.2 (s), 138.7 (s).

Methyl 2,3-Di-*O*-Benzyl-α-D-glucopyranoside (11.3).



11.2 **11.3**

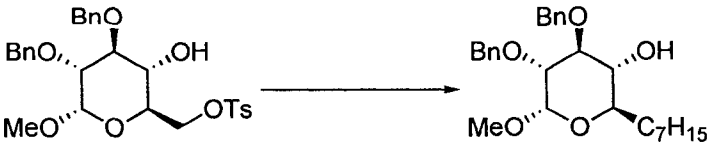
$TsOH.H_2O$ (0.58 g, 3.34 mmol) was added to a solution of **11.2** (24.70 g, 53.46 mmol) in MeOH (105 mL) and water (20 mL) and the mixture was heated at 82 °C for about 3 h. The solution was cooled to room temperature and adjusted to pH 7 with saturated aqueous $NaHCO_3$ solution. The MeOH was evaporated and the residue was dissolved in $CHCl_3$ (50 mL) and washed with saturated aqueous $NaHCO_3$ (50 mL). The organic layer was evaporated and the residue was purified by flash chromatography over silica gel (5 x 23 cm), using 1:1 EtOAc-hexane to pure EtOAc, to give **11.3**[33] (17.79 g, 90%) as a white solid: ^1H NMR ($CDCl_3$, 300 MHz) δ 1.85 (t, *J* = 5.8 Hz, 1 H), 2.20 (d, *J* = 2.5 Hz, 1 H), 3.39 (s, 3 H), 3.52 (dt, *J* = 9.5, 3.6 Hz, 2 H), 3.60-3.66 (m, 1 H), 3.70-3.85 (m, 3 H), 4.60-4.80 (m, 4 H), 5.04 (d, *J* = 11.6 Hz, 1 H), 7.27-7.40 (m, 10 H).

Methyl 2,3-Bis-*O*-benzyl-α-D-glucopyranoside 6-(4-Methylbenzenesulfonate (11.4).

11.3 **11.4**

Pyridine (0.13 mL, 1.61 mmol) followed by TsCl (0.09 g, 0.47 mmol) was added to a stirred and cooled (0 °C) solution of **11.3** (115 mg, 0.31 mmol) in CH_2Cl_2 (2 mL). The ice bath was left in place but not recharged and stirring was continued for 19 h. The mixture was diluted with CH_2Cl_2 (5 mL) and washed successively with water and saturated aqueous $CuSO_4$, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2.5 x 15 cm), using 1:2 EtOAc-hexane, gave **11.4**[20a] (136.4 mg, 84%) as a foam: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.18 (d, *J* = 2.8 Hz, 1 H), 2.44 (s, 3 H), 3.33 (s, 3 H), 3.38-3.49 (m, 2 H), 3.69-3.76 (m, 2 H), 4.23 (d, *J* = 3.6 Hz, 2 H), 4.55-4.77 (m, 4 H), 4.99 (d, *J* = 11.5 Hz, 1 H), 7.30-7.37 (m, 12 H), 7.78 (d, *J* = 8.3 Hz, 2 H).

(2*R*,3*R*,4*S*,5*R*,6*S*)-4,5-Bis(benzyloxy)-2-heptyltetrahydro-6-methoxy-2*H*-pyran-3-ol (11.5).

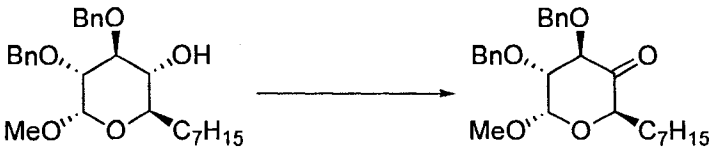


11.4 **11.5**

A solution of **11.4** (10.80 g, 20.40 mmol) in THF (32 mL) was added dropwise over 55 min to a stirred and cooled (-30 °C) mixture of CuI (8.15 g, 42.8 mmol) and $C_6H_{13}MgBr$ (72 mL, 2.0 M in Et_2O) in THF (100 mL). [This latter solution was prepared by dropwise addition of the Grignard reagent to a stirred and cooled (-70 °C) solution of the freshly purified CuI in THF.] Stirring at -25 to -30 °C was continued for 6 h. The cooling bath was left in place, but not recharged, and stirring was continued for ca 25 h, at which time the mixture was poured into cooled (0 °C) saturated aqueous NH_4Cl (200 mL) (stirring) and extracted with Et_2O (3 x 200 mL). The combined organic extracts were washed with brine (80 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (4 x 25 cm), using 15% EtOAc-hexanes, gave **11.5** (6.8 g, 76%) as a colorless oil: $[\alpha]_D$ +46.8 (*c* 2.15, $CHCl_3$); FTIR (CH_2Cl_2, cast) 3450, 3064, 3031, 2856 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.85 (t, *J* = 6.9 Hz, 3 H), 1.18-1.53 (m, 11 H), 1.74-1.83 (m, 1 H), 2.11 (d, *J* = 2.4 Hz, 1 H), 3.20 (dt, *J* = 9.2, 2.4 Hz, 1 H), 3.35 (s, 3 H), 3.45-3.53 (m, 2 H), 3.71 (t, *J* = 9.2 Hz, 1 H), 4.57 (d, *J* = 3.5 Hz, 1 H), 4.70 (AB q, *J* = 12.1 Hz, $\Delta\nu_{AB}$ = 44.6 Hz, 2 H), 4.85 (AB q, *J* = 11.5 Hz, $\Delta\nu_{AB}$ = 149.6 Hz, 2 H), 7.25-7.39 (m, 10 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 14.1 (q), 22.6 (t), 25.4 (t), 29.2 (t), 29.6 (t), 31.6 (t), 31.8 (t), 55.0 (q), 70.5 (d), 73.0 (t), 73.7 (d), 75.3 (t), 80.0 (d), 81.5 (d), 97.8 (d), 127.8 (d), 127.9

(d), 128.0 (d), 128.1 (d), 128.5 (d), 128.6 (d), 138.1 (s), 138.8 (s); exact mass (electrospray) *m/z* calcd for $C_{27}H_{38}NaO_5$ (M + Na) 465.2617, found 465.2617.

(2*R*,4*R*,5*R*,6*S*)-4,5-Bis(benzyloxy)-2-heptyldihydro-6-methoxy-2*H*-pyran-3(4*H*)-one (11.6).

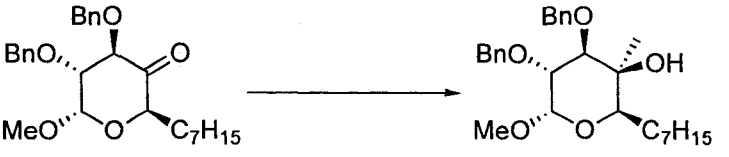


11.5 **11.6**

DMSO (2.90 mL, 40.65 mmol) in CH_2Cl_2 (8 mL) was added dropwise to a stirred and cooled (-78 °C) solution of $(COCl)_2$ (2.9 mL, 33 mmol) in CH_2Cl_2 (90 mL). Stirring at -78 °C was continued for 35 min, and then a solution of **11.5** (7.22 g, 16.3 mmol) in CH_2Cl_2 (28 mL) was added dropwise over 45 min. After 1 h 15 min at -78 °C, Et_3N (7.0 mL, 49.9 mmol) was injected over 10 min. The cooling bath was left in place, but not recharged, and stirring was continued for 18.5 h. The mixture was diluted with CH_2Cl_2 (135 mL) and aqueous NH_4Cl (60 mL), and the aqueous phase was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (5 x 27 cm), using 1:5 EtOAc-hexane, gave **11.6** (7.0 g, 100%) as a yellow oil: $[\alpha]_D$ +164.7 (*c* 1.75, CH_2Cl_2); FTIR (CH_2Cl_2, cast) 3064,

3032, 2953, 2856, 1726 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.86 (t, *J* = 6.9 Hz, 3 H), 1.18-1.56 (m, 11 H), 1.78-1.87 (m, 1 H), 3.44 (s, 3 H), 3.73 (dd, *J* = 10.0, 3.6 Hz, 1 H), 4.02 (dd, *J* = 8.4, 3.9 Hz, 1 H), 4.40 (d, *J* = 10.0 Hz, 1 H), 4.72 (d, *J* = 3.5 Hz, 1 H), 4.75 (AB q, *J* = 12.3 Hz, $\Delta\nu_{AB}$ = 93.3 Hz, 2 H), 4.80 (AB q, *J* = 11.3 Hz, $\Delta\nu_{AB}$ = 145.5 Hz, 2 H), 7.24-7.44 (m, 10 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 14.0 (q), 22.6 (t), 25.2 (t), 28.1 (t), 29.1 (t), 29.5 (t), 31.8 (t), 55.8 (q), 72.6 (d), 73.9(t), 74.3 (t), 80.4 (d), 82.9 (d), 98.4 (d), 127.8 (d), 127.9 (d), 128.0 (d), 128.1 (d), 128.3 (d), 128.4 (d), 137.8 (s), 138.9 (s), 203.2 (s); exact mass (electrospray) *m/z* calcd for $C_{27}H_{36}NaO_5$ (M + Na) 463.2460, found 463.2466.

(2*R*,3*S*,4*R*,5*R*,6*S*)-4,5-Bis(benzyloxy)-2-heptyltetrahydro-6-methoxy-3-methyl-2*H*-pyran-3-ol (11.7).

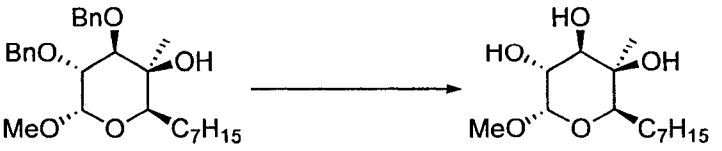


11.6 **11.7**

A solution of **11.6** (13.51 g, 30.71 mmol) in Et_2O (26 mL) was added dropwise over about 40 min to a stirred and cooled (-78 °C) mixture of MeMgI (3.0 M in Et_2O, 21.0 mL) in Et_2O (100 mL). Stirring at -78 °C was continued for 2.5 h. The mixture was diluted with saturated aqueous NH_4Cl (32 mL)

and extracted with Et_2O (2 x 50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (5 x 25 cm), using 1:5 EtOAc-hexane, gave **11.7** (13.0 g, 93%) as a yellow oil: $[\alpha]_D$ +45.4 (*c* 1.0, $CHCl_3$); FTIR ($CHCl_3$, cast) 3500, 3063, 3030, 2953, 2925 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.86 (t, *J* = 6.9 Hz, 3 H), 1.14 (s, 3 H), 1.18-1.68 (m, 12 H), 2.18 (d, *J* = 1.6 Hz, 1 H), 3.36 (s, 3 H), 3.47 (d, *J* = 10.1 Hz, 1 H), 3.56 (d, *J* = 9.7 Hz, 1 H), 3.81 (dd, *J* = 9.6, 3.7 Hz, 1 H), 4.63 (d, *J* = 3.2 Hz, 1 H), 4.64 (d, *J* = 11.3 Hz, 1 H), 4.67 (AB q, *J* = 12.0 Hz, $\Delta\nu_{AB}$ = 46.7 Hz, 2 H), 5.01 (d, *J* = 10.9 Hz, 1 H), 7.24-7.37 (m, 10 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 14.0 (q), 22.1 (q), 22.6 (t), 26.4 (t), 27.6 (t), 29.2 (t), 29.6 (t), 31.8 (t), 55.1(q), 72.7 (d), 73.1 (t), 74.3(s), 76.2 (t), 78.1 (d), 80.9 (d), 98.0 (d), 127.8 (d), 128.1 (d), 128.2 (d), 128.3 (d), 128.4 (d), 138.3 (s); exact mass (electrospray) *m/z* calcd for $C_{28}H_{40}NaO_5$ (M + Na) 479.2768, found 479.2771.

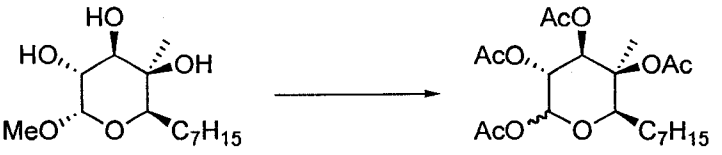
(2*R*,3*R*,4*R*,5*R*,6*S*)-2-Heptyltetrahydro-6-methoxy-3-methyl-2*H*-pyran-3,4,5-triol (11.8).



11.7 **11.8**

Pd-C (10%, 0.31 g) was added to a solution of **11.7** (2.21 g, 4.85 mmol) in MeOH (12 mL). The mixture was shaken under H_2 at 50 psi (Parr shaker) for 5.5 h and then filtered through a pad of Celite. The filtrate was evaporated to give **11.8** (1.50 g, 88%) as a white solid: mp = 92-94 °C; $[\alpha]_D$ +139.8 (*c* 1.0, $CHCl_3$); FTIR ($CHCl_3$, cast) 3396, 2924, 2856 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.85 (t, *J* = 6.9 Hz, 3 H), 1.17 (s, 3 H), 1.20-1.66 (m, 12 H), 2.48 (s, 1 H), 2.79 (d, *J* = 8.8 Hz, 1 H), 3.28 (d, *J* = 5.6 Hz, 1 H), 3.38 (s, 3 H), 3.41-3.50 (m, 2 H), 3.70 (dt, *J* = 9.2, 4.0 Hz, 1 H), 4.75 (d, *J* = 4.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 14.0 (q), 22.1 (q), 22.6 (t), 26.3 (t), 27.5 (t), 29.2 (t), 29.6 (t), 31.8 (t), 55.2 (q), 70.6 (d), 73.3 (d), 73.6(s), 74.6 (d), 99.1 (d); exact mass (electrospray) *m/z* calcd for $C_{14}H_{28}NaO_5$ (M + Na) 299.1829, found 299.1829.

Acetic Acid (3*R*,4*R*,5*S*,6*R*)-3,4,5-Triacetoxy-6-heptyl-tetrahydro-5-methylpyran-2-yl Ester (11.9).



11.8 **11.9**

Concentrated H_2SO_4 (0.2 mL) was added dropwise to a stirred and cooled (0 °C) solution of **11.8** (1.5 g, 5.4 mmol) in a mixture of Ac_2O (6.5 mL) and AcOH (6.5 mL). The cold

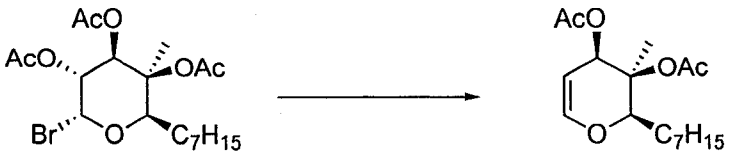
bath was left in place, but not recharged, and stirring was continued for 14 h. The mixture was poured into water (80 mL) and extracted with EtOAc (3 x 60 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (50 mL) and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (4 x 15 cm), using 1:6 EtOAc-hexane, gave **11.9** (1.70 g, 100%) as a 1:5 mixture of two epimers (^1H NMR): FTIR (CH_2Cl_2, cast) 2928, 2857, 1751, 1220 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) (two epimers) δ 0.84 (t, *J* = 7.1 Hz, 3 H), 1.16-1.66 (m, 15 H), 1.94-2.13 (eight s, 12 H), 3.30 and 3.64 (each dd, *J* = 9.7, 2.5 Hz, 1 H), 4.98 and 5.23 (each dd, *J* = 10.0 Hz, 2 H), 5.60 and 6.30 (each d, *J* = 8.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 14.0 (q), 19.0 (q), 19.1 (q), 20.4 (q), 20.5 (q), 20.6 (q), 20.7 (q), 20.8 (q), 20.9 (q), 22.3(q), 22.4 (q), 22.5 (t), 25.9 (t), 26.0 (t), 28.1 (t), 28.3 (t), 29.1 (t), 29.2 (t), 31.7 (t), 31.8 (t), 67.6(d), 69.2 (d), 72.0 (d), 75.5 (d), 76.5 (d), 80.3 (d), 82.4 (s), 83.2 (s), 89.6 (d), 92.3 (d), 169.0 (s), 169.1 (s), 169.4 (s), 169.7 (s), 169.9 (s), 170.3 (s), 170.5 (s); exact mass (electrospray) *m/z* calcd for $C_{21}H_{34}NaO_9$ (M + Na) 453.2095, found 453.2099.

Acetic Acid (2*R*,3*R*,4*R*,5*S*,6*R*)-4,5-Diacetoxy-2-bromo-6-heptyltetrahydro-5-methylpyran-3-yl Ester (11.10).

11.9 **11.10**

A solution of HBr in AcOH (45%, 15.5 mL) was added dropwise to a stirred solution of **11.9** (6.64 g, 15.47 mmol) in CH_2Cl_2 (60 mL). The mixture was stirred for 2 h, diluted with CH_2Cl_2 (50 mL), washed with saturated aqueous $NaHCO_3$ (30 mL) and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (5 x 8 cm), using 1:6 EtOAc-hexane, gave **11.10** (5.30 g, 76%) as a brown oil: $[\alpha]_D$ +226 (*c* 1.0, $CHCl_3$); FTIR ($CHCl_3$, cast) 2956, 2857, 2828, 1751, 1223 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.86 (t, *J* = 6.9 Hz, 3 H), 1.18-1.69 [m, including a singlet (3 H) at δ 1.58, 15 H in all], 2.06 (s, 9 H), 3.82 (dd, *J* = 9.9, 2.4 Hz, 1 H), 4.94 (dd, *J* = 10.2, 4.1 Hz, 1 H), 5.33 (d, *J* = 10.2 Hz, 1 H), 6.72 (d, *J* = 3.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 14.0 (q), 20.6 (q), 20.7 (q), 22.3(q), 22.7 (t), 25.6 (t), 27.8 (t), 29.0 (t), 29.1 (t), 31.7 (t), 69.1 (d), 72.4 (d), 79.0 (d), 82.8 (s), 89.5 (d), 169.5(s), 170.0s), 170.1(s); exact mass (electrospray) *m/z* calcd for $C_{19}H_{31}{}^{79}BrNaO_7$ (M + Na) 473.1151, found 473.1155.

Acetic Acid (2*R*,3*S*,4*R*)-3-Acetoxy-2-heptyl-3-methyl-3,4-dihydro-2*H*-pyran-4-yl Ester (11.11).

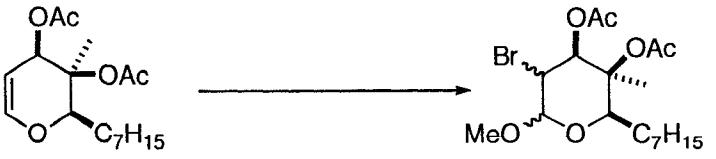


11.10 **11.11**

Zn dust (9.33 g) was tipped into a stirred solution of AcONa (11 g) and AcOH (15.6 mL) in water (22 mL), and saturated aqueous $CuSO_4$ (3 mL) was then added. The blue color disappeared, and a solution of **11.10** (1.32 g, 2.93 mmol) in Ac_2O (6 mL) was added at a fast dropwise rate. Stirring was continued for 2 h and the mixture was diluted with CH_2Cl_2 (25 mL) and filtered. The aqueous phase was extracted with CH_2Cl_2 (2 x 15 mL), and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ (15 mL) and brine (15 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (5 x 16 cm), using 1:6 EtOAc-hexane, gave **11.11** (0.76 g, 83%) as a yellow oil: $[\alpha]_D$ -106.0 (*c* 1.0, $CHCl_3$); FTIR ($CHCl_3$, cast) 2926, 2857, 1747, 1458, 1230 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.86 (t, *J* = 6.9 Hz, 3 H), 1.20-1.66 [m, including a singlet (3 H) at δ 1.58, 14 H in all], 1.83-1.93 (m, 1 H), 1.99 and 2.00 (s, 6 H), 4.08 (d, *J* = 10.9 Hz, 1 H), 4.90 (t, *J* = 10.2 Hz, 1 H), 5.38 (d, *J* = 5.3 Hz, 1 H), 6.26 (d, *J* = 6.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 14.0 (q), 20.9 (q), 21.7 (q), 21.8(q), 22.6 (t), 26.4 (t), 26.9 (t), 29.2 (t), 29.4 (t), 31.8 (t), 67.2 (d), 78.2 (s), 79.4 (d), 98.3 (d), 143.9(d), 169.5 (s), 169.9(s); exact mass

(electrospray) *m/z* calcd for $C_{17}H_{28}NaO_5$ (M + Na) 335.1829, found 335.1828.

Acetic Acid (2*R*,3*S*,4*S*)-4-Acetoxy-5-bromo-2-heptyl-tetrahydro-6-methoxy-3-methylpyran-3-yl Ester (12.1).

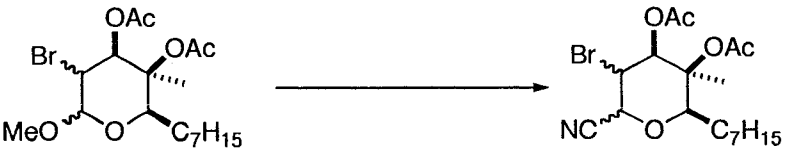


11.11 **12.1**

A solution of **11.11** (0.25 g, 0.60 mmol) in dry MeOH (6 mL) was added dropwise to a stirred and cooled (-50 °C) solution of NBS (0.106 g, 0.60 mol) in dry MeOH (4 mL). The cooling bath was left in place but not recharged and stirring was continued for 19 h. Most of the MeOH was evaporated and the residue was diluted with Et_2O (20 mL). The resulting solution was washed with 10% aqueous $Na_2S_2O_3$ (15 mL) and water (15 mL), dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2.5 x 22 cm), using 20% EtOAc-hexanes, gave **12.1** (0.339 g, 99%) as a mixture of isomers. The more polar isomer had: FTIR (neat) 2956, 2927, 2857, 1749, 1466, 1370, 1236, 1129, 1066 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.87 (t, *J* = 7.0 Hz, 3 H), 1.22-1.36 (m, 10 H), 1.58-1.67 [m, including a singlet at δ 1.52 (3 H), 4 H in all], 1.75-1.83 (m, 1 H), 1.94 (s, 3 H), 2.13 (s, 3 H), 3.41 (s, 2 H), 3.58 (s, 1 H), 3.73 (dt, *J* =

10.7, 1.2 Hz, 1 H), 4.13 (t, J = 3.7 Hz, 1 H), 4.95 (d, J = 3.5 Hz, 1 H), 5.30 (d, J = 4.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.1 (q), 20.3 (q), 20.8 (q), 22.4 (q), 22.6 (t), 26.3 (t), 27.6 (t), 29.3 (t), 29.4 (t), 31.8 (t), 46.8 (d), 55.7 (q), 71.3 (d), 75.9 (d), 80.0 (s), 100.6 (d), 169.6 (s), 169.7 (s); exact mass (electrospray) m/z calcd for $C_{18}H_{31}{}^{79}BrNaO_6$ 445.11962, found 445.11978.

Acetic Acid (2*R*,3*S*,4*S*)-4-Acetoxy-5-bromo-6-cyano-2-heptyltetrahydro-3-methylpyran-3-yl Ester (12.2).

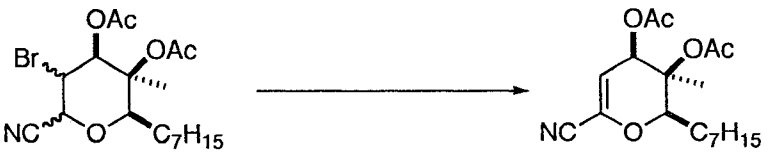


12.1 **12.2**

Me_3SiCN (2.90 mL, 20.7 mmol), followed by $BF_3.OEt_2$ (2.90 mL, 20.7 mmol), was added dropwise to a stirred and cooled (-78 °C) solution of bromoacetal **12.1** (1.30 g, 3.07 mmol) in dry CH_2Cl_2 (12 mL). The cold bath was left in place but not recharged and stirring was continued for 35 h. The mixture was diluted with CH_2Cl_2 (15 mL) and washed with saturated aqueous $NaHCO_3$ (2 x 15 mL) and water (2 x 20 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (4 x 28 cm), using 1:6 EtOAc-hexanes, gave **12.2** (0.636 g, 64%) as a yellow oil: FTIR ($CHCl_3$, cast) 2956, 2928, 2857, 1754, 1466, 1437, 1368, 1231, 1202, 1140,

1094, 1050, 1016 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.84-0.90 (m, 3 H), 1.23-1.36 (m, 10 H), 1.40-1.51 (m, 1 H), 1.59 (s, 2 H), 1.62-1.66 (m, 1 H), 1.74 (s, 1 H), 1.98 (s, 1 H), 2.07 (s, 2 H), 2.14 (s, 3 H), 3.72 (dd, *J* = 9.7, 2.2 Hz, 1 H), 4.30 (dd, *J* = 11.1, 5.8 Hz, 1 H), 5.04 (d, *J* = 5.8 Hz, 1 H), 5.22 (d, *J* = 11.1 Hz, 1 H); exact mass *m/z* calcd for $C_{16}H_{25}{}^{81}BrNO_4$ (M - C_2H_3O) 376.09464, found 376.09484.

Acetic Acid (2*R*,3*S*,4*R*)-4-acetoxy-6-cyano-2-heptyl-3,4-dihydro-3-methyl-2*H*-pyran-3-yl Ester (12.3).

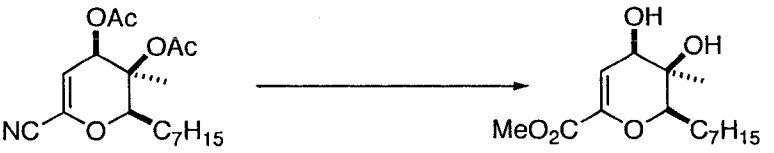


12.2 **12.3**

DBU (0.250 mL, 1.85 mmol) was added dropwise to a stirred and cooled (0 °C) solution of bromonitrile **12.2** (0.636 g, 1.24 mmol) in dry THF (20 mL). The ice bath was left in place but not recharged and stirring was continued for 3 h, by which time the solution had reached room temperature. Evaporation of the solvent and flash chromatography of the residue over silica gel (3.5 x 15 cm), using 1:6 EtOAc-hexane, gave unsaturated nitrile **12.3** (0.480 g, 94%) as an oil: $[\alpha]_D$ -46.3 (*c* 0.38, $CHCl_3$); FTIR (CH_2Cl_2, cast) 2970, 2928, 2858, 2237, 1752, 1645, 1373, 1241, 1161, 1029 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.90 (t, *J* =

7.5 Hz, 3 H), 1.24-1.40 (m, 10 H), 1.60 (s, 3 H), 1.6-1.73 (m, 1 H), 1.74-1.90 (m, 1 H), 2.045 (s, 3 H), 2.054 (s, 3 H), 4.19 (dt, J = 10.7, 1.8 Hz, 1 H), 5.49 (dd, J = 5.0, 1.4 Hz, 1 H), 5.76 (d, J = 4.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.9 (q), 20.5(q), 21.3 (q), 21.5 (q), 22.5 (t), 25.9 (t), 26.4 (t), 29.0 (t), 29.1 (t), 31.6 (t), 66.2 (d), 81.5 (d), 112.2 (d), 113.4 (s), 129.2 (s), 169.2 (s), 169.4 (s); exact mass *m/z* calcd for $C_{18}H_{27}NO_5$ 337.1889, found 337.1891.

(2*R*,3*R*,4*R*)-2-Heptyl-3,4-dihydro-3,4-dihydroxy-3-methyl-2*H*-pyran-6-carboxylic Acid Methyl Ester (12.4).

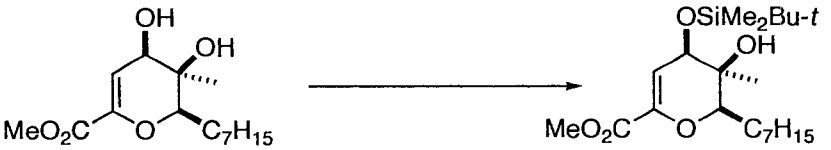


12.3 **12.4**

KOH (4.0 g, 71 mmol) was added to a stirred solution of **12.3** (0.429 g) in water (62 mL) and the mixture was refluxed (oil bath at 105-110 °C), the disappearance of the starting material being monitored by TLC (silica, 1:1 EtOAc-hexane). After 24 h another portion of KOH (0.385 g, 6.86 mmol) was added and refluxing was continued for 11 h (oil bath at 120-130 °C). At this stage reaction was complete. The mixture was cooled to room temperature and then in an ice bath, and acidified to pH 1 with hydrochloric acid (2 N). The solution was saturated with

solid NaCl and extracted with Et_2O (3 x 15 mL). The combined ether extracts were treated with ethereal CH_2N_2 until a yellow color persisted. Evaporation of the solvent and flash chromatography of the residue over silica gel (2.25 x 22 cm), using 1:1 EtOAc-hexanes, gave unsaturated ester **12.4** (0.366 g, 100%) as a yellow oil: $[\alpha]_D$ +130.6 (*c* 0.19, $CHCl_3$); FTIR (CH_2Cl_2, cast) 3446, 2954, 2926, 2857, 1733, 1653, 1438, 1373, 1267, 1140, 1102 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.89 (t, *J* = 6.9 Hz, 3 H), 1.24-1.38 (m, including a singlet, 11 H), 1.38-1.44 (m, 1 H), 1.64-1.74 (m, 2 H), 1.76-1.86 (m, 1 H), 2.0 (s, 1 H), 2.31 (d, *J* = 10.4 Hz, 1 H), 3.73 (dd, *J* = 10.0, 1.9 Hz, 1 H), 3.80 (s, 3 H), 4.04 (dd, *J* = 10.3, 2.4 Hz, 1 H), 5.95 (d, *J* = 2.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.1 (q), 20.8 (q), 22.6 (t), 25.7 (t), 27.6 (t), 29.2 (t), 29.5 (t), 31.8 (t), 52.3 (q), 68.4 (s), 69.3 (d), 82.3 (d), 112.9 (d), 144.1 (s), 162.7 (s); exact mass *m/z* calcd for $C_{15}H_{26}O_5$ 286.1780, found 286.1783.

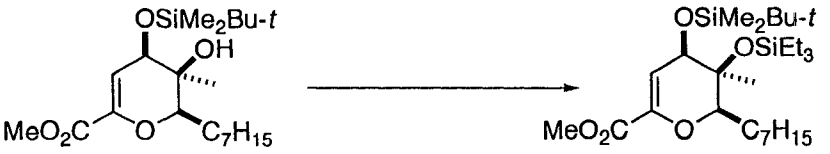
(2*R*,3*S*,4*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]-2-heptyl-3,4-dihydro-3-hydroxy-3-methyl-2*H*-pyran-6-carboxylic Acid Methyl Ester (12.5).



12.4 **12.5**

t-$BuMe_2SiOSO_2CF_3$ (140 mL, 0.607 mmol) was added dropwise to a stirred and cooled (0 °C) solution of diol **12.4** (100 mg, 0.3 mmol) and 2,6-lutidine (0.180 mL, 1.55 mmol) in CH_2Cl_2 (5 mL). Stirring at 0 °C was continued for 1 h, the ice bath was removed and stirring was continued for 4 h. The mixture was diluted with CH_2Cl_2 (5 mL) and washed with saturated aqueous $NaHCO_3$ (5 mL). The organic phase was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.75 x 20 cm), using 1:1 EtOAc-hexanes, gave **12.5** (140.2 mg, 100%) as a colorless oil: $[\alpha]_D$ -0.8 (*c* 0.73, $CHCl_3$); FTIR ($CHCl_3$, cast) 3546, 2954, 2929, 2858, 1734, 1653, 1260 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.15 (s, 3 H), 0.18 (s, 3 H), 0.86-0.94 (m, 12 H), 1.19 (s, 3 H), 1.22-1.39 (m, 9 H), 1.62-1.74 (m, 2 H), 1.84-1.97 (m, 1 H), 2.72 (s, 1 H), 3.73 (d, *J* = 10 Hz, 1 H), 3.8 (s, 3 H), 4.07 (dd, *J* = 3.0, 0.8 Hz, 1 H), 5.79 (d, *J* = 3.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ -5.1 (q), -4.2 (q), 14.0 (q), 17.9 (s), 22.5 (t), 23.0 (q), 25.6 (q), 26.0 (t), 27.3 (t), 29.0 (t), 29.4 (t), 31.7 (t), 52.1 (q), 68.0 (s), 69.5 (d), 81.6 (d), 110.1 (d), 143.6 (s), 162.9 (s); exact mass (electrospray) *m/z* calcd for $C_{21}H_{40}NaO_5Si$ (M + Na) 4223.2537, found 400.2536.

(2*R*,3*S*,4*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]-2-heptyl-3,4-dihydro-3-methyl-3-[(triethylsilyl)oxy]-2*H*-pyran-6-carboxylic Acid Methyl Ester (12.6).



12.5 **12.6**

$Et_3SiOSO_2CF_3$ (1 mL, 4.5 mmol) was added dropwise to a stirred and cooled (0 °C) solution of ester **12.5** (269 mg, 0.78 mmol) and 2,6-lutidine (0.7 mL, 6 mmol) in CH_2Cl_2 (25 mL). The ice bath was left in place but not recharged and stirring was continued for 18 h. The mixture was diluted with CH_2Cl_2 (15 mL) and washed with saturated aqueous $NaHCO_3$ (15 mL) and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3.5 x 25 cm), using hexanes, gave **12.6** (345 mg, 100%) as a colorless oil: $[\alpha]_D$ -1.9 (*c* 0.76, $CHCl_3$); FTIR ($CHCl_3$, cast) 2955, 2930, 2875, 2858, 1745, 1656, 1462, 1438, 1258 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.13 (s, 6 H), 0.54-0.69 (m, 6 H), 0.86-0.95 (m, 21 H), 1.20 (s, 3 H), 1.24-1.38 (m, 9 H), 1.59-1.67 (m, 2 H), 1.80-1.91 (m, 1 H), 3.71 (d, *J* = 10.5 Hz, 1 H), 3.77 (s, 3 H), 4.10 (br s, 1 H), 5.76 (d, *J* = 2.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ -4.56 (q), -4.46 (q), 4.9 (t), 6.5 (t), 6.6 (t), 6.8 (q), 7.0 (q), 14.1 (q), 18.4 (s), 22.6 (t), 23.1 (q), 26.0 (q), 26.3 (t), 27.7 (t), 29.2 (t),

29.6 (t), 31.8 (t), 52.1 (q), 71.3 (d), 71.4 (s), 82.9 (d), 112.3 (d), 142.5 (s), 163.2 (s); exact mass (electrospray) *m/z* calcd for $C_{27}H_{54}NaO_5Si_2$ (M + Na) 537.3402, found 514.3405.

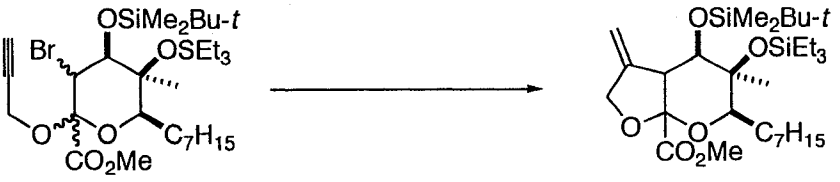
(4*S*,5*S*,6*R*)-3-Bromo-4-[(*tert*-butyldimethylsilyl)oxy]-6-heptyltetrahydro-5-methyl-2-prop-2-ynyloxy-5-[(triethylsilyl)oxy]-2*H*-pyran-2-carboxylic Acid Methyl Ester (12.7).

12.6 **12.7**

A solution of **12.6** (24.5 mg, 0.05 mmol) in CH_2Cl_2 (1 mL) was added dropwise over 1 h to a stirred and cooled (-40 °C) solution of NBS (0.0123 g, 0.06 mmol) and 2-propyn-1-ol (0.07 mL, 1.2 mmol) in CH_2Cl_2 (1 mL). The bath temperature was raised to -20 °C by addition of acetone and stirring was continued for 2 h at -20 °C. The cold bath was left in place but not recharged and stirring was continued for 21 h. The mixture was diluted with CH_2Cl_2 (10 mL) and washed with 5% aqueous $Na_2S_2O_3$ (10 mL). The organic layer was washed with water (10 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (2 x 30 cm), using 1:6 EtOAc-hexanes, gave the bromo ester **12.7** (28.3 mg, 93%) as a single isomer: $[\alpha]_D$

+4.23 (*c* 0.31, $CHCl_3$); FTIR ($CHCl_3$, cast) 3313, 2954, 2930, 2876, 2858, 2126, 1761, 1463, 1255 1160, 1110 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.13 (s, 3 H), 0.24 (s, 3 H), 0.62-0.71 (m, 6 H), 0.86 (t, *J* = 7 Hz, 3 H), 0.93-1.00 (m, 18 H), 1.18 (s, 3 H), 1.22-1.31 (m, 10 H), 1.40-1.48 (m, 1 H), 1.51-1.52 (m, 1 H), 2.41 (t, *J* = 2.4 Hz, 1 H), 3.53 (dd, *J* = 10.1, 1.8 Hz, 1 H), 3.75 (s, 3 H), 3.81 (d, *J* = 10.3 Hz, 1 H), 4.28 (dd, *J* = 15.7, 2.5 Hz, 1 H), 4.59 (d, *J* = 10.4 Hz, 1 H), 4.63 (dd, *J* = 15.8, 2.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ -3.4 (q), -2.0 (q), 6.8 (t), 7.0 (q), 14.1 (q), 19.1 (s), 22.6 (t), 22.7 (q), 26.1 (t), 27.0 (q), 28.5 (t), 29.2 (t), 29.8 (t), 31.9 (t), 52.0 (t), 52.7 (d), 53.3 (q), 74.0 (s), 76.0 (d), 78.8 (s), 79.0 (d), 100.4 (s), 167.2 (s); exact mass *m/z* calcd for $C_{28}H_{52}{}^{79}BrO_6Si_2$ (M - C_2H_5) 621.2465, found 621.2457.

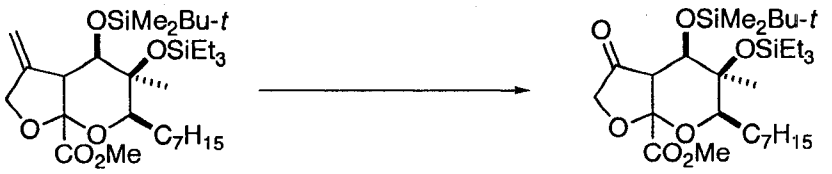
(4*R*,5*S*,6*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]-6-heptyl-hexahydro-5-methyl-3-methylene-5-[(triethylsilyl)-oxy]-7a*H*-furo[2,3-*b*]pyran-7a-carboxylic Acid Methyl Ester (12.8).



12.7 **12.8**

Et_3B in THF (21 μL, 1 M in hexanes) was added to a stirred mixture of **12.7** (20 mg, 0.03 mmol) and Bu_3SnH (14 μL, 0.047 mmol) in EtOAc (1 mL) in a flask open to the air. Stirring was continued for 3.5 h, and the mixture was diluted with Et_2O (5 mL), washed with brine and dried (Na_2SO_4). Evaporation of the solvent and flash chromatography of the residue over silica gel (1.75 x 22 cm), using 1:6 EtOAc-hexanes, gave **12.8** (13 mg, 74%) as a colorless oil: $[\alpha]_D$ -12.9 (*c* 0.04, $CHCl_3$); FTIR ($CHCl_3$, cast) 2953, 2929, 2875, 2857, 1754, 1462, 1252, 1228, 1175, 1093 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.00 (s, 3 H), 0.06 (s, 3 H), 0.63-0.73 (m, 6 H), 0.88 (t, *J* = 7 Hz, 3 H), 0.93-1.01 (m, 18 H), 1.13 (s, 3 H), 1.23-1.34 (m, 9 H), 1.44-1.64 (m, 3 H), 3.04 (d, *J* = 10 Hz, 1 H), 3.41 (d, *J* = 9.6 Hz, 1 H), 3.57 (dd, *J* = 10.0, 2.4 Hz, 1 H), 3.71 (s, 3 H), 4.37 (dt, *J* = 12.5, 1.7 Hz, 1 H), 4.51 (d, *J* = 12.5 Hz, 1 H), 5.00 (s, 1 H), 5.20 (t, *J* = 2.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ -3.4 (q), -2.5 (q), 6.9 (q), 7.1 (t), 14.1 (q), 18.5 (s), 22.0 (q), 22.7 (t), 26.0 (t), 26.5 (q), 28.6 (t), 29.2 (t), 29.6 (t), 31.8 (t), 49.0 (d), 52.3 (q), 68.7 (t), 74.3 (s), 75.6 (d), 78.8 (d), 105.1 (s), 111.5 (s), 144.1 (s), 169.2 (s); exact mass *m/z* calcd for $C_{28}H_{53}O_6Si_2$ (M - C_2H_5) 541.3381, found 541.3384.

(4*R*,5*S*,6*R*)-[4-(*tert*-Butyldimethylsilyl)oxy]-6-heptylhexahydro-5-methyl-3-oxo-5-[(triethylsilyl)oxy]-7a*H*-furo[2,3-*b*]pyran-7a-carboxylic Acid Methyl Ester (12.9).

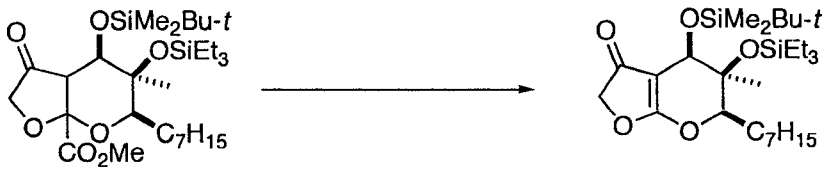


12.8 **12.9**

An O_3-O_2 stream was passed through a stirred and cooled (-78 °C) solution of **12.8** (197 mg, 0.35 mmol) in dry CH_2Cl_2 (10 mL) for 12 min. The solution was purged with O_2 for 15 min, and then Ph_3P (142 mg, 0.54 mmol) was added. The cooling bath was removed and stirring was continued for 7 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (1.75 x 22 cm), using 1:6 EtOAc-hexanes, gave keto ester **12.9** (158 mg, 80%) as a colorless oil: $[\alpha]_D$ +34.3 (*c* 0.02, $CHCl_3$); FTIR ($CHCl_3$, cast) 2954, 2929, 2876, 2857, 1770, 1739, 1463, 1258, 1231 1141 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ -0.02 (s, 3 H), 0.07 (s, 3 H), 0.58-0.68 (m, 6 H), 0.89 (t, *J* = 7 Hz, 3 H), 0.92-0.98 (m, 18 H), 1.17 (s, 3 H), 1.24-1.36 (m, 9 H), 1.48-1.54 (m, 1 H), 1.58-1.74 (m, 2 H), 2.76 (d, *J* = 9.4 Hz, 1 H), 3.61 (d, *J* = 9.5 Hz, 1 H), 3.64 (dd, *J* = 9.9, 2.5 Hz, 1 H), 3.76 (s, 3 H), 4.21 (AB q, *J* = 16.5 Hz, $\Delta\nu_{AB}$ = 80.1 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) (small impurity signals at

130-136 ppm) δ -4.6 (q), -2.7 (q), 6.9 (t), 7.0 (q), 14.1 (q), 18.5 (s), 21.6 (q), 22.7 (t), 26.0 (t), 26.4 (q), 28.5 (t), 29.2 (t), 29.5 (t), 31.8 (t), 51.9 (q), 52.7 (d), 70.6 (t), 73.6 (s), 74.6 (d), 78.9 (d), 102.7 (s), 168.5 (s), 209.4 (s); exact mass *m/z* calcd for $C_{27}H_{51}O_7Si_2$ (M - C_2H_5) 543.3173, found 543.3191.

(4*R*,5*S*,6*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]-6-heptyl-5,6-dihydro-5-methyl-5-[(triethylsilyl)oxy]-4*H*-furo[2,3-*b*]pyran-3(2*H*)-one (13.2).



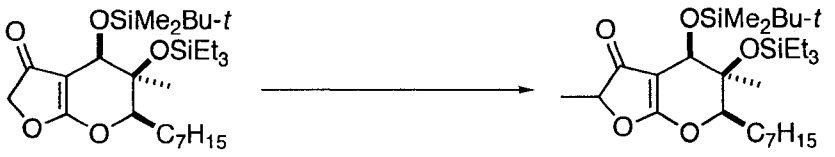
12.9 **13.2**

$(Bu_3Sn)_2O$ (3.5 mL, 6.8 mmol) was added to a stirred solution of **12.9** (158 mg, 0.28 mmol) in PhH (9 ml) and the mixture was refluxed at 85 °C for 23 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (2.75 x 10 cm), using 1:1 EtOAc-hexanes, gave the acid **13.1**, which was used immediately.

$Cu(OAc)_2.H_2O$ (0.34 g, 1.7 mmol) was added to a stirred solution of the freshly prepared acid in PhH (9.5 mL) (N_2 atmosphere). Dry pyridine (0.1 mL) was added, and stirring was continued at for 50 min. The flask was then wrapped

with aluminum foil, and $Pb(OAc)_4$ (0.80 g, 1.83 mmol) was tipped in. Stirring was continued for 50 min, and another portion of $Pb(OAc)_4$ (0.9 g, 2.1 mmol) was added, followed by dry DMF (0.9 mL). The flask was fitted with a reflux condenser and flushed well with N_2. The mixture was refluxed for 11 h (oil bath at 88 °C). PhH (4 mL) was added and refluxing was continued for 1 h. The resulting solution was cooled to room temperature, evaporated to a small volume, and applied directly to a flash chromatography column (27 x 2.75 cm) made up with silica gel in 1:20 EtOAc-hexane. Flash chromatography, using 1:20 to 1:6 EtOAc-hexanes, gave **13.2** (88 mg, 61%) as a yellow oil: $[\alpha]_D$ +6.8 (*c* 0.10, $CHCl_3$); FTIR (CH_2Cl_2, cast) 2956, 2928, 2877, 2857, 1707, 1604, 1467, 1249 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, 60 °C) δ 0.18 (s, 6 H), 0.62-0.74 (m, 6 H), 0.89-1.02 (m, 21 H), 1.26-1.37 (m, 12 H), 1.44-1.65 (m, 1 H), 2.01-2.06 (m, 2 H), 4.11 (dd, J = 7.1, 3.8 Hz, 1 H), 4.26 (s, 1 H), 4.50 (AB q, J = 15.7 Hz, $\Delta\nu_{AB}$ = 27.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100.58 MHz, 50 °C) δ -4.7, 6.89, 6.99, 14.0, 18.3, 22.7, 24.8, 26.1, 27.1, 29.1, 29.4, 31.8, 67.6, 73.4, 75.6, 90.0, 92.6, 181.4, 192.8; exact mass *m/z* calcd for $C_{26}H_{49}O_5Si_2$ (M - CH_3) 497.3119, found 497.3128.

(4*R*,5*S*,6*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]-6-heptyl-5,6-dihydro-2,5-dimethyl-5-[(triethyl-silyl)oxy]-4*H*-furo[2,3-b]pyran-3(2*H*)-one (13.3).

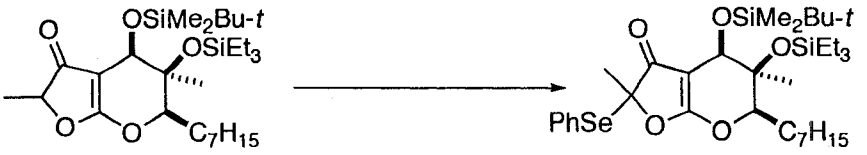


13.2 **13.3**

n-BuLi (2.5 M in hexanes, 0.1 mL, 0.23 mmol) was added to a stirred and cooled (-78 °C) solution of *i*-Pr_2NH (0.05 mL, 0.32 mmol) in dry THF (0.8 mL) and stirring was continued for 40 min. A solution of **13.2** (105 mg, 0.21 mmol) in THF (0.2 mL) was then added dropwise and stirring at -78 °C was continued for 1 h. Freshly distilled HMPA (0.03 mL, 0.17 mmol) was added rapidly followed immediately by MeI (25 μL, 0.40 mmol) which was also added quickly, and stirring at -78 °C was continued for 18 h. Then the cold bath was removed and the solution was allowed to reach to room temperature. The mixture was quenched with water (2 mL) and diluted with Et_2O (5 mL). The organic layer was washed with water, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 1:6 EtOAc-hexane, gave **13.3** (80 mg, 75%) as a yellow oil: $[\alpha]_D$ +71.2 (*c* 0.20, $CHCl_3$); FTIR (CH_2Cl_2, cast) 2956, 2929, 2877, 2857, 1706, 1602, 1467, 1249, 1086 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.14 (s, 6 H), 0.0.56-0.71 (m, 6 H), 0.82-1.00 (m, 21 H), 1.21-1.35 (m, 13 H), 1.43 (d, *J* = 7.0 Hz, 3 H), 1.56-1.60 (m, 1 H), 1.97-2.04 (br s, 1 H), 4.08 (d, *J* = 4.9 Hz, 1 H), 4.20 (t, *J* = 4.3 Hz, 1 H), 4.63-4.67 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz, 60 °C) δ -4.6, 7.0,

14.0, 16.2, 18.4, 22.7, 23.0, 26.2, 27.2, 29.1, 29.2, 29.4, 31.6, 31.8, 67.5, 73.5, 84.0, 89.9, 91.4, 179.9, 195.8; exact mass *m/z* calcd for $C_{26}H_{49}O_5Si_2$ (M - C_2H_5) 497.3119, found 497.3113.

(4*R*,5*S*,6*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]-6-heptyl-5,6-dihydro-2,5-dimethyl-2-(phenylseleno)-5-[(triethylsilyl)oxy]-4*H*-furo[2,3-b]pyran-3(2*H*)-one (13.4).

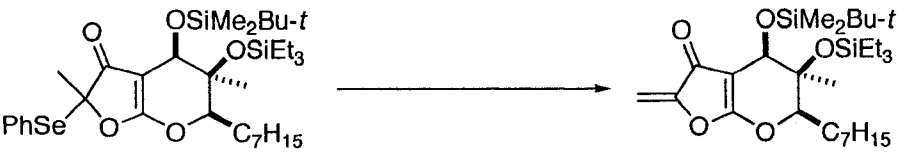


13.3 **13.4**

n-BuLi (41 μL, 0.10 mmol) was added to a stirred and cooled (-0 °C) solution of *i*-Pr_2NH (0.016 g, 0.16 mmol) in dry THF (0.3 mL). After 15 min the solution was cooled to -78 °C and **13.3** (43 mg, 0.08 mmol) in THF (0.3 mL) was added dropwise. Stirring at -78 °C was continued for 40 min and a solution of PhSeCl (0.023 g, 0.12 mmol) in THF (0.1 mL) was then added dropwise. Stirring at -78 °C was continued for 4 h and the mixture was quenched with saturated aqueous NH_4Cl (2 mL) and diluted with Et_2O (5 mL). The organic layer was washed with water, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.75 x 22 cm), using 1:8 EtOAc-hexanes, gave the unsaturated ketone **13.4** (39 mg, 70%) as a yellow oil: FTIR (CH_2Cl_2, cast)

2955, 2928, 2876, 2857, 1709, 1603, 1454, 1248, 1199, 1167, 1138, 1089, 1063, 1005 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.13 (s, 6 H), 0.51-0.64 (m, 7 H), 0.08-0.98 (m, 22 H), 1.23 1.35 (m, 10 H), 1.50-1.60 (br s, 1 H), 1.77 (s, 3 H), 1.83-1.97 (br s, 1 H), 1.98-2.11 (m, 1 H), 3.84-4.0 (m, 2 H), 7.24-7.29 (m, 2 H), 7.34 (tt, *J* = 7.3, 1.0 Hz, 1 H), 7.66 (d, *J* = 7.8 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125.3 MHz) δ -4.6, 6.8, 7.1, 14.1, 18.3, 22.7, 23.0, 24.7, 27.0, 27.4, 29.1, 29.3, 31.8, 66.3, 73.0, 90.6, 91.7, 94.0, 125.2, 129.0, 129.5, 137.8, 177.5, 193.1; exact mass *m/z* calcd for $C_{34}H_{58}O_5{}^{80}SeSi_2$ (M - CH_3) 667.27533, found 667.27426.

(4*R*,5*S*,6*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]-6-heptyl-5,6-dihydro-5-methyl-2-methylene-5-[(triethylsilyl)oxy]-4*H*-furo[2,3-b]pyran-3(2*H*)-one (13.5).



13.4 **13.5**

H_2O_2 (30% , 0.05 mL, 0.57 mmol) was added to a stirred solution of **13.4** (39 mg, 0.06 mmol) in THF (1.4 mL) and water (0.3 mL) (flask open to the air). Stirring was continued for 1.5 h, and the mixture was diluted with THF (3 mL) and water (2 mL), and extracted with Et_2O (3 x 5 mL). The combined organic extracts were dried (Na_2SO_4) and

evaporated. Flash chromatography of the residue over silica gel (2.75 x 24 cm), using 1:10 *t*-BuOMe-hexanes, gave **13.5** (29.6 mg, 76%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.17 (s, 6 H), 0.60-0.72 (m, 6 H), 0.82-1.03 (m, 21 H), 1.25-1.36 (m, 13 H), 1.55-1.60 (m, 1 H), 1.98-2.12 (m, 1 H), 4.14-4.24 (m, 1 H), 4.25-4.32 (m, 1 H), 5.08 (d, J = 2.4 Hz, 1 H), 5.49 (d, J = 2.7 Hz, 1 H).

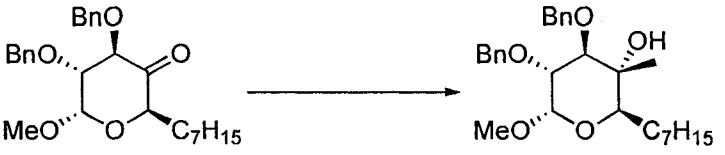
(4*R*,5*R*,6*R*)-6-heptyl-5,6-dihydro-4,5-dihydroxy-5-methyl-2-methylene-4*H*-furo[2,3-b]pyran-3(2*H*)-one (1).

13.5 **1**

HF-pyridine (70%w/w, 34 μL) was added to a stirred and cooled (0 °C) solution of **13.5** (12.3 mg, 0.04 mmol) in dry THF (1 mL) (Ar atmosphere). Stirring was continued for 25 min, the ice bath was removed and another portion of HF-pyridine (0.2 mL) was added. The progress of the reaction was monitored by TLC (silica, 1:1 EtOAc-hexanes). After 1.5 h, the reaction flask was placed in an ice bath and the mixture was diluted with Et_2O (2 mL) and quenched with saturated aqueous $NaHCO_3$ until CO_2 evolution stopped. The organic phase was dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 x 18 cm),

using 1:1 EtOAc-hexanes, gave **1** (2 mg, 29%) as a colorless oil: $[\alpha]_D$ +130.6 (*c* 0.10, $CHCl_3$); FTIR (CH_2Cl_2, cast) 3382, 2956, 2927, 2857, 1695, 1595, 1478, 1306, 1033 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ 0.91 (t, *J* = 7.2 Hz, 3 H), 1.29 (s, 3 H), 1.31-1.41 (m, 7 H), 1.41-1.52 (m, 2 H), 1.66-1.80 (m, 2 H), 1.92-1.96 (m, 1 H), 4.08 (s, 1 H), 4.46 (dd, *J* = 10.9, 2.3 Hz, 1 H), 5.27 (d, *J* = 3.1 Hz, 1 H), 5.52 (d, *J* = 3.0 Hz, 1 H); ^{13}C NMR (CD_3OD, 125.3 MHz, 50 °C) δ 14.8, 22.5, 24.1, 27.0, 29.2, 30.7, 30.8, 33.4, 67.3, 72.6, 87.5, 95.0, 97.6, 155.5, 181.0, 183.3; exact mass *m/z* calcd for $C_{16}H_{24}O_5$ 296.1624, found 296.1612.

(2*R*,3*R*,4*R*,5*R*,6*S*)-4,5-Bis(benzyloxy)-2-heptyltetrahydro-6-methoxy-3-methyl-2*H*-pyran-3-ol (14.1).

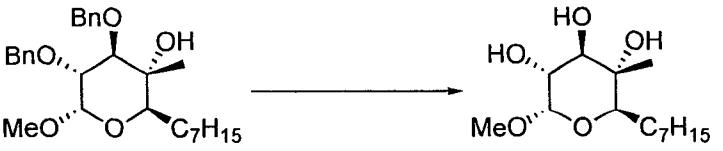


11.6 **14.1**

MeLi (1.6 M in Et_2O, 54 mL) was added to a stirred and cooled (-78 °C) solution of **11.6** (5.80 g, 13.18 mmol) in Et_2O (450 mL) and stirring at -78 °C was continued for 2 h. The mixture was diluted with aqueous NH_4Cl (50 mL) and the aqueous layer was extracted with Et_2O (2 x 40 mL). 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 38 cm), using 1:8 *t*-BuOMe-hexanes, gave **14.1** (3.77 g, 80%) as a yellow oil: $[\alpha]_D$ +15.6 (*c* 0.45, $CHCl_3$); FTIR ($CHCl_3$, cast) 3483, 3031, 2926, 2857, 1497, 1454, 1372, 1357, 1132, 1089, 1075, 1029 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.88 (t, J = 6.6 Hz, 3 H), 1.14 (s, 3 H), 1.22-1.36 (m, 9 H), 1.47-1.67 (m, 2 H), 1.81 (br s, 1 H), 3.4 (s, 3 H), 3.45 (dd, J = 10.1, 3.9 Hz, 1 H), 3.51 (d, J = 10.0 Hz, 1 H), 3.73 (d, J = 10.1 Hz, 1 H), 4.57 (d, J = 3.9 Hz, 1 H), 4.63 (d, J = 12.0 Hz, 1 H), 4.74 (AB q, J_{AB} = 12.1 Hz, $\Delta\nu_{AB}$ = 21.6 Hz, 2 H), 5.04 (d, J = 11.8 Hz, 1 H), 7.28-7.38 (m, 10 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 14.1 (q), 15.5 (q), 22.7 (t), 26.8 (t), 27.7 (t), 29.3 (t), 29.7 (t), 31.9 (t), 54.9 (q), 73.1 (t), 73.2 (d), 74.3 (s), 75.6 (t), 79.2 (d), 83.9 (d), 98.0 (d), 127.70 (d), 127.8 (d), 128.1 (d), 128.4 (d), 128.5 (d), 138.3 (s), 139 (s); exact mass (electrospray) *m/z* calcd for $C_{28}H_{40}NaO_5$ (M + Na) 479.27680, found 479.27673.

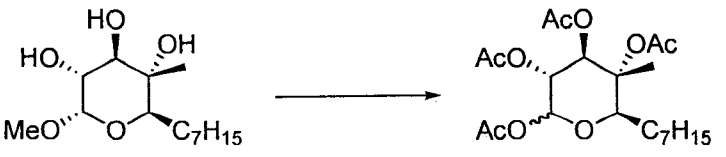
(2*R*,3*S*,4*R*,5*R*,6*S*)-2-Heptyltetrahydro-6-methoxy-3-methyl-2*H*-pyran-3,4,5-triol (14.2).



14.1 **14.2**

Pd-C (10%, 0.8 g) was added to a solution of **14.1** (5.13 g, 11.3 mmol) in MeOH (20 mL). The mixture was shaken under H_2 (50 psi, Parr shaker) for 8 h and then filtered through a pad of silica gel, using EtOAc. The filtrate was evaporated to give **14.2** (2.8 g, 90%) as a white solid: mp 104-106 °C; $[\alpha]_D$ +162.3 (*c* 0.06, $CHCl_3$); FTIR (cast) 3290, 2924, 2857, 1467, 1364, 1153, 1059 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.88 (t, *J* = 6.7 Hz, 3 H), 1.13 (s, 3 H), 1.21-1.42 (m, 10 H), 1.51-1.61 (br s, 1 H), 1.64-1.71 (m, 1 H), 2.94 (br s, 1 H), 3.05 (br s, 1 H), 3.41 (s, 3 H), 3.48 (apparent d, *J* = 10.2 Hz, 2 H), 3.69 (d, *J* = 9.8 Hz, 1 H), 3.81 (br s, 1 H), 4.72 (dd, *J* = 3.4, 1.9 Hz, 1 H); ^{13}C NMR ($CHCl_3$, 100.6 MHz) δ 13.97 (q), 14.02 (q), 22.5 (t), 26.8 (t), 27.5 (t), 29.2 (t), 29.6 (t), 31.8 (t), 55.0 (q), 71.4 (d), 73.6 (d), 73.7 (d), 76.9 (s), 98.8 (d); exact mass (electrospray) *m/z* calcd for $C_{14}H_{28}NaO_5$ (M + Na) 299.18289, found 299.18296.

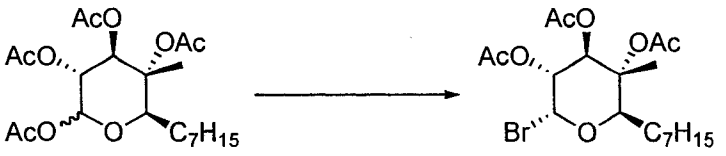
Acetic Acid (3*R*,4*R*,5*R*,6*R*)-3,4,5-Triacetoxy-6-heptyl-tetrahydro-5-methylpyran-2-yl Ester (14.3).



14.2 **14.3**

Concentrated H_2SO_4 (0.6 mL) was added dropwise to a stirred and cooled (0 °C) solution of **14.2** (4.28 g, 15.5 mmol) in a mixture of Ac_2O (18.5 mL) and AcOH (18.5 mL). The cold bath was left in place, but not recharged, and stirring was continued for 20 h. The mixture was poured into water (100 mL) and extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with water (50 mL), saturated aqueous $NaHCO_3$ (50 mL) and brine (50 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (5 x 15 cm), using 25% EtOAc-hexanes, gave **14.3** (6.63 g, 100%) as a 1:5 mixture of epimers: $[\alpha]_D$ +60.7 (*c* 0.45, $CHCl_3$); FTIR ($CHCl_3$, cast) 2929, 2858, 1754, 1370, 1224 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) (two epimers) δ 0.88 (t, *J* = 6.2 Hz, 3 H), 1.18-1.32 (m, 9 H), 1.38-1.48 (m including a singlet at δ 1.39, 6 H in all), 1.94-2.17 (eight s, 12 H in all), 4.54 and 4.79 (both t, *J* = 5.5 Hz, 1 H in all), 5.00 and 5.06 (both dd, *J* = 10.3, 4.1 Hz, 1 H in all), 5.68 and 5.99 (both d, *J* = 10.4, 8.5 Hz, 1 H in all), 5.87-6.22 (d, *J* = 4.1, 9.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 13.97 (q), 14.04 (q), 20.5 (q), 20.8 (q), 20.9 (q), 22.1 (q), 22.6 (t), 25.8 (t), 27.1 (t), 29.1 (t), 29.2 (t), 31.8 (t), 69.1 (d), 70.3 (d), 71.3 (d), 82.8 (s), 88.9 (d), 169.3 (s), 169.8 (s), 169.9 (s), 170.2 (s); exact mass (electrospray) *m/z* calcd for $C_{21}H_{34}NaO_9$ (M + Na) 453.20950, found 453.20956.

Acetic Acid (2*R*,3*R*,4*R*,5*R*,6*R*)-4,5-Diacetoxy-2-bromo-6-heptyltetrahydro-5-methylpyran-3-yl Ester (14.4).

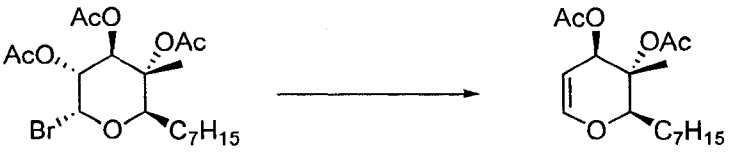


14.3 **14.4**

A solution of HBr in AcOH (45%, 21.5 mL) was added dropwise to a stirred solution of **14.3** (6.72 g, 15.7 mmol) in CH_2Cl_2 (60 mL). Stirring was continued for 5 h, and the mixture was diluted with CH_2Cl_2 (40 mL), washed with ice-water (25 mL), saturated aqueous $NaHCO_3$ (25 mL) and brine (25 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (5 x 15 cm), using 15% EtOAc-hexanes, gave **14.4** (5.24 g, 75%) as a yellow oil: $[\alpha]_D$ +176.8 (*c* 1.2, $CHCl_3$); FTIR (neat) 2928, 2858, 1750, 1369, 1247, 1223 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.88 (t, *J* = 7.1 Hz, 3 H), 1.22-1.38 (m, 9 H), 1.42 (s, 3 H), 1.46-1.55 (m, 3 H), 1.96 (s, 3 H), 2.09 (s, 6 H), 4.72 (dd, *J* = 10.2, 4.5 Hz, 1 H), 4.95 (t, *J* = 6.2 Hz, 1 H), 6.01 (d, *J* = 10.2 Hz, 1 H), 6.63 (d, *J* = 4.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 14.1 (q), 14.7 (q), 20.73 (q), 20.74 (q), 22.0 (q), 22.6 (t), 25.5 (t), 26.9 (t), 29.06 (t), 29.12 (t), 31.7 (t), 70.5 (d), 70.7 (d), 74.7 (d), 82.0 (s), 87.8 (d), 169.6 (s), 170.0 (s), 170.1 (s); exact mass (electrospray)

m/z calcd for $C_{19}H_{31}{}^{79}BrNaO_7$ (M + Na) 473.11454, found 473.11455.

Acetic Acid (2*R*,3*R*,4*R*)-3-Acetoxy-2-heptyl-3,4-dihydro--3-methyl-2*H*-pyran-4-yl Ester (14.5).



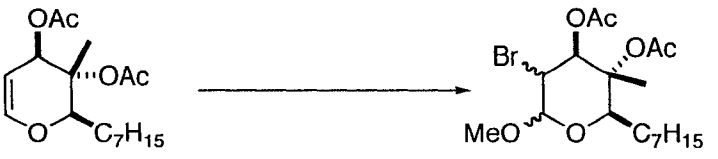
14.4 **14.5**

Zn dust (35.0 g) was tipped into a stirred solution of AcONa (41.0 g) and AcOH (60 mL) in water (75 mL), and saturated aqueous $CuSO_4$ (12 mL) was then added. The blue color disappeared. A solution of **14.4** (4.90 g, 10.9 mmol) in Ac_2O (20 mL) was then added at a fast dropwise rate, and stirring was continued for 3 h. The mixture was diluted with CH_2Cl_2 (70 mL) and filtered through a pad of Celite. **CAUTION:** The Zn dust and Celite can spontaneously burst into flame. The material should be covered with sand and kept wet with water. The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (50 mL) and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (5 x 27 cm), using 1:10 *t*-BuOMe-hexane, gave **14.5** (3.03 g, 90%) as a colorless oil: $[\alpha]_D$ -18.0 (*c* 0.6, $CHCl_3$); FTIR ($CHCl_3$, cast) 2955, 2928, 2858, 1748, 1650, 1370, 1234 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.89

(t, J = 7.0 Hz, 3 H), 1.24-1.37 [m, including a singlet (3 H) at δ 1.35, 13 H in all], 1.43-1.50 (m, 1 H), 1.61-1.68 (m, 1 H), 1.99 and 2.10 (two singlets, 6 H in all), 4.62 (dd, J = 6.0, 2.7 Hz, 1 H), 4.75 (dd, J = 10.6, 1.9 Hz, 1 H), 6.06 (s, 1 H), 6.37 (dd, J = 6.0, 1.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 13.98 (q), 14.14 (q), 20.9 (q), 21.9 (q), 22.5 (t), 26.0 (t), 27.0 (t), 29.1 (t), 29.3 (t), 31.7 (t), 69.0 (d), 78.0 (d), 80.7 (s), 100.3 (d), 145.4 (d), 169.86 (s), 169.94 (s); exact mass (electrospray) m/z calcd for $C_{17}H_{28}NaO_5$ (M + Na) 335.18289, found 335.18294.

Sequence with correct relative stereochemistry, using TES and TBDMS protection.

Acetic Acid (2*R*,3*R*,4*S*)-4-Acetoxy-5-bromo-2-heptyl-tetrahydro-6-methoxy-3-methylpyran-3-yl Ester (15.1).

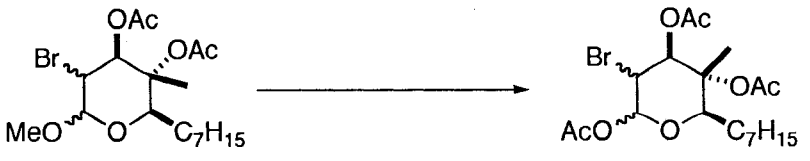


14.5 **15.1**

A solution of **14.5** (69 mg, 0.17 mmol) in dry MeOH (1.5 mL) was added dropwise to a stirred and cooled (-40 °C) solution of NBS (36 mg, 0.20 mmol) in dry MeOH (1 mL). The cooling bath was left in place but not recharged and stirring was continued for 23 h. Most of the MeOH was

evaporated and the residue was diluted with Et_2O (5 mL). The resulting solution was washed with 10% aqueous $Na_2S_2O_3$ (3 mL) and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 1:6 EtOAc-hexane, gave **15.1** (80.0 mg, 86%) as a mixture of isomers: $[\alpha]_D$ +17.14 (*c* 0.07, $CHCl_3$); FTIR (neat) 2972, 2857, 1756, 1452, 1371, 1238, 1153, 1075, 1046, 1021 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, *J* = 6.9 Hz, 3 H), 1.20-1.40 (m, 12 H), 1.45-1.55 (m, 3 H), 1.93 (s, 3 H), 2.14 (s, 3 H), 3.57 (s, 3 H), 3.71 (dd, *J* = 10.5, 8.7 Hz, 1 H), 4.45-4.53 (m, 2 H), 5.85 (d, *J* = 10.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.88 (q), 13.95 (q), 20.6 (q), 22.0 (q), 22.5 (t), 26.0 (t), 27.3 (t), 29.1 (t), 29.3 (t), 31.7 (t), 50.8 (d), 57.4 (q), 74.0 (d), 74.5 (d), 83.6 (s), 103.7 (d), 169.7 (s), 169.9 (s); exact mass (electrospray) *m/z* calcd for $C_{18}H_{31}{}^{79}BrO_6Na$ (M + Na) 445.11962, found 445.111977.

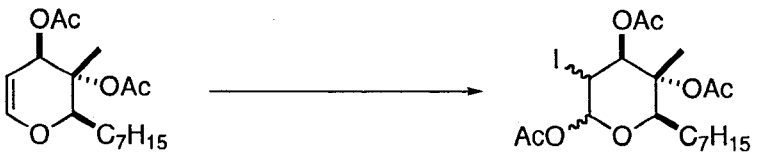
Acetic Acid (4*S*,5*S*,6*R*)-4,5-Diacetoxy-3-bromo-6-heptyl-tetrahydro-5-methylpyran-2-yl Ester (15.2).



15.1 **15.2**

Concentrated H_2SO_4 (2 drops) was added to a stirred and cooled (0 °C) solution of **15.1** (41 mg, 0.09 mmol) in Ac_2O (1 mL). The ice bath was left in place but not recharged, and stirring was continued for 3 h. Solid Na_2CO_3 (50.0 mg) was then added and the mixture was diluted with Et_2O (5 mL), washed with water, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 16 cm), using 1:6 EtOAc-hexane, gave **15.2** (33 mg, 76%) as a mixture of two isomers: $[\alpha]_D$ +134.97 (*c* 0.02, $CHCl_3$); FTIR (neat) 2928, 2858, 1760, 1433, 1371, 1237, 1218, 1122, 1073, 1014 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.87 (t, *J* = 6.5 Hz, 3 H), 1.18-1.33 (m, 10 H), 1.37 (s, 3 H), 1.38-1.51 (m, 2 H), 1.19 (s, 3 H), 2.14 (s, 3 H), 2.19 (s, 3 H), 4.01 (dd, *J* = 11.1 Hz, 1 H), 4.82 (m, 1 H), 6.02 (d, *J* = 11.1 Hz, 1 H), 6.22 (d, *J* = 3.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.3 (q), 14.1 (q), 20.6 (q), 20.7 (q), 22.1 (q), 22.6 (t), 25.8 (t), 27.1 (t), 29.05 (t), 29.14 (t), 31.8 (t), 47.0 (d), 71.5 (d), 72.3 (d), 83.4 (s), 90.3 (d), 170.0 (s), 169.8 (s), 169.9 (s); exact mass *m/z* (electrospray) calcd for $C_{19}H_{31}IO_3Na$ 521.10068 (M + Na), found 521.10055.

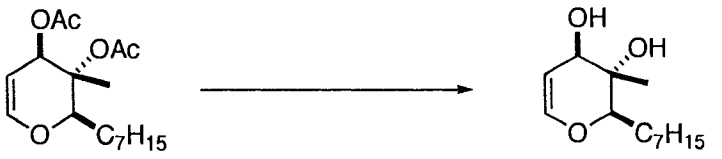
Acetic Acid (4*S*,5*R*,6*R*)-4,5-Diacetoxy-6-heptyltetrahydro-3-iodo-5-methylpyran-2-yl Ester (15.4).



14.5 **15.4**

AcOH (23 μL, 0.4 mmol), followed by NIS (75 mg, 0.33 mmol), was added to a stirred solution of **14.5** (65 mg, 0.20 mmol) in CH_2Cl_2 (3.5 mL) and stirring was continued for 7 h. The resulting solution was washed with 10% aqueous $Na_2S_2O_3$ (5 mL), extracted with EtOAc (5 mL x 3), dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 25 cm), using 1:6 EtOAc-hexane, gave **15.4** (96.0 mg, 93%) as a mixture of two isomers. The more polar isomer had: $[\alpha]_D$ +27.39 (*c* 0.10, $CHCl_3$): FTIR ($CHCl_3$, cast) 2972, 2857, 1759, 1367, 1214, 1066, 1035 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.87 (t, *J* = 6.7 Hz, 3 H), 1.21-1.33 (m, 9 H), 1.36 (s, 3 H), 1.40-1.52 (m, 3 H), 1.93 (s, 3 H), 2.15 (s, 6 H), 3.93 (dd, *J* = 11.3, 9.7 Hz, 1 H), 4.56 (t, *J* = 6.5 Hz, 1 H), 5.86 (d, *J* = 11.3 Hz, 1 H), 5.90 (d, *J* = 9.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.6 (q), 14.1 (q), 20.7 (q), 20.8 (q), 22.0 (q), 22.6 (t), 25.9 (t), 27.4 (t), 28.0 (d), 29.1 (t), 29.3 (t), 31.8 (t), 75.3 (d), 75.6 (d), 83.0 (s), 94.8 (d), 168.5 (s), 169.5 (s), 169.9 (s); exact mass *m/z* (electrospray) calcd for $C_{19}H_{31}IO_3Na$ 521.10068 (M + Na), found 521.10055.

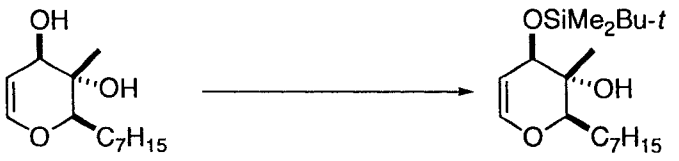
(2*R*,3*S*,4*R*)-2-Heptyl-3,4-dihydro-3-methyl-2*H*-pyran-3,4-diol (16.1).



14.5 **16.1**

K_2CO_3 (1.66 g, 12.0 mmol) was added to a stirred solution of **14.5** (1.22 g, 3.2 mmol) in MeOH (10 mL). After 30 min, the mixture was diluted with water (10 mL) and extracted with CH_2Cl_2 (2 x 15 mL). The combined organic extracts were washed with brine (15 mL), dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (3 x 16 cm), using 50% EtOAc-hexanes, gave **16.1** (0.89 g, 100%) as a white solid: mp 59-60 °C; $[\alpha]_D$ +14.0 (*c* 0.03, $CHCl_3$); FTIR ($CHCl_3$, cast) 3264, 2955, 2924, 2853, 1647, 1464, 1378, 1232, 1135, 1083 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.89 (t, *J* = 9.2 Hz, 3 H), 1.15 (s, 3 H), 1.21-1.40 (m, 9 H), 1.50-1.64 (m, 2 H), 1.68-1.82 (m, 1 H), 1.96 (br s, 1 H), 2.12 (br s, 1 H), 3.67 (dd, *J* = 10.3, 2.1 Hz, 1 H), 4.23 (s, 1 H), 4.68 (dd, *J* = 6.0, 2.1 Hz, 1 H), 6.29 (dd, *J* = 6.0, 1.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 14.0 (q), 14.4 (q), 22.5 (t), 26.4 (t), 27.2 (t), 29.1 (t), 29.4 (t), 31.7 (t), 71.0 (s), 72.8 (d), 81.3 (d), 103.3 (d), 144.3 (d); exact mass *m/z* calcd for $C_{13}H_{24}NaO_3$ (M + Na) 251.16177, found 251.16204.

(2*R*,3*R*,4*R*)-4-[*tert*-Butyldimethylsilyl)oxy]-2-heptyl-3,4-dihydro-3-methyl-2*H*-pyran-3-ol (16.3).

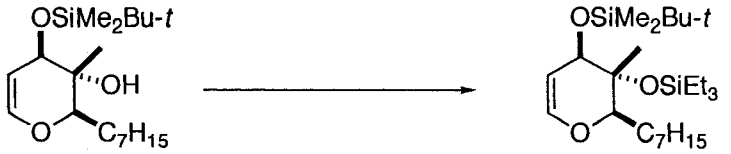


16.1 **16.3**

t-$BuMe_2SiOSO_2CF_3$ (1.3 mL, 5.62 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **16.1** (0.55 g, 2.4 mmol) and 2,6-lutidine (0.85 mL, 7.2 mmol) in CH_2Cl_2 (30 mL). The ice bath was left in place but not recharged and stirring was continued for 4 h. The mixture was diluted with CH_2Cl_2 (20 mL) and washed with saturated aqueous $NaHCO_3$ (15 mL) and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (24 x 2.5 cm), using 1:16 EtOAc-hexane, gave **16.3** (0.79 g, 88%) as a yellow oil: $[\alpha]_D$ -35.71 (*c* 0.07, $CHCl_3$); FTIR ($CHCl_3$, cast) 3493, 2956, 2929, 2858, 1650, 1472, 1463, 1389, 1379, 1253, 1235, 1132, 1086 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.10 (s, 6 H), 0.85-0.92 (m, 12 H), 1.16 (s, 3 H), 1.23-1.36 (m, 9 H), 1.51-1.57 (m, 1 H), 1.65-1.71 (m, 2 H), 1.86 (s, 1 H), 3.67-3.71 (m, 1 H), 4.12 (s, 1 H), 4.61 (dd, *J* = 6.1, 2.5 Hz, 1 H), 6.24 (dd, *J* = 6.1, 1.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ -4.9 (q), -4.5 (q), 14.0 (q), 15.9 (q), 18.0 (s), 22.5 (t), 25.7 (q), 26.5 (t), 27.4 (t), 29.1 (t), 29.4 (t), 31.7 (t), 71.3 (s), 72.3 (d), 81.5 (d), 104.4 (d), 142.9

(d); exact mass *m/z* calcd for $C_{19}H_{38}O_3Si$ 342.25903, found 342.25857.

(2*R*,3*R*,4*R*)-4-[*tert*-Butyldimethylsilyl)oxy]-2-heptyl-3,4-dihydro-3-methyl-3-[(triethylsilyl)oxy]-2*H*-pyran (16.4).

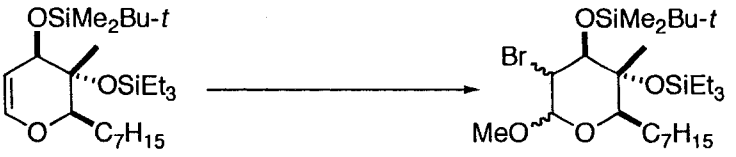


16.3 **16.4**

$Et_3SiOSO_2CF_3$ (5.0 mL, 22.5 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **16.3** (1.28 g, 3.71 mmol) and 2,6-lutidine (3.1 mL, 26.6 mmol) in CH_2Cl_2 (80 mL). The ice bath was left in place but not recharged and stirring was continued for 10 h. The mixture was diluted with CH_2Cl_2 (30 mL) and washed with saturated aqueous $NaHCO_3$ (50 mL) and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 25 cm), using hexanes, gave **16.4** (1.70 g, 100%) as a colorless oil: $[\alpha]_D$ -40.99 (*c* 0.06, $CHCl_3$); FTIR ($CHCl_3$, cast) 2956, 2929, 2876, 2858, 1650, 1462, 1253, 1154, 1119, 1092, 1071, 1006 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.08 (s, 3 H), 0.10 (s, 3 H), 0.61 (q, *J* = 7.7 Hz, 6 H), 0.87-0.96 (m, 21 H), 1.21 (s, 3 H), 1.24-1.34 (m, 9 H), 1.48-1.54 (m, 2 H), 1.76-1.84 (m, 1 H), 3.63 (d, *J* = 11.2 Hz, 1 H), 3.91 (d, *J* = 3.6 Hz, 1 H),

4.63 (dd, J = 6.2, 3.5 Hz, 1 H), 6.20 (dd, J = 6.2, 1.0 Hz, 1 H) ; ^{13}C NMR ($CDCl_3$, 100 MHz) δ -4.4 (q), -4.0 (q), 6.7 (t), 7.0 (q), 14.0 (q), 18.0 (s), 18.9 (q), 22.6 (t), 26.9 (t), 27.8 (t), 29.1 (t), 29.4 (t), 31.7 (t), 71.4 (d), 74.7 (s), 82.1 (d), 103.3 (d), 142.2 (d); exact mass m/z calcd for $C_{25}H_{52}O_3Si_2$ 456.34549, found 456.34408.

(2*R*,3*R*,4*S*)-5-Bromo-4-[(*tert*-butyldimethylsilyl)oxy]-2-heptyltetrahydro-6-methoxy-3-methyl-3-[(triethylsilyl)oxy]-pyran (16.5).

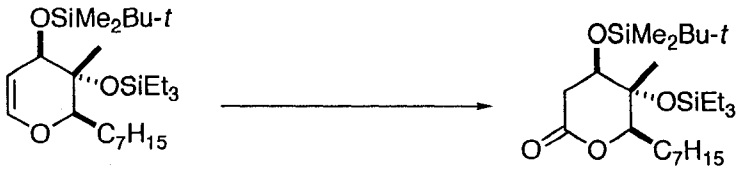


14.5 **16.5**

A solution of **14.5** (22 mg, 0.05 mmol) in dry MeOH (0.2 mL) and CH_2Cl_2 (0.2 mL) was added dropwise to a stirred and cooled (-40 °C) solution of NBS (15 mg, 0.08 mmol) in dry MeOH (0.5 mL). The cooling bath was left in place but not recharged and stirring was continued for 1 h. The solution was washed with water (2 mL), dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 23 cm), using 3% EtOAc-hexane, gave **16.5** (17.2 mg, 63%) as a mixture of isomers: $[\alpha]_D$ +14.00 (c 0.03, $CHCl_3$): FTIR ($CHCl_3$, cast) 3460, 3056, 2931, 1713, 1665, 1502, 1444, 1352, 1261, 1158, 1112, 1083, 1020 cm^{-1}; ^1H NMR ($CDCl_3$, 400

MHz) δ 0.16 (s, 3 H), 0.22 (s, 3 H), 0.61-0.69 (m, 6 H), 0.87-0.99 (m, 21 H), 1.14 (s, 2 H), 1.24-1.35 (m, 11 H), 1.60-1.72 (m, 2 H), 3.18 (d, J = 10.8 Hz, 1 H), 3.41 (s, 1 H), 3.55 (s, 3 H), 3.79 (d, J = 9.2 Hz, 1 H), 4.39 (d, J = 8.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ -3.8 (q), -3.2 (q), 7.0 (t), 7.2 (q), 14.0 (q), 16.1 (q), 18.7 (s), 22.5 (t), 26.3 (q), 26.9 (t), 29.2 (t), 29.4 (t), 29.6 (t), 31.7 (t), 56.4 (q), 57.1 (d), 79.5 (d), 80.0 (s), 83.2 (d), 103.5 (d); exact mass m/z calcd for $C_{22}H_{46}{}^{79}BrO_4Si_2$ (M - t-Bu) 509.21179, found 509.21027.

(4*R*,5*R*,6*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]-6-heptyltetrahydro-5-methyl-5-[(triethylsilyl)oxy]-2*H*-pyran-2-one (17.1).



16.4 **17.1**

PCC (0.63 g, 2.92 mmol) was added to a stirred solution of **16.4** (0.67 g, 1.5 mmol) in CH_2Cl_2 (9 mL) at room temperature. Stirring was continued for 8.5 h and the solvent was evaporated. Flash chromatography of the residue over silica gel (2.5 x 26 cm), using 1:20 EtOAc-hexane, gave **17.1** (0.72 g, 96%) as a yellow oil: $[\alpha]_D$ -1.20

(*c* 0.05, $CHCl_3$); FTIR ($CHCl_3$, cast) 2956, 2928, 2876, 2857, 1743, 1463, 1253, 1145, 1095, 1004 cm^{-1}; ^1H NMR ($CHCl_3$, 400 MHz) δ 0.08 (s, 3 H), 0.09 (s, 3 H), 0.61 (q, *J* = 7.7 Hz, 6 H), 0.86-0.97 (m, 21 H), 1.24-1.36 (m, 13 H), 1.60-1.72 (m, 1 H), 1.84-1.97 (m, 1 H), 2.45 (dd, *J* = 17.4, 2.9 Hz, 1 H), 3.04 (dd, *J* = 17.4, 5.2 Hz, 1 H), 3.79-3.83 (m, 1 H), 4.11 (dt, *J* = 11.4, 1.8 Hz, 1 H); ^{13}C NMR ($CHCl_3$, 125 MHz) δ -5.0 (q), -4.5 (q), 6.7 (t), 7.0 (q), 14.1 (q), 17.8 (t), 21.4 (q), 22.6 (t), 25.7 (q), 26.8 (t), 29.1 (t), 29.3 (t), 31.8 (t), 37.1 (t), 73.5 (d), 74.0 (s), 87.8 (d), 170.0 (s); exact mass *m/z* calcd for $C_{25}H_{52}O_4Si_2$ 472.34042, found 472.33979.

1,1,1-Trifluoromethanesulfonic Acid (2*R*,3*R*,4*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]-2-heptyl-3,4-dihydro-3-methyl-3-[(triethylsilyl)oxy]-2*H*-pyran-6-yl Ester (17.2).

17.1 **17.2**

A solution of **17.1** (1.60 g, 2.64 mmol) in THF (12 mL) was added dropwise to a stirred and cooled (-78 °C) solution of $(Me_3Si)_2NK$ (0.5 M in PhMe, 10.3 mL, 5.15 mmol). The mixture was stirred for 1.5 h and then 2-[*N*,*N*-

bis(trifluoromethylsulfonylamino]pyridine[32] (1.80 g, 5.02 mmol) in THF (11 mL) was added quickly and stirring was continued for 2.5 h. The cold bath was replaced by an ice bath and stirring was continued for 5 min. The mixture was quenched with buffer solution (pH = 7, 10 mL) and extracted with Et_2O (3 x 15 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (3 x 25 cm), using 2% EtOAc-hexane, gave **17.2** (1.66 g, 81% or 90% after correction for recovered starting material) as a colorless oil: $[\alpha]_D$ -7.64 (*c* 0.45, CH_2Cl_2); FTIR (CH_2Cl_2, cast) 2956, 2930, 2877, 2858, 1700, 1463, 1429, 1249, 1212, 1167, 1143, 1114, 1088, 1054, 1005 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ 0.11 (s, 3 H), 0.12 (s, 3 H), 0.62 (q, *J* = 8.1 Hz, 6 H), 0.87-0.65 (m, 21 H), 1.25-1.35 (m, 12 H), 1.41-1.65 (m, 2 H), 2.00-2.14 (m, 1 H), 3.94 (dd, *J* = 5.1, 1.9 Hz, 1 H), 4.06 (dt, *J* = 11.4, 1.8 Hz, 1 H), 4.77 (d, *J* = 5.0 Hz, 1 H); ^{13}C NMR (CD_2Cl_2, 125 MHz) δ -4.9 (q), -4.2 (q), 7.0 (t), 7.1 (q), 14.2 (q), 18.2 (s), 21.3 (q), 23.0 (t), 25.8 (q), 27.3 (t), 28.4 (t), 29.4 (t), 29.6 (t), 32.2 (t), 71.3 (d), 74.7 (s), 88.5 (d), 89.3 (d), 118.9 (q, *J* = 320 Hz), 149.6 (s); exact mass (electrospray) *m/z* calcd for $C_{26}H_{51}F_3NaO_6SSi_2$ (M + Na) 627.27892, found 627.27878.

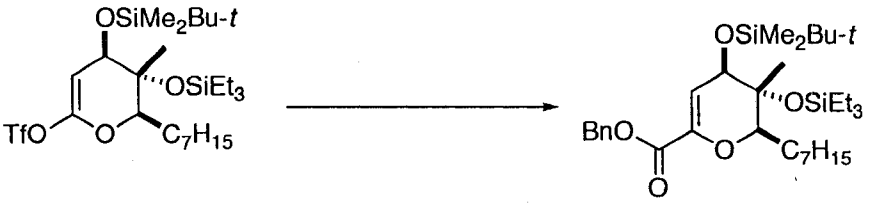
(2*R*,3*R*,4*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]-2-heptyl-3,4-dihydro-3-methyl-3-[(triethylsilyl)oxy]-2*H*-pyran-6-carboxylic Acid Methyl Ester (17.3).

17.2 **17.3**

$Pd(OAc)_2$ (0.65 g, 2.9 mmol), followed by Ph_3P (0.22 g, 0.84 mmol), Et_3N (0.80 mL, 5.7 mmol) and MeOH (5.0 mL, 123 mmol) was added to a stirred solution of **17.2** (1.66 g, 2.74 mmol) in DMF (45 mL). The mixture was purged with CO for 10 min and stirred under CO (balloon filled with CO) at room temperature for 17 h. Et_2O (40 mL) was added and the mixture was filtered through a pad of Celite. 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 25 cm), using 1:25 EtOAc-hexane, gave **17.3** (1.22 g, 64%) as a yellow oil: $[\alpha]_D$ -76.98 (*c* 0.02, $CHCl_3$); FTIR ($CHCl_3$, cast) 2956, 2930, 2876, 2858, 1746, 1735, 1656, 1463, 1438, 1387, 1260, 1156, 1124, 1104, 1048, 1006 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.11 (s, 3 H), 0.13 (s, 3 H), 0.59 (q, J = 7.6 Hz, 6 H), 0.85-0.95 (m, 21 H), 1.22-1.38 (m, 13 H), 1.44 (s, 1 H), 1.79-1.82 (m, 1 H), 3.80 (s, 3 H), 3.85 (dt, J = 10.9, 0.3 Hz, 1 H), 3.91

(d, J = 4.3 Hz, 1 H), 5.91 (d, J = 4.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ -4.7 (q), -4.0 (q), 6.7 (t), 7.0 (q), 14.1 (q), 18.0 (s), 19.9 (q), 22.6 (t), 25.8 (q), 27.0 (t), 27.5 (t), 29.1 (t), 29.5 (t), 31.8 (t), 52.2 (q), 70.8 (d), 74.4 (s), 83.5 (d), 111.3 (d), 141.7 (s), 163.5 (s); exact mass (electrospray) m/z calcd for $C_{27}H_{54}NaO_5Si_2$ (M + Na) 537.34020, found 537.34023.

(2*R*,3*R*,4*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]-2-heptyl-3,4-dihydro-3-methyl-3-[(triethylsilyl)oxy]-2*H*-pyran-6-carboxylic Acid Benzyl Ester (17.4).



17.2 **17.4**

$Pd(OAc)_2$ (44 mg, 0.20 mmol), followed by Ph_3P (10.7 mg, 0.04 mmol), Et_3N (0.04 mL, 0.35 mmol) and BnOH (0.52 mL, 5.03 mmol) was added to a stirred solution of **17.2** (105.8 mg, 0.17 mmol) in DMF (2 mL). The mixture was purged with CO for 5 min and stirred under CO (balloon filled with CO) at room temperature for 11 h. The solution was applied directly to a column of flash chromatography silica gel (2 x 25 cm), and chromatographed using 3% EtOAc-hexane, to give **17.4** (75.0 mg, 73%, or 76% after correction for

recovered **17.2**) as a yellow oil: $[\alpha]_D$ -22.57 (*c* 0.07, $CHCl_3$); FTIR ($CHCl_3$, cast) 2960, 2930, 2876, 2858, 1734, 1653, 1457, 1258, 1155, 1103, 1123, 1045, 1006 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.10 (s, 3 H), 0.12 (s, 3 H), 0.56-0.62 (m, 6 H), 0.86-0.94 (m, 21 H), 1.23-1.38 (m, 13 H), 1.40-1.45 (m, 1 H), 1.80-1.85 (m, 1 H), 3.85 (d, *J* = 11.0 Hz, 1 H), 3.93 (s, 1 H), 5.26 (s, 2 H), 5.94 (d, *J* = 4.2 Hz, 1 H), 7.31-7.38 (m, 5 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ -4.7 (q), -4.1 (q), 6.6 (t), 6.9 (q), 14.0 (q), 18.0 (s), 19.7 (q), 22.6 (t), 25.7 (q), 26.9 (t), 27.4 (t), 29.1 (t), 29.4 (t), 31.7 (t), 66.4 (t), 70.9 (d), 74.3 (s), 83.3 (d), 111.5 (d), 127.7 (d), 127.9 (d), 128.3 (d), 135.8 (s), 141.7 (s), 162.7 (s); exact mass (electrospray) *m/z* calcd for $C_{33}H_{58}NaO_5Si_2$ (M + Na) 613.37150, found 613.37174.

(4*S*,5*R*,6*R*)-3-Bromo-4-[(*tert*-butyldimethylsilyl)oxy]-6-heptyltetrahydro-5-methyl-2-(prop-2-ynyloxy)-5-[(triethylsilyl)oxy]-2*H*-pyran-2-carboxylic Acid Methyl Ester (18.1).

17.3 **18.1**

A solution of **17.3** (1.18 g, 2.41 mmol) in CH_2Cl_2 (25 mL) was added dropwise over 50 min to a stirred and cooled

(-50 °C) solution of NBS (1.06 g, 5.17 mmol) and powdered 4Å molecular sieves (3.20 g) in 2-propyn-1-ol (25 mL, 0.43 mol). The cold bath was left in place but not recharged and stirring was continued for 20 h. The mixture was filtered through a pad of Celite, using CH_2Cl_2. Evaporation of the filtrate and flash chromatography of the residue over silica gel (3 x 28 cm), using 1:20 EtOAc-hexane, gave **18.1** (1.31 g, 87%) as a mixture of isomers: $[\alpha]_D$ +9.70 (*c* 0.22, $CHCl_3$); FTIR ($CHCl_3$, cast) 3313, 2955, 2928, 2876, 2857, 1743, 1462, 1436, 1414, 1379, 1362, 1257, 1104, 1051, 1006 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) (signals for major isomer) δ 0.14 (s, 3 H), 0.17 (s, 3 H), 0.62-0.68 (m, 6 H), 0.88-0.98 (21 H), 1.25-1.34 (m, 13 H), 1.58-1.74 (m, 2 H), 2.47 (t, J = 2.5 Hz, 1 H), 3.49 (dd, J = 10.3, 1.8 Hz, 1 H), 3.82 (s, 3 H), 4.11 (d of AB q, J = 2.5 Hz, J_{AB} = 15.4 Hz, $\Delta\nu_{AB}$ = 83.8 Hz, 2 H), 4.06 (d, J = 4.7 Hz, 1 H), 4.35 (d, J = 4.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) (signals for major isomer) δ -4.1 (q), -3.9 (q), 7.2 (t), 7.3 (q), 14.1 (q), 17.9 (q), 18.3 (s), 22.7 (t), 26.1 (q), 26.2 (t), 27.0 (t), 28.1 (t), 29.3 (t), 29.7 (t), 31.9 (t), 52.0 (t), 52.6 (q), 55.1 (d), 73.2 (d), 74.8 (s), 76.6 (s), 77.7 (d), 99.9 (s), 166.3 (s); exact mass (electrospray) *m/z* calcd for $C_{30}H_{57}{}^{79}BrNaO_6Si_2$ (M + Na) 671.27693, found 671.27713.

(4*R*,5*R*,6*R*)-4-[(*tert*-Butylsilyl)oxy]-6-heptylhexahydro-5-methyl-3-methylene-5-[(triethylsilyl)oxy]-7a*H*-furo[2,3-*b*]pyran-7a-carboxylic Acid Methyl Ester (18.2).

18.1 **18.2**

Et_3B in THF (1 M in hexanes, 1.45 mL, 1.45 mmol) was added to a stirred mixture of **18.1** (1.31 g, 1.97 mmol) and Bu_3SnH (0.70 mL, 2.35 mmol) in EtOAc (21 mL) in a flask open to the air. Stirring was continued for 1 h, and the mixture was diluted with Et_2O (15 mL), washed with water and dried (Na_2SO_4). Evaporation of the solvent and flash chromatography of the residue over silica gel (3 x 28 cm), using 1:25 EtOAc-hexane, gave **18.2** (0.95 g, 86%) as an oil. The ^{13}C NMR spectrum showed a number of minor signals, which we suspect are due either to the presence of two isomers or two rotamers in a 4:1 ratio: $[\alpha]_D$ +29.28 (*c* 0.04, $CHCl_3$); FTIR ($CHCl_3$, cast) 2955, 2928, 2876, 2857, 1744, 1463, 1253, 1234, 1139, 1106, 1073, 1017 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.16 (s, 3 H), 0.19 (s, 3 H), 0.68 (q, J = 7.9 Hz, 6 H), 0.87-0.98 (m, 21 H), 1.20 (s, 3 H), 1.22-1.32 (m, 10 H), 1.55-1.63 (m, 2 H), 2.94 (d, J = 10.0 Hz, 1 H), 3.57-3.60 (m, 1 H), 3.83 (s, 3 H), 4.06 (d, J = 6.5 Hz, 1 H), 4.52-

4.65 (m, 2 H), 5.02-5.05 (m, 1 H), 5.63 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ -4.3 (q), -4.1 (q), 7.25 (q), 7.32 (t), 14.1 (q), 17.5 (q), 18.4 (s), 22.7 (t), 26.4 (t), 26.4 (q), 28.1 (t), 29.3 (t), 29.4 (t), 31.9 (t), 49.4 (d), 52.6 (q), 72.5 (t), 76.8 (s), 77.1 (d), 79.2 (d), 104.9 (s), 109.2 (t), 143.6 (s), 168.2 (s); exact mass (electrospray) *m/z* calcd for $C_{30}H_{58}O_6NaSi_2$ 593.36642 (M + Na), found 593.36687.

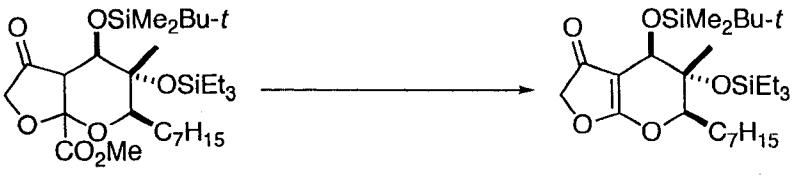
(4*R*,5*R*,6*R*)-4-[(*tert*-Butylsilyl)oxy]-6-heptyl-hexahydro-5-methyl-3-oxo-5-[(triethylsilyl)oxy]-7a*H*-furo[2,3-*b*]pyran-7a-carboxylic Acid Methyl Ester (18.3).

18.2 **18.3**

An O_3-O_2 stream was passed through a stirred and cooled (-78 °C) solution of **18.2** (0.95 g, 1.7 mmol) in dry CH_2Cl_2 (40 mL) for 5 min. The solution was purged with O_2 for 10 min, and then Ph_3P (0.58 g, 1.03 mmol) was added. The cooling bath was removed and stirring was continued for 4 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (3 x 28 cm), using 1:20 EtOAc-hexane, gave **18.3** (0.92 g, 98%) as a colorless oil: $[\alpha]_D$ +10.55 (*c* 0.03, $CHCl_3$); FTIR ($CHCl_3$, cast) 2955, 2929, 2977,

2858, 1770, 1746, 1463, 1257, 1224, 1199, 1156, 1122, 1094, 1065, 1012 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.13 (s, 3 H), 0.18 (s, 3 H), 0.58 (q, J = 7.9 Hz, 6 H), 0.87-0.98 (m, 21 H), 1.25-1.32 (m, 13 H), 1.63-1.78 (m, 2 H), 3.30 (s, 1 H), 3.70 (d, J = 11.4 Hz, 1 H), 3.81 (s, 3 H), 4.07 (s, 1 H), 4.22 (AB q, J_{AB} = 15.8 Hz, $\Delta\nu_{AB}$ = 110.3 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ -5.3 (q), -4.8 (q), 6.4 (t), 6.9 (q), 14.1 (q), 17.8 (s), 22.6 (q), 22.7 (t), 25.6 (q), 27.2 (t), 29.2 (t), 29.6 (t), 30.7 (t), 31.9 (t), 51.9 (d), 52.8 (q), 70.3 (t), 73.2 (s), 73.9 (d), 83.6 (d), 101.2 (s), 169.1 (s), 208.3 (s); exact mass (electrospray) *m/z* calcd for $C_{29}H_{56}NaO_7Si_2$ (M + Na) 595.34568, found 595.34846.

(4*R*,5*R*,6*R*)-4-[(*tert*-Butylsilyl)oxy]-6-heptyl-5,6-dihydro-5-methyl-5-[(triethylsilyl)oxy]-4*H*-furo[2,3-b]pyran-3(2*H*)-one (18.5).



18.3 **18.5**

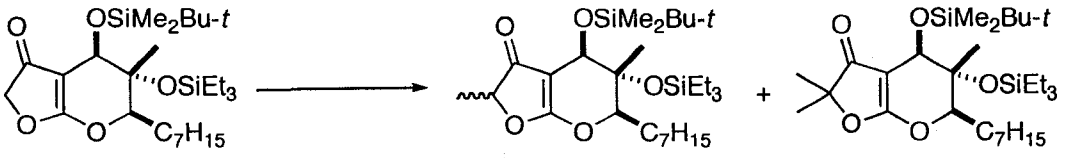
$(Bu_3Sn)_2O$ (8.0 mL, 15.6 mmol) was added to a stirred solution of **18.3** (0.39 g, 0.68 mmol) in PhH (20 ml) and the mixture was refluxed at 85 °C for 18 h. Evaporation of the solvent and flash chromatography of the residue over silica

gel (3 x 15 cm), using 1:2 to 1:1 EtOAc-hexane, gave the parent acid **18.4** as a yellow oil, which was used immediately.

$Cu(OAc)_2.H_2O$ (0.80 g, 4.0 mmol) was added to a stirred solution of the freshly prepared acid in PhH (10 mL) (N_2 atmosphere). After 12 min the flask was wrapped with aluminum foil and $Pb(OAc)_4$ (1.10 g, 2.52 mmol) was tipped in. After 15 min dry pyridine (0.28 mL) was added, and stirring was continued for 30 min. Another portion of $Pb(OAc)_4$ (1.30 g, 2.98 mmol) was added, followed by PhH (7 mL). After a further 1 h, another portion of $Pb(OAc)_4$ (0.56 g, 1.29 mmol) followed by DMF (2 mL) was added. The flask was fitted with a reflux condenser and flushed well with N_2 and the mixture was refluxed for 12 h (oil bath at 85 °C). The resulting solution was cooled to room temperature, evaporated to a small volume, and applied directly to a flash chromatography column (3 x 25 cm) made up with silica gel. Flash chromatography, using 1:15 EtOAc-hexanes, gave **18.5** (0.24 g, 68%): $[\alpha]_D$ +29.99 (*c* 0.02, $CHCl_3$); FTIR ($CHCl_3$, cast) 2956, 2928, 2857, 1706, 1606, 1471, 1250, 1172, 1148, 1070, 1006 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.13 (s, 3 H), 0.18 (s, 3 H), 0.53 (q, J = 8.0 Hz, 6 H), 0.83-0.93 (m, 21 H), 1.20-1.37 (m, 10 H), 1.40 (s, 3 H), 1.48-1.65 (m, 1 H), 2.00-2.10 (m, 1 H), 4.16 (d, J = 1.4 Hz, 1 H), 4.27 (d, J = 11.8 Hz, 1 H), 4.48 (AB q, J_{AB} = 15.7 Hz, $\Delta\nu_{AB}$ = 41.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ -5.5 (q), -

4.7 (q), 6.5 (t), 6.8 (q), 14.0 (q), 18.0 (s), 22.4 (q), 22.6 (t), 25.8 (q), 27.1 (t), 29.0 (t), 29.2 (t), 30.3 (t), 31.8 (t), 66.4 (d), 74.4 (s), 74.7 (t), 91.5 (s), 91.6 (d), 181.6 (s), 193.6 (s); exact mass (electrospray) *m/z* calcd for $C_{27}H_{52}NaO_5Si_2$ (M + Na) 535.32455, found 535.32433.

(4*R*,5*R*,6*R*)-4-[(*tert*-Butylsilyl)oxy]-6-heptyl-5,6-dihydro-2,5-dimethyl-5-[(triethylsilyl)oxy]-4*H*-furo[2,3-b]pyran-3(2*H*)-one (19.2) and (4*R*,5*R*,6*R*)-4-[(*tert*-Butylsilyl)oxy]-6-heptyl-5,6-dihydro-2,2,5-trimethyl-5-[(triethylsilyl)oxy]-4*H*-furo[2,3-*b*]pyran-3(3*H*)-one (19.1).



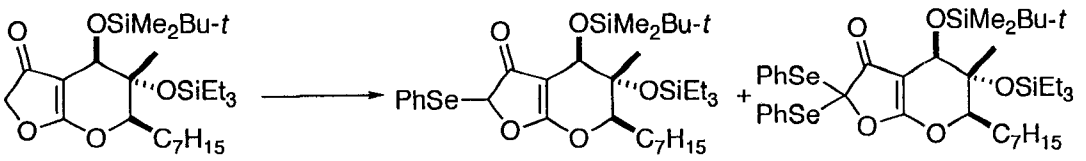
18.5 **19.2** **19.1**

A solution of **18.5** (0.17 g, 0.34 mmol) in THF (2 mL) was added dropwise over about 10 min to a stirred and cooled (-78 °C) solution of $(Me_3Si)_2NK$ (0.5 M in PhMe, 0.80 mL, 0.38 mmol) and stirring was continued for 1 h. HMPA (0.05 mL), followed by CH_3I (41.0 μL, 0.68 mmol) was then added. The mixture was stirred for 12 h at -78 °C, quenched with water (3 mL) and extracted with Et_2O (5 mL x 3). The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (2 x 25 cm), using 1:15 *t*-BuOMe-

hexane, gave **19.2** (70.0 mg, 40%) as a mixture of epimers and a bis-methylated product **19.1** (48.80 mg, 27%). The mono-methylated product **19.2** was an epimeric mixtures: $[\alpha]_D$ +71.65 (*c* 0.04, $CHCl_3$); FTIR ($CHCl_3$, cast) 2956, 2929, 2877, 2857, 1704, 1605, 1470, 1248, 1178, 1149, 1071, 1005 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.10-0.20 (m, 6 H), 0.48-0.58 (m, 6 H), 0.82-0.94 (m, 21 H), 1.22-1.36 (m, 10 H), 1.41-1.50 (m, 7 H), 2.00-2.16 (m, 1 H), 4.12 (dt, *J* = 12.3, 1.0 Hz, 1 H), 4.27 (d, *J* = 11.7 Hz, 1 H), 4.51 (q, *J* = 6.2 Hz, 0.44 H), 4.65 (q, *J* = 6.9 Hz, 0.44 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ -5.6 (q), -5.5 (q), -4.69 (q), -4.68 (q), 6.50 (t), 6.6 (t), 6.8 (q), 6.9 (q), 14.1 (q), 15.9 (q), 16.5 (q), 18.01 (s), 18.03 (s), 22.46 (q), 22.52 (q), 22.62 (t), 25.81 (q), 25.84 (q), 27.1 (t), 28.95 (t), 29.02 (t), 29.16 (t), 29.19 (t), 30.27 (t), 30.44 (t), 31.75 (t), 31.7 (t), 31.8 (t), 66.6 (d), 66.7 (d), 74.4 (s), 74.5 (s), 83.0 (d), 83.1 (d), 90.1 (s), 90.4 (s), 91.2 (d), 91.4 (d), 180.0 (s), 180.1 (s), 196.4 (s), 196.6 (s); exact mass (electrospray) *m/z* calcd for $C_{28}H_{55}O_5Si_2$ (M + H) 527.35826, found 527.35947.

The bis-methylated product had: ^1H NMR ($CDCl_3$, 400 MHz) δ 0.10 (s, 3 H), 0.21 (s, 3 H), 0.54 (q, *J* = 7.8 Hz, 6 H), 0.84-0.91 (m, 21 H), 1.22-1.36 (m, 10 H), 1.39 (s, 3 H), 1.42 (s, 3 H), 1.44 (s, 3 H), 1.51-1.62 (m, 1 H), 2.03-2.12 (m, 1 H), 4.13 (d, *J* = 1.9 Hz, 1 H), 4.26 (d, *J* = 11.7 Hz, 1 H).

(4*R*,5*R*,6*R*)-4-[(*tert*-Butylsilyl)oxy]-6-heptyl-5,6-dihydro-5-methyl-2-(phenylseleno)-5-[(triethylsilyl)oxy]-4*H*-furo[2,3-b]pyran-3(2*H*)-one (20.2) and (4*R*,5*R*,6*R*)-4-[(*tert*-Butylsilyl)oxy]-6-heptyl-5,6-dihydro-5-methyl-2,2-bis(phenylseleno)-5-[(triethylsilyl)oxy]-4*H*-furo[2,3-b]-pyran-3(2*H*)-one (20.1).



18.5 **20.2** **20.1**

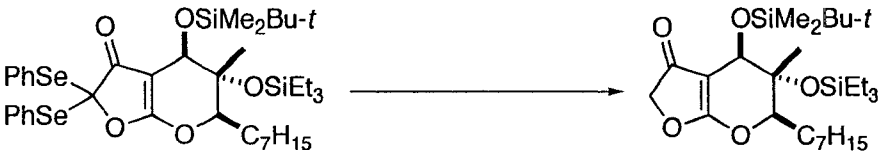
$(Me_3Si)_2NK$ (0.5 M in PhMe, 0.36 mL, 0.18 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of **18.5** (83.3 mg, 0.16 mmol) in dry THF (3 mL) and stirring was continued for 1 h. Freshly distilled Me_3SiCl (30 μL, 0.24 mmol) was then added. The mixture was stirred for 35 min at -78 °C, the cold bath was removed and stirring was continued for 50 min. The mixture was recooled to -78 °C and PhSeCl (39.9 mg, 0.21 mmol) in THF (2.2 mL) was added. After 10 min, the cold bath was replaced by an ice bath and stirring was continued for 40 min. The mixture was quenched with water and extracted with Et_2O (5 mL x 3). The combined organic extracts were washed with water and brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (2.8 x 28 cm), using 1:20 *t*-BuOMe-hexane, gave **20.2** (40.6 mg, 40%, 52% after correction for

recovered **18.5**) as a yellow oil and the corresponding bis-selenide **20.1** (20 mg, 15%). The mono-selenide **20.2** had: $[\alpha]_D$ -95.65 (*c* 0.06, $CHCl_3$); FTIR (CH_2Cl_2, cast) 2956, 2929, 2876, 2857, 1707, 1606, 1460, 1251, 1150, 1134, 1067, 1005 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.10 (s, 3 H), 0.16 (s, 3 H), 0.49-0.54 (m, 6 H), 0.82-0.93 (m, 21 H), 1.28-1.36 (m, 9 H), 1.37 (s, 3 H), 1.42-1.50 (m, 2 H), 1.82-1.92 (m, 1 H), 4.11 (d, *J* = 1.9 Hz, 1 H), 4.25 (d, *J* = 11.7 Hz, 1 H), 5.94 (s, 1 H), 7.27-7.33 (m, 3 H), 7.67-7.69 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ -5.5 (q), -4.4 (q), 6.5 (t), 6.8 (q), 14.1 (q), 18.0 (s), 22.3 (s), 22.7 (t), 26.0 (q), 27.1 (t), 29.1 (t), 29.2 (t), 30.0 (t), 31.8 (t), 66.5 (d), 74.4 (s), 83.7 (d), 91.4 (s), 91.7 (d), 125.7 (s), 128.9 (d), 129.1 (d), 135.7 (d), 179.6 (s), 191.2 (s); exact mass (electrospray) *m/z* calcd for $C_{33}H_{56}NaO_5SeSi_2$ (M + Na) 691.27237, found 691.27249.

The bis-selenide **20.1** had: $[\alpha]_D$ +78.98 (*c* 0.05, $CHCl_3$); FTIR ($CHCl_3$, cast) 2957, 2928, 2876, 2856, 1705, 1605, 1461, 1265, 1151, 1135, 1068, 1005 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.13 (s, 3 H), 0.15 (s, 3 H), 0.56 (q, *J* = 7.8 Hz, 6 H), 0.80-0.96 (m, 21 H), 1.08-1.22 (m, 2 H), 1.26-1.34 (m, 12 H), 1.52-1.71 (m, 1 H), 4.06 (d, *J* = 2.0 Hz, 1 H), 4.17 (d, *J* = 12.0 Hz, 1 H), 7.14-7.18 (m, 2 H), 7.23-7.27 (m, 2 H), 7.36-7.54 (m, 4 H), 7.79-7.82 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ -5.5 (q), -4.3 (q), 6.5 (t), 7.0 (q), 14.0 (q), 17.9 (s), 22.2 (q), 22.6 (t), 26.0 (q), 27.0 (t),

29.0 (t), 29.1 (t), 29.4 (t), 31.8 (t), 66.5 (d), 74.4 (s), 90.3 (s), 91.4 (d), 126.3 (s), 127.3 (s), 128.6 (d), 128.8 (d), 129.1 (d), 129.4 (d), 136.8 (d), 137.5 (d), 177.2 (s), 191.5 (s); exact mass (electrospray) *m/z* calcd for $C_{39}H_{60}NaO_5Se_2Si_2$ (M + Na) 847.22019, found 847.21986.

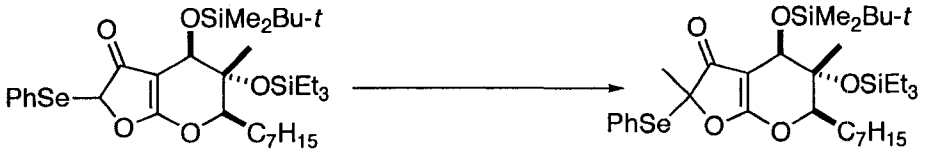
(4*R*,5*R*,6*R*)-4-[(*tert*-Butylsilyl)oxy]-6-heptyl-5,6-dihydro-5-methyl-5-[(triethylsilyl)oxy]-4*H*-furo[2,3-b]pyran-3(2*H*)-one (18.5).



20.1 **18.5**

Ph_3P (78 mg, 0.24 mmol) was added to a stirred solution of the bis-selenide **20.1** (86.0 mg, 0.10 mmol) in CH_2Cl_2 (8 mL) in a flask open to air. After 4 h, more Ph_3P (50 mg, 0.15 mmol) and water (2 mL) were added, and stirring was continued for 0.5 h. The mixture was then washed with water and the organic phase was dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2.5 x 23 cm), using 1:25 to 1:10 EtOAc-hexane, gave **18.5** (45.0 mg, 84%).

(4*R*,5*R*,6*R*)-4-[(*tert*-Butylsilyl)oxy]-6-heptyl-5,6-dihydro-2,5-dimethyl-2-(phenylseleno)-5-[(triethylsilyl)-oxy]-4*H*-furo[2,3-b]pyran-3(2*H*)-one (20.3).

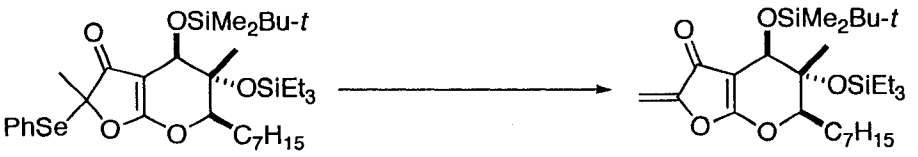


20.2 **20.3**

$(Me_3Si)_2NK$ (0.5 M in PhMe, 0.19 mL, 0.10 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of **20.2** (48.3 mg, 0.07 mmol) in dry THF (3 mL) and stirring was continued for 1 h. MeI (36 μL, 0.58 mmol) was then added dropwise. Stirring at -78 °C was continued for 2.5 h and the mixture was quenched with water and extracted with Et_2O (3 mL x 3). The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2.5 x 24 cm), using 1:10 EtOAc-hexanes, gave **20.3** (47.7 mg, 97%) as a yellow oil: $[\alpha]_D$ +198.53 (*c* 0.03, $CHCl_3$); FTIR ($CHCl_3$, cast) 2955, 2928, 2876, 2856, 1704, 1605, 1459, 1360, 1293, 1250, 1205, 1153, 1061, 1004 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.12 (s, 3 H), 0.23 (s, 3 H), 0.60 (q, *J* = 7.6 Hz, 6 H), 0.83-0.90 (m, 13 H), 0.96 (t, *J* = 11.0 Hz, 8 H), 1.23-1.34 (m, 10 H), 1.42-1.47 (m, 4 H), 1.68 (s, 3 H), 2.07 (q, *J* = 10.5 Hz, 1 H), 4.21 (d, *J* = 1.9 Hz, 1 H), 4.33 (d, *J* = 11.3 Hz, 1 H), 7.32-7.43 (m, 3 H), 7.72-7.76 (m, 2 H); ^{13}C NMR

($CDCl_3$, 100 MHz) δ -5.6 (q), -4.8 (q), 6.5 (t), 7.0 (q), 13.9 (q), 18.0 (s), 22.4 (q), 22.5 (t), 23.7 (q), 25.7 (q), 27.0 (t), 28.8 (t), 29.1 (t), 30.3 (t), 31.6 (t), 66.8 (d), 74.3 (s), 89.7 (s), 91.7 (d), 92.1 (s), 125.8 (s), 128.9 (d), 129.1 (d), 137.7 (d), 177.8 (s), 194.3 (s); exact mass (electrospray) *m/z* calcd for $C_{34}H_{59}O_5SeSi_2$ (M + H) 683.30608, found 683.30566.

(4*R*,5*R*,6*R*)-4-[(*tert*-Butylsilyl)oxy]-6-heptyl-5,6-dihydro-5-methyl-2-methylene-5-[(triethylsilyl)oxy]-4*H*-furo[2,3-b]pyran-3(2*H*)-one (4).

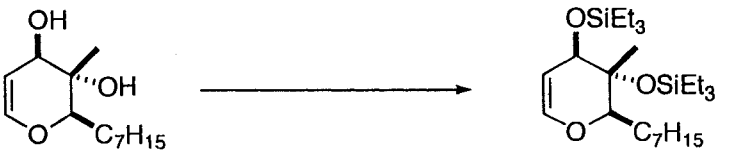


20.3 **4**

H_2O_2 (30%, 0.76 mL, 8.7 mmol) was added to a stirred solution of **20.3** (50.4 mg, 0.08 mmol) in THF (5 mL) and water (1 mL) (flask open to the air). Stirring was continued for 10 h, and the mixture was diluted with water (5 mL) and extracted with Et_2O (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 21 cm), using 1:15 EtOAc-hexane, gave **4** (33.8 mg, 87%) as a colorless oil: $[\alpha]_D$ +43.32 (*c* 0.02, CH_2Cl_2); FTIR (CH_2Cl_2, cast) 2956, 2929, 2977, 2857, 1734, 1706, 1610, 1454, 1251,

1139, 1118, 1071, 1005 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.15 (s, 3 H), 0.21 (s, 3 H), 0.54 (q, *J* = 7.6 Hz, 6 H), 0.83-0.95 (m, 21 H), 1.23-1.48 (m, 10 H), 1.43 (s, 3 H), 1.58-1.61 (m, 1 H), 2.01-2.20 (m, 1 H), 4.19 (d, *J* = 1.8 Hz, 1 H), 4.36 (d, *J* = 11.8 Hz, 1 H), 5.09 (d, *J* = 2.7 Hz, 1 H), 5.49 (d, *J* = 2.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ -5.3 (q), -4.6 (q), 6.8 (t), 7.0 (q), 14.2 (q), 18.3 (s), 22.7 (q), 23.0 (t), 26.0 (q), 27.5 (t), 29.4 (t), 29.6 (t), 30.6 (t), 32.2 (t), 66.8 (d), 75.1 (s), 92.7 (d), 93.0 (s), 94.9 (t), 153.8 (s), 177.7 (s), 180.7 (s); exact mass *m/z* calcd for $C_{28}H_{52}NaO_5Si_2$ (M + Na) 547.32455, found 547.32471.

(2*R*,3*R*,4*R*)-2-Heptyl-3,4-dihydro-3-methyl-3,4-bis[(triethylsilyl)oxy]-2*H*-pyran (22.1).

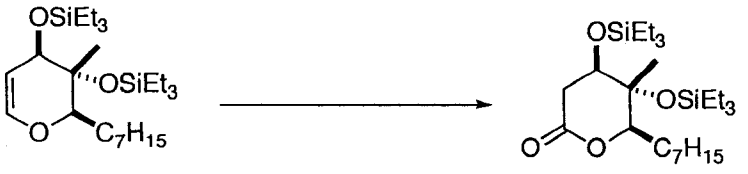


16.1 **22.1**

$Et_3SiOSO_2CF_3$ (2.5 mL, 11.3 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **16.1** (0.84 g, 3.7 mmol) and 2,6-lutidine (1.5 mL, 12.9 mmol) in CH_2Cl_2 (42 mL). The ice bath was left in place but not recharged and stirring was continued for 14 h. The mixture was diluted with CH_2Cl_2 (20 mL) and washed with saturated aqueous $NaHCO_3$ (15 mL) and brine, dried (Na_2SO_4) and evaporated. Flash

chromatography of the residue over silica gel (3 x 24 cm), using hexanes, gave **22.1** (1.7 g, 100%) as a colorless oil: $[\alpha]_D$ -37.1 (*c* 0.07, $CHCl_3$); FTIR ($CHCl_3$, cast) 3068, 2956, 2923, 2876, 1651, 1458, 1239 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.60-0.66 (m, 12 H), 0.89 (t, *J* = 7.1 Hz, 3 H), 0.93-1.00 (m, 18 H), 1.16 (s, 3 H), 1.28-1.31 (m, 9 H), 1.45-1.55 (m, 1 H), 1.61-1.69 (m, 2 H), 3.58 (dd, *J* = 9.2, 3.7 Hz, 1 H), 4.13 (br s, 1 H), 4.63 (dd, *J* = 6.1, 2.7 Hz, 1 H), 6.2 (dd, *J* = 6.1, 1.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 5.6 (t), 6.7 (t), 7.0 (q), 7.1 (q), 14.1 (q), 22.7 (t), 26.8 (t), 27.7 (t), 29.2 (t), 29.5 (t), 31.9 (t), 73.1 (q), 74.5 (s), 82.4 (d), 103.9 (d), 142.8 (d); exact mass *m/z* calcd for $C_{25}H_{52}O_3Si_2$ 456.34549, found 456.34430.

(4*R*,5*R*,6*R*)-6-Heptyltetrahydro-5-methyl-4,5-bis[(triethylsilyl)oxy]-2*H*-pyran-2-one (22.2).

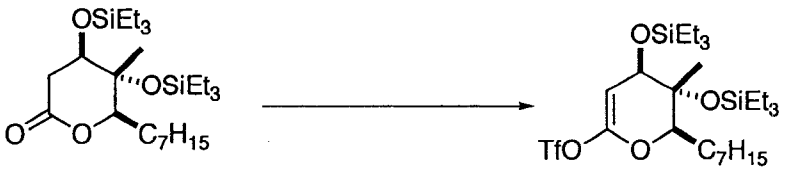


22.1 **22.2**

PCC (1.75 g, 8.12 mmol) was added to a stirred solution of **22.1** (1.76 g, 3.85 mmol) in CH_2Cl_2 (30 mL) at room temperature. Stirring was continued for 8 h and the solvent was evaporated. Flash chromatography of the

residue over silica gel (3 x 25 cm), using 1:10 EtOAc-hexanes, gave **22.2** (1.19 g, 66%) as a yellow oil: $[\alpha]_D$ +10.8 (*c* 0.05, $CHCl_3$); FTIR ($CHCl_3$, cast) 2956, 2926, 2877, 1745, 1548 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.59-0.64 (m, 12 H), 0.88 (t, *J* = 7.1 Hz, 3 H), 0.91-0.98 (m, 18 H), 1.25-1.33 (m, 12 H), 1.58-1.61 (m, 2 H), 1.82-1.90 (m, 1 H), 2.45 (dd, *J* = 17.5, 3.9 Hz, 1 H), 3.04 (dd, *J* = 17.5, 5.4 Hz, 1 H), 3.85 (t, *J* = 3.8 Hz, 1 H), 4.07 (d, 8.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 4.9 (t), 6.7 (t), 6.8 (q), 7.0 (q), 14.1 (q), 20.3 (q), 22.6 (t), 26.7 (t), 29.1 (t), 29.3 (t), 31.3 (t), 31.8 (t), 37.3 (t), 73.5 (d), 74.1 (s), 87.4 (d), 169.9 (s); exact mass *m/z* calcd for $C_{25}H_{52}O_4Si_2$ 472.34042, found 472.34166.

1,1,1-Trifluoromethanesulfonic Acid (2*R*,3*R*,4*R*)-2-Heptyl-3,4-dihydro-3-methyl-3,4-bis[(triethylsilyl)oxy]-2*H*-pyran-6-yl Ester (22.3).



22.2 **22.3**

A solution of **22.2** (1.19 g, 1.96 mmol) in THF (9 mL) was added dropwise to a stirred and cooled (-78 °C) solution of $(Me_3Si)_2NK$ in PhMe (0.5 M, 8.00 mL, 4.00 mmol. The

mixture was stirred for 1 h and then 2-[*N*,*N*-bis(trifluoromethylsulfonylamino]pyridine[32] (1.34 g, 3.74 mmol) in THF (8 mL) was added quickly and stirring was continued for 2 h. The mixture was quenched with buffer solution (pH = 7, 20 mL) and extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (3 x 25 cm), using 3% EtOAc-hexanes, gave **22.3** (1.33g, 87%) as a colorless oil: $[\alpha]_D$ -19.6 (*c* 0.69, CH_2Cl_2); FTIR (CH_2Cl_2, cast) 2958, 2935, 2879, 1700, 1459, 1430, 1213 cm^{-1}; ^1H NMR (CD_2Cl_2, 500 MHz) δ 0.59-0.66 (m, 12 H), 0.88 (t, *J* = 7.1 Hz, 3 H), 0.92-0.99 (m, 18 H), 1.28-1.30 (m, 12 H), 1.49-1.58 (m, 2 H), 1.91-1.99 (m, 1 H), 4.00 (dt, *J* = 11.2, 1.3 Hz, 1 H), 4.04 (dd, *J* = 4.4, 1.6 Hz, 1 H), 4.72 (d, *J* = 4.4 Hz, 1 H); ^{13}C NMR (CD_2Cl_2, 125.7 MHz) δ 5.4 (t), 6.9 (t), 7.1 (q), 14.2 (q), 20.0 (q), 23.0 (t), 27.1 (t), 28.1 (t), 29.4 (t), 29.5 (t), 32.2 (t), 71.9 (d), 74.6 (s), 88.1 (d), 89.8 (d), 118.9 (apparent d, *J* = 320 Hz), 150.0 (s); exact mass (electrospray) *m/z* calcd for $C_{26}H_{51}F_3NaO_6SSi_2$ (M + Na) 627.27892, found 627.27839.

(2*R*,3*R*,4*R*)-2-Heptyl-3,4-dihydro-3-methyl-3,4-bis[(triethylsilyl)oxy]-2*H*-pyran-6-carboxylic Acid Methyl Ester (22.4).

22.3 **22.4**

$Pd(OAc)_2$ (0.57 g, 2.5 mmol), followed by Ph_3P (175 mg, 0.67 mmol), Et_3N (0.64 mL, 4.6 mmol) and MeOH (4 mL, 98 mmol) was added to a stirred solution of **22.3** (1.35 g, 2.23 mmol) in DMF (36 mL). The mixture was purged with CO for 10 min and stirred under CO (balloon filled with CO) at room temperature for 18 h. Et_2O (40 mL) was added and the mixture was filtered through a pad of Celite. 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 25 cm), using 2% *t*-BuOMe in hexanes, gave **22.4** (0.91 g, 83%) as a yellow oil: $[\alpha]_D$ -17.1 (*c* 0.45, $CHCl_3$); FTIR ($CHCl_3$, cast) 2956, 2931, 2877, 1747, 1734, 1656, 1459, 1267, 1240, 1154 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.58-0.69 (m, 12 H), 0.87-1.00 (m, 21 H), 1.21 (s, 3 H), 1.26-1.32 (m, 9 H), 1.55-1.62 (m, 2 H), 1.71-1.80 (m, 1 H), 3.76 (d, *J* = 10.9 Hz, 1 H), 3.80 (s, 3 H), 4.11 (d, *J* = 3.4 Hz, 1 H), 5.91 (d, *J* = 3.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 5.4 (t), 6.7 (t), 6.9 (q), 7.1 (q), 14.1 (q), 17.7 (q), 22.6 (t), 26.8 (t), 27.5 (t), 29.1 (t), 29.5 (t), 31.8 (t), 52.2 (q), 70.2 (d), 74.1 (s), 83.5 (d), 112.0 (d), 142.3 (s), 163.3 (s); exact mass (electrospray)

m/z calcd for $C_{27}H_{54}NaO_5Si_2$ (M + Na) 537.34020, found 537.34054.

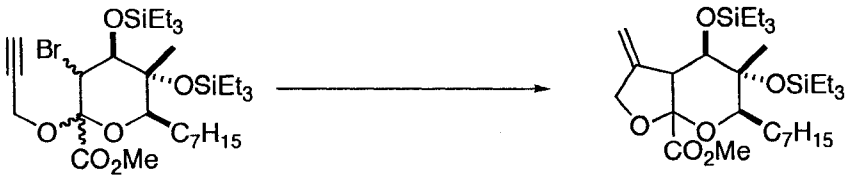
(4*S*,5*R*,6*R*)-3-Bromo-6-heptyltetrahydro-5-methyl-2-(2-propyn-1-yloxy)-4,5-bis[(triethylsilyl)oxy]-2*H*-pyran-2-carboxylic Acid Methyl Ester (22.5).

22.4 **22.5**

A solution of **22.4** (0.90 g, 1.8 mmol) in CH_2Cl_2 (19 mL) was added dropwise over 50 min to a stirred and cooled (-50 °C) solution of NBS (0.82 g, 4.0 mmol) and powdered 4Å molecular sieves in 2-propyn-1-ol (19 mL, 0.33 mol). The bath temperature was allowed to rise rapidly to -20 °C and stirring was continued for 2 h at -20 °C. The cold bath was left in place but not recharged and stirring was continued for 21 h. The mixture was diluted with CH_2Cl_2 (20 mL) and filtered through a pad of Celite, using CH_2Cl_2. Evaporation of the filtrate and flash chromatography of the residue over silica gel (3 x 25 cm), using 1:20 *t*-BuOMe-hexanes, gave **22.5** (1.2 g, 98%) as a mixture of isomers: $[\alpha]_D$ +15.5 (*c* 0.45, $CHCl_3$); FTIR ($CHCl_3$, cast) 3313, 2955, 2928, 2877, 2124, 1770, 1751, 1459, 1240, 1137 cm^{-1}; ^1H NMR ($CDCl_3$, 500

MHz) δ 0.61-0.75 (m, 12 H), 0.89 (t, *J* = 6.6 Hz, 3 H), 0.93-1.04 (m, 18 H), 1.25-1.33 (m, 12 H), 1.55-1.67 (m, 3 H), 2.46 (t, *J* = 2.5 Hz, 1 H), 3.45 (d, *J* = 10.1 Hz, 1 H), 3.82 (s, 3 H), 4.03 (dd, *J* = 15.5, 2.9 Hz, 1 H), 4.09 (d, *J* = 4.6 Hz, 1 H), 4.19 (dd, *J* = 15.5, 3.0 Hz, 1 H), 4.36 (d, *J* = 4.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 5.3 (t), 7.0 (q), 7.1 (t), 7.3 (q), 14.1 (q), 17.7 (q), 22.7 (t), 27.0 (t), 27.8 (t), 29.3 (t), 29.6 (t), 31.9 (t), 51.9 (t), 52.6 (q), 55.2 (d), 73.4 (d), 74.8 (s), 76.3 (s), 77.8 (d), 88.0 (d), 99.9 (s), 166.3 (s); exact mass (electrospray) *m/z* calcd for $C_{30}H_{57}{}^{79}BrNaO_6Si_2$ (M + Na) 671.27693, found 671.27722.

(4*R*,5*R*,6*R*)-6-Heptylhexahydro-5-methyl-3-methylene-4,5-bis[(triethylsilyl)oxy]-7a*H*-furo[2,3-b]pyran-7a-carboxylic Acid Methyl Ester (22.6).

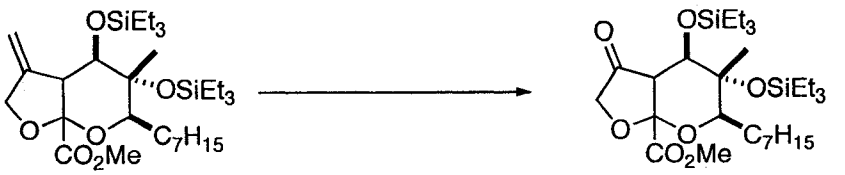


22.5 **22.6**

Et_3B in THF (1.35 mL, 1 M in hexanes) was added to a stirred mixture of **22.5** (1.19 g, 1.79 mmol) and Bu_3SnH (0.65 mL, 2.18 mmol) in EtOAc (20 mL) in a flask open to the air. Stirring was continued for 1 h, and the mixture was diluted

with Et_2O (15 mL), washed with brine and dried (Na_2SO_4). Evaporation of the solvent and flash chromatography of the residue over silica gel (3 x 25 cm), using 1:25 *t*-BuOMe-hexanes, gave **22.6** (0.51 g, 51%) as a colorless oil: $[\alpha]_D$ +16.4 (*c* 0.20, $CHCl_3$); FTIR ($CHCl_3$, cast) 2955, 2923, 2877, 1744, 1461, 1235, 1141 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.63-0.68 (m, 6 H), 0.71-0.77 (m, 6 H), 0.88 (t, *J* = 7.1 Hz, 3 H), 0.95 (t, *J* = 7.8 Hz, 9 H), 1.04 (t, *J* = 7.8 Hz, 9 H), 1.18 (s, 3 H), 1.25-1.33 (m, 10 H), 1.54-1.62 (m, 2 H), 2.93 (d, *J* = 9.8 Hz, 1 H), 3.56 (apparent br s, 1 H), 3.83 (s, 3 H), 4.07 (d, *J* = 6.6 Hz, 1 H), 4.55 (dd, *J* = 12.6, 1.7 Hz, 1 H), 4.64 (dd, *J* = 12.6, 2.4 Hz, 1 H), 5.01 (d, 2.4 Hz, 1 H), 5.58 (dd, *J* = 4.5, 2.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 5.1 (t), 7.1 (q), 7.2 (t), 7.3 (q), 14.1 (q), 17.1 (q), 22.7 (t), 26.3 (t), 27.9 (t), 29.2 (t), 29.4 (t), 31.9 (t), 49.5 (d), 52.6 (q), 72.6 (t), 76.5 (s), 76.8 (d), 79.2 (d), 105.0 (s), 109.0 (t), 143.8 (s), 168.2 (s); exact mass (electrospray) *m/z* calcd for $C_{30}H_{58}NaO_6Si_2$ 593.36642, found 593.36643.

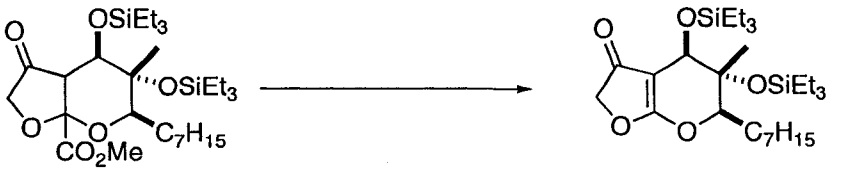
(4*R*,5*R*,6*R*)-6-Heptylhexahydro-5-methyl-3-oxo-4,5-bis[(triethylsilyl)oxy]-7a*H*-furo[2,3-b]pyran-7a-carboxylic Acid Methyl Ester (22.7).



22.6 **22.7**

An O_3-O_2 stream was passed through a stirred and cooled (-78 °C) solution of **22.6** (0.51 g, 0.91 mmol) in dry CH_2Cl_2 (20 mL) for 10 min. The solution was purged with O_2 for 15 min, and then Ph_3P (0.31 g, 1.2 mmol) was added. The cooling bath was removed and stirring was continued for 4.5 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (3 x 25 cm), using 1:25 *t*-BuOMe-hexanes, gave **22.7** (0.51 g, 100%) as a colorless oil: $[\alpha]_D$ +12.7 (*c* 0.08, $CHCl_3$); FTIR ($CHCl_3$, cast) 2956, 2924, 2877, 1770, 1747, 1460, 1223, 1157, 1012 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.58-0.72 (m, 12 H), 0.72-1.04 (m, 21 H), 1.11 (s, 3 H), 1.27 (s, 9 H), 1.42-1.59 (m, 3 H), 3.12 (dd, *J* = 10.1, 1.5 Hz, 1 H), 3.25 (dd, *J* = 7.0, 0.8 Hz, 1 H), 3.86 (s, 3 H), 4.05 (d, *J* = 7.0 Hz, 1 H), 4.17 (ddd, *J* = 30.2, 16.3, 0.8 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 5.1 (t), 6.91 (t), 6.93 (q), 7.2 (q), 14.1 (q), 16.8 (q), 22.7 (t), 26.4 (t), 28.6 (t), 29.2 (t), 29.3 (t), 31.9 (t), 51.8 (d), 53.0 (q), 71.5 (t), 75.5 (s), 75.6 (d), 80.0 (d), 103.8 (s), 167.7 (s), 208.4 (s); exact mass (electrospray) *m/z* calcd for $C_{29}H_{56}NaO_7Si_2$ (M + Na) 595.34568, found 595.34545.

(4*R*,5*R*,6*R*)-6-Heptyl-5,6-dihydro-5-methyl-4,5-bis[(triethylsilyl)oxy]-4*H*-furo[2,3-b]pyran-3(2*H*)-one (23.2).



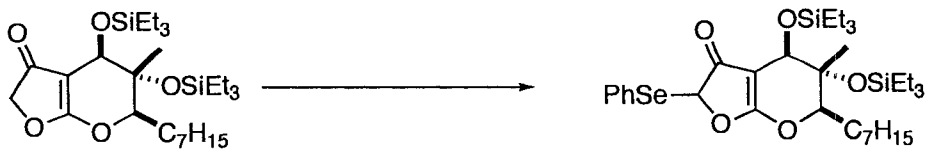
22.7 **23.2**

$(Bu_3Sn)_2O$ (6.35 mL, 12.3 mmol) was added to a stirred solution of **22.7** (0.31 g, 0.55 mmol) in PhH (15 ml) and the mixture was refluxed at 85 °C for 19 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (3 x 15 cm), using 1:2 EtOAc-hexanes, gave the parent acid **23.1**, which was used immediately.

$Cu(OAc)_2.H_2O$ (1.28 g, 6.40 mmol) was added to a stirred solution of the above freshly prepared acid in PhH (16 mL) (N_2 atmosphere). After 12 min the flask was wrapped with aluminum foil and $Pb(OAc)_4$ (1.25 g, 2.86 mmol) was tipped in. Dry pyridine (0.4 mL) was then added, and stirring was continued for 30 min. Another portion of $Pb(OAc)_4$ (0.9 g, 2.1 mmol) was added, followed by PhH (2 mL). After a further 75 min, another portion of $Pb(OAc)_4$ (0.10 g, 0.23 mmol), followed by DMF (1.5 mL) was added. The flask was fitted with a reflux condenser and flushed well with N_2 and the mixture was refluxed for 12 h (oil bath at 85 °C). The

resulting solution was cooled to room temperature, evaporated to a small volume, and applied directly to a flash chromatography column (3 x 25 cm) made up with silica gel. Flash chromatography, using 1:15 EtOAc-hexanes, gave **23.2** (0.2 g, 74%) as a yellow oil: $[\alpha]_D$ +53.6 (*c* 0.04, $CHCl_3$); FTIR ($CHCl_3$, cast) 2955, 2933, 2875, 1706, 1606, 1470 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.50-0.58 (m, 6 H), 0.64-0.72 (m, 6 H), 0.85-0.95 (m, 21 H), 1.25-1.42 (m, 9 H), 1.43 (s, 3 H), 1.43-1.57 (m, 2 H), 2.10-2.13 (m, 1 H), 4.19 (d, J = 1.9 Hz, 1 H), 4.29 (dt, J = 11.3, 1.8 Hz, 1 H), 4.50 (AB q, J_{AB} = 15.7 Hz, $\Delta\nu_{AB}$ = 63.8 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 4.6 (t), 6.5 (t), 6.8 (q), 6.9 (q), 14.0 (q), 22.2 (q), 22.6 (t), 27.1 (t), 29.0 (t), 29.2 (t), 30.1 (t), 31.2 (t), 66.2 (d), 74.4 (s), 74.7 (t), 91.68 (d), 91.72 (s), 181.5 (s), 193.7 (s); exact mass (electrospray) *m/z* calcd for $C_{27}H_{52}NaO_5Si_2$ (M + Na) 535.32455, found 535.32495.

(4*R*,5*R*,6*R*)-6-Heptyl-5,6-dihydro-5-methyl-2-(phenylseleno)-4,5-bis[(triethylsilyl)oxy]-4*H*-furo[2,3-b]pyran-3(2*H*)-one (23.3).



23.2 **23.3**

$(Me_3Si)_2NK$ (0.5 M in PhMe, 1.00 mL, 0.50 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of **23.2** (0.23 g, 0.45 mmol) in dry THF (7 mL) and stirring was continued for 50 min. Freshly distilled Me_3SiCl (90 μL, 0.71 mmol) was then added. The mixture was stirred for 0.5 h at -78 °C, the cold bath was removed and stirring was continued for 0.5 h. The mixture was recooled to -78 °C and PhSeCl (107 mg, 0.56 mmol) in THF (4 mL) was added. After 10 min, the cold bath was replaced by an ice bath and stirring was continued for 40 min. The mixture was quenched with water and extracted with Et_2O (10 mL x 3). 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 28 cm), using 1:25 *t*-BuOMe-hexanes, gave **23.3** (0.11 g, 39%, 66% after correction for recovered **23.2**) as a yellow oil and what we assume to be the corresponding bis-selenide (68 mg, 19%). Selenide **23.3** had: $[\alpha]_D$ -492.8 (*c* 0.01, $CHCl_3$); FTIR ($CHCl_3$, cast) 2955, 2931, 2875, 1707, 1606, 1459, 1235, 1148 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.52 (dq, *J* = 7.8, 1.5 Hz, 6 H), 0.66 (dq, *J* = 7.8, 1.3 Hz, 6 H), 0.84-0.96 (m, 21 H), 1.25-1.36 (m, 10 H), 1.39 (s, 3 H), 1.41-1.54 (m, 1 H), 1.89-1.98 (m, 1 H), 4.16 (d, *J* = 1.9 Hz, 1 H), 4.27 (d, *J* = 11.6 Hz, 1 H), 5.99 (s, 1 H), 7.26-7.34 (m, 3 H), 7.69-7.71 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 4.6 (t), 6.5 (t), 6.8 (q), 7.0 (q), 14.1 (q), 22.1 (q), 22.6 (t), 27.1 (t), 29.06 (t),

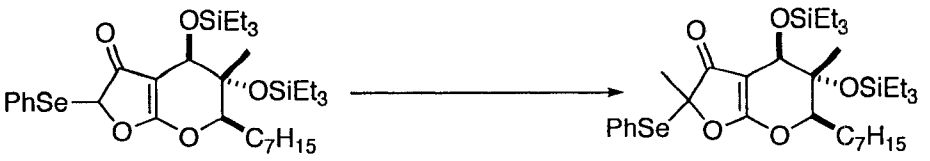
29.12 (t), 29.8 (t), 31.8 (t), 66.3 (d), 74.4 (s), 84.4 (d), 91.6 (s), 91.9 (d), 126.4 (s), 128.7 (d), 129.2 (d), 135.3 (d), 179.6 (s), 191.1 (s); exact mass (electrospray) *m/z* calcd for $C_{33}H_{56}NaO_5SeSi_2$ (M + Na) 691.27237, found 691.27200.

The bis-selenide was not characterized, its structure being inferred by its reconversion into the starting ketone.

Conversion of presumed bis-selenide into 23.2.

Ph_3P (40 mg, 0.12 mmol) was added to a stirred solution of the bis-selenide (46 mg, 0.056 mmol) in CH_2Cl_2 (5 mL) in a flask open to air. After 1 h, more Ph_3P (32 mg, 0.098 mmol), CH_2Cl_2 (3 mL) and water (3 mL) were added, and stirring was continued for 3 h. The mixture was then washed with water, and the organic phase was dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2.8 x 26 cm), using 1:25 to 1:10 EtOAc-hexane, gave **23.2** (23 mg, 82%).

(4*R*,5*R*,6*R*)-6-Heptyl-5,6-dihydro-2,5-dimethyl-2-(phenylseleno)-4,5-bis[(triethylsilyl)oxy]-4*H*-furo[2,3-b]pyran-3(2*H*)-one (23.4).

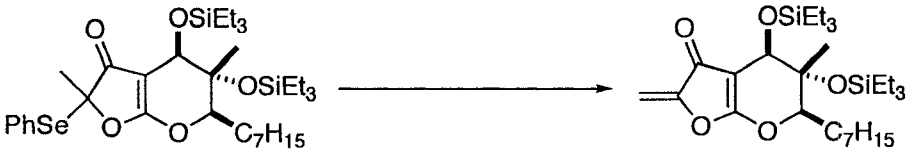


23.3 **23.4**

$(Me_3Si)_2NK$ (0.5 M in PhMe, 0.45 mL, 0.23 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of **23.3** (0.11 g, 0.16 mmol) in dry THF (6 mL) and stirring was continued for 45 min. MeI (81 μL, 1.3 mmol) was then added dropwise. Stirring at -78 °C was continued for 2.5 h and the mixture was quenched with water and extracted with Et_2O (5 mL x 3). 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 28 cm), using 1:20 *t*-BuOMe-hexanes, gave **23.4** (0.1 g, 91%) as a yellow oil: $[\alpha]_D$ -115.6 (*c* 0.02, $CHCl_3$); FTIR ($CHCl_3$, cast) 2956, 2927, 2875, 1729, 1706, 1606, 1458, 1290, 1082 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.49-0.74 (m, 12 H), 0.82-0.98 (m, 21 H), 1.22-1.38 (m, 12 H), 1.39-2.15 (m, including a singlet, 6 H in all), 4.11 (apparent s, 1 H), 4.23 (apparent d, *J* = 9.6 Hz, 1 H), 7.26-7.42 (m, 3 H), 7.68-7.75 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 4.7 (t), 6.5 (t), 6.9 (q), 7.0 (q), 14.1 (q), 22.1 (q), 22.7 (t), 22.9 (q), 27.1 (t), 29.07 (t), 29.13 (t), 29.6 (t), 31.8 (t), 66.6 (d), 74.5 (s), 91.4 (s), 91.37 (d), 91.42 (s), 125.6 (s), 128.9 (d), 129.0 (d), 129.2 (d), 137.4 (d), 137.7 (d), 177.8 (s), 194.5 (s);

exact mass (electrospray) *m/z* calcd for $C_{34}H_{58}NaO_5SeSi_2$ (M + Na) 705.28802, found 705.28799.

(4*R*,5*R*,6*R*)-6-Heptyl-5,6-dihydro-5-methyl-2-methylene-4,5-bis[(triethylsilyl)oxy]-4*H*-furo[2,3-b]pyran-3(2*H*)-one (23.5).

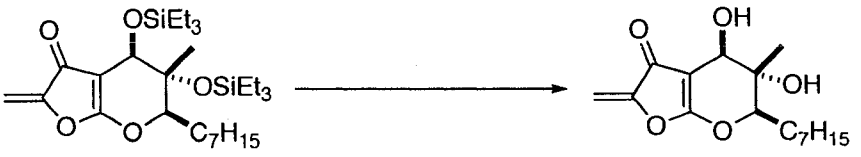


23.4 **23.5**

H_2O_2 (30%, 1.5 mL, 17 mmol) was added to a stirred solution of **23.4** (98 mg, 0.15 mmol) in THF (10 mL) and water (2 mL) (flask open to the air). Stirring was continued for 11 h, and the mixture was diluted with water (5 mL) and extracted with Et_2O (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (3 x 25 cm), using 1:15 *t*-BuOMe-hexanes, gave **23.5** (70 mg, 93%) as a yellow oil: $[\alpha]_D$ +95.5 (*c* 0.01, $CHCl_3$); FTIR ($CHCl_3$, cast) 2956, 2930, 2875, 1729, 1705, 1611, 1454, 1268, 1137, 1075 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.51-0.56 (dq, *J* = 7.4, 1.8 Hz, 6 H), 0.66-0.71 (dq, *J* = 7.4, 1.4 Hz, 6 H), 0.85-0.90 (m, 12 H), 0.94 (t, *J* = 7.7 Hz, 9 H), 1.22-1.40 (m, 9 H), 1.44 (s, 3 H), 1.56-1.59 (m, 2 H), 2.09-2.18 (m, 1 H), 4.21 (d, *J* = 1.9 Hz, 1 H), 4.36 (dd, *J* = 10.3, 1.6 Hz, 1 H),

5.08 (d, J = 2.7 Hz, 1 H), 5.49 (d, J = 2.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 4.6 (t), 6.5 (t), 6.8 (d), 6.9 (d), 14.0 (q), 22.2 (q), 22.6 (t), 27.1 (t), 29.0 (t), 29.2 (t), 30.0 (t), 31.7 (t), 66.1 (d), 74.6 (s), 92.3 (d), 92.9 (s), 95.2 (t), 153.2 (s), 177.3 (s), 180.6 (s); exact mass (electrospray) m/z calcd for $C_{28}H_{52}NaO_5Si_2$ (M + Na) 547.32455, found 547.32458.

(4*R*,5*S*,6*R*)-6-heptyl-5,6-dihydro-4,5-dihydroxy-5-methyl-2-methylene-4*H*-furo[2,3-b]pyran-3(2*H*)-one (*ent*-benesudon) (3).



23.5 **3**

HF-pyridine (ca 70% HF in pyridine, 0.05 mL) was added dropwise to a stirred solution of **23.5** (17.0 mg, 0.058 mmol) in dry THF (5 mL) in an open flask. After 11 h, more THF (5 mL) was added, and stirring was continued for another 12 h. The mixture was quenched with saturated aqueous $NaHCO_3$ until CO_2 evolution stopped. The organic phase was washed with water, saturated aqueous Cu_2SO_4 and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 8 cm), using 1:1 EtOAc-hexanes, gave *ent*-benesudon (**3**) (5.1 mg, 53%) as a

colorless oil: $[\alpha]_D$ +124.2 (*c* 0.11, $CHCl_3$); FTIR ($CHCl_3$, cast) 3399, 2957, 2927, 2857, 1693, 1593, 1469 cm^{-1}; ^1H NMR (CD_3OD, 500 MHz, room temperature) δ 0.90 (t, *J* = 7.1 Hz, 3 H), 1.27-1.46 (m, 12 H), 1.55-1.60 (m, 1 H), 1.69-1.75 (m, 1 H), 2.07-1.98 (m, 1 H), 4.21 (d, *J* = 1.7 Hz, 1 H), 4.47 (dt, *J* = 11.5, 1.7 Hz, 1 H), 5.26 (d, *J* = 3.1 Hz, 1 H), 5.52 (d, *J* = 3.1 Hz, 1 H); ^{13}C NMR (CD_3OD, 125.7 MHz, room temperature) δ 182.9, 179.3, 154.9, 97.2, 94.3, 93.0, 72.6, 66.8, 32.9, 30.3, 30.23, 30.18, 27.9, 23.7, 20.7, 14.4; exact mass (electrospray) *m/z* calcd for $C_{16}H_{24}NaO_5$ (M + Na) 319.15159, found 319.15133.

The NMR spectra were also run at 50 °C: ^1H NMR (CD_3OD, 500 MHz, 50 °C) δ 0.89 (t, *J* = 7.5 Hz, 3 H), 1.25-1.48 (m, including a singlet at δ 1.35, 12 H in all), 1.53-1.62 (m, 1 H), 1.71-1.78 (m, 1 H), 1.98-2.06 (m, 1 H), 4.22 (d, *J* = 1.5 Hz, 1 H), 4.45 (dt, *J* = 11.5, 2.0 Hz, 1 H), 5.23 (d, *J* = 3.0 Hz, 1 H), 5.50 (d, *J* = 3.0 Hz, 1 H); ^{13}C NMR (CD_3OD, 125.7 MHz, 50 °C) δ 182.91 (s), 179.34 (s), 155.08 (s), 96.97 (t), 94.39 (s), 92.98 (d), 72.63 (s), 66.99 (d), 32.83 (t), 30.28 (t), 30.10 (t), 27.79 (t), 23.57 (t), 20.56 (q), 14.27 (q).

Natural benesudon had: $[\alpha]_D$ -120.5 (*c* 0.10, $CHCl_3$); ^1H NMR (CD_3OD, 500 MHz, 50 °C) δ 0.89 (t, *J* = 7.5 Hz, 3 H), 1.25-1.48 (m, including a singlet at δ 1.35, 12 H in all), 1.53-1.62 (m, 1 H), 1.71-1.78 (m, 1 H), 1.98-2.06 (m, 1 H), 4.22 (d, *J* = 1.5 Hz, 1 H), 4.45 (dt, *J* = 11.5, 2.0 Hz, 1

H), 5.23 (d, J = 3.0 Hz, 1 H), 5.50 (d, J = 3.0 Hz, 1 H); ^{13}C NMR (CD_3OD, 125.7 MHz, 50 °C) δ 182.91 (s), 179.35 (s), 155.04 (s), 96.96 (t), 94.38 (s), 92.99 (d), 72.63 (s), 67.00 (d), 32.83 (t), 30.28 (t), 30.10 (t), 27.79 (t), 23.58 (t), 20.56 (q), 14.27 (q).

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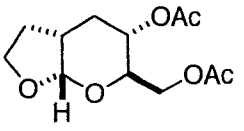
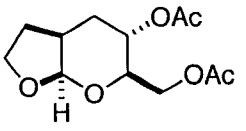


δ 5.33

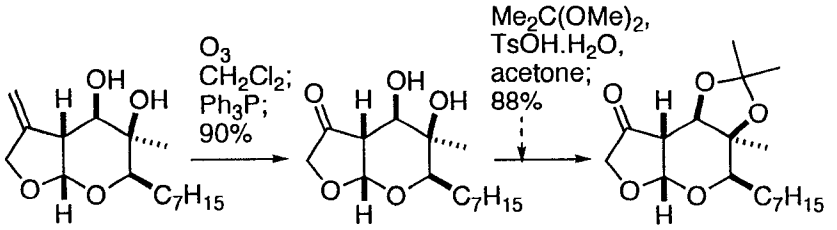
i



δ 5.14

ii

(12) (a) We also considered hydride abstraction:



iii **iv** **v**

Treatment of **v** with Ph_3CBF_4[13] produced a complex mixture. The structure of **iii** was confirmed by X-ray analysis. (b) At the beginning, Haikang Yang was working on this project (see reference 9b). Later this project was assigned to me and I repeated some of his initial experiments, and some spectral data have

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(23) See reference 12. Compound **iii**, whose structure was confirmed by X-ray analysis, was made from **11.7**. Hence the stereochemistry of **11.7** at the quaternary carbon is established.

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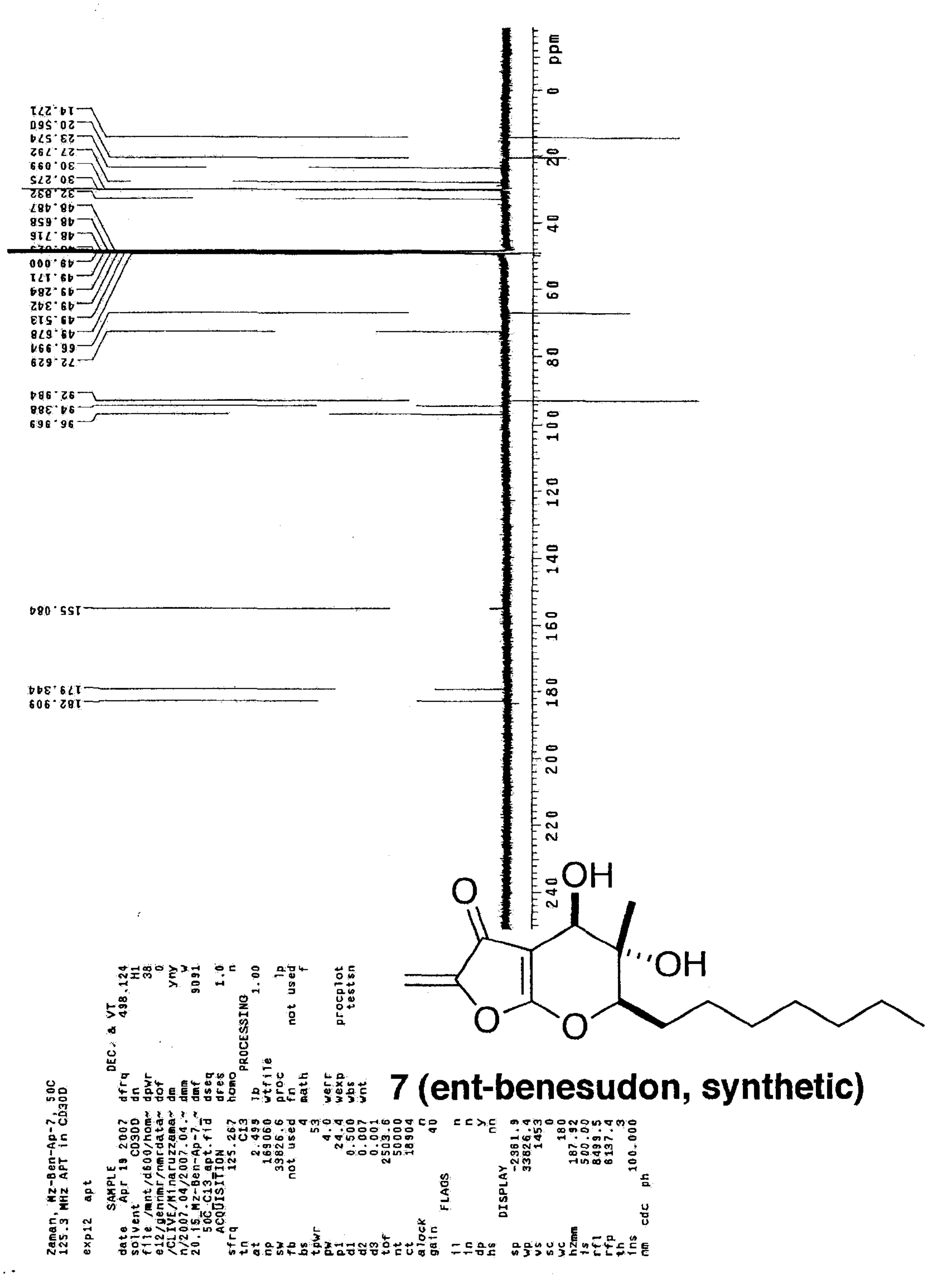
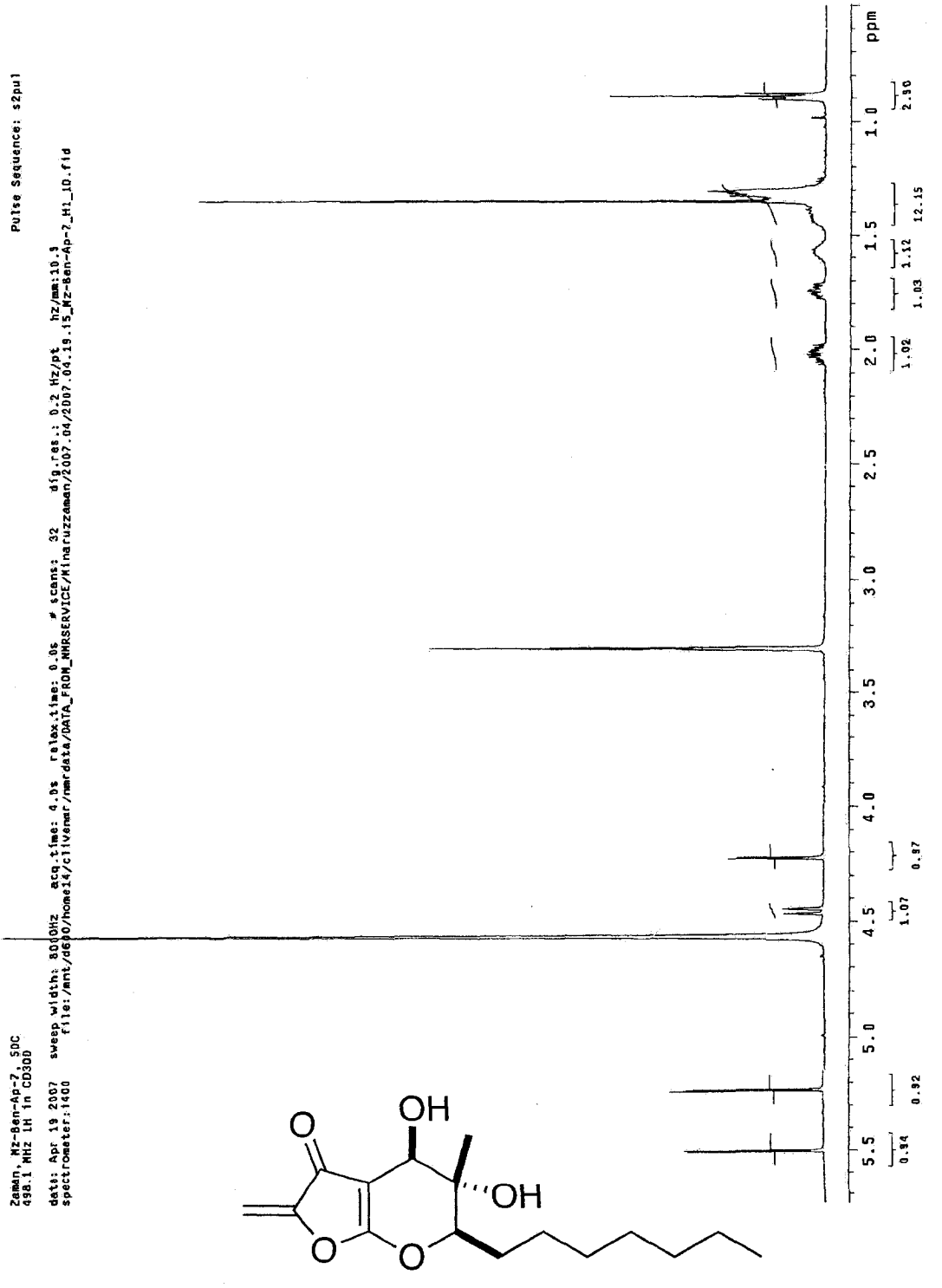


7 (ent-benesudon, synthetic)



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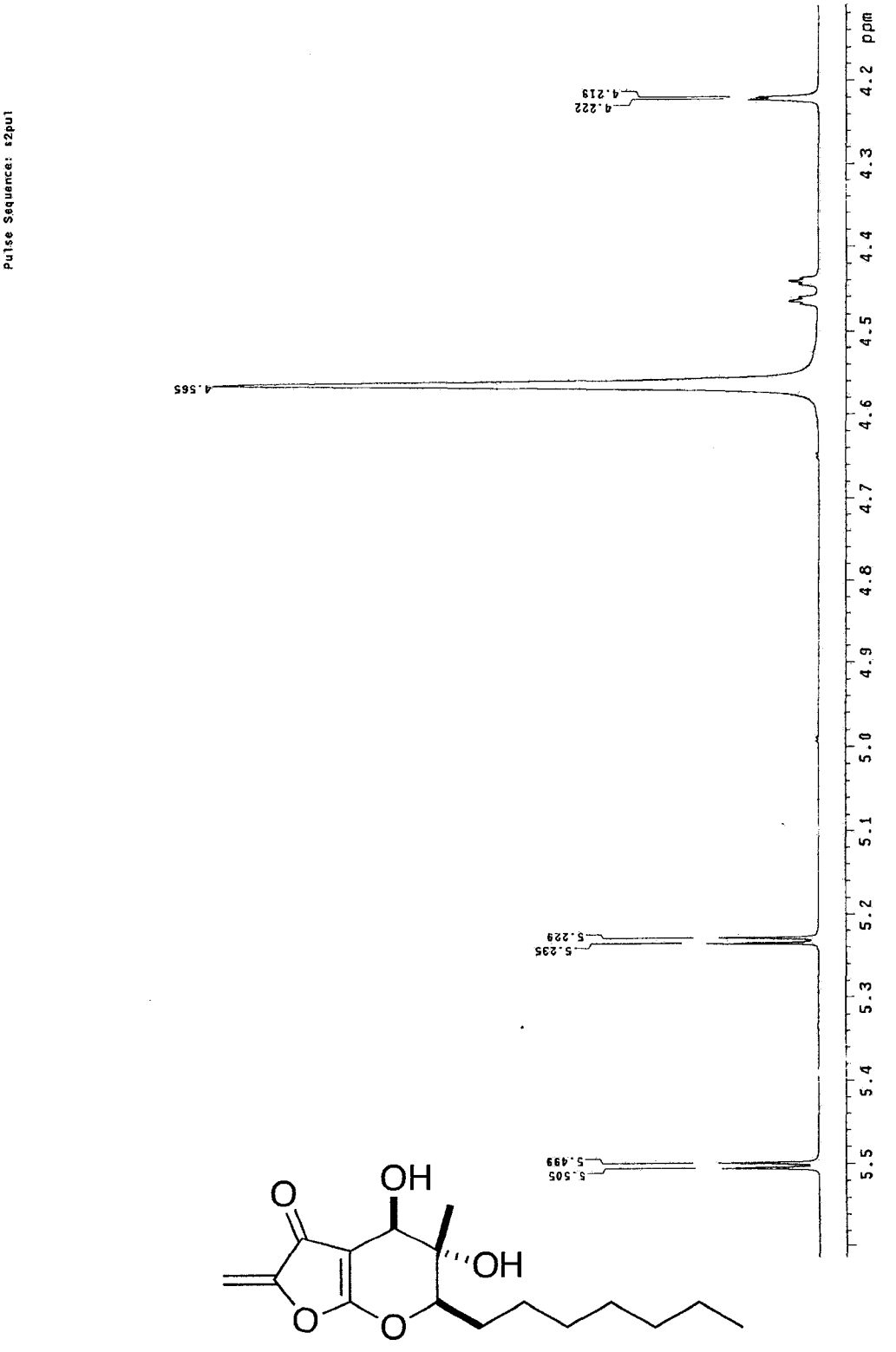

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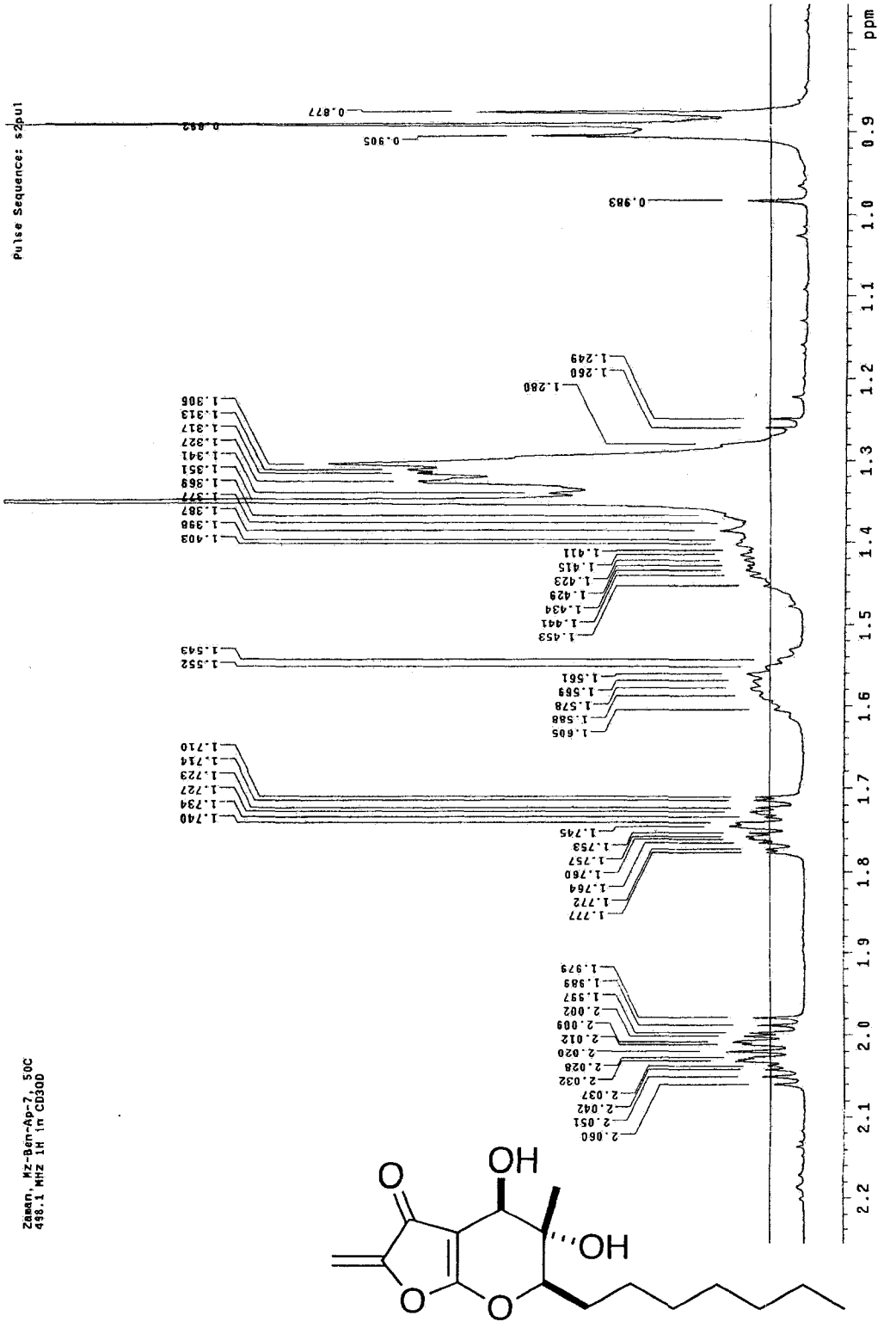

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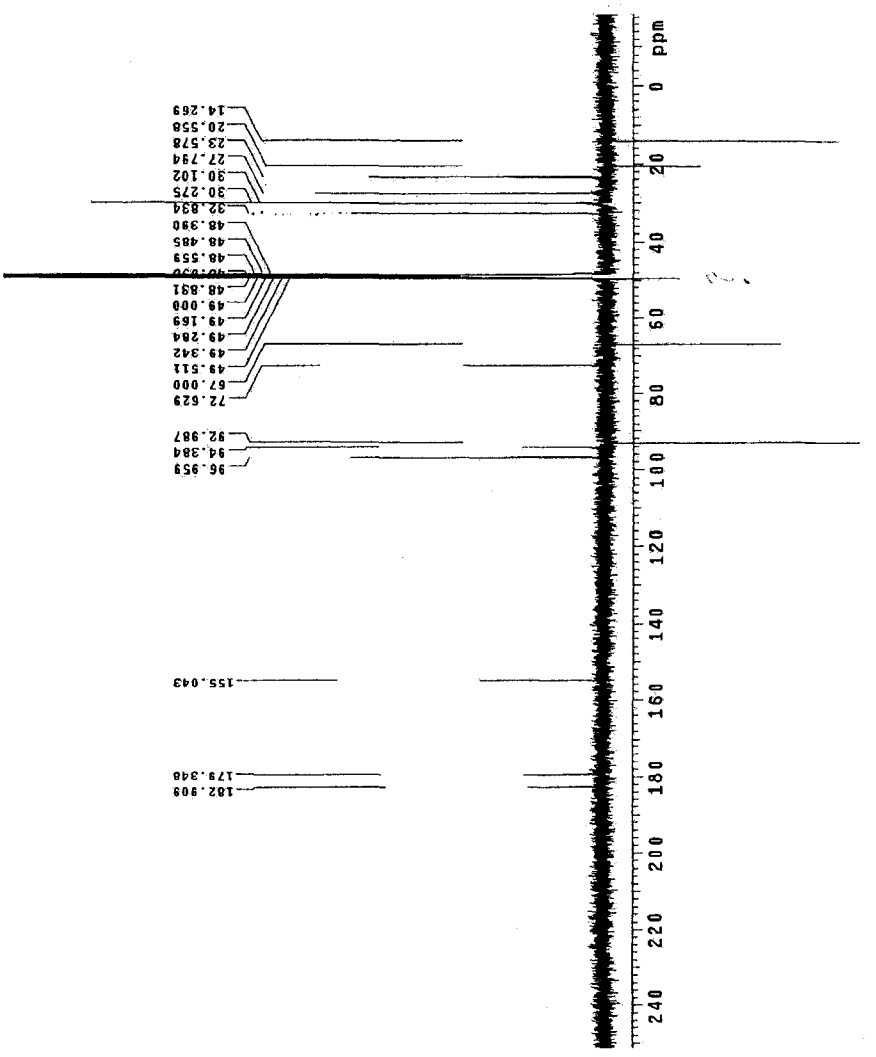
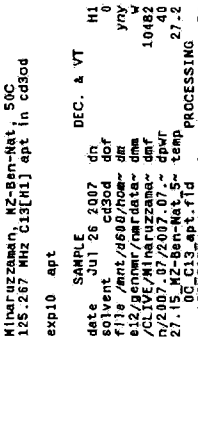
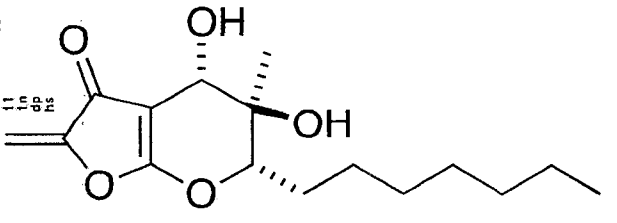
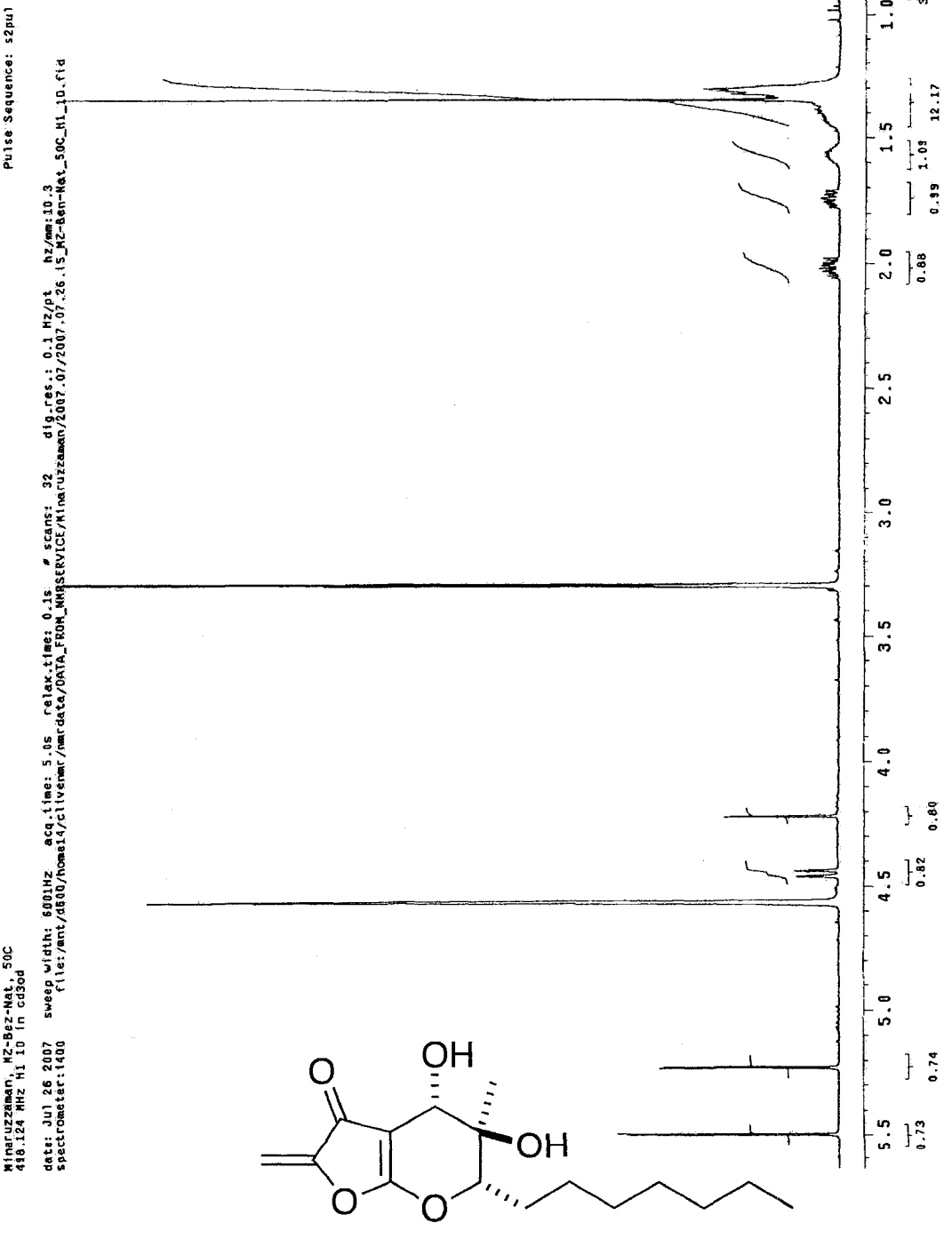






Natural benesudon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Minaruzzaman, MZ-Bez-Nat, 50C
418.124 MHz H1 10 in cd3od
date: Jul 26 2007 sweep width: 6001Hz acq.time: 5.0s relax.time: 0.1s # scans: 32 dig.res.: 0.1 Hz/pt hz/mm:10.3
spectrometer:1400 file:/mnt/d600/home14/clivenmr/nmrdata/DATA_FROM_NMRSERVICE/Minaruzzaman/2007.07/2007.07.26.15_MZ-Ben-Nat_50C_H1_1D.fid
O
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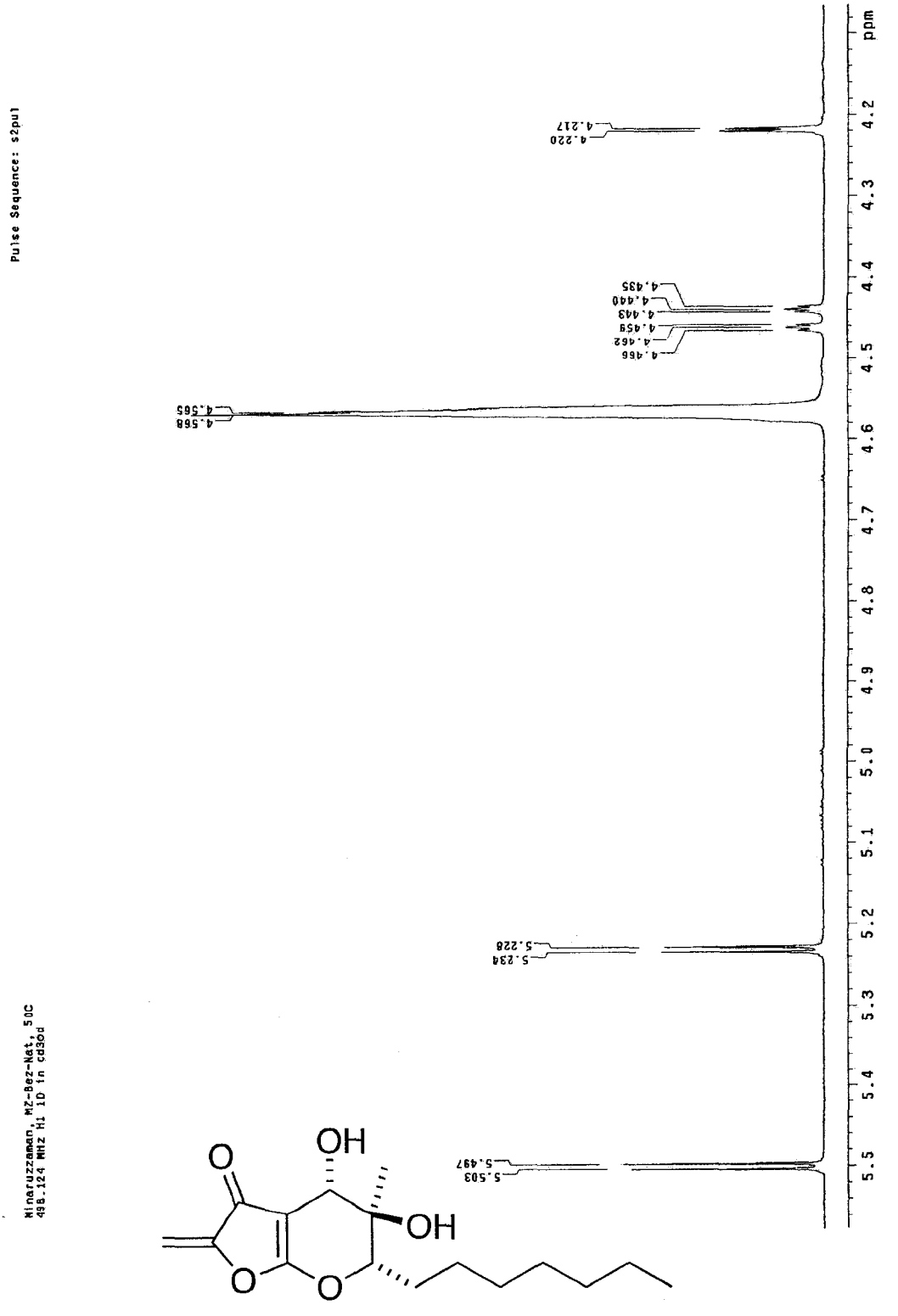
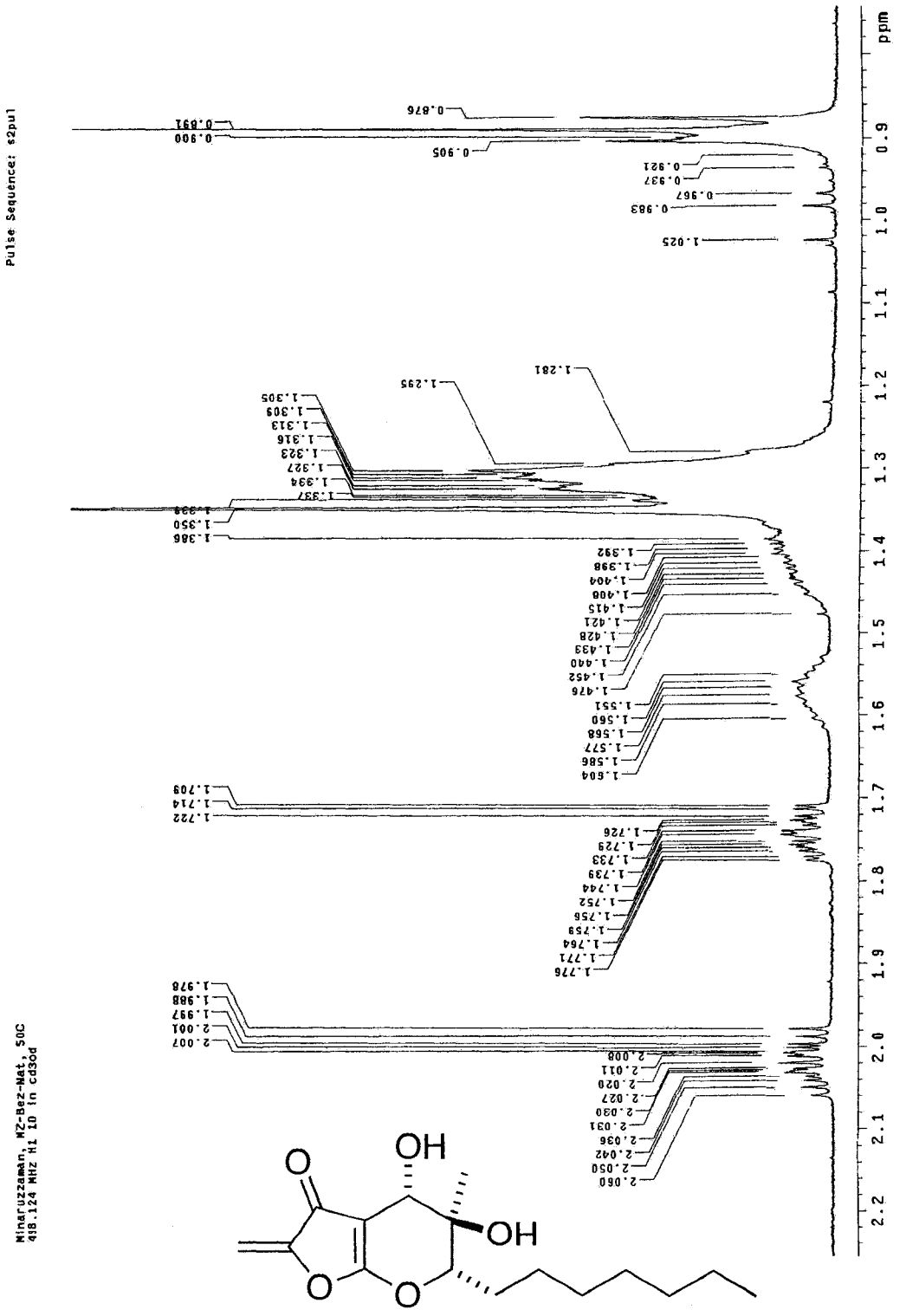
Natural benesudon



Natural benesudon



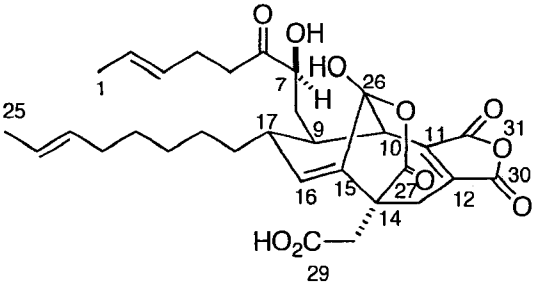
Natural benesudon

Chapter III

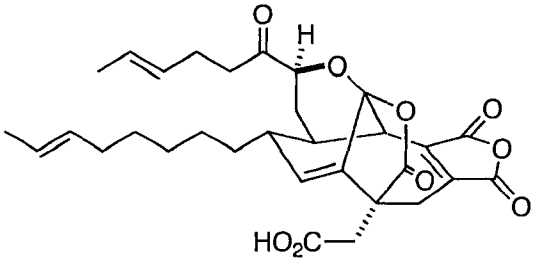
A Synthetic Studies on the Anticancer Agent CP-225,917

1. INTRODUCTION

Two of the leading causes of death in Canada are cancer and cardiovascular disease.[1] It has been shown that hypercholesterolemia is a major risk factor for developing cardiovascular disease.[2] As a result, pharmaceutical companies invest significant amounts of time and money in the isolation and development of compounds that show cholesterol-lowering activity. In the late 1990s Pfizer laboratories reported the isolation and structure elucidation of two new natural products, phomoidride A (CP-225,917) (**1**) and phomoidride B (CP-263,114) (**2**) which are fungal metabolites extracted from an unidentified fungus growing on the twigs of a Juniper tree in Texas.[3] These substances were shown to significantly inhibit the enzyme squalene synthase (from rat liver) with IC_{50} values of 43 μM and 160 μM, respectively. This enzyme has been shown to play a critical role in the biosynthesis of cholesterol. In addition to inhibiting squalene synthase, the substances were also shown to inhibit another enzyme known as Ras farnesyl transferase (from rat brain) with IC_{50} values of 6 μM and 20 μM, respectively.[4] Mutations in this protein have been shown to be involved in approximately 30% of all human cancers. These mutations result in the uncontrolled transduction of intracellular signals by the protein leading to unregulated cellular growth. Inhibitors of this



1 Phomoidride A (CP-225,917): C-7 = *S*
3 Phomoidride C: C-7 = *R*



2 Phomoidride B (CP-263,114): C-7 = *S*
4 Phomoidride D: C-7 = *R*

protein could lead to the development of more effective treatments for cancer patients.[5]

In addition to these promising biological activities, the two compounds also present a unique challenge to synthetic organic chemists. Along with six stereogenic centers, the CP molecules also contain a bridgehead double bond contained within a bicyclo[4.3.1]deca-15,16-diene carbon framework, a quaternary center held within a caged γ-lactone acetal or hemiacetal, a maleic anhydride moiety and two pendant olefinic side chains. The relative stereochemistry of both compounds was assigned by Kaneko and his group by extensive NMR studies.[3]

To date four total syntheses and a number of synthetic studies[6] have been reported. The first total synthesis of racemic CP-225,917 (**1**) (open form) and CP-263,114 (**2**) (closed form) was reported in 1999 from Nicolaou's laboratories.[7] Compound **2** can be generated from compound **1** by treatment with methanesulfonic acid,[3] and the reverse transformation – conversion of **2** into **1** – has been achieved

under controlled basic conditions.[7] Attempts to grow crystals of CP compounds for X-ray analysis were unsuccessful. Therefore the absolute configuration of the two compounds was determined by chemical synthesis.[8] It turned out that compounds **1** and **2** synthesized by the Nicolaou group were actually the enantiomers of the natural substances.[9] Shortly after Nicolaou's publications, three additional elegant syntheses of CP molecules appeared from the Shair,[10] Fukuyama,[11] and Danishefsky[12] groups. The latter described the synthesis of racemic **1**, and the Shair and Fukuyama groups made optically active **2**, Fukuyama's work leading to the first asymmetric synthesis of the natural enantiomer and Shair's to the unnatural enantiomer. Like Nicolaou's approach, neither Shair nor Fukuyama claimed any synthesis of **1** from **2**.[13] The Danishefsky group first isolated a naturally occurring phomoidride epimeric to **2** at C-7 from various fermentation broths provided by Pfizer scientists.[14]

Later this finding was corroborated by Sulikowski and co-workers, who demonstrated that both epimers of the ring-opened and ring- closed phomoidrides could be isolated from fungal cultures.[15] Further studies indicated that the relative ratios of these four compounds largely depend upon pH and fermentation time, with **1** and **2** being the major isolates in all cases. The Sulikowski group also suggested that phomoidride B (**2**) is the primary biosynthetic product and the remaining three are derived from **2**. Compounds **3**

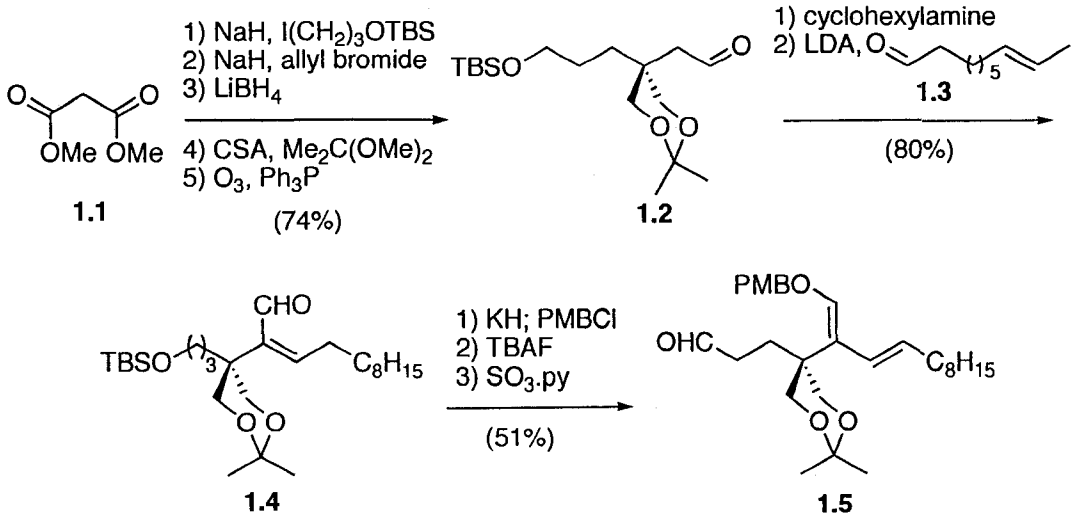
and **4**, epimeric at C-7 to **1** and **2** respectively, were named phomoidrides C (**3**) and D (**4**); no biological studies have been reported for them.

1.1 Nicolaou's Asymmetric Synthesis

In 1999 Nicolaou and his group reported the first total synthesis of CP compounds (in their racemic form)[7,16] by a route that involved an intramolecular Diels-Alder reaction as a key step to generate the core skeleton. The absolute configuration of the CP compounds, however, remained unknown despite many attempts to prepare a crystalline derivative for X-ray crystallography. Subsequently, in 2000, the first asymmetric total synthesis which established the absolute configuration, from the same laboratory was published. The approach relied upon modifying the racemic route using an asymmetric Diels-Alder reaction.

The required diene **1.5** was assembled by double alkylation of commercially available dimethyl malonate **1.1** (Scheme 1).

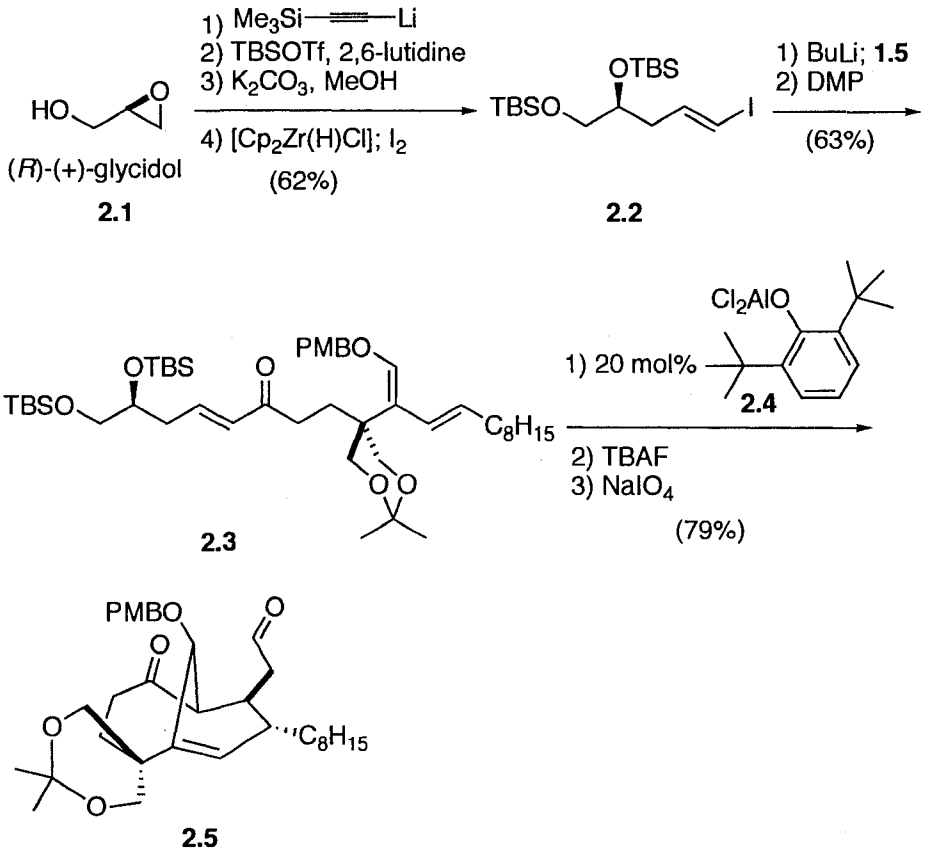
SCHEME 1. Synthesis of the Diels-Alder Precursor



After a double alkylation of dimethyl malonate (**1.1**), the two ester groups were reduced to alcohols, which were protected as an acetonide. Ozonolysis then gave aldehyde **1.2**. Reaction of the cyclohexylenamine of **1.2** with aldehyde **1.3** provided the corresponding unsaturated aldehyde **1.4**, which was further reacted with KH and *para*-methoxybenzyl chloride to give diene **1.5**.

The arbitrarily chosen *R* enantiomer of glycidol **2.1** was opened with TMS-acetylide, quenched with TBSOTf, followed by alkylation and hydroiodination to give vinyl iodide **2.2**. This intermediate was converted to the corresponding vinyllithium reagent by metal-halogen exchange, coupled with racemic aldehyde **1.5** and oxidized to provide enone **2.3**.

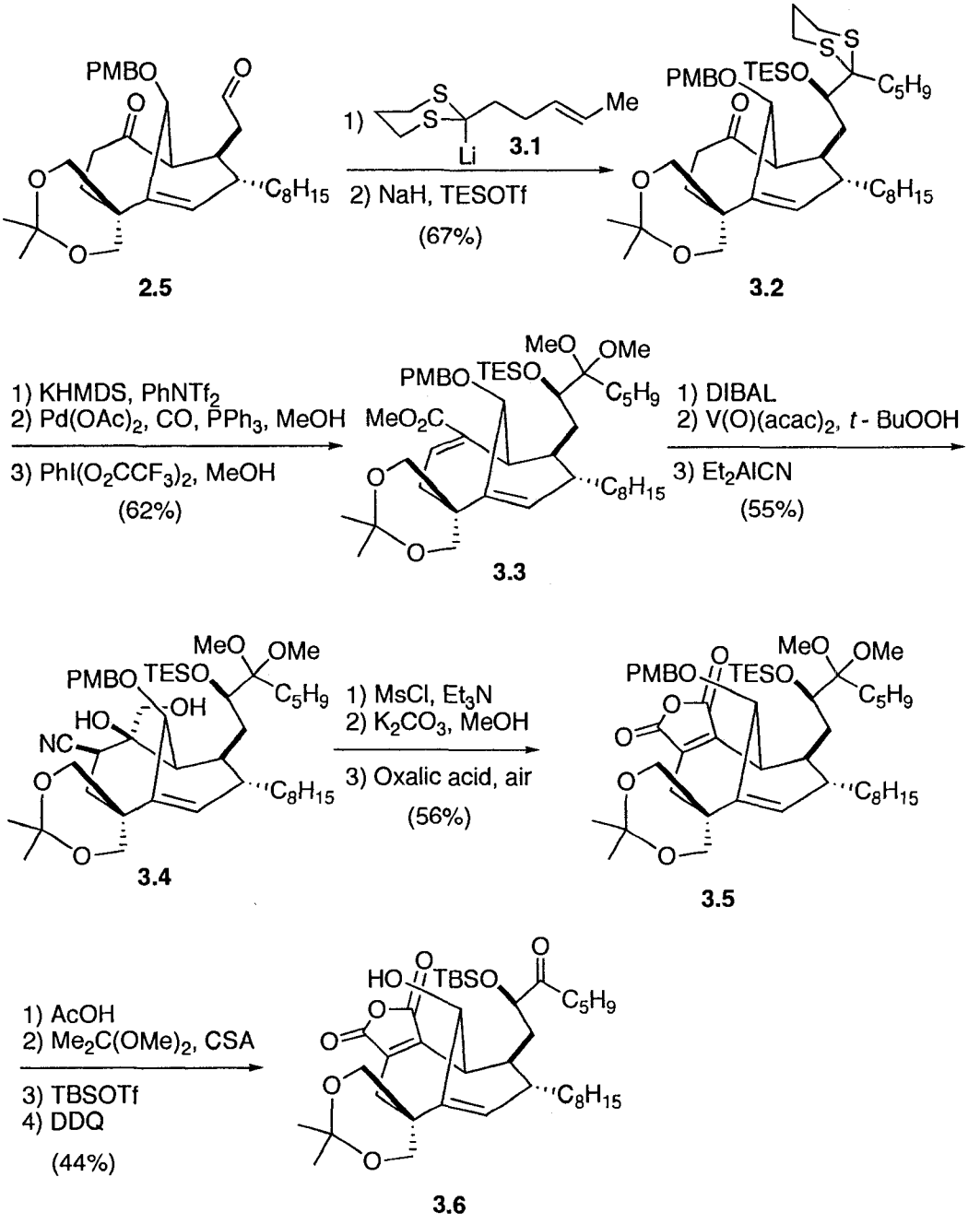
SCHEME 2. Asymmetric Construction of the Core Structure



The requisite [4.3.1] core structure was then assembled through an unusual (it gives a bridgehead olefin) intramolecular Diels-Alder reaction in the presence of the Lewis acid **2.4**. The cycloadducts were produced as a mixture of diastereomers (5.7:1). These were deprotected, chromatographically separated, and oxidatively cleaved with $NaIO_4$ to provide enantiomerically enriched aldehyde **2.5** (Scheme 2).

The derived ketone **3.2** was converted into its vinyl triflate which was then submitted to Pd-catalyzed

SCHEME 3. Synthesis of the Maleic Anhydride Unit

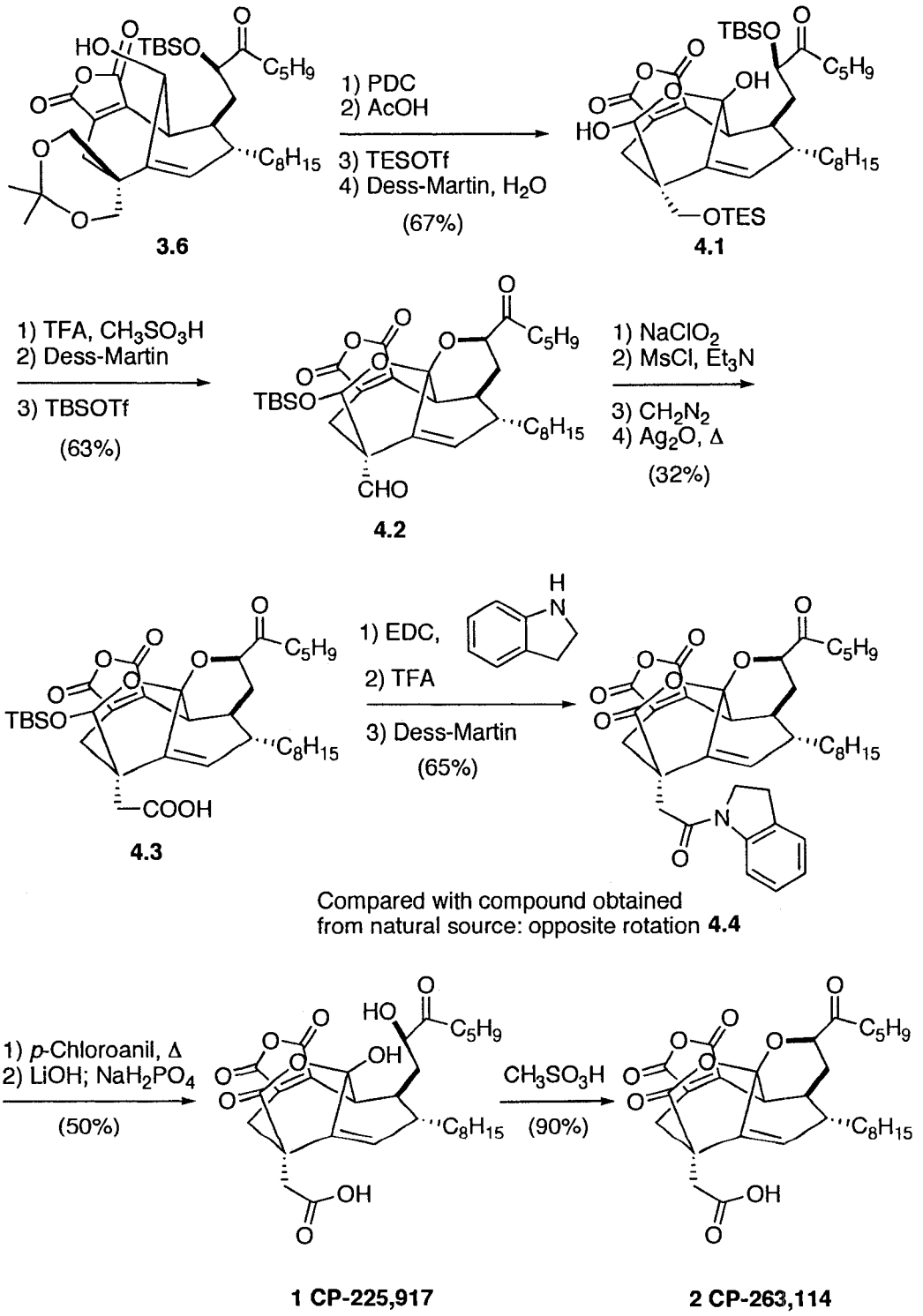


carboxymethylation to furnish an α,β-unsaturated ester; subsequent dithiane deprotection yielded **3.3** (Scheme 3).

The methyl ester **3.3** was reduced to an allylic alcohol and epoxidized. Epoxide opening with Et_2AlCN gave diol **3.4**. Completion of the anhydride function was accomplished by a cascade of reactions. This involved conversion of the primary alcohol function in **3.4** to a mesylate, base assisted epoxide formation, and β-elimination from the intermediate cyano-epoxide. This sequence was followed by cyclization to an imino butenolide, tautomerization to an 2-aminofuran, and autoxidation by triplet oxygen. Finally, extrusion of ammonia yielded the maleic anhydride **3.5**.[17]

After a series of protection and deprotection steps, **3.5** was transformed into bridgehead alcohol **3.6**. This was oxidized by PDC to the corresponding bridgehead ketone (Scheme 4). Subsequent acetonide removal allowed one of the released primary alcohols to form a lactol with the bridgehead carbonyl and the remaining hydroxyl group was protected as a triethylsilyl ether (**4.1**) (Scheme 4).[8,17c] Upon exposure of the lactol to DMP the γ-hydroxylactol **4.1** was formed. This was desilylated and then oxidized to aldehyde **4.2**. One carbon homologation was done by a modified Arndt-Eistert protocol to give rise to acid **4.3**. The acid was coupled with indoline, using DCC. Then acid-mediated TBS ether deprotection, and oxidation of the lactol subunit to a lactone using DMP, furnished **4.4**, the amide derivative of CP-263,114 (**2**). The Nicolaou group determined the absolute configuration of the natural product by comparing **4.4** to the analogous indoline

SCHEME 4. Preparation of γ-Hydroxylactone and Completion of the Total Synthesis



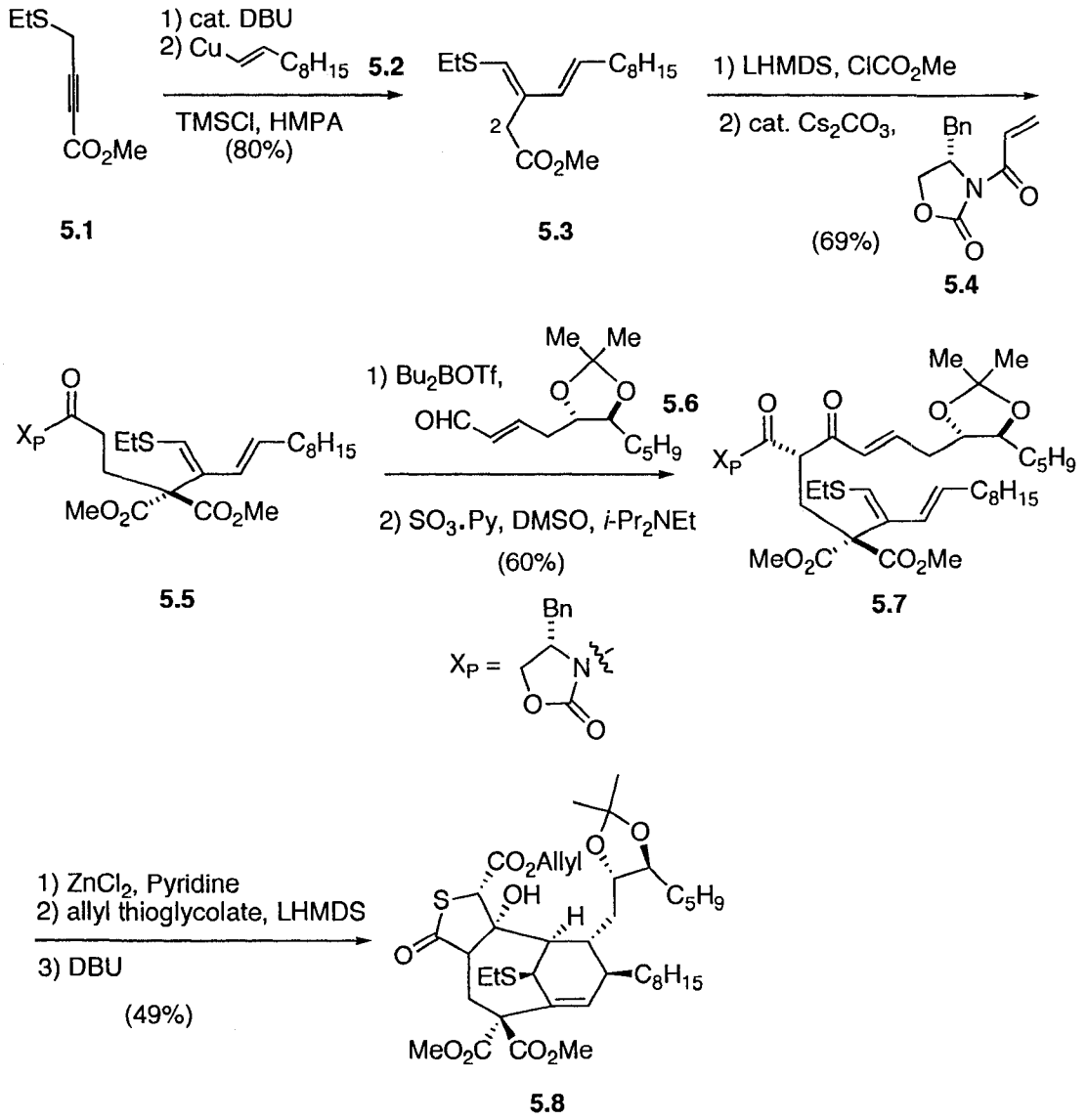
derivative from natural CP-263,114 (**2**). The synthetic material possessed the opposite optical rotation to the natural fungal metabolite. In the final steps of the synthesis, LiOH hydrolysis gave CP-225,917 (**1**). Treatment of CP-225,917 (**1**) with methanesulfonic acid provided[3] CP-263,114 (**2**) in 90% yield.

1.2 Fukuyama's Enantioselective Synthesis of the Natural Isomer of CP-263,114 (2)

Like Nicolaou's approach, Fukuyama and his colleagues used an intramolecular Diels-Alder reaction to synthesize the bicyclic core structure of CP-263,114. Their journey started with the isomerization of **5.1** to an allene, and subsequent 1,4-addition of **5.2** then yielded the diene **5.3** (Scheme 5). After introduction of a second carbomethoxy group at C-2 of **5.3**, Michael addition of the resulting malonate to the chiral acrylamide **5.4** gave diester **5.5**. Boron-mediated diastereoselective aldol reaction of **5.5** with aldehyde **5.6**, followed by Parikh-Doering oxidation, furnished the Diels-Alder precursor **5.7** which was then cyclized using $ZnCl_2$. The Evan's chiral auxiliary was displaced by the action of lithium allyl thioglycolate and an intramolecular type aldol reaction then furnished the bridgehead olefin **5.8** as a single diastereomer.[18]

The construction of the maleic anhydride unit and completion of the synthesis are presented in Scheme 6.

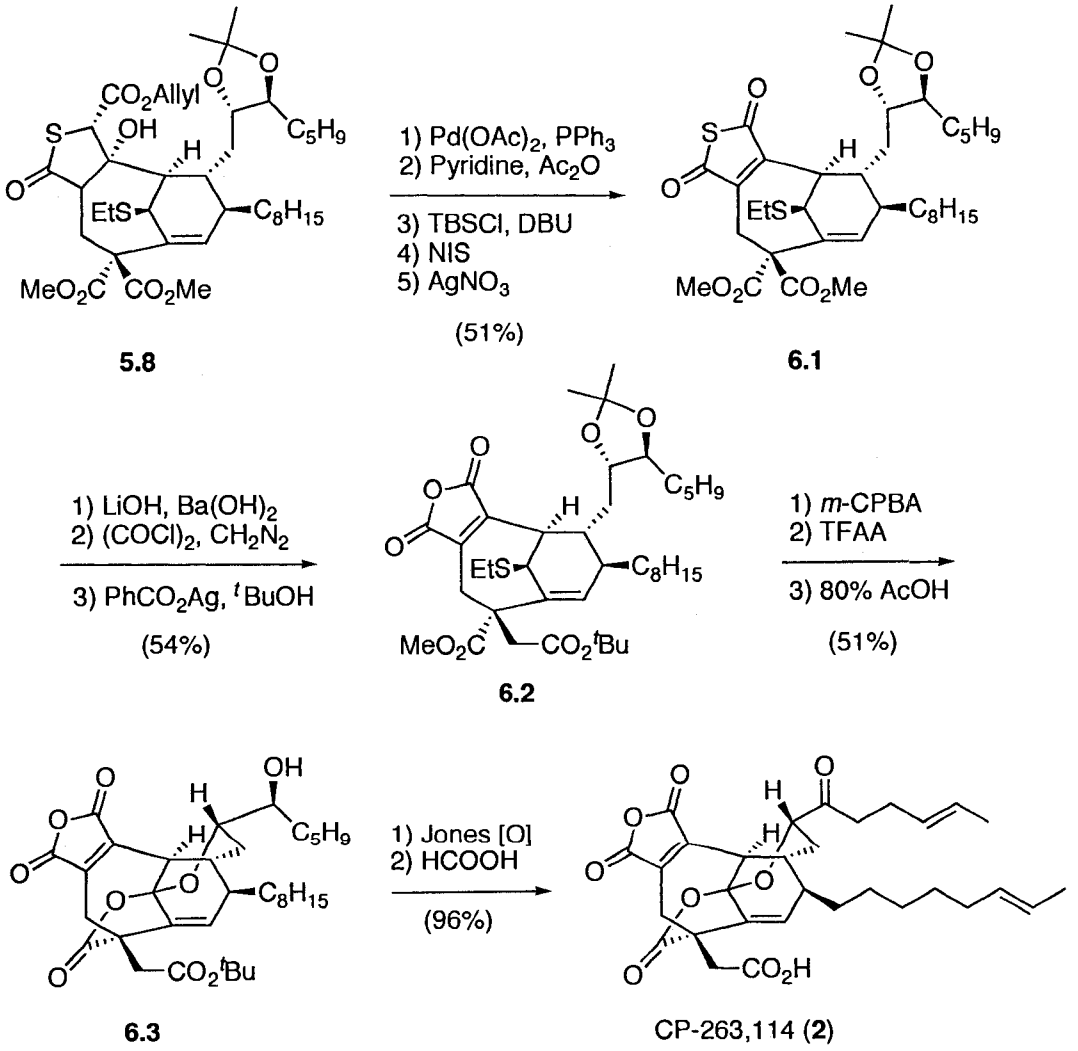
SCHEME 5. Synthesis of the Core Structure



After Pd-catalyzed deprotection of the allyl group followed by dehydration and decarboxylation, a thiobutenolide was formed. This was converted into thiomaleic anhydride **6.1** in three steps via a 2-silyloxythiophene. Successive treatment of **6.1** with $LiOH/Ba(OH)_2$ caused selective hydrolysis of the less hindered methyl ester into a

carboxylate, and concomitant hydrolysis of the thiomaleic anhydride furnished the desired maleic anhydride. One carbon homologated ester **6.2** was then reached by the Arndt-Eistert procedure. A Pummerer rearrangement was now applied and the acetonide was deprotected to build up the cyclic acetal. The maleic anhydride survived all these steps. Finally Jones oxidation and removal of the *t*-butyl

SCHEME 6. The Completion of the Synthesis.



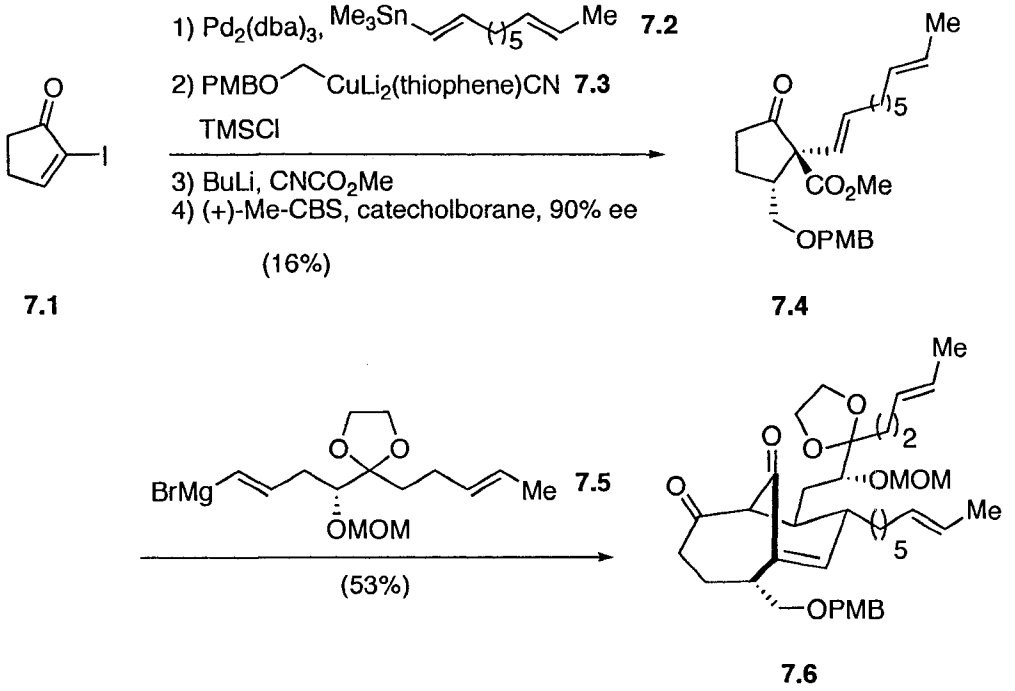
5.8 **6.1** **6.2** **6.3** CP-263,114 (**2**)

group afforded the natural enantiomer of CP-263,114 (**2**) which is depicted above in the correct absolute configuration.

1.3 Shair's Synthesis of (+)-CP-263,114 (2)

Shair and his group masterfully developed a three-step tandem cyclization to build up the highly functionalized [4.3.1]bicyclic core structure of CP-263,114 (**2**) as a key step in their synthesis.[19,17c]

SCHEME 7. Early Steps of Shair's Approach

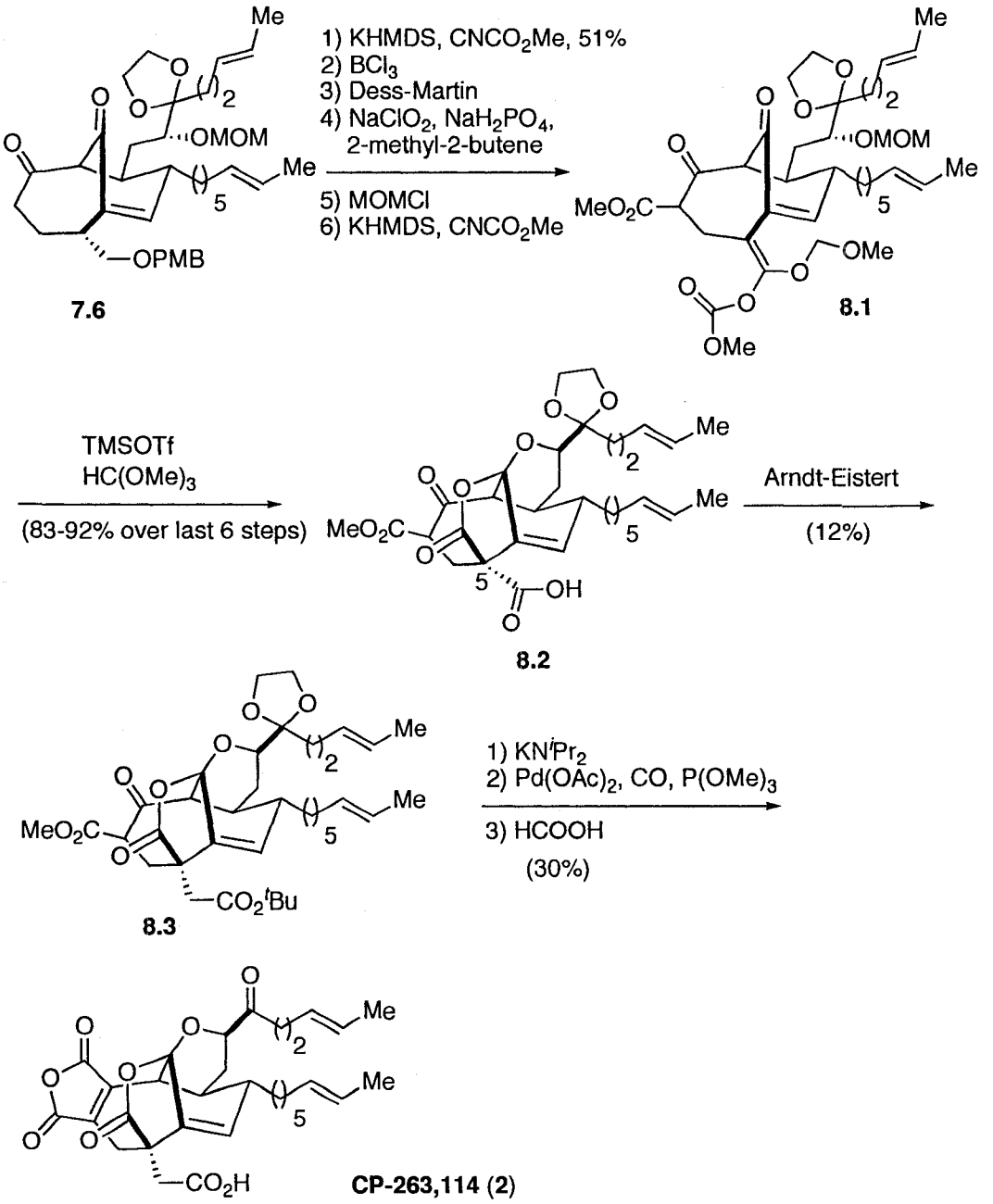


The synthetic route started with a Pd(0)-catalyzed cross coupling between iodo-enone **7.1** and vinyl stannane **7.2** (Scheme 7). Conjugate addition with cuprate **7.3**, *C*-

acylation using Mander's reagent and then Corey's oxazaborolidine-mediated kinetic resolution afforded β-keto ester **7.4**. Grignard reagent **7.5**, derived from (*R*)-glyceraldehyde, was coupled with optically pure ketone **7.4** to afford a bromomagnesium alkoxide that underwent anionic oxy-Cope rearrangement followed by spontaneous Dieckmann-like cyclization to produce the core structure **7.6**.

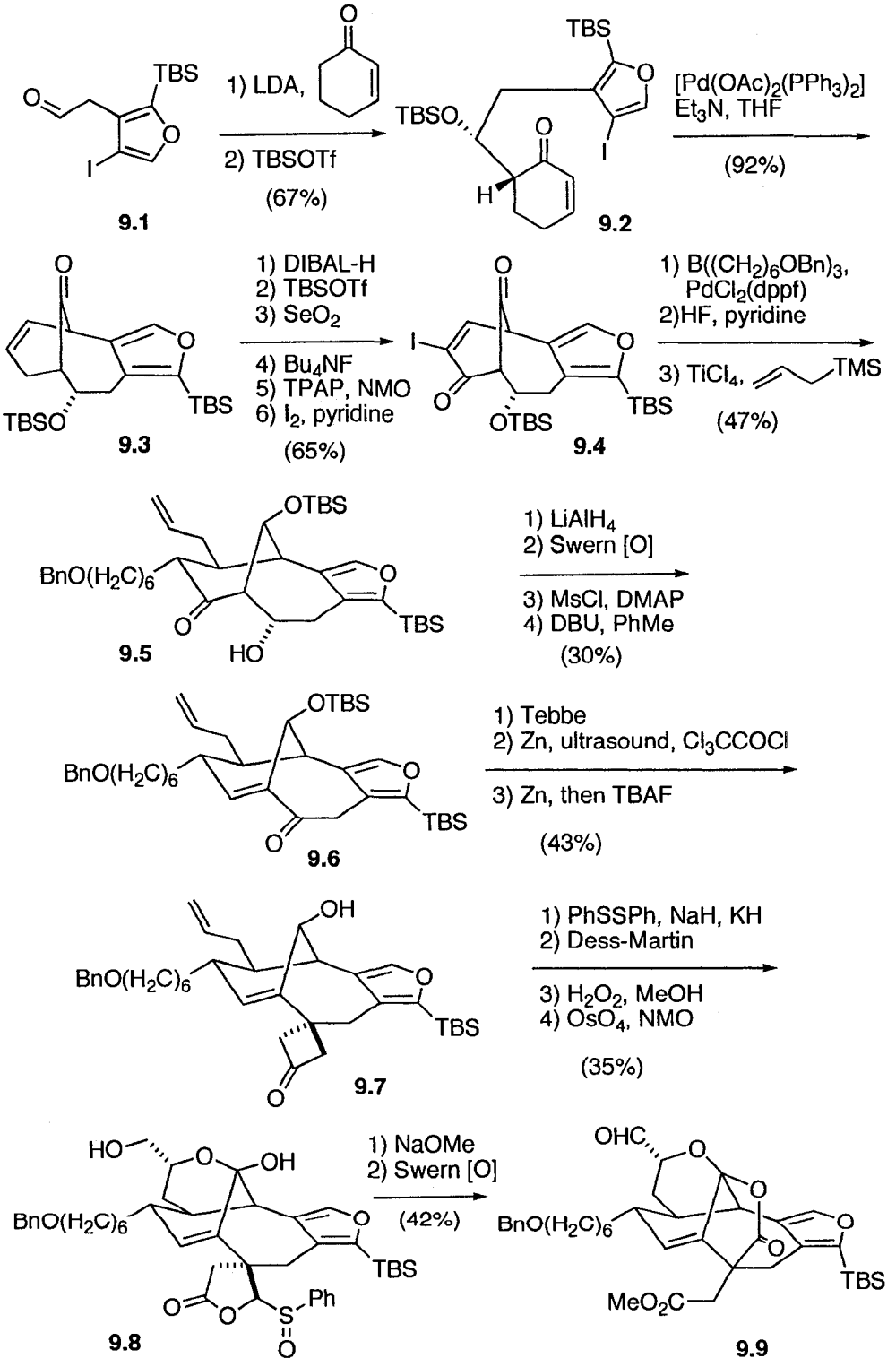
The next task was the formation of the maleic anhydride subunit and pseudoester cage ring system. After *C*-acylation, the primary PMB ether subunit of **7.6** was converted into enol carbonate **8.1** using a five step protocol (Scheme 8). Exposure of **8.1** to TMSOTf and trimethyl orthoformate initiated an unprecedented Fries-like cascade reaction to form the lactone and C-5 quaternary center which also liberated the free acid (**8.1**→**8.2**). As in the routes used by Fukuyama and Nicolaou, the acid was homologated by Arndt-Eistert reaction which gave very low yield. The low yield was attributed to the sensitivity of the substrate **8.2** rather than any inefficiency of the reaction. Following homologation, the β-keto ester **8.3** was converted into a vinyl triflate, which was then carbonylated. Although this step required a high pressure of CO due to the surrounding steric hindrance it did serve to build up the maleic anhydride moiety and at that stage acid-mediated ester deprotection afforded the unnatural enantiomer of CP-263,114 (**2**).

SCHEME 8. Final Steps of the Synthesis



1.4 Danishefsky's Approach to CP Molecules: Insight into the C-7 Configuration

SCHEME 9. Assembly of the Carbocyclic Core of CP Molecules

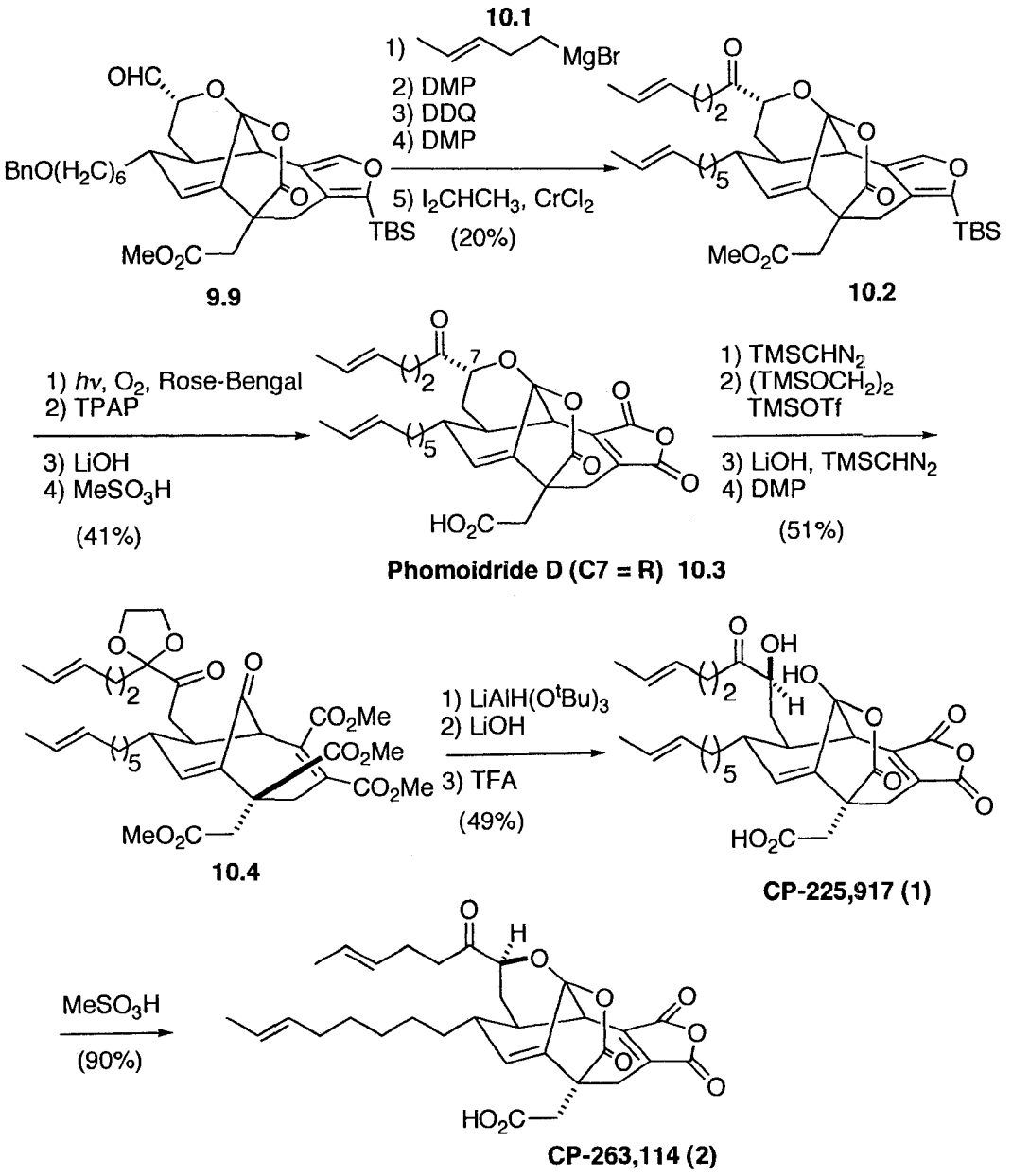


The synthesis began with an aldol addition between 2-cyclohexanone and **9.1**, followed by Heck vinylation to afford the desired bicyclic ring system **9.3** (Scheme 9). The diastereoselectivity of the aldol reaction was 8:1. The fused furan ring serves as a masked maleic anhydride that will be revealed late in the synthesis, and the olefin in **9.3** is ideally positioned for subsequent elaboration of the bridgehead olefin. Compound **9.3** was converted into iodo enone **9.4**, an intermediate that is suitably poised for Suzuki-Miyaura cross coupling and Sakurai type allylation.[14,17c,20] This sequence provided the desired trans side chain stereochemistry found in the natural product. The bridgehead olefin was then installed through a series of chemoselective oxidative manipulations, followed by a β-elimination of a mesylate to give **9.6**.

Danishefsky's group took a unique approach to install the quaternary center. After Tebbe olefination of **9.6**, a cyclobutanone was formed regioselectively using dichloroketene and selective desilylation then gave **9.7**. This was then regioselectively sulfenylated by deprotonation and reaction with diphenyl disulfide. The sulfenylation step controls the selectivity of a subsequent Bayer-Villiger oxidation, as well as a fragmentation of the resulting lactone. After sulfenylation, the bridgehead secondary alcohol was oxidized by Dess-Martin periodinane and the sulfenylated cyclobutanone moiety was subjected to regiospecific Bayer-Villiger reaction, followed by

oxidation of the resulting sulfenyl lactones to the corresponding sulfoxides. Dihydroxylation of the allyl group then provided **9.8**. The bridgehead double bond was deactivated by the α-carbonyl group. Saponification and

SCHEME 10. Completion of the Total Synthesis



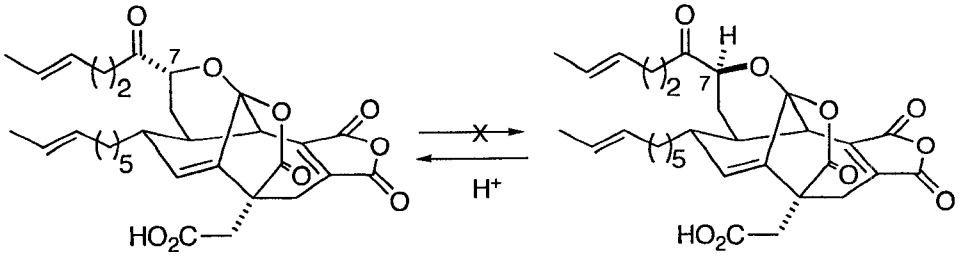
oxidation produced lactone **9.9** which has the required quaternary center as well as the remaining two rings found in the CP molecules.

The side chain at C-7 was installed by addition of Grignard reagent **10.1** to the aldehyde group of **9.9**. Three additional steps then served to elaborate the second side chain at C-17 so as to arrive at the methyl ester **10.2**.

Unmasking of the anhydride unit was accomplished via the action of singlet oxygen and Ley oxidation.[21] Base hydrolysis and acidification then gave compound **10.3**, which proved to be the C-7 epimer (i.e. phomoidride D). Ultimately phomoidride D (**4**) was converted to **1** in a seven step sequence, thus completing the racemic total synthesis of racemic CP-263,114.

During their epimerization studies, the Danishefsky group uncovered useful information regarding the stereochemical preference at C-7 (Scheme 11). Conversion of material from the 7*S* to the 7*R* configuration (**2** → **4**)

SCHEME 11. Attempted C-7 Epimerization



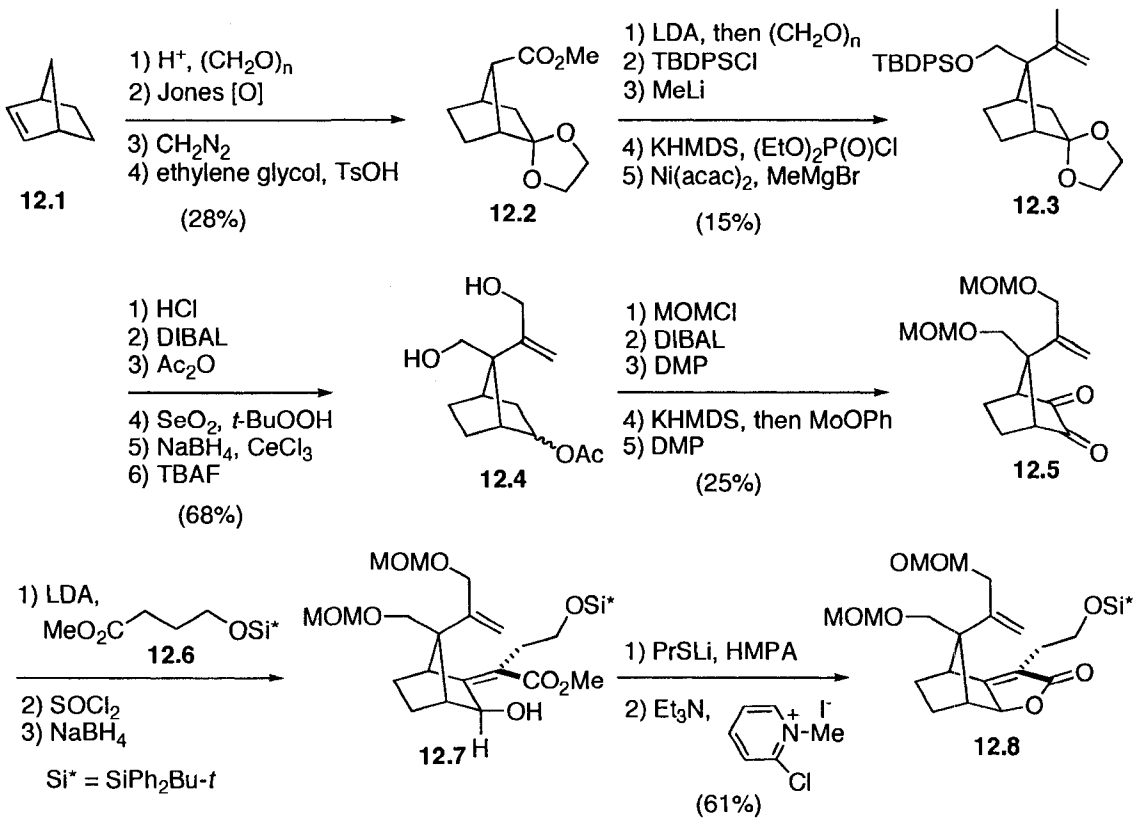
4 Phomoidride D: C-7 = *R* **2 Phomoidride B (CP-263,114): C-7 = *S***

occurred readily while epimerization in the reverse direction could not be effected under any conditions. These results suggested that compounds containing the *R* configuration at C-7 represent the thermodynamically favored epimeric series.

1.5 Clive's First Generation Thermal Cope Approach: Synthetic Studies Related to CP-225,917 (1)

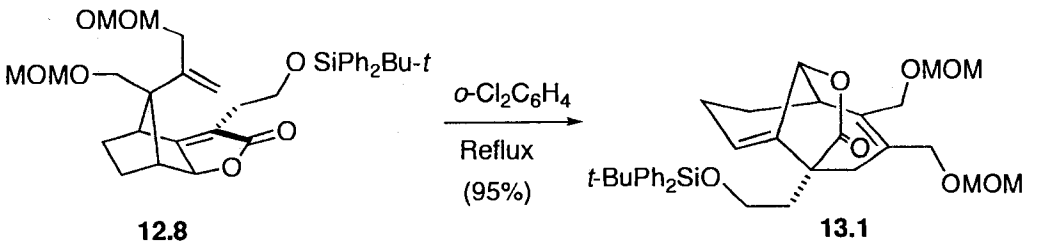
During the initial synthetic approach, Clive and his group used oxy-Cope rearrangement to build up the carbocyclic core.[6n,22] The synthesis began by converting norbornene (**12.1**) into ester acetal **12.2** in four steps (Scheme 12). A bridgehead hydroxymethyl group was introduced by reaction with paraformaldehyde and LDA and, after protection of the hydroxyl group, the ester was treated with methyllithium to obtain a methyl ketone. This was homologated to an isoprene unit by Kumada coupling. The acetal **12.3** was deprotected by acid, converted to a mixture of epimeric acetates and subjected to allylic oxidation, reduction and deprotection to give diol **12.4.** Protection of the hydroxyls as MOM ethers and removal of the acetyl group with DIBAL gave an alcohol which was oxidized to a ketone. This was converted into an α-hydroxyketone using Vedej's protocol, followed by Dess-Martin oxidation to diketone **12.5.** That compound was condensed with the enolate derived from the protected ester **12.6.**

SCHEME 12. Synthesis of Oxy-Cope Precursor



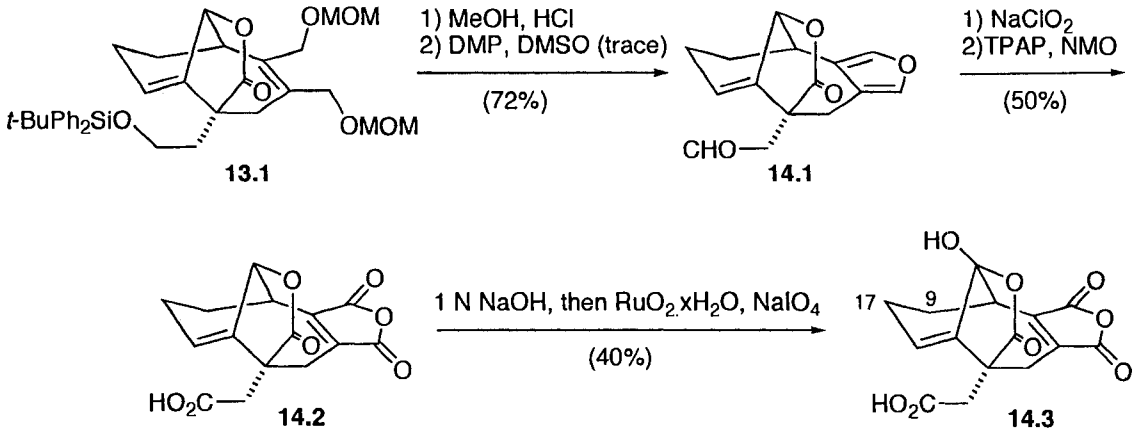
Diastereoselective reduction then gave alcohol **12.7**. After demethylation of the ester, the free acid was lactonized using Mukaiyama's reagent to yield the strained butenolide **12.8**.

SCHEME 13. Cope Rearrangement



Clive's first efforts to synthesize the core structure of CP-225,917 (**1**) were based on thermal Cope, oxy-Cope, anionic oxy-Cope or corresponding siloxy oxy-Cope rearrangements. The tricyclic lactone (**13.1**) was assembled smoothly by refluxing the strained lactone (**12.8**) in 1,2-dichlorobenzene (Scheme 13). This rearranged carbocycle contains all the carbons needed for elaboration into the core model of CP molecules.

SCHEME 14. Building Anhydride Unit



Global deprotection with acid gave a triol which was subjected to Dess-Martin oxidation to afford furan aldehyde **14.1**. Subsequent sodium chlorite oxidation converted the aldehyde into a carboxylic acid, and the unexpected oxidation of the furan to a regioisomeric mixture of hydroxybutenolides also occurred. Both regioisomers were equally suitable for perruthenate oxidation. Finally,

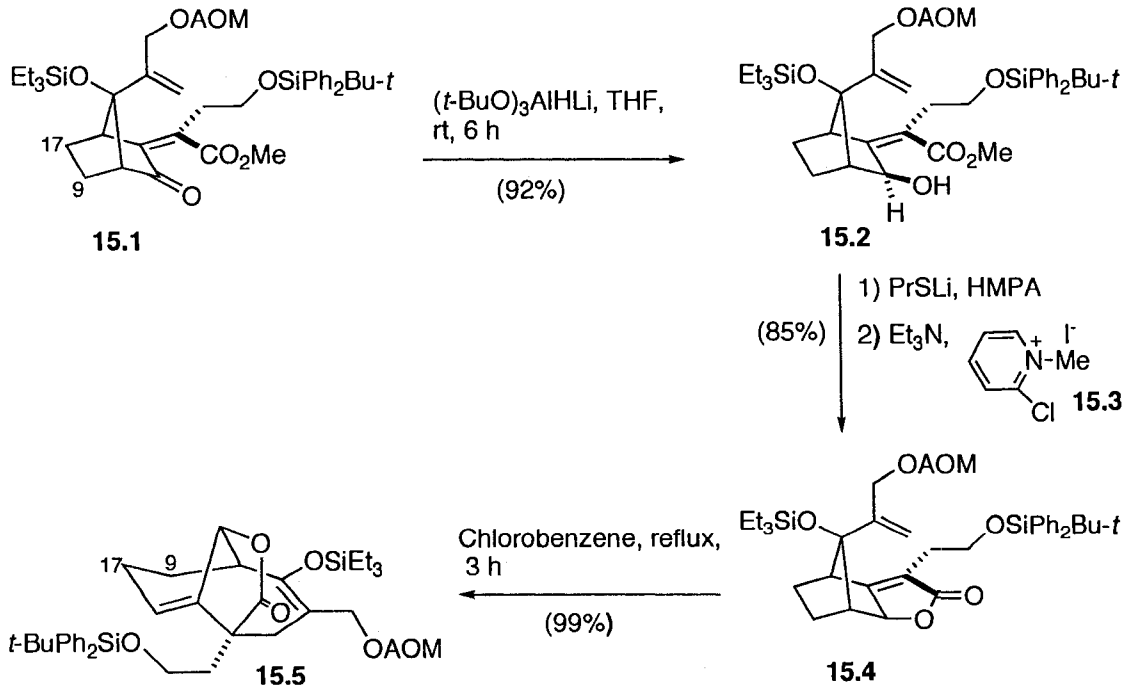
installation of the hemiacetal was done by ruthenium dioxide to afford the fully oxygenated core structure **14.3** that lacks only the two alkyl side chains at C-9 and C-17.

From the above discussion, it is clear that the natural isomer of CP-225,917 (**1**) has not been synthesized yet, and there is still room to discover new routes and methodologies to synthesize these challenging synthetic targets using a smaller number of steps and in better overall yield.

2. RESULTS AND DISCUSSION

The first generation approach towards **1** and **2** explored in this laboratory is based on a thermal Cope rearrangement or its variants such as oxy-Cope or siloxy-Cope rearrangement. The analog **15.5** of the natural core structure of CP molecules was synthesized by applying this synthetic plan (Scheme 15).[23] Ketone **15.1** was reduced stereoselectively to the desired *exo* alcohol **15.2**, using $(t\text{-BuO})_3AlHLi$, and the ester group was demethylated with PrSLi. Finally, the hydroxy acid was lactonized using Mukaiyama's reagent[24] **15.3** to afford **15.4**. The bridgehead

SCHEME 15.

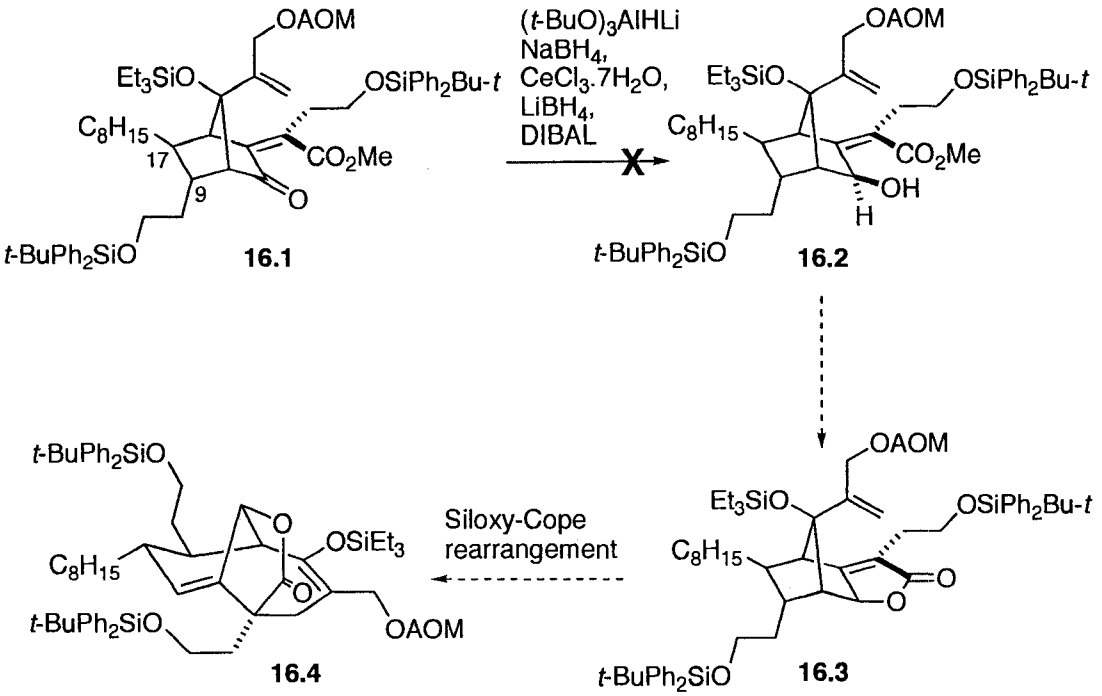


AOM = *p*-anisyloxymethyl, *p* - $MeOC_6H_4OCH_2$

olefin **15.5**, without the C-17 and C-9 side chains, was smoothly produced by thermal siloxy-Cope rearrangement in refluxing chlorobenzene.

These experiments serve as a model for more advanced work towards CP-225,917 itself.

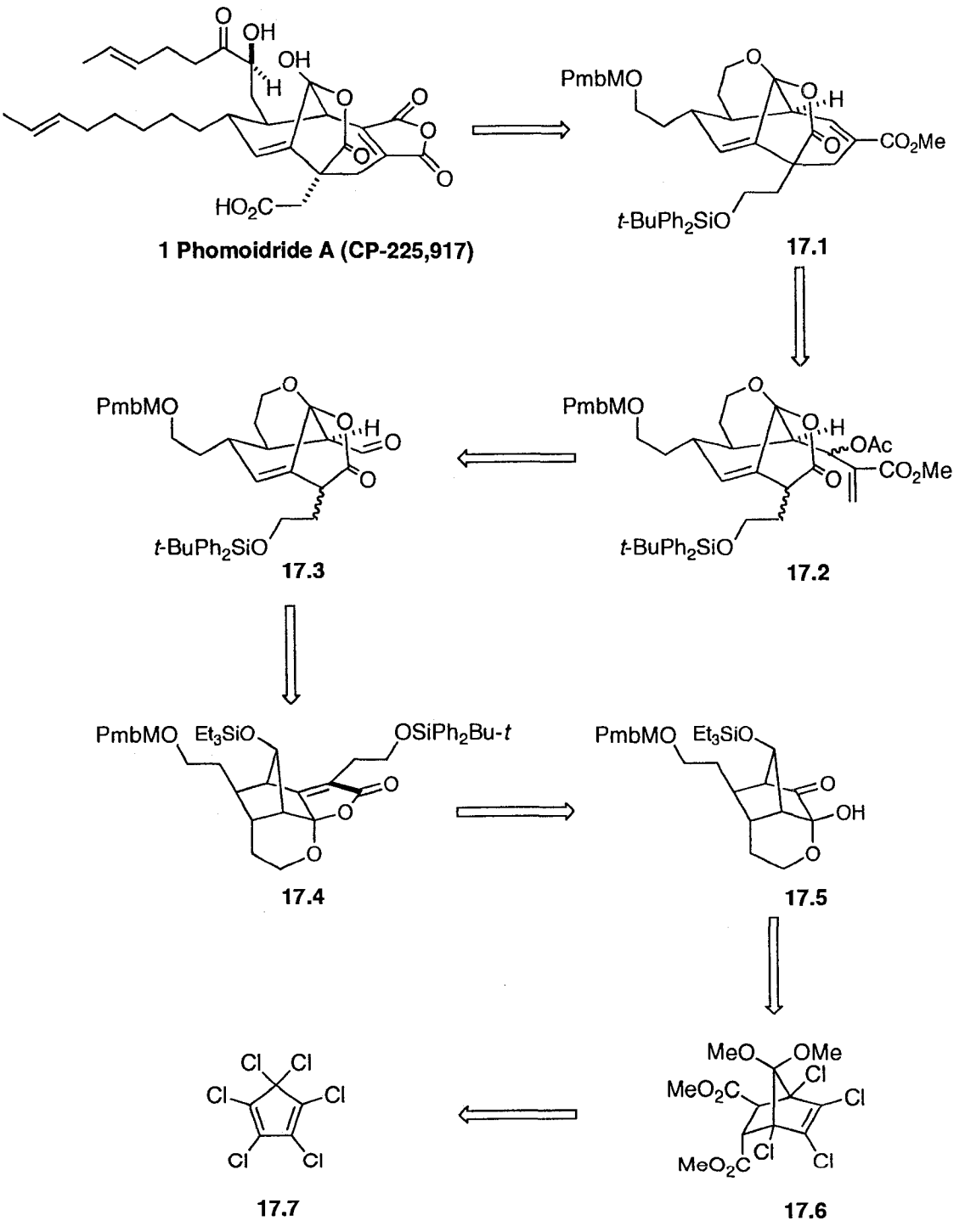
SCHEME 16.



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

With these optimized conditions in hand, the natural core structure **16.4** of CP molecules became the next target. Ketone **16.1** with two additional side chains at C-17 and C-9 was made[25] in order to reach **16.4**. However, all attempts to reduce ketone **16.1** using a variety of reducing agents gave

SCHEME 17. Synthetic Strategy



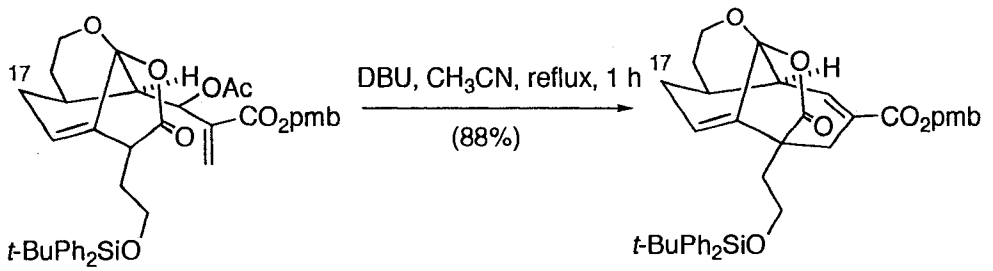
either decomposition products or unreacted starting material (Scheme 16). When $LiAlH_4$ was used, it reduced both ester and keto groups of **16.1**.[25] Clearly, the synthetic plan of Scheme 16 failed at the first step.

Consequently, alternative retrosynthetic plans were sought. The second generation route, which does not involve Cope rearrangement, is summarized in Scheme 17.

It was envisioned that CP-225,917 could be derived from the core structure **17.1** by converting the α,β-unsaturated ester into an anhydride subunit and elaborating the two side chains. The core structure **17.1** would, in turn, come from allylic acetate **17.2** via an intramolecular conjugate displacement reaction (ICD reaction), which is a type of S_N2' process. The Morita-Baylis-Hillman[26] adduct **17.2** would be accessible from aldehyde **17.3**, and the latter is the expected Bu_4NF-mediated fragmentation product of **17.4**. Butenolide **17.4** should be accessible from the hemiacetal **17.5** by esterification and intramolecular Wittig olefination. The hemiacetal **17.5** can be prepared from the readily available starting material hexachlorocyclopentadiene (**17.7**) via **17.6**, itself made by Diels-Alder reaction.

A general method to construct a broad range of carbocycles using a metal-free intramolecular conjugate displacement (ICD) reaction was reported from this laboratory.[27] The analog **18.2** of the natural core structure of **1** was synthesized using this ICD reaction (Scheme 18). The ring closure formally resembles both a conjugate

SCHEME 18. Application of ICD reaction

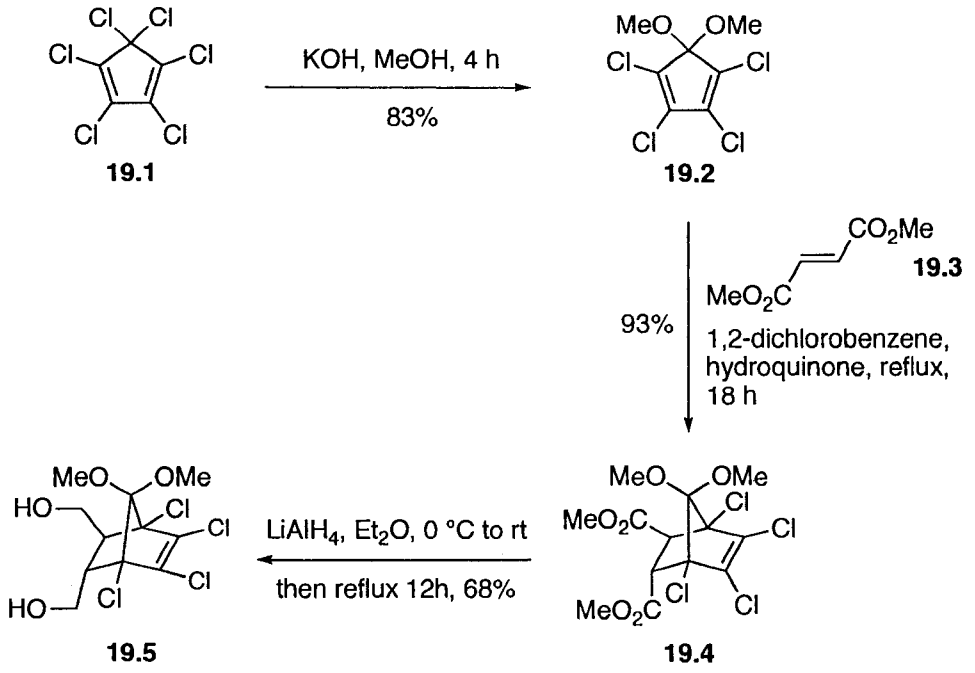


18.1 **18.2**

addition and an S_N2' displacement. Compound **18.2**, however, does not have the alkyl side chain at C-17 that is present in natural CP-225,917 (**1**). My initial assignment was to prepare a different analog of the natural core structure with the required functionalized alkyl side chain at C-17.

My synthesis began with the conversion of hexachloro-cyclopentadiene (**19.1**) to 1,2,3,4-tetrachloro-5,5-dimethoxy-cyclopenta-1,3-diene (**19.2**) using KOH-MeOH (Scheme 19).[28] This cyclic electron deficient diene has been successfully utilized in many Diels-Alder reactions with a wide variety of dienophiles possessing both electron rich and electron deficient groups. It gives very high *endo* selectivity and it can serve as a masked cyclopentadienone, which itself is not suitable for the Diels-Alder reaction as it dimerizes very easily.[29] Diene **19.2** was subjected to Diels-Alder cycloaddition with *trans*-dimethyl fumarate **19.3** in refluxing 1,2-dichlorobenzene to produce the diester

SCHEME 19



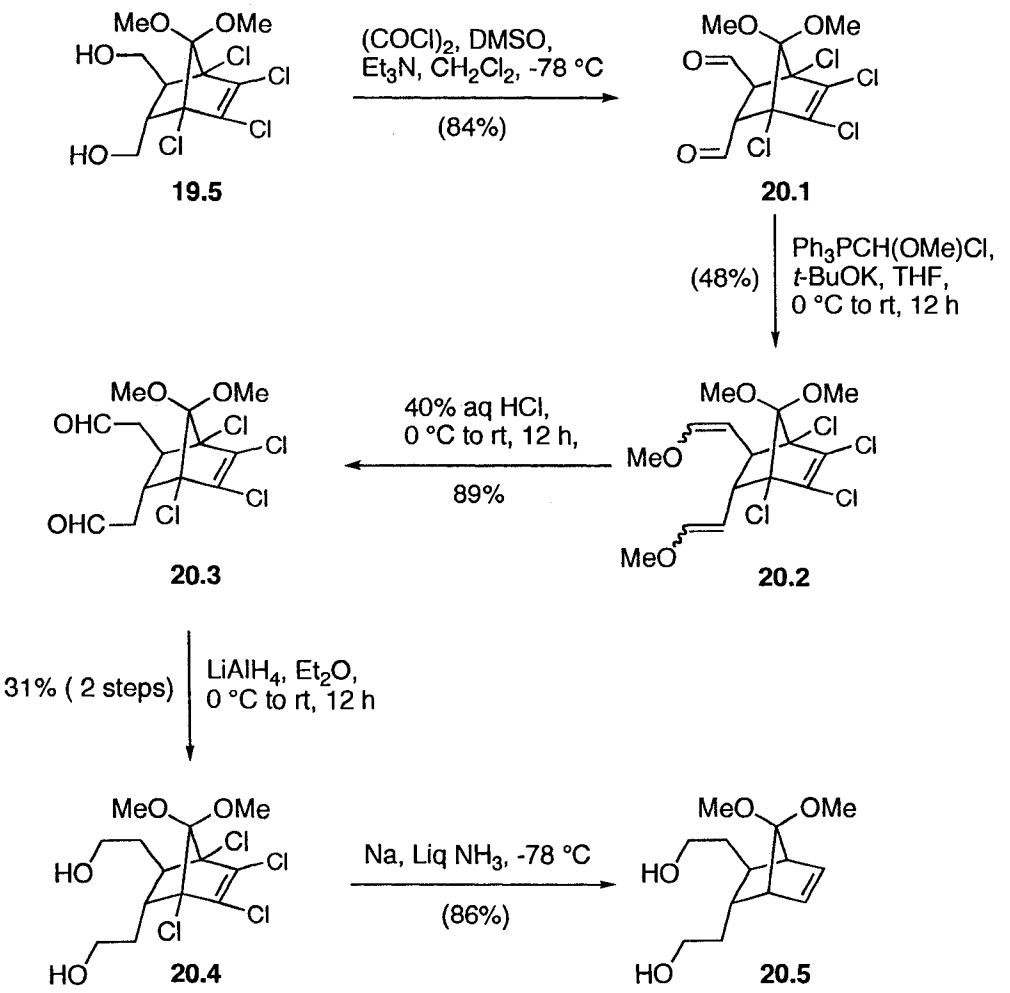
19.4 which was reduced to diol **19.5**. Later, one of the hydroxymethyl side chains of **19.5** will be used to construct the C-17 side chain of the natural product.

Both primary hydroxyl groups of **19.5** were homologated by one carbon so as to form diol **20.4**. Our intention was to use one of the side chains in **20.4** to form the six-membered cyclic ether which is present in CP-263,114 (**2**). The second side chain of **20.5** will be used to build up the C-17 side chains of **1** and **2**.

Both hydroxyls of **20.5** were oxidized under Swern conditions to afford the unstable dialdehyde **20.1** which was treated immediately with the Wittig salt, $Ph_3PCH(OMe)Cl$ in the presence of *t*-BuOK (Scheme 20). The resulting bis enol

ethers **20.2** were not separable using flash chromatography. The unstable bisaldehyde **20.3** was obtained as a single

SCHEME 20

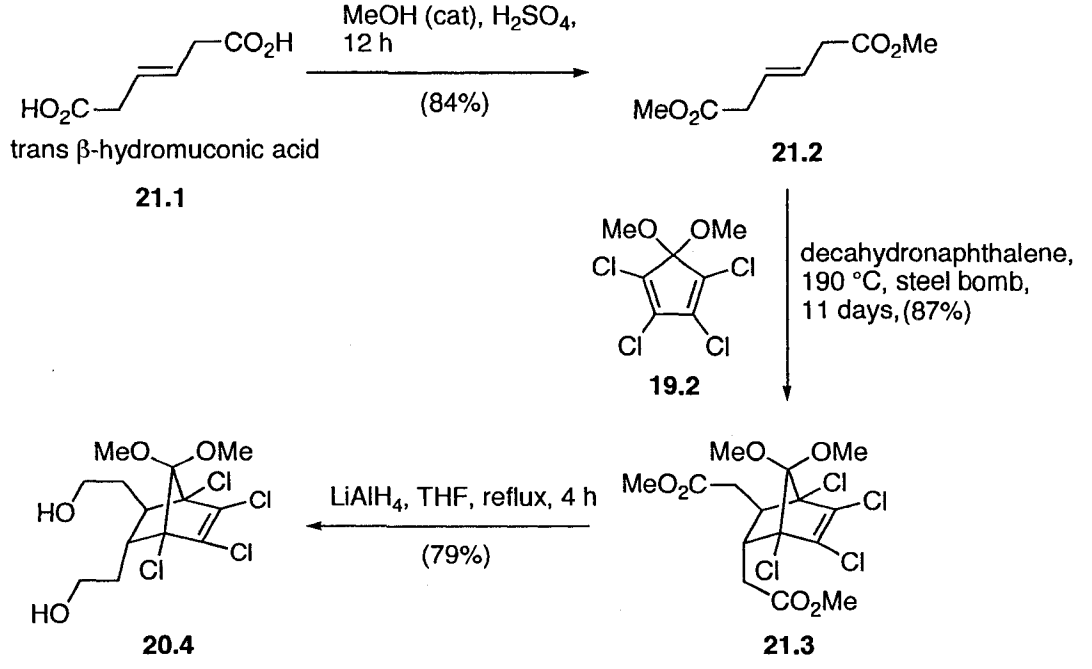


isomer after hydrolysis with 40% aqueous HCl. The material was immediately reduced with $LiAlH_4$ to afford the tetrachlorinated and homologated bis alcohol **20.4** in moderate yield. The compound was dechlorinated under Birch reduction conditions to give **20.5**. This five-step sequence

produced the desired diol **20.5** in only 10% overall yield. Both intermediate aldehydes **20.1** and **20.3** are unstable and require immediate processing. Beside these limitations, the yields were not reproducible.

These facts caused us to seek an alternative and higher-yielding protocol to homologate **19.5**. Initially, we adopted the route used by Leighton.[61] *trans*-β-Hydromuconic acid **21.1** was esterified to bis ester **21.2** under Fischer esterification conditions (Scheme 21).[30] Diels-Alder reaction between (*E*)-3-hexenedioic acid dimethyl ester **21.2** and 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene (**19.2**) required prolonged (ca 11 days) heating at 190 °C to produce the adduct **21.3**. This was reduced by $LiAlH_4$ to diol **20.4**.

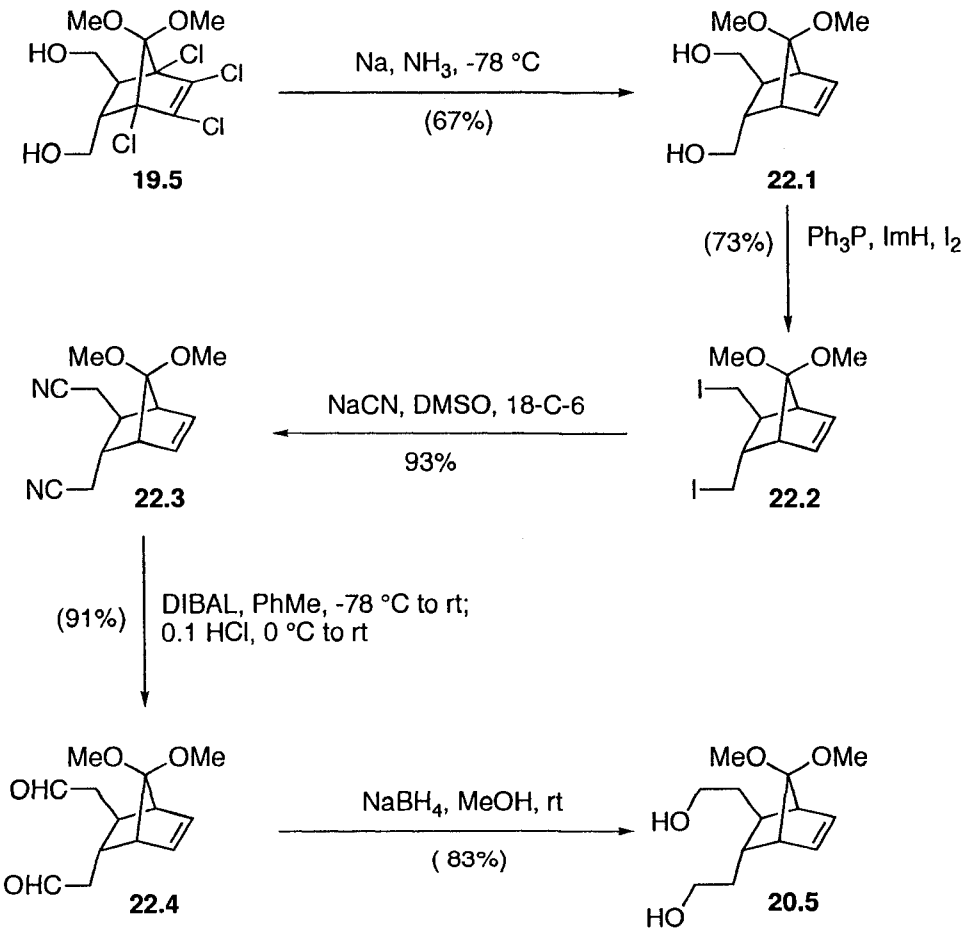
SCHEME 21



Obviously, an 11 day reaction period at nearly 200 °C, using a steel bomb, was inconvenient. Moreover, *trans*-β-hydromuconic acid **21.1** is quite expensive, and so this sequence was abandoned.

Eventually, a five-step route was developed to produce the homologated diol **20.5** from **19.5** in high and reproducible yield (Scheme 22).

SCHEME 22

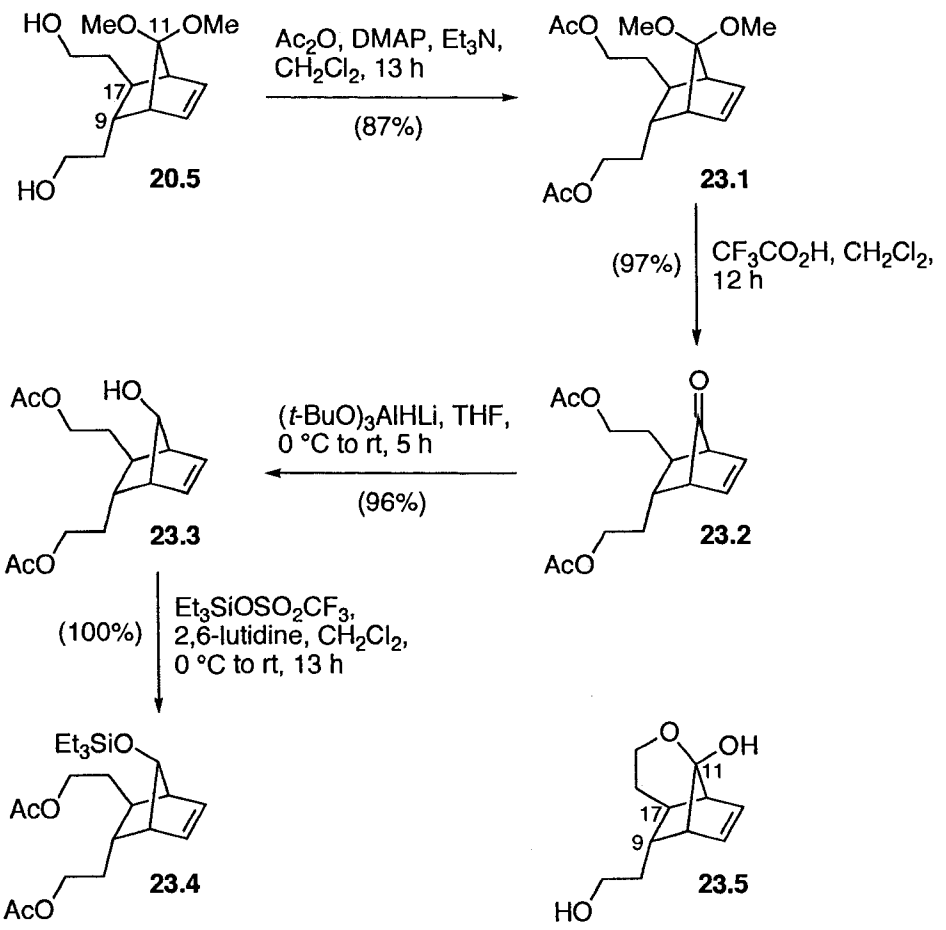


At the beginning, attempts were made by Dr. Che-Chien Chang of this laboratory to replace both -OH groups of **19.5** by iodine or to convert them into mesylates so as to be in a position to carry out a nucleophilic displacement with cyanide ion. However, this first approach was not successful. It was not clear whether the sterically demanding chlorine atoms in **19.5** or an inductive effect of those halogens inhibited the desired substitution. Based on these possibilities, it was decided to remove all four chlorine atoms from **19.5** at the very beginning. The experiments with this new approach were amply rewarded, as the diol **20.5** could be formed in high yield using inexpensive reagents. Diol **19.5** was dehalogenated with Na in liquid ammonia at -78 °C to produce **22.1** which was transformed into diiodide **22.2** by Appel-type reaction. Both iodides were displaced in high yield by the one carbon synthon $^{-}$CN, using NaCN and DMSO in the presence of a catalytic amount of 18-crown-6. The bis cyanide **22.3** was reduced smoothly to bis aldehyde **22.4** using DIBAL, and then further reduction by $NaBH_4$ afforded the diol **20.5**. This five step sequence gave an overall yield of 34% and each step was easily reproducible.

Unlike the two other aldehydes **20.1** and **20.3**, the intermediate aldehyde **22.4** (Scheme 22) which does not have four chlorine atoms was stable and easy to handle. In my own work I adopted this method.

With a viable route in hand to prepare multigram

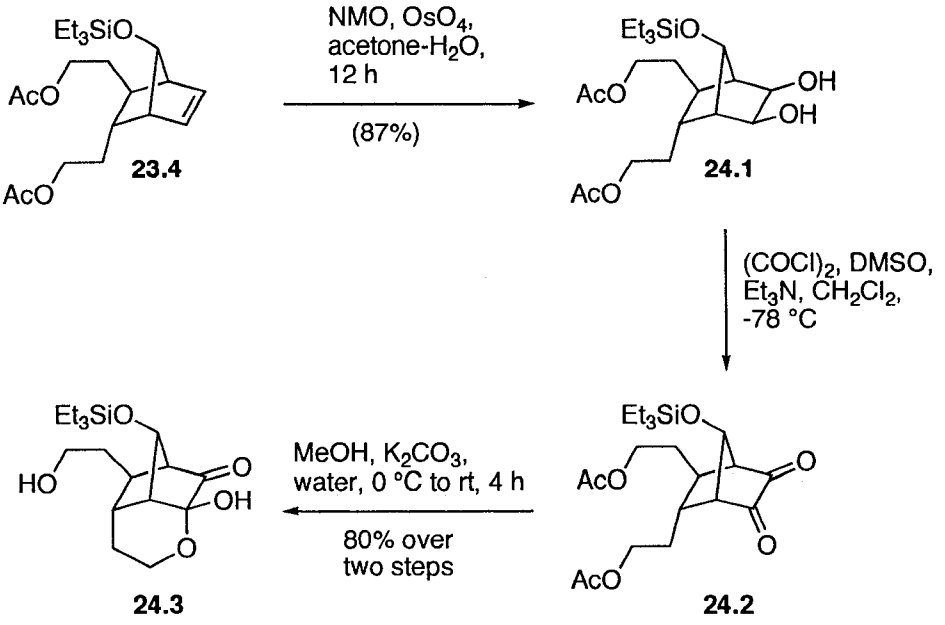
SCHEME 23



quantities of **20.5**, we were ready to generate the cyclic ether ring that is present in CP-263,114 (**2**). The homologated diol **20.5** was bis-acetylated using acetic anhydride and DMAP and this step was followed by acid hydrolysis of the acetal **23.1** to release ketone **23.2** (Scheme 23). The acetylation step prior to acid hydrolysis was necessary in order to prevent formation of the undesired hemiacetal **23.5**.

Facially selective reduction of ketone **23.2** to alcohol **23.3** was accomplished by slow addition of $(t\text{-BuO})_3AlHLi$ in THF at 0 °C. The facial selectivity is important in order to avoid steric congestion on the same side as the carbon-carbon double bond. The secondary alcohol of **23.3** was protected by silylation to avoid premature fragmentation (see later).

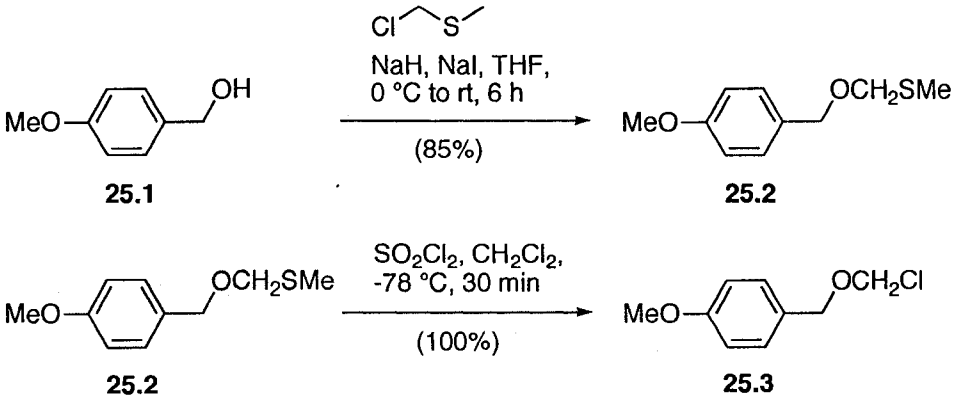
SCHEME 24



Olefin **23.4** was stereoselectively dihydroxylated (catalytic OsO_4, NMO) to furnish vicinal diol **24.1** (Scheme 24) whose oxidation under Swern conditions gave diketone **24.2.** This diketone is unstable to silica gel. Therefore, the crude diketone was immediately exposed to K_2CO_3-MeOH-water for deacetylation, leading to hemiacetal **24.3.**

The next task was to protect the primary hydroxyl group of **24.3** in presence of the sensitive tertiary hemiacetal hydroxyl. Initially, PMBCl (*p*-methoxybenzyl chloride) was tried but the experiments were unrewarding. It was then found that freshly prepared PmbmCl[32] (4-methoxybenzyloxymethyl chloride) in the presence of *i*-Pr_2NEt served to protect the alcohol as a Pmbm ether without any decomposition of the starting material. When other bases such as *i*-Pr_2NH and Et_3N were tried instead of Hünig's base, extensive decomposition occurred. This protecting group should be removable under mild oxidative conditions.

SCHEME 25

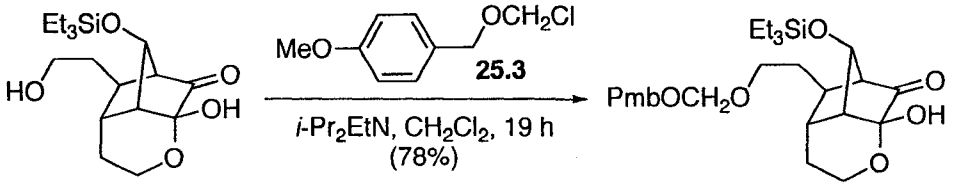


PMBMCl, itself is unstable and has to be prepared immediately before the use by a two step procedure (Scheme 25). Treating the sodium salt of *p*-methoxybenzyl alcohol with chloromethyl methyl sulfide gave the sulfur compound **25.2** which was treated with sulfuryl chloride in methylene

chloride at -78 °C to afford the required chloride **25.3**. Sulfur compound **25.2** and PMBMCl **25.3**, are both too unstable to store and were used right after preparation.

As indicated above, alcohol **24.3** was regioselectively protected as its Pmbm ether by treating it with an excess of PMBM-Cl in CH_2Cl_2 in the presence of *i*-Pr_2NEt at room temperature for about 19 h (Scheme 26).

SCHEME 26



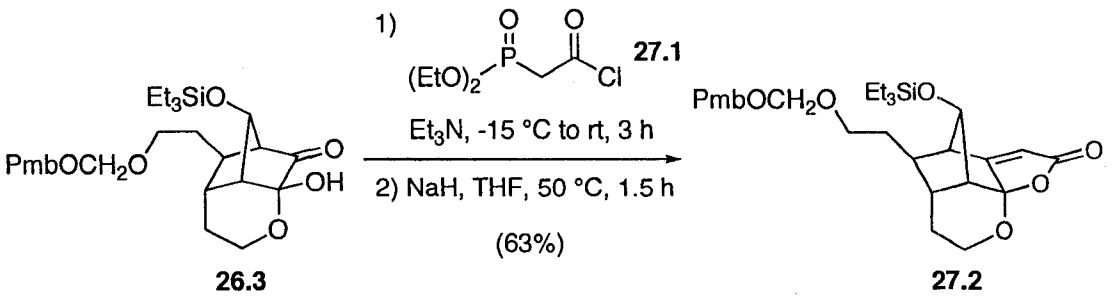
24.3 **26.3**

During this study only the primary hydroxyl group of **24.3** was masked, leaving the tertiary hydroxyl group untouched even in the presence of excess PMBMCl.

The butenolide **27.2** was then synthesized starting from ketol **26.3**, as outlined in Scheme 27.

Conversion of commercially available diethylphosphonoacetic acid into its acid chloride **27.1** was done using $(COCl)_2$ and a catalytic amount of DMF in CH_2Cl_2. Esterification of alcohol **26.3** with acid chloride **27.1** was then accomplished in the presence of Et_3N. The intermediate

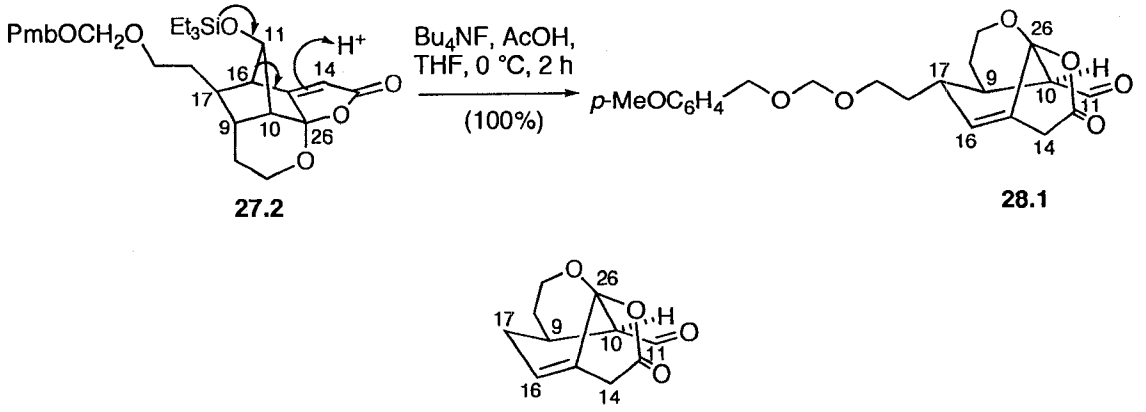
SCHEME 27



26.3 **27.2**

phosphonate is very susceptible to hydrolytic reversal to **26.3**, and so the Wittig olefination was done *in situ* under reflux, without isolation of the phosphonate, to yield butenolide **27.2**.

SCHEME 28



27.2 **28.1**

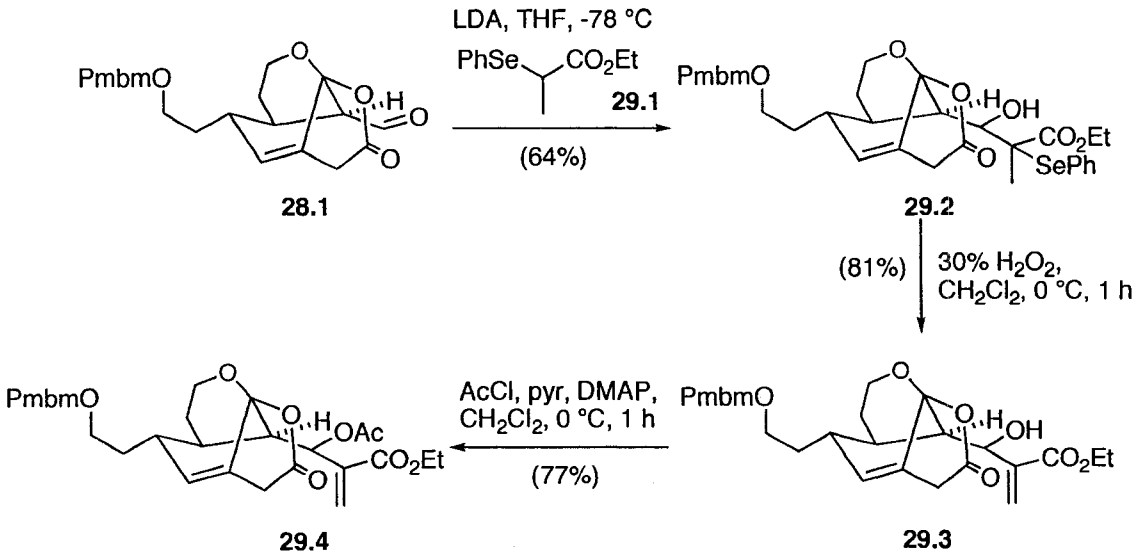
28.2

Desilylation of butenolide **27.2** with fluoride ion, caused spontaneous strain-assisted fragmentation to release the required aldehyde **28.1** in quantitative yield as a single isomer (Scheme 28). The structure of **28.1** was

determined by extensive NMR studies as well as by NMR comparison with **28.2** which had been made during previous studies in this laboratory[27] and whose structure was established by X-ray analysis.

The precursor for the planned intramolecular conjugate displacement (ICD) reaction was prepared in three steps starting from aldehyde **28.1** (Scheme 29). After deprotonation of seleno ester **29.1** with LDA at -78 °C, the selenium-stabilized carbanion was added to aldehyde **28.1**. This reaction led to a mixture of two products **29.2** (5:1) which were separable by flash chromatography (Scheme 29). The stereochemistry at the hydroxy-bearing carbon was not determined. Subsequent selenoxide fragmentation gave the corresponding allylic alcohol **29.3** which was acylated using AcCl to form **29.4**. In principle, the allylic alcohol might

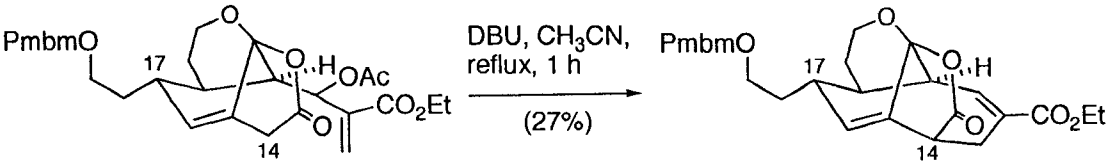
SCHEME 29



be accessible by Morita-Baylis-Hillman reaction, if aldehyde epimerization does not occur, but this approach was not tried.

Treatment of the resulting alkene **29.4** with a base, such as DBU in refluxing CH_3CN afforded the carbocycle **30.1** (Scheme 30). The allylic leaving group and the classical Michael acceptor appear to be mutually reinforcing in this metal-free carbocyclization. The yield was poor, but we did not attempt to optimize it as this was simply a model study.

SCHEME 30

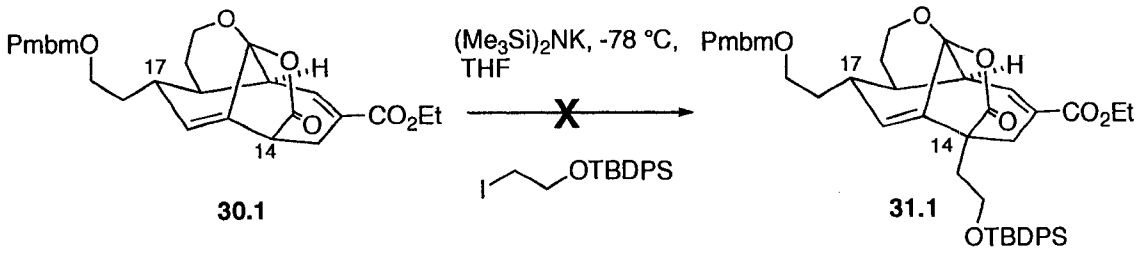


29.4 **30.1**

The above experiments accomplished the synthesis of an analog of the natural core structure of CP molecules 1 and **2**. The analog **30.1** has the required functional group at C-17 but it does not have the other important functionality at C-14 for the synthesis of the complete core structure.

With lactone **30.1** in hand, attempts were made to alkylate it at C-14 (Scheme 31), but the desired product **31.1** was not obtained. Consequently, we turned our attention to a route in which the side chain at C-14 is

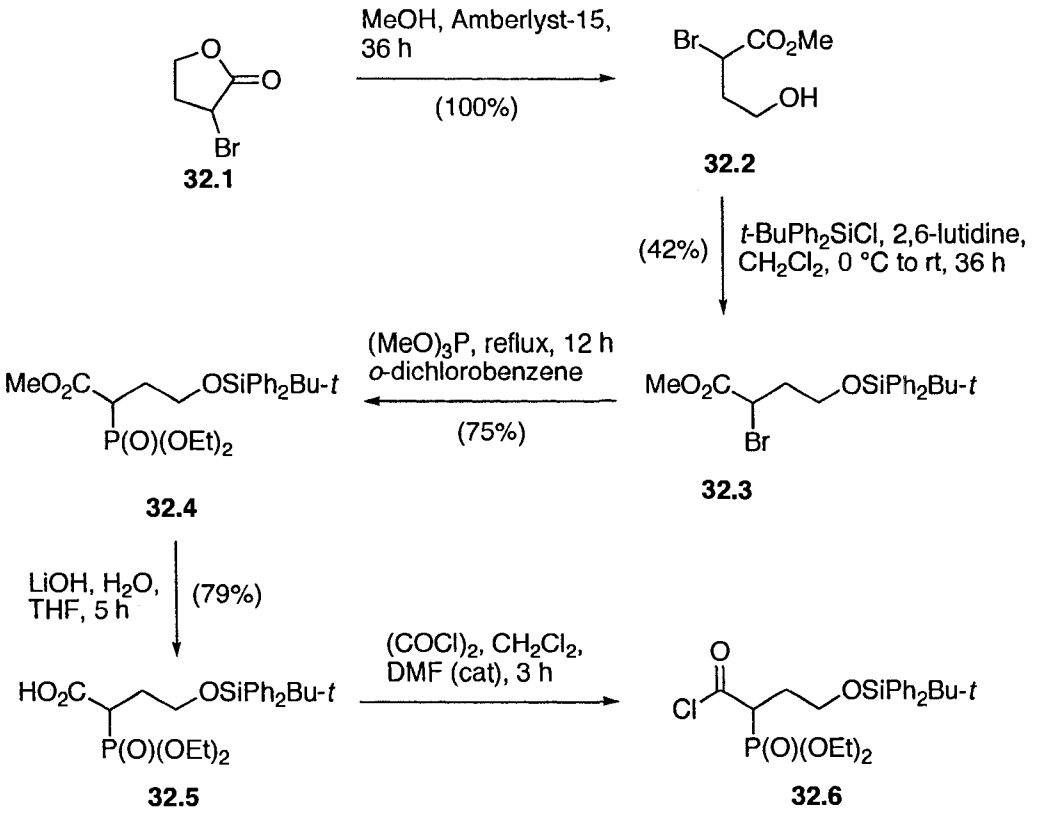
SCHEME 31



introduced at an earlier stage.

We planned to attach the eventual C-14 substituent during the synthesis of the butenolide subunit. For this purpose it was necessary to synthesize the acid chloride **32.6** and this was achieved in five steps starting from *2*-bromo-γ-butyrolactone **32.1** (Scheme 32). Solvolytic cleavage of the lactone ring in the presence of Amberlyst-15 and MeOH afforded the corresponding methyl ester **32.2.** In this reaction, the carbon-bromine bond remained unaffected. Compound **32.2** is known and can also be synthesized by photoirradiation of α-bromobutyrolactone.[33] The primary alcohol was protected as its *tert*-butyldiphenylsilyl derivative **32.3** albeit in low yield. Decomposition occurred during the aqueous NH_4Cl workup. Refluxing the α-bromo ester with trimethyl phosphite in 1,2-dichlorobenzene served to generate the α-phosphonoester **32.4** which was hydrolyzed by LiOH in aqueous THF to yield acid **32.5.** This acid was then transformed into the corresponding acid chloride using $(COCl)_2$ and a catalytic amount of DMF in CH_2Cl_2.

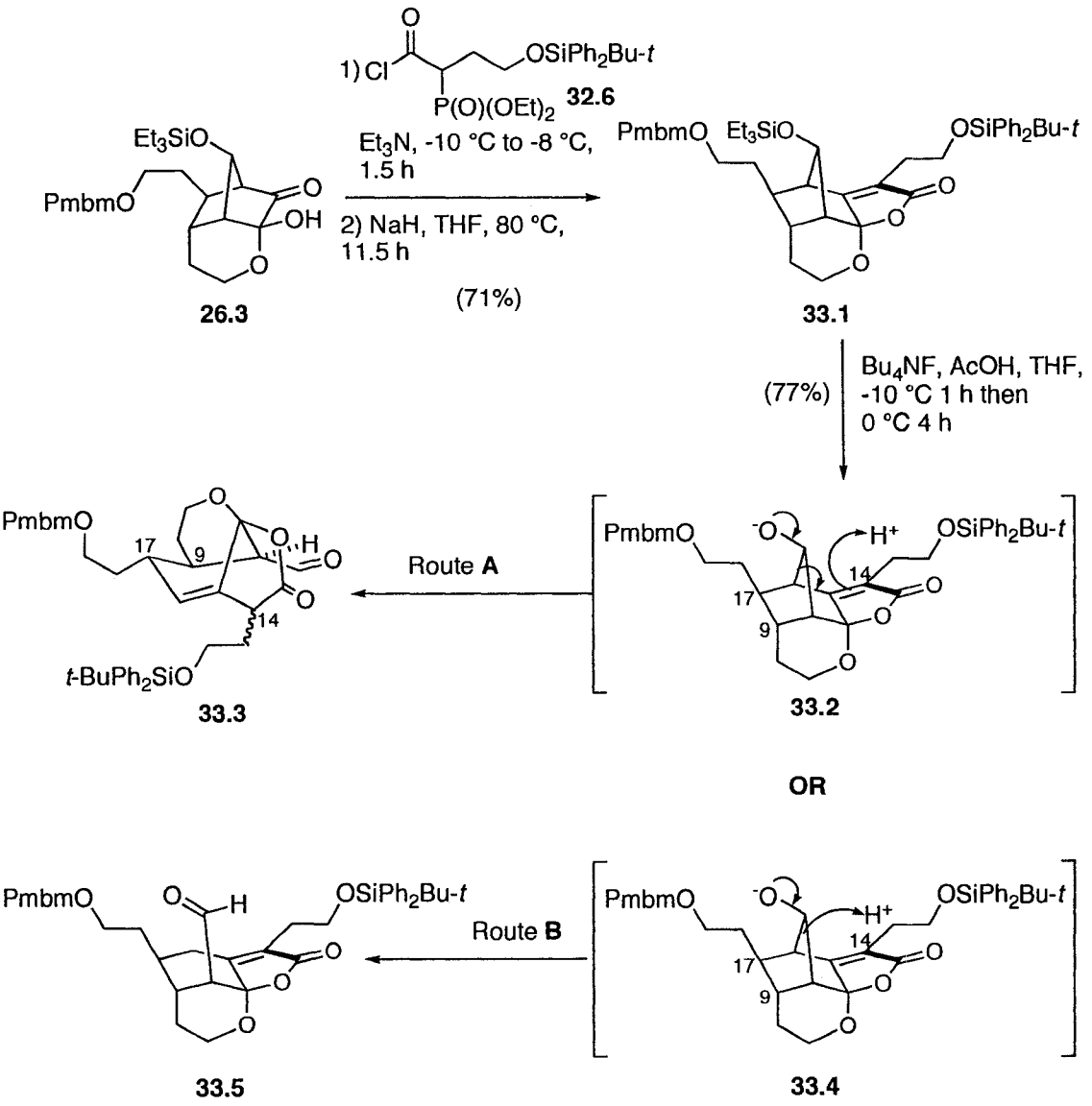
SCHEME 32



The acid chloride **32.6**, prepared in situ from freshly recrystallized acid **32.5**, was treated with ketol **26.3** in order to form an ester. The intermediate phosphonate is very sensitive to water and has a tendency to undergo hydrolytic reversal to ketol **26.3**. For this reason, without isolation the intermediate phosphonate ester was subjected to Horner-Emmons-Wadsworth conditions (NaH, reflux, THF, 80 °C, 11.5 h) to afford the desired butenolide **33.1** (Scheme 33). This butenolide already has the required side chain at C-14. Conversion of the ketol into the butenolide required a longer reaction time and higher

temperature than for the conversion **26.3** → **27.2** shown in Scheme 27. Presumably, steric congestion is responsible in the present case. We assumed that fluoride ion assisted fragmentation reaction of **33.1** would be straightforward as

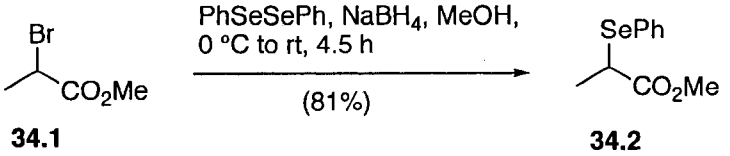
SCHEME 33



was the case with **27.2**. However, **33.1** behaved differently and, in order to obtain the desired aldehyde **33.3** by route **A** of Scheme 33, the temperature had to be kept between -10 °C and 0 °C and it was found that the amount of Bu_4NF should be no more than 1.1 equiv. If the temperature is not maintained carefully, then the undesired aldehyde **33.5** becomes the major product (see route B of Scheme 33). An excess of Bu_4NF, or a longer reaction time or a higher temperatures (> 0 °C) gives a large amount of what we assume to be the primary alcohol resulting from desilylation of the C-14 side chain (H instead of $SiPh_2Bu$-*t* in **33.3**). The material was not characterized, however, and our assumption is based just on its high chromatographic polarity. Aldehyde **33.3** was a 3:2 mixture of C-14 diastereomers.

With optimized conditions for fragmentation in hand, we turned our attention to the synthesis of the natural core structure of CP-225,917 (**1**).

SCHEME 34



34.1 **34.2**

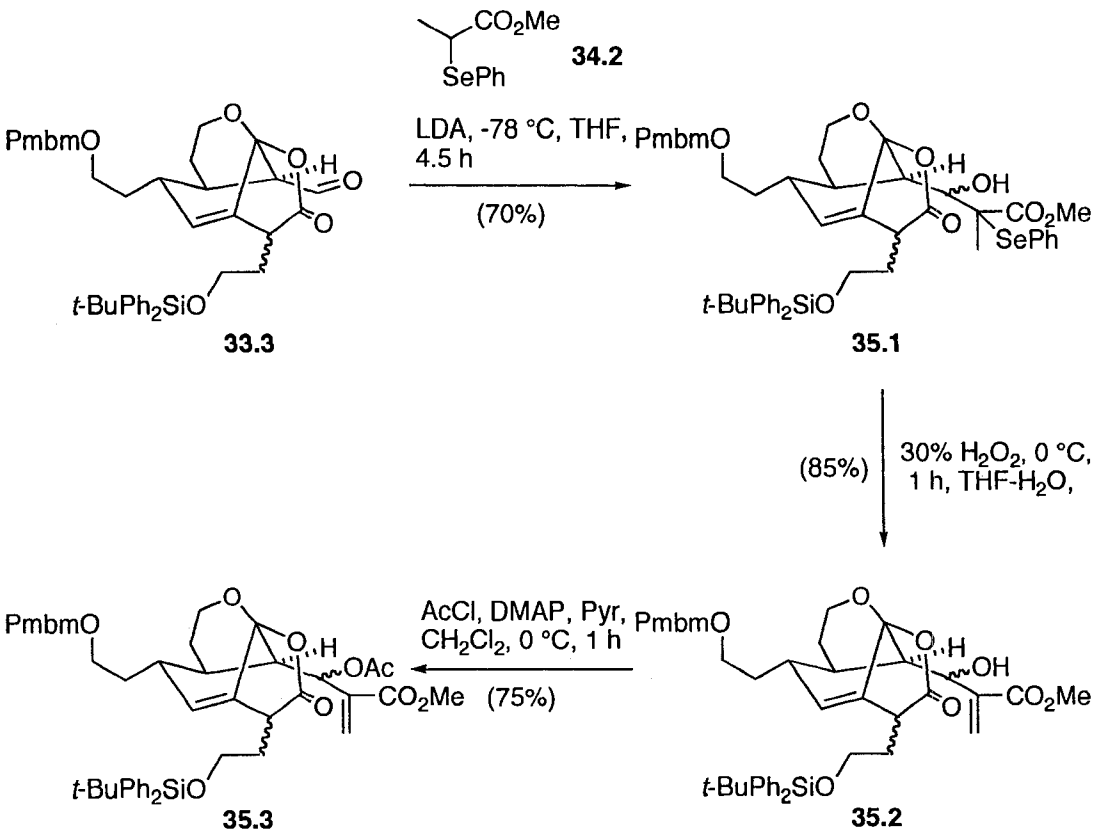
To prepare the Baylis-Hillman subunit, the selenium-mediated method is a reliable route,[34] and for synthesizing

the ICD reaction precursor **35.3**, the required methyl 2-(phenylseleno)propionate **34.2** was made from methyl 2-bromopropionate **34.1** by displacing the bromine with the reagent made from PhSeSePh and $NaBH_4$ in MeOH (Scheme 34). We had previously used the ethyl ester but, as our supply was exhausted we decided to make the methyl ester as it would lead to simpler NMR spectra.

Aldehyde **33.3** was alkylated with the lithium salt derived from **34.2** and the aldol products **35.1** were isolated as a mixture of isomers. Without separation, the isomer mixture was advanced to the next step. Phenylseleno esters **35.1** were oxidized with H_2O_2 and the resulting selenoxide fragmentation produced the Baylis-Hillman adduct **35.2** as an inseparable mixture of C-14 isomers. The allylic hydroxyl group was acetylated to prepare it for the subsequent ICD reaction (Scheme 35). Work in this laboratory has shown that the selenium-based method is much more reliable than the classical Baylis-Hillman conditions. Throughout the series **35.1**→**35.2**→**35.3** the products were chromatographically inseparable mixtures of isomers.

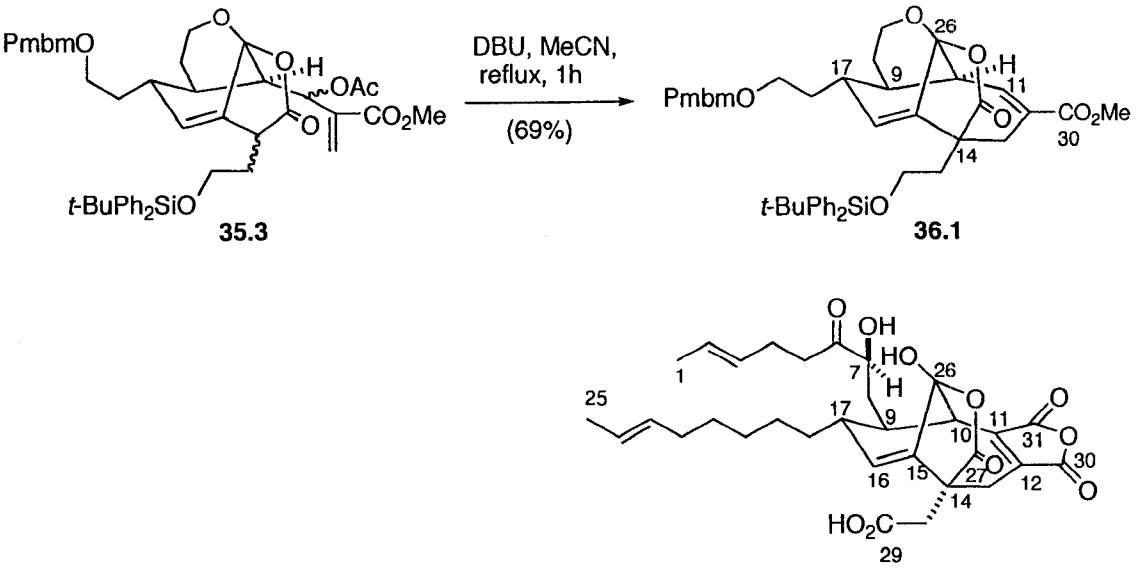
Compounds **35.3** were subjected without separation to the ICD reaction. In this study, the electron-withdrawing group in the acceptor double bond was a methyl ester and the allylic leaving group was an acetate. When the alkene **35.3** was treated with DBU in refluxing CH_3CN for 1 h, it cyclized smoothly to afford the bicyclic natural core structure **36.1** of CP molecules **1** and **2** as a single isomer.

SCHEME 35



The core structure **36.1** is highly functionalized with side chains at C-17, C-9 and C-14. The product has a classical Michael acceptor, which we hope can be manipulated further to build up the anhydride unit required to complete the total synthesis of 1.

SCHEME 36



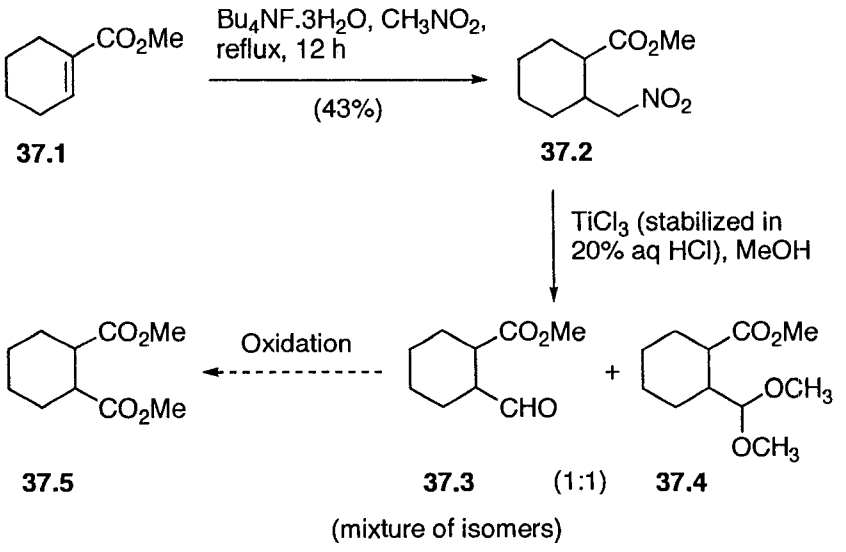
1 Phomoidride A (CP-225,917): C-7 = *S*

After synthesizing the highly functionalized core structure, we decided to make the maleic anhydride unit of the CP molecules. The core structure **36.1** has an α,β-unsaturated methyl ester at C-11, C-12 and C-30 and one more carbon needs to be incorporated to form C-31 so as to build up the anhydride. We initiated a model study to make the maleic anhydride subunit from a substrate containing an α,β-unsaturated methyl ester.

For the model study, methyl 1-cyclohexene-1-carboxylate **37.1** was synthesized from cyclohexanecarboxylic acid according to the literature procedure.[35] When the ester **37.1** was treated with $Bu_4NF.3H_2O$ as a base in refluxing CH_3NO_2, the Michael addition product **37.2** was isolated as a single isomer (Scheme 37). We then attempted

to convert the nitro group of **37.2** to an aldehyde using aqueous $TiCl_3$ and MeOH.[36] The desired aldehyde **37.3** was obtained as a mixture of stereoisomers along with the corresponding acetal **37.4** (1:1). Further oxidation of the aldehyde would lead to the diester **37.5**, but this possibility was not pursued because the $TiCl_3$-mediated oxidation of the nitro group of **37.2** gave a very low yield as well as a mixture of inseparable isomers. Also the acidic conditions seem quite harsh for use on CP-like molecules.

SCHEME 37

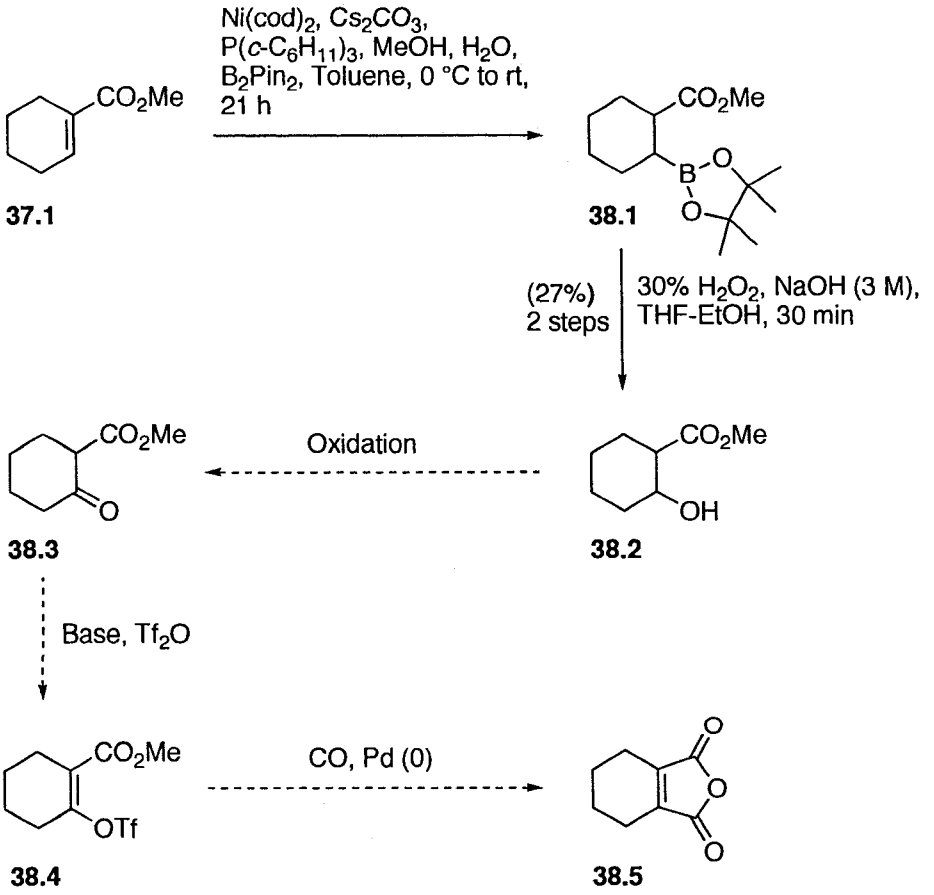


An alternative and better plan was to convert the unsaturated ester into the β-hydroxy ester **38.2** (Scheme 38). The hydroxyl group would then be oxidized to form the β-keto ester **38.3** and this step would be followed by formation of

enol triflate **38.4.** Subsequent carbonylation using CO and Pd(0) would then serve to generate the desired maleic anhydride **38.5.**

To implement this plan, the first step was β-boration of **37.1** using Ni(0) as a catalyst and bis(pinacolato)diboron in PhMe at room temperature.[37] The boronic ester **38.1** was not purified by chromatography due to its instability on silica gel. After workup, the crude boronic ester **38.1** was oxidized by basic H_2O_2 to afford β-

SCHEME 38

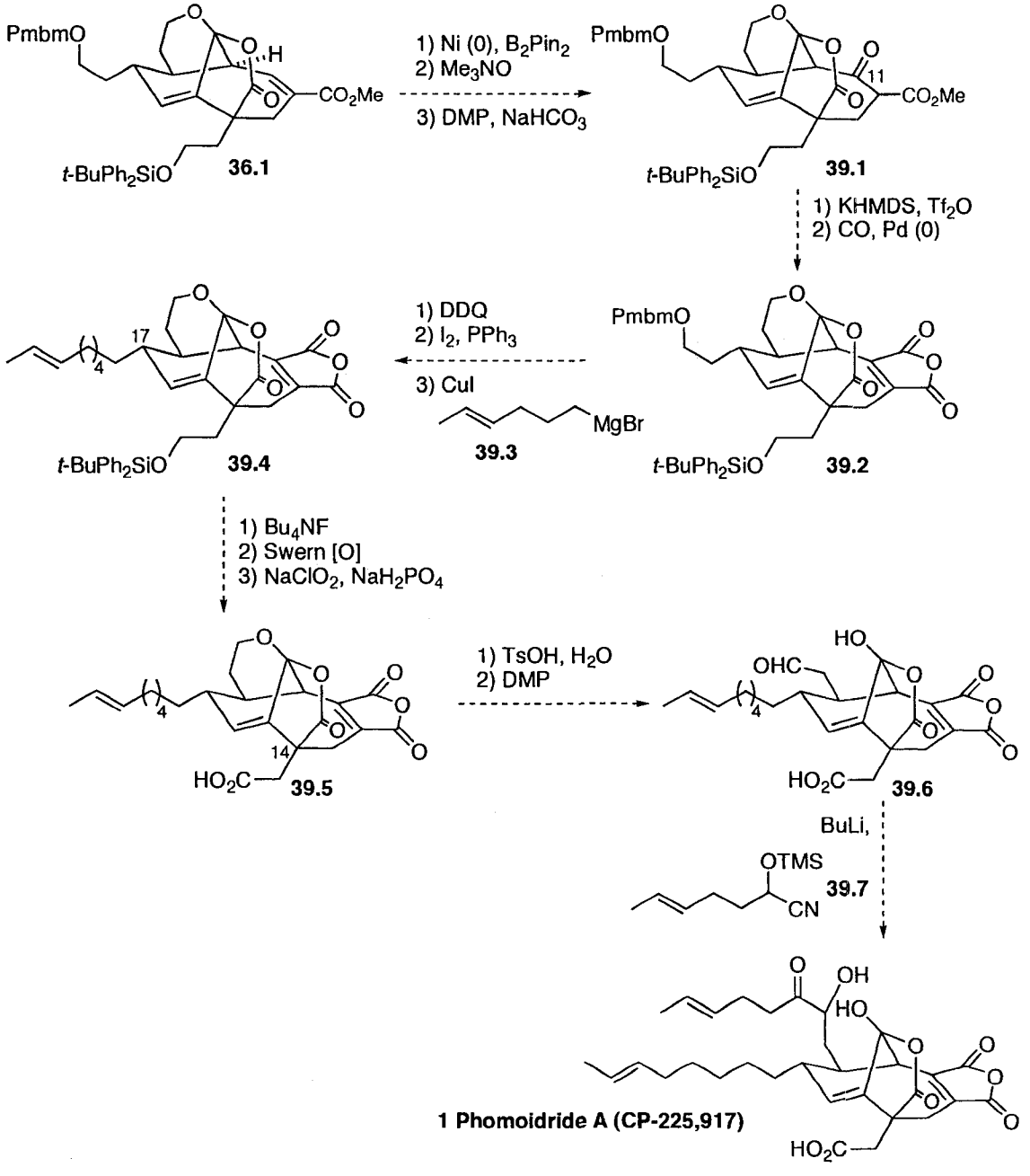


hydroxy ester **38.2** as a single isomer. The yield was low but the reaction was not optimized. This conjugate boron addition should be possible in the presence of a bridgehead olefin which is part of the core structure **36.1** of CP molecules.

Further investigations along these lines leading to the total synthesis of CP-225,917 (**1**) are currently underway in these laboratories.

3. FUTURE WORK

SCHEME 39

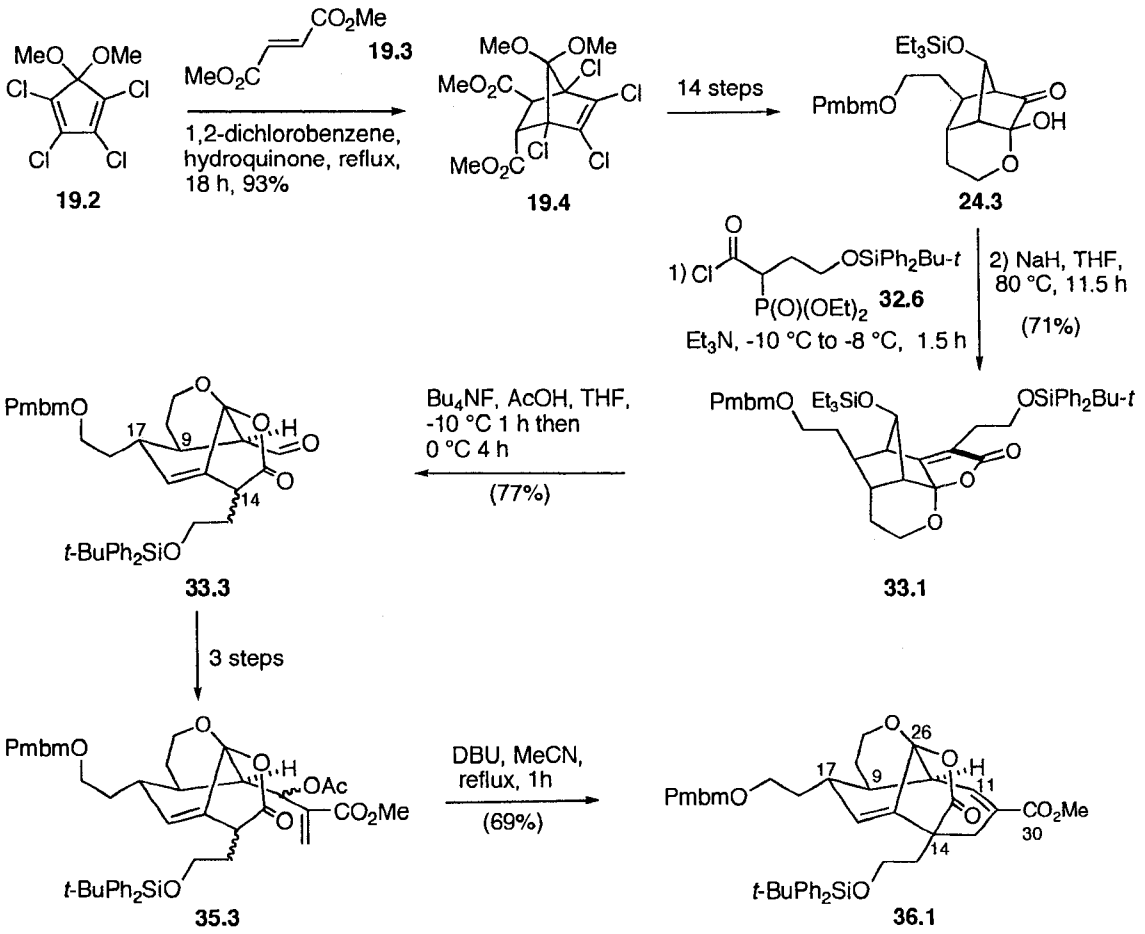


It is our hope that CP-225,917 (**1**) can be synthesized from the functionalized core structure **36.1** according to the plans pictured in Scheme 39. On the basis of the successful model study in Scheme 38, the α,β-unsaturated methyl ester unit in **36.1** should be convertible into a β-hydroxy ester via Ni(0)- and B_2Pin_2-mediated β-boration and subsequent oxidation.[37] Oxidation of the hydroxyl group at C-11 to a ketone will give β-keto ester **39.1**. At that point conversion to an enol triflate, followed by Pd(0) catalyzed carbonylation, would furnish the maleic anhydride unit (**39.1** → **39.2**). It should be possible to install the olefin side chain at C-17 (**39.2** → **39.4**) by following the sequence: i) deprotection of the PMBM ether with DDQ. ii) transformation of the primary hydroxyl group to an iodide by reaction with Ph_3P and I_2 and iii) organocuprate mediated homologation using the cuprate derived from the Grignard reagent **39.3**. The required carboxylic acid group at C-14 can be unmasked by Bu_4NF assisted deprotection of the silyl ether **39.4** and then a two-step oxidation will lead to acetal **39.5**. Acid catalyzed cleavage of the cyclic acetal **39.5**, followed by Dess-Martin oxidation will produce aldehyde **39.6**. The umpolung chemistry[38] with cyanohydrin **39.7** will furnish the target compound CP-225,917 (**1**), although we are not certain if stereochemical adjustment of the resulting alcohol will be required.

4 CONCLUSION

In summary, my research has developed a route to the highly functionalized natural core structure of CP-225,917 (**1**) in seventeen linear steps in 2.3% overall yield, starting from 1,1-dimethoxy-2,3,4,5-tetrachlorocyclopentadiene. A summary of the route to our most advanced compound (**36.1**) is given in Scheme 40.

SCHEME 40

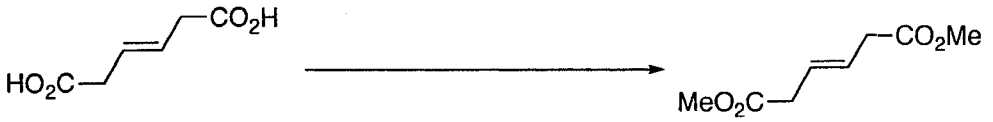


The route is based on two novel methodologies: fluoride-initiated and strain-assisted fragmentation (**33.1→33.3**) and a metal-free all carbon intramolecular displacement (ICD) reaction (**35.3→36.1**).

In a simple model study, an α,β-unsaturated ester has been converted into a β-hydroxy ester and this route may solve the challenging problem of constructing the maleic anhydride unit present in CP molecules. Further synthetic efforts to these ends are underway in this laboratory.

5. Experimental

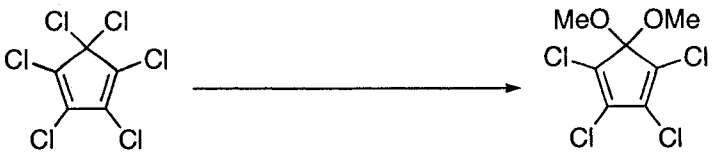
(*E*)-Hex-3-enedioic acid dimethyl ester (21.2).[30]



21.1 **21.2**

Concentrated H_2SO_4 (0.1 mL) was added to a stirred solution of **21.1** (0.21 g, 1.46 mmol) in MeOH (10 mL) at room temperature and the mixture was then heated at 70 °C for 12 h and then cooled. The MeOH was evaporated and the residue was diluted with brine (3 mL) and extracted with Et_2O (2 x 10 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (10 mL), water (10 mL) and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (3 x 15 cm), using 1:1 EtOAc-hexane, gave **21.2** (0.21 g, 84%) as a yellow oil: FTIR (CH_2Cl_2 cast) 3002, 2956, 2847, 1740, 1437, 1410, 1255, 1198, 1165, 1012 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.08 (dd, *J* = 3.8, 1.9 Hz, 4 H), 3.67 (s, 6 H), 5.66-5.71 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 37.6 (t), 51.8 (q), 125.9 (d), 171.9 (s); exact mass *m/z* calculated for $C_8H_{12}O_4$ 172.07356, found 172.07378.

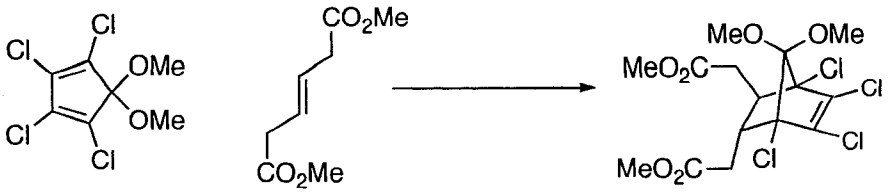
1,2,3,4-Tetrachloro-5,5-dimethoxy-cyclopenta-1,3-diene (19.2).[28]



19.1 **19.2**

KOH (14 g, 0.25 mol) in MeOH (80 mL) was added dropwise over 2 h to a stirred solution of **19.1** (30 g, 0.11 mol) in MeOH (95 mL) at room temperature. The reaction mixture was stirred for an additional 2 h and then poured onto chopped ice (400 mL). After the ice had melted, the mixture was extracted with CH_2Cl_2 (3 x 35 mL) and the combined organic extracts were dried (Na_2SO_4) and evaporated. The residue was distilled through a vacuum-jacketed Vigreaux column at 65 °C under vacuum (0.5 mm Hg) to yield **19.2** (24 g, 83%) as a yellow oil: FTIR ($CHCl_3$ cast) 3003, 2951, 2839, 1644, 1614, 1457, 1314, 1244, 1213, 1175, 1127, 1099, 1067 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.35 (s, 6 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 51.9 (q), 104.7 (s), 128.5 (s), 129.4 (s); exact mass (electrospray) *m/z* calculated for $C_7H_6Cl_4NaO_2$ (M + Na) 284.90141, found 284.90151.

(1*R*,2*S*,3*S*,4*S*)-rel-(1,4,5,6-Tetrachloro-7,7-dimethoxy-3-(methoxycarbonylmethyl)bicyclo[2.2.1]hept-5-en-2-yl)acetic Acid Methyl Ester (21.4).



19.2 **21.2** **21.4**

Dimethyl *trans*-3-hexene-1,6-dioate **21.2** (1.81 g, 10.5 mmol) was added to a solution of 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene **19.2** (5.0 g, 19 mmol) in decahydronaphthalene (1.6 mL) in a steel bomb. The bomb was purged with Ar for 20 min, then sealed and heated in an oil bath at 190 °C for 12 days, and then allowed to cool. The reaction mixture was transferred with CH_2Cl_2 (10 mL) and filtered through a pad of silica gel, using CH_2Cl_2 (50 mL). Evaporation of the filtrate and flash chromatography of the black residue over silica gel (4 x 31 cm), using 1:7 EtOAc-hexane, gave **21.4** (4.0 g, 87%) as a yellow oil: FTIR (CH_2Cl_2 cast) 2995, 2953, 2846, 1740, 1607, 1438, 1607, 1438, 1376, 1321, 1272, 1202, 1173 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.16-2.32 (m, 2 H), 2.66-3.04 (m, 4 H), 3.54 (s, 3 H), 3.60 (s, 3 H), 3.68 (s, 3 H), 3.69 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 35.0 (t), 35.4 (t), 48.9 (q), 49.2 (q), 51.4 (d), 51.9 (d), 51.9 (q), 52.6 (q), 77.6 (s), 77.7 (s), 111.5 (s), 128.7 (s), 131.8 (s), 172.1 (s), 172.9 (s); exact mass (electrospray) *m/z* calculated for $C_{15}H_{18}Cl_4NaO_6$ (M + Na) 456.97497, found 456.97549.

(1*R*,2*S*,3*S*,4*S*)-rel-2-[1,4,5,6-Tetrachloro-3-(2-hydroxyethyl)-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-yl]ethanol (20.4).

21.4 **20.4**

A solution of crude **21.4** (3.0 g, 6.9 mmol) in THF (15 mL) was added dropwise by syringe pump over 1 h to a stirred solution of $LiAlH_4$ (0.57 g, 15 mmol) in THF (14 mL). The mixture was refluxed for 4 h, cooled to room temperature and quenched with NaOH (2 N, 5 mL). The mixture was passed through a pad of silica gel (6 x 4 cm) covered by $MgSO_4$, using Et_2O as a rinse. Evaporation of the solvent and flash chromatography of the residue over silica gel (4.5 x 12 cm), using 1:1 EtOAc-hexane, gave **20.4** (2.05 g, 79%) as a yellow oil: FTIR (CH_2Cl_2, cast) 3349, 2950, 2882, 2845, 1604, 1456, 1265, 1199, 1142, 1110, 1059, 1030 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.35-1.46 (m, 1 H), 1.78 (dd, J = 11.2, 5.6 Hz, 1 H), 1.87-1.98 (m, 2 H), 2.21-2.32 (m, 1 H), 2.49-2.56 (m, 1 H), 2.72 (br s, 2 H), 3.54 (s, 3 H), 3.57 (s, 3 H), 3.68-3.76 (m, 1 H), 3.75-3.85 (m, 3 H); ^{13}C NMR (CD_2Cl_2, 125 MHz) δ 33.6 (t), 33.8 (t), 49.0 (q), 51.0 (q), 51.4 (d), 52.6 (d), 60.8 (t), 61.9 (t), 78.6 (s), 78.7

(s), 111.7 (s), 128.8 (s), 131.7 (s); exact mass (electrospray) *m/z* calculated for $C_{13}H_{18}Cl_4NaO_4$ (M + Na) 400.98514, found 400.98549.

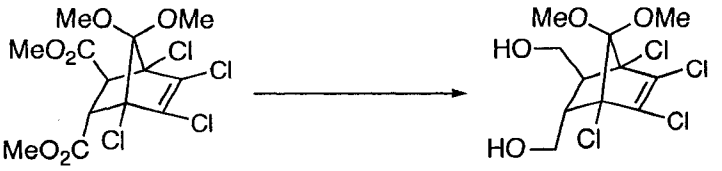
(1*R*,2*R*,3*R*,4*S*)-rel-1,4,5,6-Tetrachloro-7,7-dimethoxy-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic Acid Dimethyl Ester (19.4).

19.2 **19.4**

A mixture of 1,1-dimethoxy-2,3,4,5-tetrachlorocyclopentadiene **19.2** (8.56 g, 32.4 mmol), dimethyl fumarate (4.60 g, 31.9 mmol) and hydroquinone (30 mg) in *o*-dichlorobenzene (3 mL) was refluxed for 18 h. The mixture was cooled to room temperature and applied directly to a column of flash chromatography silica gel (4.5 x 23 cm). The column was developed with 1:7 EtOAc-hexane to give the adduct **19.4** (12 g, 93%) as a viscous liquid: FTIR (CH_2Cl_2 cast) 2997, 2954, 2846, 1740, 1608, 1437, 1243, 991 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.22 (d, *J* = 5.2 Hz, 1 H), 3.55 (s, 3 H), 3.57 (s, 3 H), 3.75 (s, 3 H), 3.79 (s, 3 H) 4.06 (d, *J* = 5.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 51.7 (d), 52.4 (q), 52.5 (d), 52.6 (q), 52.7 (q), 53.4 (q), 75.7 (s), 111.65 (s), 129.9 (s), 131.4 (s), 167.6 (s), 169.6 (s);

exact mass (electrospray) *m/z* calculated for $C_{13}H_{14}Cl_4NaO_6$ (M + Na) 428.94367, found 428.94405.

(1*R*,2*S*,3*S*,4*S*)-rel-(1,4,5,6-Tetrachloro-3-hydroxymethyl-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-yl)-methanol (19.5).

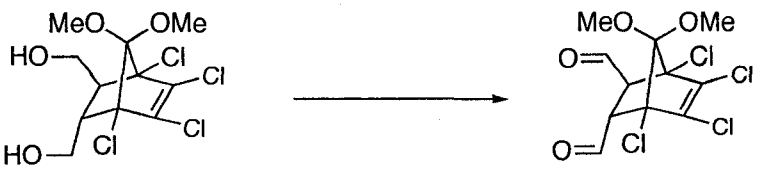


19.4 **19.5**

A solution of **19.4** (8.0 g, 19.6 mmol) in Et_2O (25 mL) was added slowly to a stirred and cooled (0 °C) solution of $LiAlH_4$ (1.29 g, 34.0 mmol) in Et_2O (85 mL). After the addition the ice bath was removed, the solution was allowed to warm to room temperature, and it was then refluxed at 40 °C for 12 h. The stirred mixture was cooled and quenched by sequential addition of EtOAc (5 mL), water (1.5 mL), NaOH (2 N, 1.5 mL) and water (5 mL). After 10 min the mixture was filtered through a pad of silica gel (6 x 5 cm) covered by a layer of $MgSO_4$, using Et_2O as a rinse. Evaporation of the filtrate and flash chromatography of the residue over silica gel (4.5 x 21 cm), using 1:3 EtOAc-hexane, gave **19.5** (4.6 g, 68%) as a white solid: FTIR (CH_2Cl_2 cast) 3328, 2952, 2847, 1605, 1450, 1266, 1199, 1177, 1118, 1039 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.96-2.00 (m, 1 H), 2.67-2.72 (m, 1

H), 2.95 (br s, 2 H), 3.24 (t, J = 10.3 Hz, 1 H), 3.54 (s, 3 H), 3.58 (s, 3 H), 3.92 (t, J = 10.0 Hz, 1 H), 4.00 (dt, J = 10.5, 3.7 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 51.5 (d), 52.7 (d), 53.7 (q), 53.8 (q), 61.9 (t), 62.0 (t), 76.3 (s), 76.5 (s), 111.8 (s), 128.6 (s), 131.7 (s); exact mass (electrospray) m/z calculated for $C_{11}H_{14}Cl_4NaO_4$ (M + Na) 372.95384, found 372.95364.

(1*R*,2*S*,3*S*,4*S*)-rel-1,4,5,6-Tetrachloro-7,7-dimethoxybicyclo[2.2.1]hept-5-ene-2,3-dicarbaldehyde (20.1).

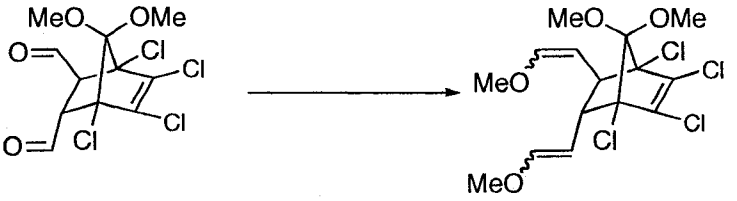


19.5 **20.1**

DMSO (1.33 mL, 18.7 mmol) was added dropwise to $(COCl)_2$ (0.90 mL, 9.4 mmol) in CH_2Cl_2 (12 mL) at -78 °C. After 15 min, a solution of **19.5** (1.09 g, 3.11 mmol) in CH_2Cl_2 (6 mL) was added dropwise over 15 min. Stirring was continued for 1 h, and then Et_3N (3.3 mL, 23.7 mmol) was added dropwise over 5 min. After 1 h, the ice bath was removed and stirring was continued for 20 min. The mixture was quenched with water. The organic layer was separated and passed through a pad of silica gel (4 x 4 cm), using CH_2Cl_2. Evaporation of the filtrate gave the unstable but pure dialdehyde **20.1** (0.91 g, 84%) as a yellow oil: FTIR ($CHCl_3$,

cast) 2954, 2848, 1730, 1606, 1461, 1244, 1207, 1179, 1127, 1033 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.01 (d, *J* = 4.5 Hz, 1 H), 3.79 (dd, *J* = 4.5, 0.3 Hz, 1 H), 3.55 (s, 3 H), 3.79 (s, 3 H), 9.84 (s, 1 H), 9.91 (d, *J* = 0.3 Hz, 1 H); ^{13}C NMR (CD_2Cl_2, 125 MHz) δ 52.1 (d), 53.5 (d), 54.4 (q), 59.3 (q), 75.6 (s), 76.0 (s), 112.7 (s), 130.4 (s), 131.4 (s), 196.6 (d), 197.1 (d); exact mass (electrospray) *m/z* calculated for $C_{11}H_{10}Cl_4NaO_4$ (M + Na) 368.92254, found 368.92253.

(1*R*,2*S*,3*S*,4*S*)-rel-1,2,3,4-Tetrachloro-7,7-dimethoxy-5,6-bis(2-methoxyvinyl)bicyclo[2.2.1]hept-2-ene (20.2).



20.1 **20.2**

A solution of *t*-BuOK (1.09 g, 9.23 mmol) in THF (7 mL) was added to a stirred and cooled (0 °C) suspension of $MeOCHPh_3PCl$ (3.25 g, 9.48 mmol) in THF (15 mL). Stirring was continued for 15 min and then a solution of **20.1** (0.91 g, 2.6 mmol) in THF (6 mL) was added dropwise over 20 min. After the addition the mixture was stirred at 0 °C for 3 h, the ice bath was removed and stirring was continued for 14 h. The mixture was quenched with saturated aqueous $NaHCO_3$ (10 mL) and extracted with Et_2O (3 x 10 mL). The combined

organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (3 x 25 cm), using 1% Et_3N in 1:10 EtOAc-hexane, gave **20.2** (0.48 g, 48%) as a mixture of isomers: FTIR (CH_2Cl_2, cast) 2950, 2842, 1655, 1605, 1394, 1318, 1265, 1212, 1155, 1115, 1039 cm^{-1}.

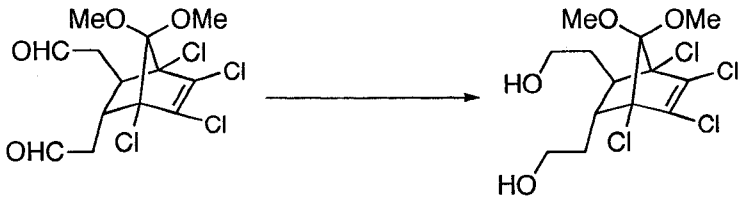
(1*R*,2*S*,3*S*,4*S*)-rel-[1,4,5,6-Tetrachloro-7,7-dimethoxy-3-(2-oxoethyl)bicyclo[2.2.1]hept-5-en-2-yl]acetaldehyde (20.3).

20.2 **20.3**

Hydrochloric acid (40%v/v, 3 mL) was added dropwise over 20 min to a stirred and cooled (0 °C) solution of **20.2** (0.44 g, 1.3 mmol) in THF (9 mL). Stirring was continued at 0 °C for 2 h, the ice bath was removed and stirring was continued for 16 h. The mixture was diluted with water (10 mL) and extracted with Et_2O (10 mL x 3). The combined organic extracts were dried (Na_2SO_4) and evaporated to give the crude unstable **20.3** (0.36 g, 89%) as a yellow oil: FTIR (CH_2Cl_2, cast) 2952, 2845, 2730, 1725, 1607, 1458, 1388, 1265, 1200, 1177, 1121, 1025 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.27 (dd, J = 10.8, 5.6 Hz, 1 H), 2.24-2.51 (m, 1 H),

2.83-2.89 (m, 2 H), 3.10-3.26 (m, 2 H), 3.54 (s, 3 H), 3.61 (s, 3 H), 9.76 (s, 1 H), 9.78 (s, 1 H); ^{13}C NMR (CD_2Cl_2, 125 MHz) δ 44.9 (t), 45.4 (t), 46.6 (q), 47.1 (q), 51.5 (d), 52.7 (d), 111.5 (s), 128.7 (s), 131.8 (s), 199.5 (d), 200.1 (d); exact mass (electrospray) *m/z* calculated for $C_{13}H_{14}Cl_4NaO_4$ (M + Na) 396.95384, found 396.95358.

(1*R*,2*S*,3*S*,4*S*)-rel-2-[1,4,5,6-Tetrachloro-3-(2-hydroxyethyl)-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-yl]ethanol (20.4).



20.3 **20.4**

A solution of crude **20.3** (0.37 g, 0.98 mmol) in Et_2O (15 mL) was added dropwise over 10 min to a stirred and cooled (0 °C) solution of $LiAlH_4$ (55.0 mg, 1.39 mmol) in Et_2O (30 mL). After 2 h, the cold bath was removed and stirring was continued at room temperature for 12 h. The reaction was quenched with NaOH (2 N, 6 mL) and the solution was passed through a pad of silica gel (2 x 3 cm) covered by Na_2SO_4, using Et_2O as a rinse. Evaporation of the solvent and flash chromatography of the residue over silica gel (3 x 15 cm), using 1:1 EtOAc-hexane, gave **20.4** (0.13 g, 31%

over 2 steps) as a yellow oil: FTIR (CH_2Cl_2, cast) 3349, 2950, 2882, 2845, 1604, 1456, 1265, 1199, 1142, 1110, 1059, 1030 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.35-1.46 (m, 1 H), 1.78 (dd, *J* = 11.2, 5.6 Hz, 1 H), 1.87-1.98 (m, 2 H), 2.21-2.32 (m, 1 H), 2.49-2.56 (m, 1 H), 2.72 (br s, 2 H), 3.54 (s, 3 H), 3.57 (s, 3 H), 3.68-3.76 (m, 1 H), 3.75-3.85 (m, 3 H); ^{13}C NMR (CD_2Cl_2, 125 MHz) δ 33.6 (t), 33.8 (t), 49.0 (q), 51.0 (q), 51.4 (d), 52.6 (d), 60.8 (t), 61.9 (t), 78.6 (s), 78.7 (s), 111.7 (s), 128.8 (s), 131.7 (s); exact mass (electrospray) *m/z* calculated for $C_{13}H_{18}Cl_4NaO_4$ (M + Na) 400.98514, found 400.98549.

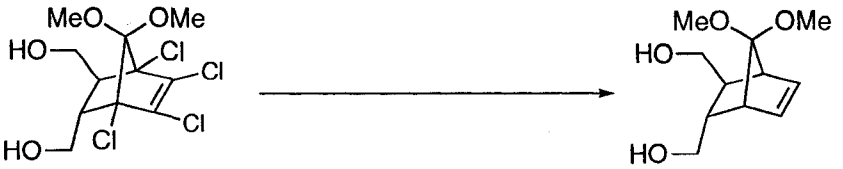
(1*R*,2*S*,3*S*,4*S*)-rel-2-[3-(2-Hydroxyethyl)-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-yl]ethanol (20.5).

20.4 **20.5**

Liquid NH_3 (350 mL), followed by small pieces of Na (1.13 g, 49.4 mmol) were added to a cooled (-78 °C) and stirred solution of **20.4** (1.14 g, 3.0 mmol) in THF (50 mL). The blue solution was stirred for 3 h at -78 °C and then the cold bath was removed. Within 30 min the blue color disappeared, and the mixture was carefully quenched with

NH_4Cl (5 g) and saturated aqueous NH_4Cl (10 mL). The mixture was stirred for 4 h to allow the NH_3 to evaporate. Finally water (20 mL) was added to the residue which was extracted with EtOAc (20 mL x 3). The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (4.5 x 23 cm), using 10% MeOH-EtOAc, gave **20.5** (0.62 g, 86%) as a yellow oil: FTIR (CH_2Cl_2 cast) 3388, 2935, 2832, 1452, 1288, 1226, 1195, 1121, 1061 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.11-1.14 (m, 1 H), 1.36-1.52 (m, 2 H), 1.86-1.92 (m, 2 H), 1.94-2.01 (m, 1 H), 2.08 (br s, 2 H), 2.56 (t, *J* = 1.7 Hz, 1 H), 2.80-2.82 (m, 1 H), 3.13 (s, 3 H), 3.19 (s, 3 H), 3.58-3.72 (m, 4 H), 6.00 (apparent q, *J* = 3.2 Hz, 1 H), 6.24 (dq, *J* = 3.6, 0.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 35.9 (t), 36.8 (t), 39.4 (d), 43.4 (d), 48.3 (q), 48.7 (q), 49.6 (d), 51.6 (d), 61.7 (t), 62.3 (t), 119.1 (s), 130.4 (d), 135.7 (d); exact mass (electrospray) *m/z* calculated for $C_{13}H_{22}NaO_4$ (M + Na) 265.14103, found 265.14099.

(1*R*,2*S*,3*S*,4*S*)-rel-[3-Hydroxymethyl-7,7-dimethoxy-bicyclo[2.2.1]hept-5-en-2-yl]methanol (22.1).

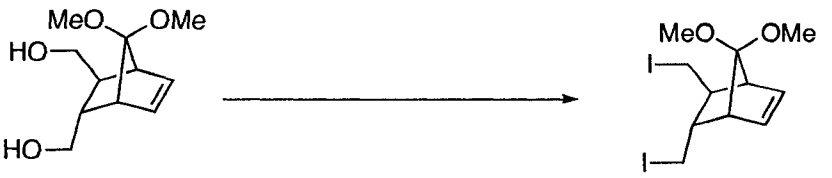


19.5 **22.1**

Liquid NH_3 (600 mL), followed by small pieces of Na (4.9 g, 0.21 mol) were added to a cooled (-78 °C) and stirred solution of **19.5** (4.64 g, 13.2 mmol) in THF (180 mL). The blue solution was stirred for 4 h at -78 °C and then the cold bath was removed. Within 40 min the solution became colorless and the mixture was carefully quenched by adding solid NH_4Cl (22 g) in portions, and the flask was left open for 2 h to allow the NH_3 to evaporate. Finally water (100 mL) was added to the residue which was extracted with EtOAc (50 mL x 3). The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (4.5 x 17 cm), using EtOAc, gave **22.1** (2.0 g, 67%) as a yellow oil: FTIR (neat) 3355, 2938, 2832, 1457, 1286, 1119, 1081, 1061, 1028 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.34-1.39 (m, 1 H), 2.21-2.26 (m, 1 H), 2.67 (s, 1 H), 2.80 (br s, 1 H), 2.88 (s, 1 H), 2.95 (br s, 1 H), 3.10-3.18 [m, including a singlet at δ 3.14 (3 H), 4 H in all], 3.19 (s, 3 H), 3.61-3.65 (m, 1 H), 3.73-3.78 (m, 1 H), 3.85 (t, J = 9.3 Hz, 1 H), 6.00 (dd, J = 6.2, 3.3 Hz, 1 H), 6.27 (ddd, J = 6.2, 3.5, 0.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 43.9 (d), 47.4 (d), 47.5 (d), 47.9 (d), 49.5 (q), 51.9 (q), 64.0 (t), 65.2

(t), 119.0 (s), 130.4 (d), 135.3 (d); exact mass (electrospray) *m/z* calculated for $C_{11}H_{18}NaO_4$ (M + Na) 237.10973, found 237.10988.

(1*R*,2*S*,3*S*,4*S*)-rel-5,6-Di(iodomethyl)-7,7-dimethoxybicyclo[2.2.1]hept-2-ene (22.2).

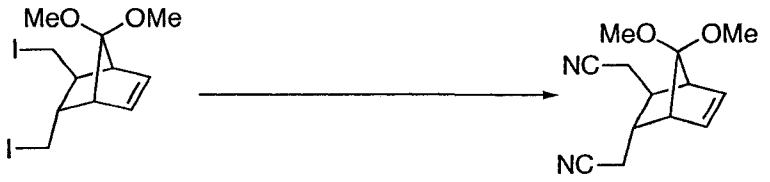


22.1 **22.2**

Ph_3P (6.1 g, 23.3 mmol), I_2 (5.5 g, 21.5 mmol) and imidazole (1.59 g, 68.1 mmol) were added sequentially to a stirred and cooled (0 °C) solution of **22.1** (2.0 g, 9.4 mmol) in CH_2Cl_2 (10 mL) and PhH (50 mL). After 30 min the ice bath was removed and stirring was continued for 12 h. The mixture was diluted with CH_2Cl_2 (75 mL) and washed with water (75 mL) and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (4.5 x 23 cm), using hexane to 1:8 EtOAc-hexane, gave **22.2** (2.93 g, 73%) as a light yellow oil: FTIR (neat) 3062, 2982, 2954, 2934, 2828, 1452, 1424, 1301, 1282, 1248, 1147, 1119, 1076 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.48-1.56 (m, 1 H), 2.30-2.37 (m, 1 H), 2.85 (t, *J* = 10.4 Hz, 1 H), 2.10 (br s, 1 H), 3.18 (s, 3 H), 3.19 (br s, 1 H), 3.22 (s, 3 H), 3.31 (dd, *J* = 9.5, 6.1 Hz, 1 H), 3.46 (t, *J* = 9.0 Hz, 1 H), 3.67

(dd, J = 9.4, 7.4 Hz, 1 H), 6.12 (dd, J = 6.1, 3.2 Hz, 1 H), 6.34 (ddd, J = 6.2, 3.6, 0.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 9.2 (t), 47.8 (d), 49.8 (d), 51.3 (d), 51.5 (d), 51.8 (q), 52.4 (q), 118.6 (s), 130.5 (d), 136.2 (d); exact mass m/z calculated for $C_{11}H_{16}I_2O_2$ 433.92398, found 433.92442.

(1*R*,2*S*,3*S*,4*S*)-rel-(3-Cyanomethyl-7,7-dimethoxy-bicyclo[2.2.1]hept-5-en-2-yl)acetonitrile (22.3).

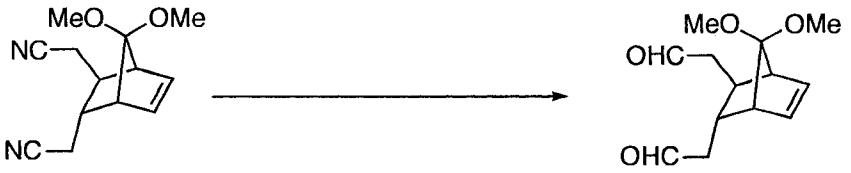


22.2 **22.3**

NaCN (6.63 g, 134.7 mmol), followed by a catalytic amount of 18-crown-6 were added to a solution of **22.2** (2.93 g, 6.75 mmol) in DMSO (50 mL) and the solution was heated at 40 °C for 12 h, then cooled to room temperature, diluted with EtOAc (100 mL) and quenched with water (60 mL). The aqueous layer was extracted with EtOAc (30 x 3 mL) and the combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (4.5 x 16 cm), using 1:1 EtOAc-hexane, gave **22.3** (1.45 g, 93%) as a light yellow oil: FTIR (neat) 2978, 2939, 2246, 1427, 1283, 1240, 1121, 1084, 1049 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.36-1.44 (m, 1 H), 2.15-2.25 (m, 2 H), 2.30-2.40 (m, 1 H), 2.72-2.85 (m, 3 H),

3.06 (br s, 1 H), 3.15 (s, 3 H), 3.22 (s, 3 H), 6.11-6.15 (m, 1 H), 6.34-6.38 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.1 (t), 20.8 (t), 39.3 (d), 42.9 (d), 48.5 (q), 49.2 (q), 49.6 (d), 52.1 (d), 118.3 (s), 118.9 (s), 119.3 (s), 130.9 (d), 136.1 (d); exact mass (electrospray) *m/z* calculated for $C_{13}H_{16}NaN_2O_2$ (M + Na) 255.11040, found 255.11056.

(1*R*,2*S*,3*S*,4*S*)-rel-[7,7-Dimethoxy-3-(2-oxoethyl)-bicyclo[2.2.1]hept-5-en-2-yl]acetaldehyde (22.4).



22.3 **22.4**

DIBAL (1 M in PhMe, 19 mL, 19 mmol) was added dropwise over 20 min to a stirred and cooled (-78 °C) solution of **22.3** (1.48 g, 6.38 mmol) in PhMe (60 mL). Stirring at -78 °C was continued for 1 h and the cold bath was then replaced by an ice bath. Stirring was continued for 30 min, the ice bath was removed and stirring was continued for 10 min. Hydrochloric acid (0.5 N, 105 mL) was added and the mixture was stirred for 18 h. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. The residue was passed through a pad of silica gel (4 x 4 cm), using 1:2 EtOAc-hexane, to afford **22.4**

(1.39 g, 91%) as a yellow oil: FTIR (CH_2Cl_2, cast) 2938, 2831, 2724, 1721, 1121, 1081 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.52 (dd, *J* = 7.0, 5.5 Hz, 1 H), 2.25-2.40 (m, 2 H), 2.53-2.59 (m, 2 H), 2.87-3.06 (m, 3 H), 3.12 (s, 3 H), 3.22 (s, 3 H), 6.02 (dd, *J* = 6.2, 3.3 Hz, 1 H), 6.29-6.32 (m, 1 H), 9.73 (d, *J* = 1.1 Hz, 1 H), 9.78 (d, *J* = 0.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 36.0 (d), 39.5 (d), 47.8 (t), 48.0 (t), 48.7 (q), 48.8 (q), 49.5 (d), 51.8 (d), 119.0 (s), 130.7 (d), 135.9 (d), 201.6 (d), 202.3 (d); exact mass (electrospray) *m/z* calculated for $C_{13}H_{18}NaO_4$ (M + Na) 261.10973, found 261.11006.

(1*R*,2*S*,3*S*,4*S*)-rel-2-[3-(2-Hydroxyethyl)-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-yl]ethanol (20.5).

22.4 **20.5**

$NaBH_4$ (0.65 g, 17.2 mmol) was added in portions to a stirred solution of **22.4** (1.39 g, 5.84 mmol) in MeOH (56 mL) and stirring was continued for 10 h. The mixture was evaporated and the residue was partitioned between EtOAc (50 mL) and water (30 mL). The aqueous layer was extracted with EtOAc (25 mL x 3) and the combined organic extracts

were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (4.5 x 15 cm), using 10:1 EtOAc-MeOH, gave **20.5** (1.18 g, 83%), as a colorless oil: FTIR (CH_2Cl_2 cast) 3388, 2935, 2832, 1452, 1288, 1226, 1195, 1121, 1061 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.11-1.14 (m, 1 H), 1.36-1.52 (m, 2 H), 1.86-1.92 (m, 2 H), 1.94-2.01 (m, 1 H), 2.08 (br s, 2 H), 2.56 (t, *J* = 1.7 Hz, 1 H), 2.80-2.82 (m, 1 H), 3.13 (s, 3 H), 3.19 (s, 3 H), 3.58-3.72 (m, 4 H), 6.00 (apparent q, *J* = 3.2 Hz, 1 H), 6.24 (dq, *J* = 3.6, 0.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 35.9 (t), 36.8 (t), 39.4 (d), 43.4 (d), 48.3 (q), 48.7 (q), 49.6 (d), 51.6 (d), 661.7 (t), 62.3 (t), 119.1 (s), 130.4 (d), 135.7 (d); exact mass (electrospray) *m/z* calculated for $C_{13}H_{22}NaO_4$ (M + Na) 265.14103, found 265.14099.

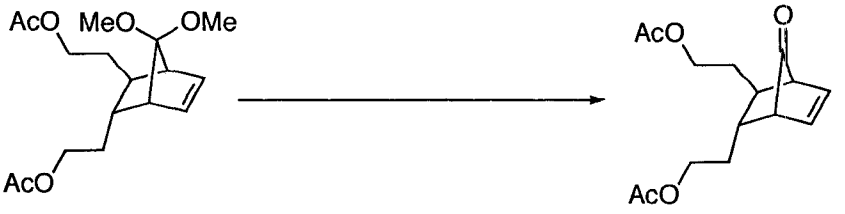
(1*R*,2*S*,3*S*,4*S*)-rel-Acetic acid 2-[3-(2-acetoxyethyl)-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-yl]ethyl Ester (23.1).

20.5 **23.1**

DMAP (60 mg, 0.49 mmol), Ac_2O (2.9 mL, 31 mmol) and Et_3N (3.4 mL, 24.6 mmol) were added sequentially to a

stirred solution of **20.5** (1.18 g, 4.88 mmol) in CH_2Cl_2 (50 mL). Stirring was continued for 13 h, the mixture was diluted with CH_2Cl_2 (50 mL) and the organic phase was washed with water (50 mL) and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (4.5 x 15 cm), using 1:2 EtOAc-hexane, gave **23.1** (1.37 g, 87%) as a colorless oil: FTIR (CH_2Cl_2 cast) 3019, 2917, 2849, 1732, 1366, 1247, 1217, 1121, 1036 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.00-1.04 (m, 1 H), 1.40-1.46 (m, 1 H), 1.51-1.58 (m, 1 H), 1.87-2.00 (m, 3 H), 2.04 (s, 3 H), 2.05 (s, 3 H), 2.57 (t, *J* = 1,9 Hz, 1 H), 2.84 (br s, 1 H), 3.14 (s, 3 H), 3.18 (s, 3 H), 4.00-4.11 (m, 4 H), 6.01 (dd, *J* = 5.8, 2.6 Hz, 1 H), 6.22-6.25 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.0 (q), 21.0 (q), 31.4 (t), 32.5 (t), 39.6 (d), 43.7 (d), 47.8 (q), 48.4 (q), 49.5 (d), 51.7 (d), 63.5 (t), 64.1 (t), 119.1 (s), 130.4 (d), 135.7 (d), 171.1 (s), 171.1 (s); exact mass (electrospray) *m/z* calculated for $C_{17}H_{26}NaO_6$ (M + Na) 349.16216, found 349.16202.

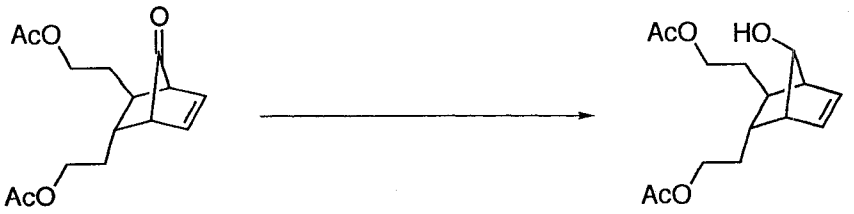
(1*R*,2*S*,3*S*,4*S*)-rel-Acetic acid 2-[3-(2-Acetoxyethyl)-7-oxobicyclo[2.2.1]hept-5-en-2-yl]ethyl Ester (23.2).



23.1 **23.2**

CF_3CO_2H (7.8 mL, 105 mmol) was added to a stirred solution of **23.1** (1.37 g, 4.20 mmol) in CH_2Cl_2 (40 mL). Stirring was continued for 12 h and the solution was then evaporated. Flash chromatography of the residue over silica gel (4.5 x 13 cm), using 1:2 EtOAc-hexane, gave **23.2** (1.14 g, 97%), as a yellow oil: FTIR (CH_2Cl_2 cast) 2957, 2849, 1779, 1739, 1435, 1368, 1242, 1038 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.20-1.25 (m, 1 H), 1.48-1.64 (m, 2 H), 1.68-1.82 (m, 2 H), 1.86-1.94 (m, 1 H), 2.06 (s, 6 H), 2.70 (d, *J* = 3.8 Hz, 1 H), 2.94 (t, *J* = 3.6 Hz, 1 H), 4.00-4.20 (m, 4 H), 6.44 (apparent q, *J* = 3.5 Hz, 1 H), 6.60 (dq, *J* = 3.8, 1.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.9 (q), 32.3 (t), 32.6 (t), 38.9 (d), 40.3 (d), 50.4 (d), 51.6 (d), 62.4 (t), 62.6 (t), 130.7 (d), 133.4 (d), 170.9 (s), 204.0 (s); exact mass (electrospray) *m/z* calculated for $C_{15}H_{20}NaO_5$ (M + Na) 303.12030, found 303.12069.

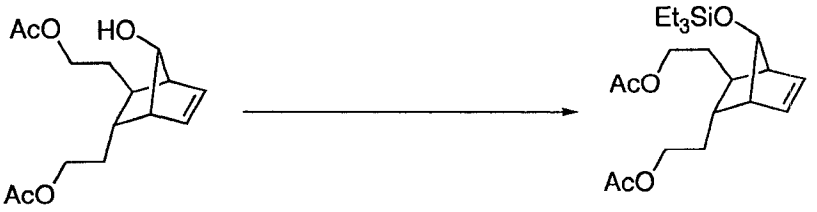
(1*R*,2*S*,3*S*,4*S*,7-*syn*)-rel-Acetic Acid 2-[3-(2-Acetoxyethyl)-7-hydroxybicyclo[2.2.1]hept-5-en-2-yl]ethyl Ester (23.3).



23.2 **23.3**

(t-BuO)$_3$AlHLi (1 M solution in THF, 13 mL, 46.2 mmol) was added dropwise over 15 min to a stirred and cooled (0 °C) solution of **23.2** (1.20 g, 4.29 mmol) in THF (100 mL). Stirring at 0 °C was continued for 2 h, the cold bath was removed and stirring was continued for 3 h. The mixture was quenched with saturated aqueous sodium potassium tartrate (5 mL), and the resulting mixture was stirred at room temperature for 15 min and then diluted with EtOAc (50 mL). The organic extract was dried (Na_2SO_4) and evaporated. The residue was filtered through a pad of silica gel (5 x 4 cm), using EtOAc (50 mL). Evaporation of the filtrate and flash chromatography of the residue over silica gel (4.5 x 20 cm), using 1:1 EtOAc-hexane, gave **23.3** (1.15 g, 96%), as a yellow oil: FTIR (neat) 3461, 2960, 2917, 1731, 1367, 1247, 1036 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.04-1.09 (m, 1 H), 1.46-1.56 (m, 1 H), 1.61-1.70 (m, 1 H), 2.00-2.10 (m, 9 H), 2.10-2.18 (m, 1 H), 2.42 (br s, 1 H), 2.65 (br s, 1 H), 3.77 (s, 1 H), 4.04-4.14 (m, 4 H), 5.88 (dd, J = 6.1, 3.2 Hz, 1 H), 6.10 (dd, J = 6.1, 3.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.0 (q), 31.5 (t), 32.2 (t), 39.8 (d), 42.9 (d), 49.6 (d), 50.3 (d), 63.9 (t), 64.3 (t), 84.7 (d), 131.6 (d), 136.4 (d), 170.0 (s); exact mass (electrospray) m/z calculated for $C_{15}H_{22}NaO_5$ (M + Na) 305.13594, found 305.13589.

(1*R*,2*S*,3*S*,4*S*,7-*syn*)-rel-Acetic Acid 2-[3-(2-Acetoxyethyl)-7-(triethylsilanyloxy)bicyclo[2.2.1]hept-5-en-2-yl]-ethyl Ester (23.4).

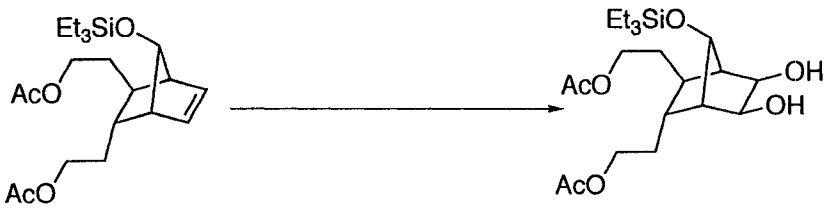


23.3 **23.4**

2,6-Lutidine (2.2 mL, 19 mmol), followed by $Et_3SiOSO_2CF_3$ (1.73 mL, 8.03 mmol) were added to a stirred and cooled (0 °C) solution of **23.3** (1.15 g, 4.06 mmol) in CH_2Cl_2 (60 mL). The ice bath was removed after 40 min and stirring was continued for 13 h. The mixture was quenched with saturated aqueous $NaHCO_3$ (30 mL) and the organic phase was washed with water (50 mL) and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (4.5 x 18 cm), using 1:8 to 1:5 EtOAc-hexane, gave **23.4** (1.67 g, 100%) as a pale yellow oil: FTIR (neat) 2958, 1740, 1458, 1366, 1243, 1112, 1036 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.56 (q, *J* = 7.8 Hz, 6 H), 0.94 (t, *J* = 7.9 Hz, 9 H), 1.01-1.10 (m, 1 H), 1.42-1.53 (m, 1 H), 1.60-1.70 (m, 1 H), 1.98-2.16 [m, including singlets at δ 2.04 (3 H) and 2.05 (3 H), 9 H in all], 2.33 (br s, 1 H), 2.55 (br s, 1 H), 3.62 (s, 1 H), 4.02-4.16 (m, 4 H), 5.86 (dd, *J* = 6.1, 3.3 Hz, 1 H), 6.08-6.12 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 4.6 (t), 4.6 (t), 6.7 (q), 20.9 (q), 20.9 (q), 31.3 (t), 32.1 (t), 39.7 (d), 43.1 (d), 49.9 (d), 50.8 (d), 63.8 (t), 64.3 (t), 84.7 (d), 131.3 (d), 136.1 (d), 171.0 (s), 171.1

(s); exact mass (electrospray) *m/z* calculated for $C_{21}H_{36}NaO_5Si$ (M + Na) 419.22242, found 419.22247.

(1*R*,2*S*,3*S*,4*S*,7-*syn*)-rel-Acetic Acid 2-[3-(2-Acetoxy-ethyl)-5,6-dihydroxy-7-(triethylsilanyloxy)bicyclo[2.2.1]-hept-2-yl]ethyl Ester (24.1).

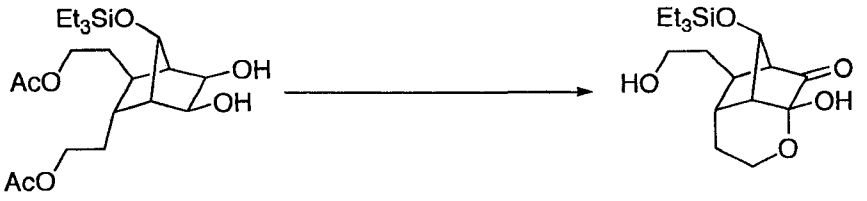


23.4 **24.1**

NMO (0.74 g, 6.32 mmol), followed by a solution of OsO_4 (0.1 M solution in PhMe, 2.2 mL) were added to a stirred and cooled (0 °C) solution of **23.4** (1.67 g, 4.22 mmol) in acetone (67 mL) and water (16 mL). Stirring was continued at 0 °C for 30 min, the cooling bath was removed and stirring was continued for 12 h. The solution was quenched with $Na_2S_2O_3$ (0.8 g) and stirring was continued for 30 min. Acetone was removed under water pump vacuum and the residue was diluted with water (30 mL) and extracted with EtOAc (3 x 30 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (4.5 x 23 cm), using 1:1 EtOAc-hexane to pure EtOAc, gave **24.1** (1.51 g, 87%) as a yellow oil: FTIR ($CHCl_3$ cast) 3420, 2956, 2914, 2877, 1740, 1242, 1117, 1036 cm^{-1}; ^1H

NMR ($CDCl_3$, 500 MHz) δ 0.60 (q, *J* = 8.0 Hz, 6 H), 0.96 (t, *J* = 8.2 Hz, 9 H), 1.56-1.67 (m, 1 H), 1.71-1.88 (m, 3 H), 1.92-2.01 (m, 2 H), 2.03-2.12 [m, including singlets at δ 2.05 (3 H) and δ 2.06 (3 H), 8 H in all], 3.60 (d, *J* = 7.0 Hz, 1 H), 3.98 (d, *J* = 6.7 Hz, 1 H), 4.04-4.16 (m, 4 H), 4.43 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 4.5 (t), 6.7 (q), 20.8 (q), 20.9 (q), 28.9 (t), 34.0 (t), 38.4 (d), 42.3 (d), 51.4 (d), 51.5 (d), 63.5 (t), 63.6 (t), 67.2 (d), 72.3 (d), 76.6 (d), 171.2 (s), 171.2 (s); exact mass (electrospray) *m/z* calculated for $C_{21}H_{38}NaO_7Si$ (M + Na) 453.22790, found 453.22757.

(4*R*,4a*S*,5*S*,6*R*,7as,8*S*)-rel-Hexahydro-7a-hydroxy-8-(2-hydroxyethyl)-5-[(triethylsilyl)oxy]-4,6-methanocyclopenta-[b]pyran-7(2*H*)-one (24.3).



24.1 **24.3**

DMSO (0.95 mL, 10.0 mmol) was added over 2 min to a stirred and cooled (-78 °C) solution of $(COCl)_2$ (0.75 mL, 7.9 mmol) in CH_2Cl_2 (80 mL). After 15 min, **24.1** (0.82 g, 1.90 mmol) in CH_2Cl_2 (40 mL) was added dropwise over 15 min. Stirring was continued for 1.5 h and then Et_3N (2.0 mL, 14.4

mmol) was added dropwise over 15 min. After 1.5 h, the cold bath was removed and stirring was continued for 15 min. The mixture was quenched with water and the organic phase was passed through a pad of silica gel (3 x 4 cm), using EtOAc as a rinse, and evaporated.

The crude diketone **24.2** was dissolved in MeOH (125 mL) and cooled to 0 °C. K_2CO_3 (355 mg, 2.57 mmol) and water (2.1 mL) were added, the ice bath was removed and stirring was continued for 4 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (3 x 15 cm), using 1:1 EtOAc-hexane, gave **24.3** 0.52 g (80% over two steps) as a yellow oil: FTIR ($CHCl_3$ cast) 3378, 2956, 2877, 1762, 1459, 1414, 1294, 1237, 1152, 1122, 1091 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.63 (q, J = 8.0 Hz, 6 H), 0.97 (t, J = 8.2 Hz, 9 H), 1.56 (br s, 1 H), 1.57-2.00 (m, 2 H), 2.01-2.22 (m, 2 H), 2.19-2.24 (m, 1 H), 2.51-2.59 (m, 2 H), 3.06 (br s, 1 H), 3.59 (dt, J = 12.0, 2.8 Hz, 1 H), 3.69 (t, J = 5.8 Hz, 2 H), 3.92 (q, J = 4.0 Hz, 1 H), 4.49 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 4.5 (t), 6.6 (q), 25.3 (t), 36.2 (d), 37.1 (d), 38.2 (t), 50.6 (d), 59.2 (d), 60.9 (t), 61.1 (t), 74.3 (d), 97.1 (s), 212.3 (s); exact mass (electrospray) m/z calculated for $C_{17}H_{30}NaO_5Si$ (M + Na) 365.17547, found 365.17538.

1-Methoxy-4-[[(methylthio)methoxy]methyl]benzene (25.2).

25.1 **25.2**

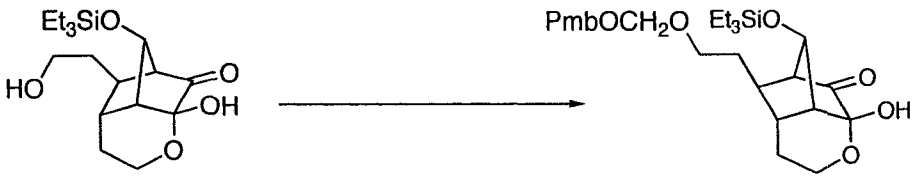
4-Methoxybenzyl alcohol **25.1** (2.3 mL, 18.5 mmol) was added dropwise to a stirred slurry of NaI (2.7 g, 18 mmol) and NaH (0.9 g, 3.7 mmol) in THF (20 mL) at room temperature (vigorous H_2 evolution). After H_2 evolution had ceased, the mixture was cooled to 0 °C and chloromethyl methyl sulfide (1.7 mL, 20.3 mmol) in THF (6 mL) was added dropwise over 20 min. The mixture was stirred at 0 °C for 2 h, the cooling bath was removed and stirring was continued for 5.5 h. Water (28 mL) was carefully added and then Et_2O (20 mL). The aqueous phase was extracted with Et_2O (2 x 15 mL) and the combined organic extracts were dried (K_2CO_3) and evaporated. Flash chromatography of the residue over silica gel (3 x 12 cm), using 1:8 EtOAc-hexane, gave **25.2** (2.95 g, 85%) as a colorless oil. The material is unstable and was used immediately in the next step: FTIR (neat) 2998, 2955, 2917, 2835, 1613, 1586, 1514, 1465, 1441, 1381, 1302, 1249, 1174, 1110, 1061, 1036 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.19 (s, 3 H), 3.82 (s, 3 H), 4.56 (s, 2 H), 4.67 (s, 2 H), 6.89 (d, J = 8.7 Hz, 2 H), 7.29 (d, J = 8.8 Hz, 2 H); exact mass m/z calculated for $C_{10}H_{14}O_2S$ 198.07146, found 198.07154.

1-[(Chloromethoxy)methyl]-4-methoxybenzene (25.3).[32]

25.2 **25.3**

SO_2Cl_2 (1.25 mL, 15.66 mmol) was added dropwise over 10 min to a stirred and cooled (-78 °C) solution of **25.2** (2.95 g, 14.9 mmol) in CH_2Cl_2 (40 mL). After 30 min, the cold bath was removed and stirring was continued for 5 min. The solvent was evaporated under water pump vacuum and then under oil pump vacuum for 30 min to afford pure **25.3** (2.78 g, 100%) as a yellow oil. The reagent is unstable and it should be used immediately after its preparation: FTIR (neat) 3000, 2956, 2837, 1612, 1586, 1515, 1465, 1303, 1249, 1175, 1102, 1035 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.82 (s, 3 H), 4.69 (s, 2 H), 5.50 (s, 2 H), 6.91 (d, *J* = 8.7 Hz, 2 H), 7.27 (t, *J* = 6.1 Hz, 2 H); exact mass *m/z* calculated for $C_9H_{11}ClO_2$ 186.04475, found 186.04496.

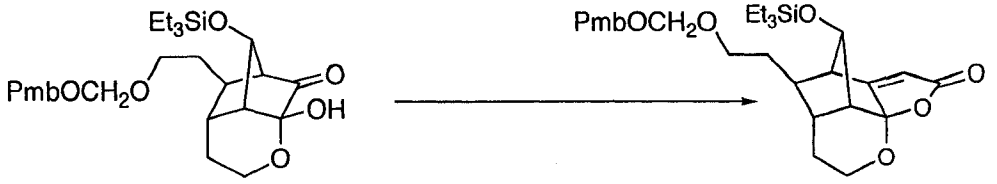
(4*R*,4a*S*,5*S*,6*R*,7as,8*S*)-rel-Hexahydro-7a-hydroxy-8-[[[(4-methoxyphenyl)methoxy]methoxy]ethyl]-5-[(triethylsilyl)oxy]-4,6-methanocyclopenta-[b]pyran-7(2*H*)-one (26.3).



24.3 **26.3**

i-Pr_2NEt (0.64 mL, 3.52 mmol), followed by freshly prepared $PMBOCH_2Cl$ (0.60 g, 3.3 mmol) in CH_2Cl_2 (12 mL) were added to a stirred solution of alcohol **24.3** (0.25 g, 0.73 mmol) in dry CH_2Cl_2 (32 mL). The solution was stirred for 19 h and then evaporated. Flash chromatography of the residue over silica gel (4.5 x 23 cm), using 1:2 EtOAc-hexane, gave **26.3** 0.28 g (78%) as a yellow oil: FTIR (CH_2Cl_2 cast) 3351, 2955, 2876, 1762, 1613, 1515, 1465, 1248, 1152, 1091, 1035 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.63 (q, *J* = 7.8 Hz, 6 H), 0.97 (t, *J* = 8.1 Hz, 9 H), 1.56 (d, *J* = 11.6 Hz, 1 H), 1.88-1.96 (m, 2 H), 2.04-2.14 (m, 2 H), 2.20-2.22 (m, 1 H), 2.50-2.55 (m, 1 H), 2.58 (s, 1 H), 3.10 (s, 1 H), 3.55-3.63 (m, 3 H), 3.82 (s, 3 H), 3.90 (q, *J* = 5.2 Hz, 1 H), 4.49 (s, 1 H), 4.52 (d, *J* = 1.5 Hz, 2 H), 4.71 (AB q, J_{AB} = 6.8 Hz, $\Delta\nu_{AB}$ = 5.2 Hz, 2 H), 6.89 (d, *J* = 4.5 Hz, 2 H), 7.27 (d, *J* = 4.5 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 4.6 (t), 6.8 (q), 25.4 (t), 35.5 (t), 36.3 (d), 37.7 (d), 50.7 (d), 55.3 (q), 59.3 (d), 61.3 (t), 66.1 (t), 69.0 (t), 74.4 (d), 94.3 (t), 97.2 (s), 113.9 (d), 129.9 (d), 159.3 (s), 212.1 (s); exact mass (electrospray) *m/z* calculated for $C_{26}H_{40}NaO_7Si$ (M + Na) 515.24355, found 515.24374.

Compound 27.2.



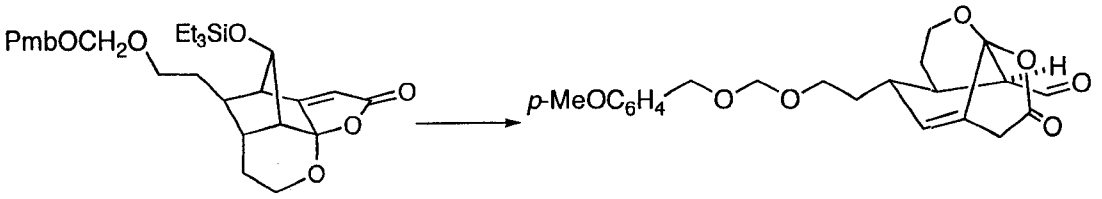
26.3 **27.2**

$(COCl)_2$ (0.12 mL, 1.32 mmol), followed by DMF (1 drop) were added dropwise to a stirred and cooled (0 °C) solution of $(EtO)_2P(O)CH_2CO_2H$ (116 mg, 0.59 mmol) in CH_2Cl_2 (1 mL). After 15 min, the ice bath was removed and stirring continued for 2.5 h. The solvent was evaporated under water pump vacuum with protection from moisture, N_2 being admitted to the flask at the end of the evaporation. The excess of $(COCl)_2$ and solvent were then removed under oil pump vacuum. CH_2Cl_2 (1 mL) was injected into the flask and the solution was cooled to -15 °C. A solution of **26.3** (65 mg, 0.13 mmol) in CH_2Cl_2 (3 mL) was added with stirring, followed by dropwise addition (over ca 5 min) of Et_3N (75 μL, 0.66 mmol). The temperature was kept at -10 to -15 °C for 2 h and then allowed to rise to 0 °C over about 1 h. The cold bath was then removed and stirring was continued for 15 min. The solvent was evaporated under water pump vacuum with protection from moisture, N_2 being admitted to the flask at the end of the evaporation. THF (3 mL) was injected and the mixture was stirred for 10 min. The resulting suspension was transferred to a centrifuge tube sealed with a septum and the mixture was centrifuged for 5 min. The supernatant liquid was added to a stirred and

cooled (0 °C) solution of NaH (95%w/w, 10 mg, 0.33 mmol) in THF (1 mL). The solid in the centrifuge tube was swirled with dry THF (3 x 2 mL) and the mixture was centrifuged for 5 min each time. The supernatant liquid was added to the above suspension containing NaH. The ice bath was removed and stirring was continued for 10 min. The reaction flask was then lowered into a preheated oil bath set at 50 °C. Stirring at this temperature was continued for 1.5 h, and the mixture was cooled to room temperature and then filtered through a pad of silica gel (1.5 x 3 cm) covered by a layer of $MgSO_4$ (ca 1 cm thick). Evaporation of the filtrate and flash chromatography of the residue over silica gel (1.5 x 20 cm), using 1:3 EtOAc-hexane, gave **27.2** (43 mg, 63%) as a colorless oil: FTIR (CH_2Cl_2 cast) 2954, 2876, 1781, 1650, 1613, 1586, 1514, 1463, 1414, 1379, 1302, 1248, 1222, 1177, 1122, 1094, 1036, 1012 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.60 (q, *J* = 8.3 Hz, 6 H), 0.95 (t, *J* = 7.9 Hz, 9 H), 1.82-1.90 (m, 1 H), 1.90-1.96 (m, 2 H), 1.98-2.04 (m, 1 H), 2.20 (dd, *J* = 12.9, 5.5 Hz, 1 H), 2.65 (s, 1 H), 2.68-2.73 (m, 1 H), 3.02 (s, 1 H), 3.58-3.66 (m, 2 H), 3.77-3.84 [(m, including a singlet at δ 3.81 (3 H), 4 H in all], 3.90 (s, 1 H), 4.01 (t, *J* = 7.0 Hz, 1 H), 4.53 (s, 2 H), 4.73 (s, 2 H), 5.57 (s, 1 H), 6.89 (d, *J* = 8.7 Hz, 2 H), 7.27 (d, *J* = 8.8 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 4.6 (t), 6.7 (q), 24.9 (t), 34.6 (t), 36.5 (d), 41.9 (d), 46.6 (d), 53.8 (d), 55.3 (q), 62.2 (t), 66.3 (t), 69.1 (t), 82.2 (d), 94.3 (t), 108.6 (s), 111.1 (d), 113.9 (d), 129.4 (d), 129.9 (s),

159.3 (s), 172.0 (s), 173.0 (s); exact mass (electrospray) *m/z* calculated for $C_{28}H_{40}NaO_7Si$ (M + Na) 539.24355, found 515.24347.

Compound 28.1.

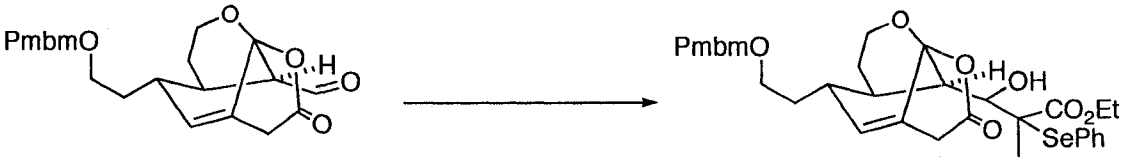


27.2 **28.1**

AcOH (10 μL, 0.17 mmol) and Bu_4NF (1 M solution in THF, 0.15 mL, 0.15 mmol) were added dropwise to a stirred and cooled (-7 °C) solution of **27.2** (43.0 mg, 0.08 mmol) in THF (2 mL). After 30 min an ice bath (0 °C) was put in place and stirring at 0 °C was continued for 2 h. The reaction was quenched at 0 °C with saturated aqueous NH_4Cl (0.5 mL), the cold bath was removed and stirring was continued for 5 min. The mixture was diluted with water (1 mL) and extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 10 cm), using 1:1 EtOAc-hexane, gave **28.1** (33.0 mg, 100%) as a yellow oil: FTIR (CH_2Cl_2, cast) 2935, 2878, 1803, 1723, 1613, 1515, 1466, 1381, 1249, 1201, 1172, 1109, 1060, 1035 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.55-1.64 (m, 3 H), 1.93-2.02

(m, 1 H), 2.27-2.33 (m, 1 H), 2.85 (d, J = 5.3 Hz, 1 H), 2.90 (s, 1 H), 3.15 and 3.20 (two s, 1 H in all), 3.36 and 3.40 (two dd, J = 4.2, 2.3 Hz, 1 H in all), 3.64 (t, J = 6.2 Hz, 2 H), 3.72-3.84 [m, including a singlet at δ 3.81 (3 H), 4 H in all], 3.96 (dd, J = 11.8, 5.9 Hz, 1 H), 4.53 (s, 2 H), 4.73 (s, 2 H), 6.05 (s, 1 H), 6.89 (dd, J = 6.8, 1.9 Hz, 2 H), 7.25-7.27 (m, 2 H), 9.63 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 31.6 (t), 33.6 (t), 34.6 (t), 35.4 (d), 37.5 (d), 53.6 (d), 55.3 (q), 62.7 (t), 65.6 (t), 69.4 (t), 94.6 (t), 102.2 (s), 113.9 (d), 127.6 (s), 129.4 (d), 129.8 (s), 131.5 (d), 159.4 (s), 172.5 (s), 199.3 (d); exact mass (electrospray) m/z calculated for $C_{22}H_{26}NaO_7$ (M + Na) 425.15708, found 425.15690.

Compound 29.2.



28.1 **29.2**

n-BuLi (2.5 M in hexane, 0.12 mL, 0.28 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of i-Pr_2NH (30.3 mg, 0.30 mmol) in THF (0.8 mL). Stirring was continued for 35 min and a solution of ethyl 2-(phenylseleno)propionate (80 mg, 0.31 mmol) in THF (1 mL) was added over 5 min. Stirring was continued for 1 h and a

solution of **28.1** (37.4 mg, 0.09 mmol) in THF (1.5 mL) was added dropwise over 5 min. Stirring was continued for 3.5 h and the mixture was quenched with saturated aqueous NH_4Cl (0.5 mL). The cooling bath was removed and stirring was continued for 5 min. The mixture was diluted with water (0.5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2.5 x 24 cm), using 1:3 to 1:1 EtOAc-hexane, gave **29.2** (39 mg, 64%) as a yellow oil, which was a mixture of isomers. The major isomer had: FTIR (CH_2Cl_2, cast) 3470, 2935, 2874, 1801, 1709, 1514, 1465, 1439, 1382, 1249, 1169, 1107, 1062, 1034 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.14 (t, J = 7.1 Hz, 3 H), 1.41-1.49 (m, 2 H), 1.72-1.88 (m, 2 H), 1.89-1.98 (m, 1 H), 2.16-2.20 (m, 1 H), 2.32 (dd, J = 9.3, 2.4 Hz, 1 H), 2.97 (s, 1 H), 3.03 (dd, J = 3.2, 2.1 Hz, 2 H), 3.53 (br s, 1 H), 3.65-3.77 (m, 4 H), 3.81 (s, 4 H), 3.83-3.88 (m, 2 H), 3.95-4.04 (m, 2 H), 4.56 (s, 2 H), 4.77 (s, 2 H), 5.90 (s, 1 H), 6.88 (d, J = 4.4 Hz, 2 H), 7.28-7.31 (m, 4 H), 7.39 (t, J = 7.4 Hz, 1 H), 7.55 (dd, J = 8.1, 1.2 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.6 (q), 16.6 (q), 31.5 (t), 33.9 (d), 34.9 (t), 35.2 (t), 37.9 (d), 44.8 (d), 55.3 (q), 61.2 (t), 61.5 (s), 62.4 (t), 66.4 (t), 68.5 (d), 69.3 (t), 94.5 (t), 104.3 (s), 113.9 (d), 113.9 (d), 126.8 (s), 126.8 (s), 128.9 (d), 129.5 (d), 129.7 (d), 129.8 (s), 137.8 (d), 159.4 (s), 172.2 (s), 174.0 (s); exact mass (electrospray)

m/z calculated for $C_{33}H_{40}NaO_9{}^{80}Se$ (M + Na) 683.17297, found 683.17298.

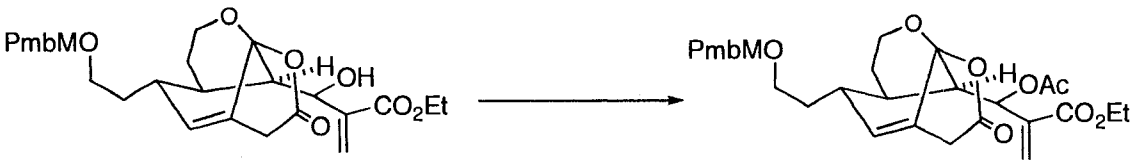
Compound 29.3.

29.2 **29.3**

H_2O_2 (30%, 0.05 mL) was added to a stirred and cooled (0 °C) solution of **29.2** (34.0 mg, 0.05 mmol) in CH_2Cl_2 (1 mL). Stirring was continued for 1 h and the mixture was quenched with 10% aqueous $Na_2S_2O_3$ (1 mL). The ice bath was removed after 5 min and stirring was continued for 10 min. The mixture was diluted with water (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 21 cm), using 1:1 EtOAc-hexane, gave **29.3** (21 mg, 81%) as a colorless oil: FTIR ($CHCl_3$, cast) 3492, 2937, 1799, 1707, 1613, 1515, 1466, 1381, 1249, 1168, 1107, 1064, 1036 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.32 (t, *J* = 7.1 Hz, 3 H), 1.49 (dt, *J* = 13.4, 2.8 Hz, 1 H), 1.84-1.97 (m, 3 H), 2.24 (br s, 1 H), 2.47 (dd, *J* = 10.4, 2.4 Hz, 1 H), 2.65 (d, *J* = 6.9 Hz, 1 H), 2.90 (s, 1 H), 3.03 (dt, *J* = 21.2, 1.6 Hz, 1 H), 3.22 (ddd, *J* = 21.3, 4.4, 2.8 Hz, 1 H), 3.70-3.77 (m, 3 H), 3.81 (s, 3 H), 3.91

(dd, J = 12.0, 6.2 Hz, 1 H), 4.22 (ddd, J = 10.0, 7.1, 1.7 Hz, 2 H), 4.30 (dd, J = 10.3, 6.9 Hz, 1 H), 4.55 (s, 2 H), 4.76 (d, J = 1.6 Hz, 2 H), 5.74 (s, 1 H), 6.04 (t, J = 1.4 Hz, 1 H), 6.27 (s, 1 H), 6.89 (dt, J = 4.5, 2.1 Hz, 2 H), 7.27 (dt, J = 4.5, 2.1 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.1 (q), 31.7 (t), 32.7 (d), 34.7 (t), 35.0 (t), 37.6 (d), 48.6 (d), 55.3 (q), 61.1 (t), 62.6 (t), 66.4 (t), 69.3 (t), 69.4 (d), 94.6 (t), 104.3 (s), 113.9 (d), 126.0 (t), 126.7 (s), 129.4 (d), 129.8 (s), 130.2 (d), 143.3 (s), 159.3 (s), 166.7 (s), 172.9 (s); exact mass (electrospray) m/z calculated for $C_{27}H_{34}NaO_9$ (M + Na) 525.20950, found 525.20977.

Compound 29.4.



29.3 **29.4**

DMAP (1 mg, 0.008 mmol), pyridine (60 μL, 0.72 mmol) and AcCl (24 μL, 0.36 mmol) were added in that order to a stirred and cooled (0 °C) solution of **29.3** (21.0 mg, 0.04 mmol) in CH_2Cl_2 (1.5 mL). Stirring was continued for 1 h and the mixture was diluted with water (0.5 mL) and 10% HCl (0.2 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over

silica gel (2 x 18 cm), using 1:1 EtOAc-hexane, gave **29.4** (17.0 mg, 77%) as a colorless oil: FTIR ($CHCl_3$, cast) 2962, 2876, 1800, 1742, 1713, 1613, 1514, 1370, 1298, 1245, 1224, 1169, 1097, 1065, 1028 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.29 (t, *J* = 7.1 Hz, 3 H), 1.48-1.55 (m, 2 H), 1.69-1.78 (m, 1 H), 1.90-2.00 (m, 1 H), 2.02 (s, 3 H), 2.24-2.30 (m, 1 H), 2.58 (dd, *J* = 11.2, 2.4 Hz, 1 H), 2.71 (br s, 1 H), 3.16 (dd, *J* = 3.2, 2.1 Hz, 2 H), 3.60-3.70 (m, 2 H), 3.74 (dt, *J* = 12.2, 2.9 Hz, 1 H), 3.82 (s, 3 H), 3.90 (dd, *J* = 12.0, 6.0 Hz, 1 H), 4.18 (q, *J* = 7.2 Hz, 2 H), 4.54 (s, 2 H), 4.74 (s, 2 H), 5.43 (d, *J* = 11.2 Hz, 1 H), 5.82 (s, 1 H), 6.05 (s, 1 H), 6.33 (s, 1 H), 6.90 (dt, *J* = 8.6, 2.0 Hz, 2 H), 7.27 (dt, *J* = 8.5, 1.7 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.0 (q), 21.0 (q), 31.5 (t), 33.6 (d), 34.4 (t), 34.8 (t), 36.9 (d), 47.8 (d), 55.3 (q), 61.2 (t), 62.4 (t), 65.7 (t), 69.2 (t), 69.7 (d), 94.5 (t), 103.6 (s), 113.9 (d), 125.5 (s), 127.0 (t), 129.4 (d), 129.7 (s), 142.2 (s), 159.3 (s), 165.5 (s), 169.3 (s), 173.0 (s); exact mass (electrospray) *m/z* calculated for $C_{29}H_{36}NaO_{10}$ (M + Na) 567.22007, found 567.22025.

Compound 30.1.

29.4 **30.1**

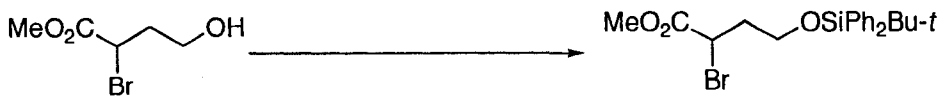
DBU (28 μL, 0.13 mmol) was added to a stirred solution of **29.4** (17 mg, 0.03 mmol) in MeCN (1.5 mL). The mixture was refluxed for 1 h, cooled to room temperature and then filtered through a pad of silica gel (ca 1.5 x 2.5 cm), using 1:2 EtOAc-hexane. Evaporation of the filtrate and flash chromatography of the residue over silica gel (2 x 18 cm), using 1:1 EtOAc-hexane, gave **30.1** (4.0 mg, 27%) as a colorless oil: FTIR ($CHCl_3$, cast) 2935, 2881, 1786, 1707, 1613, 1248, 1174, 1158, 1113, 1096, 1038 1002 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.84-0.90 (m, 1 H), 1.27 (t, *J* = 8.4 Hz, 3 H), 1.49-1.54 (m, 1 H), 1.64-1.70 (m, 1 H), 1.97-2.04 (m, 1 H), 2.29 (s, 1 H), 2.41 (t, *J* = 7.1 Hz, 1 H), 2.71-2.78 (m, 1 H), 2.93-2.96 (m, 1 H), 3.07 (d, *J* = 15.9 Hz, 1 H), 3.56-3.64 (m, 2 H), 3.71-3.73 (m, 1 H), 3.81 (s, 3 H), 3.90 (dt, *J* = 11.2, 3.5 Hz, 1 H), 3.99-4.03 (m, 1 H), 4.16 (q, *J* = 5.5 Hz, 2 H), 4.52 (s, 2 H), 4.72 (s, 2 H), 5.77 (s, 1 H), 6.78-6.80 (m, 1 H), 6.89 (d, *J* = 4.5 Hz, 2 H), 7.24-7.27 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.2, 33.2, 36.1, 36.3, 38.3, 40.7, 43.6, 47.3, 55.4, 61.4, 61.5, 65.7, 69.4, 94.6, 106.1, 114.0, 128.8, 129.5, 129.8, 131.9, 135.0, 138.3, 159.4, 167.6, 174.7; exact mass (electrospray) *m/z* calculated for $C_{27}H_{32}NaO_8$ (M + Na) 507.19894, found 507.19906.

2-Bromo-4-hydroxybutanoic Acid Methyl Ester (32.2).[33]

32.1 **32.2**

A solution of 2-bromo-γ-butyrolactone **32.1** (4.77 g, 28.9 mmol) and Amberlyst-15 (10.8 g) in anhydrous MeOH (130 mL) was stirred for 36 h at room temperature. The mixture was filtered through a pad of Celite and the pad was washed with MeOH (50 mL). Evaporation of the filtrate and flash chromatography of the residue over silica gel (4.5 x 21 cm), using 1:1 EtOAc-hexane, gave **32.2** (5.6 g, 100%) as a yellow oil: FTIR ($CHCl_3$, cast) 3998, 2955, 2889, 1740, 1438, 1274, 1156, 1054 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.65 (s, 1 H), 2.16-2.25 (m, 1 H), 2.30-2.39 (m, 1 H), 3.79-3.83 [m, including a singlet at δ 3.79 (3 H), 5 H in all], 4.51 (dd, J = 8.2, 6.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 37.2 (t), 42.7 (d), 53.1 (q), 59.7 (t), 170.5 (s); exact mass (electrospray) m/z calculated for $C_5H_9{}^{79}BrNaO_3$ (M + Na) 218.96273, found 218.96271.

2-Bromo-4-(*tert*-butyldiphenylsilanyloxy)butyric Acid Methyl Ester (32.3).



32.2 **32.3**

2,6-Lutidine (6.75 mL, 57.7 mmol) was added over ca 5 min to a stirred and cooled (0 °C) solution of **32.2** (5.69 g, 28.9 mmol) and *t*-$BuMe_2SiCl$ (9.7 mL, 37.4 mmol) in CH_2Cl_2 (70 mL). The ice bath was removed after 1 h and stirring was continued for 32 h. The mixture was quenched with saturated aqueous NH_4Cl (20 mL), diluted with water (30 mL), and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (4.5 x 19 cm), using 2% EtOAc-hexane, gave **32.3** (5 g, 42%) as a colorless oil: FTIR ($CHCl_3$, cast) 3071, 3050, 2955, 2932, 2885, 2858, 1744, 1472, 1428, 1272, 1154, 1112 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.06 (s, 9 H), 2.12-2.20 (m, 1 H), 2.32-2.41 (m, 1 H), 3.72-3.85 [m, including a singlet at δ 3.78 (3 H), 5 H in all], 4.63 (dd, *J* = 8.6, 5.9 Hz, 1 H), 7.37-7.47 (m, 6 H), 7.64-7.69 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.2 (s), 26.8 (q), 37.5 (t), 42.8 (d), 52.9 (q), 60.7 (t), 127.7 (d), 129.8 (d), 133.2 (s), 133.3 (s), 135.5 (d), 135.6 (d), 170.4 (s); exact mass (electrospray) *m/z* calculated for $C_{21}H_{27}BrNaO_3Si$ (M + Na) 457.08051, found 457.08027.

4-(*tert*-Butyldiphenylsilanyloxy)-2-(dimethoxy-phosphoryl)butyric Acid Methyl Ester (32.4).

32.3 **32.4**

A solution of **32.3** (5.0 g, 11.5 mmol) and $(MeO)_3P$ (2.5 mL, 20.7 mmol) in 1,2-dichlorobenzene (5 mL) was refluxed for 12 h. The mixture was cooled to room temperature and applied directly to a column of flash chromatography silica gel (4.5 x 22 cm) made up with 3% EtOAc-hexane. Flash chromatography, using 3% EtOAc-hexane to pure EtOAc, gave **32.4** (4.1 g, 75%) as a colorless oil: FTIR ($CHCl_3$, cast) 3072, 3049, 2955, 2857, 1739, 1463, 1429, 1261, 1190, 1160, 1112, 1054, 1031 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.04 (s, 9 H), 2.09-2.14 (m, 1 H), 2.21-2.25 (m, 1 H), 3.39 (ddd, *J* = 23.5, 11.0, 3.5 Hz, 1 H), 3.59-3.64 (m, 1 H), 3.70-3.75 [m, including a singlet at δ 3.72 (3 H), 4 H in all], 3.79 (d, *J* = 11.0 Hz, 3 H), 3.80 (d, *J* = 11.0 Hz, 3 H), 7.36-7.45 (m, 6 H), 7.61-7.65 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.2 (s), 26.8 (q), 29.7 (d, *J* = 4.5 Hz, t), 41.4 (d, *J* = 131.3 Hz, d), 52.5 (q), 53.3 (d, *J* = 6.6 Hz, q), 53.4 (d, *J* = 6.5 Hz, q), 61.6 (d, *J* = 15.6 Hz, t), 127.7 (d), 129.7 (d), 133.3 (s), 133.4 (s), 135.50 (d), 135.51 (d), 169.4 (d, *J* = 4.9 Hz, s); exact mass (electrospray) *m/z* calculated for $C_{23}H_{33}NaO_6PSi$ (M + Na) 487.16763, found 487.16797.

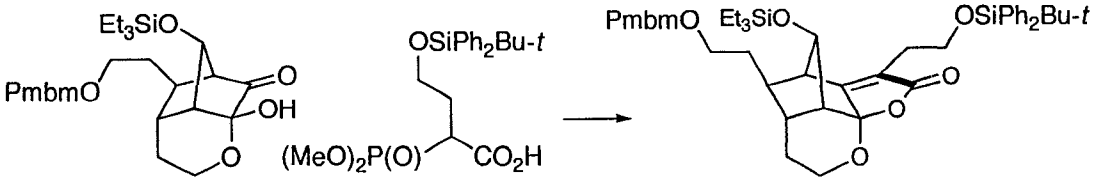
4-(*tert*-Butyldiphenylsilanyloxy)-2-(dimethoxy-phosphoryl)butyric Acid (32.5).

32.4 **32.5**

A solution of $LiOH.H_2O$ (235 mg, 5.6 mmol) in water (4.5 mL) was added to a stirred solution of **32.4** (1.3 g, 2.8 mmol) in THF (10 mL). Stirring was continued for 5 h and the reaction mixture was quenched with 10% HCl (5 mL) to pH = 3). The mixture was diluted with brine (5 mL) and solid NaCl was added to saturate the aqueous phase. The mixture was extracted with EtOAc (3 x 10 mL) and the combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 9 cm), using EtOAc, gave **32.5** (0.99 g, 79%) as a white solid: mp 93-94 °C; FTIR ($CHCl_3$, cast) 3072, 3049, 3012, 2999, 2957, 2933, 2890, 2858, 1727, 1609, 1463, 1428, 1389, 1220, 1188, 1112, 1059, 1035 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.04 (s, 9 H), 2.0-2.11 (m, 1 H), 2.19-2.29 (m, 1 H), 3.43 (ddd, *J* = 23.6, 10.4, 3.2 Hz, 1 H), 3.65-3.77 (m, 2 H), 3.80 (d, *J* = 10.8 Hz, 3 H), 3.84 (d, *J* = 11.2 Hz, 3 H), 7.36-7.43 (m, 6 H), 7.64-7.67 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.2 (s), 26.8 (q), 29.7 (d, *J* = 4.9 Hz, t), 41.6 (d, *J* = 130.8 Hz, d), 53.4 (d, *J* = 6.8 Hz, q), 54.0 (d, *J* = 6.8 Hz, q), 61.4 (d, *J* = 15.0 Hz, t), 127.7 (d), 129.7 (d), 133.3 (s), 133.4

(s), 135.50 (d), 135.52 (d), 170.4 (s); exact mass (electrospray) *m/z* calculated for $C_{22}H_{31}NaO_6PSi$ (M + Na) 473.15198, found 473.15203.

Compound 33.1.



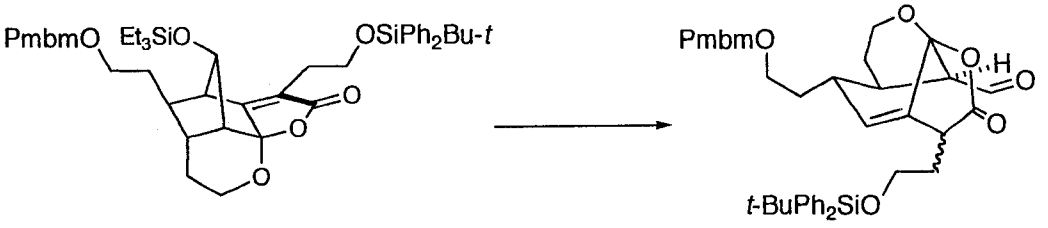
26.3 **32.5** **33.1**

$(COCl)_2$ (0.14 mL, 1.6 mmol), followed by DMF (1 drop) were added dropwise to a stirred and cooled (0 °C) solution of acid **32.5** (234 mg, 0.52 mmol) in CH_2Cl_2 (2 mL). After 15 min, the ice bath was removed and stirring continued for 3 h. The solvent was evaporated under water pump vacuum with protection from moisture, N_2 being admitted to the flask at the end of the evaporation. The excess of $(COCl)_2$ and solvent were then removed under oil pump vacuum. CH_2Cl_2 (1 mL) was injected into the flask and the solution was cooled to -10 °C. A solution of **26.3** (160 mg, 0.33 mmol) in CH_2Cl_2 (2 mL) was added, followed by dropwise addition (over ca 5 min) of Et_3N (0.22 mL, 1.63 mmol). The mixture was stirred at -10 °C to -8 °C for 1.5 h, the cold bath was removed and stirring continued for 15 min. The solvent was evaporated under water pump vacuum with protection from moisture, N_2 being admitted to the flask at the end of the evaporation.

THF (3 mL) was injected and the mixture was stirred for 3 min. The resulting suspension was transferred to a centrifuge tube capped with a septum and centrifuged for 5 min. The supernatant liquid was added to a stirred and cooled (0 °C) solution of NaH (95%w/w, 20 mg, 0.78 mmol) in THF (1 mL). The solid in the centrifuge tube was swirled with dry THF (3 x 2 mL) and the mixture was centrifuged for 5 min each time. The supernatant liquid was added to the above suspension containing NaH. The ice bath was removed and stirring was continued for 10 min. The reaction flask was then lowered into a preheated oil bath set at 80 °C. Stirring at this temperature was continued for 11.5 h, and the mixture was cooled to room temperature and then filtered through a pad of silica gel (2.5 x 3 cm) covered by $MgSO_4$ (ca 1 cm). Evaporation of the filtrate and flash chromatography of the residue over silica gel (2.5 x 18 cm), using 1:7 EtOAc-hexane, gave **33.1** (184 mg, 71%) as a yellow oil: FTIR (CH_2Cl_2 cast) 2954, 2876, 1769, 1514, 1458, 1248, 1111, 1087, 1037 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.54 (q, *J* = 7.9 Hz, 6 H), 0.90 (t, *J* = 7.9 Hz, 9 H), 1.05 (s, 9 H), 1.80-2.01 (m, 4 H), 2.10-2.14 (m, 1 H), 2.42-2.48 (m, 1 H), 2.51-2.57 (m, 1 H), 2.59 (br s, 1 H), 2.65-2.69 (m, 1 H), 2.85 (s, 1 H), 3.54-3.60 (m, 2 H), 3.72-3.82 [m, including a singlet at δ 3.81 (3 H), 7 H in all], 3.93-3.97 (m, 1 H), 4.52 (s, 2 H), 4.69 (s, 2 H), 6.88 (dt, *J* = 4.7, 2.0 Hz, 2 H), 7.26 (dt, *J* = 5.1, 1.7 Hz, 2 H), 7.35-7.44 (m, 6 H), 7.64-7.68 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 4.6

(t), 6.7 (q), 19.2 (s), 25.2 (t), 26.9 (q), 27.9 (t), 34.9 (t), 36.6 (d), 41.8 (d), 46.7 (d), 53.2 (d), 55.3 (q), 61.7 (t), 62.0 (t), 66.4 (t), 69.0 (t), 81.9 (d), 94.2 (t), 107.1 (s), 113.9 (d), 121.2 (s), 127.7 (d), 129.4 (d), 129.4 (d), 129.67 (d), 129.69 (d), 129.9 (s), 133.5 (s), 133.6 (s), 135.5 (d), 159.3 (s), 166.1 (s), 172.9 (s); exact mass (electrospray) *m/z* calculated for $C_{46}H_{62}NaO_8Si_2$ (M + Na) 821.38755, found 821.38736.

Compound 33.3.



33.1 **33.3**

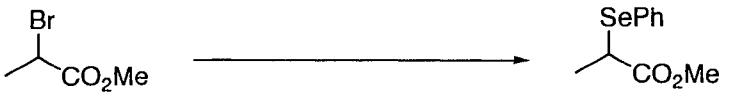
AcOH (8 μL, 0.14 mmol) and Bu_4NF (50 μL, 0.05 mmol, 1 M solution in THF) were added dropwise to a stirred and cooled (-10 °C) solution of **33.1** (22.8 mg, 0.04 mmol) in THF (1 mL). After 1 h an ice bath (0 °C) was put in place and stirring at 0 °C was continued for 4 h. The reaction was quenched with saturated aqueous NH_4Cl (0.5 mL) at 0 °C. The ice bath was removed and stirring was continued for 5 min. The mixture was diluted with water (1 mL) and extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the

residue over silica gel (2.5 x 20 cm), using 1:1 EtOAc-hexane, gave **33.3** (15 mg, 77%) as a colorless oil, which was a separable 3:2 mixture of diastereomers. In subsequent experiments we isolated only the more polar isomer in 70% yield. The more polar isomer had: FTIR (CH_2Cl_2, cast) 2932, 2858, 1794, 1723, 1613, 1514, 1471, 1248, 1167, 1110, 1035 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.07 (s, 9 H), 1.49-1.56 (m, 3 H), 1.92-2.01 (m, 1 H), 2.02-2.12 (m, 2 H), 2.22-2.29 (m, 1 H), 2.84 (br s, 1 H), 2.87 (br s, 1 H), 3.47-3.52 (m, 1 H), 3.60 (t, *J* = 5.9 Hz, 2 H), 3.74 (dt, *J* = 13.3, 3.1 Hz, 1 H), 3.80 (s, 3 H), 3.82-3.88 (m, 1 H), 3.94-3.99 (m, 2 H), 4.52 (s, 2 H), 4.71 (s, 2 H), 5.91 (t, *J* = 2.0, 1 H), 6.89 (dd, *J* = 4.6, 2.1 Hz, 2 H), 7.25 (dd, *J* = 4.7, 2.1 Hz, 2 H), 7.37-7.46 (m, 6 H), 7.65-7.69 (m, 4 H), 9.53 (d, *J* = 1.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.2 (s), 26.9 (q), 31.3 (t), 33.6 (t), 34.5 (t), 35.1 (d), 37.3 (d), 37.3 (d), 53.5 (d), 55.3 (q), 60.7 (t), 62.7 (t), 65.6 (t), 69.3 (t), 94.5 (t), 100.7 (s), 113.9 (d), 127.7 (d), 127.8 (d), 129.4 (d), 129.7 (d), 130.3 (d), 132.2 (s), 133.4 (s), 133.6 (s), 135.6 (d), 159.4 (s), 175.2 (s), 199.5 (d); exact mass (electrospray) *m/z* calculated for $C_{40}H_{48}NaO_8Si$ (M + Na) 707.30107, found 707.30158.

The less polar (and minor) isomer was not fully characterized or obtained absolutely pure: FTIR (CH_2Cl_2, cast) 2932, 2859, 1774, 1722, 1613, 1514, 1472, 1428, 1249, 1163, 1111, 1032 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.01-1.12

(m, 10 H), 1.26 (s, 1 H), 1.45-1.52 (m, 1 H), 1.56-1.61 (m, 2 H), 1.75-1.82 (m, 1 H), 1.85-1.97 (m, 1 H), 2.18-2.29 (m, 2 H), 2.84 (s, 1 H), 3.47-3.65 (m, 3 H), 3.69-3.77 (m, 1 H), 3.78-3.92 [m, including a singlet at δ 3.81 (3 H), 5 H in all], 4.50-4.55 (m, 2 H), 4.68-4.75 (m, 2 H), 5.93 (t, *J* = 1.3 Hz, 1 H), 6.88 (d, *J* = 11.1 Hz, 2 H), 7.24-7.28 (m, 2 H), 7.36-7.45 (m, 6 H), 7.65-7.69 (m, 4 H), 9.63 (s, 1 H); exact mass (electrospray) *m/z* calculated for $C_{40}H_{48}NaO_8Si$ (M + Na) 707.30107, found 707.30158.

2-(Phenylseleno)propionic Acid Methyl Ester (34.2).

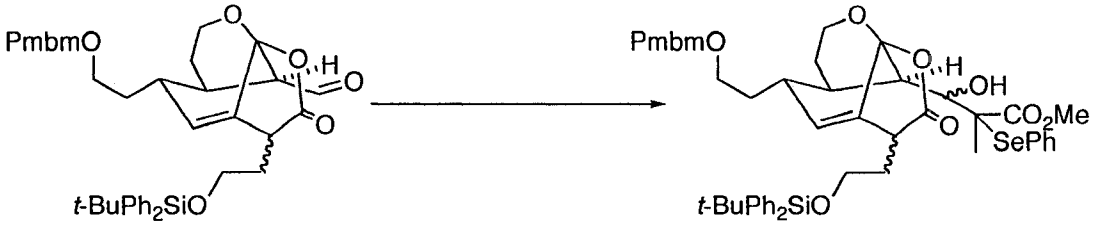


34.1 **34.2**

$NaBH_4$ (2.4 g, 63.4 mmol) was added in several portions to a stirred and cooled (0 °C) solution of PhSeSePh (4.0 g, 12.8 mmol) in MeOH (75 mL). After the addition **34.1** (4.01 g, 24.0 mmol) in MeOH (30 mL) was added dropwise. Stirring was continued for 2 h, the ice bath was removed and stirring was continued for 2.5 h. The solution was quenched with water (30 mL) and diluted with Et_2O (30 mL). The aqueous phase was extracted with Et_2O (15 mL x 3), and all the combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over

silica gel (4.5 x 21 cm), using 3% EtOAc-hexane to EtOAc-1:6 hexane, gave **34.2** (4.74 g, 81%) as a yellow oil: FTIR ($CHCl_3$, cast) 3072, 3058, 2991, 2950, 2928, 1730, 1579, 1477, 1450, 1438, 1376, 1333, 1258, 1213, 1148, 1062, 1022 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.55 (d, *J* = 7.1 Hz, 3 H), 3.65 (s, 3 H), 3.78 (q, *J* = 7.2 Hz, 1 H), 7.26-7.38 (m, 3 H), 7.58-7.62 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.6 (q), 37.1 (q), 52.0 (d), 127.6 (s), 128.5 (d), 128.9 (d), 135.7 (d), 173.7 (s); exact mass (electrospray) *m/z* calculated for $C_{10}H_{12}NaO_2{}^{80}Se$ (M + Na) 266.98947, found 266.98959.

Compound 35.1.

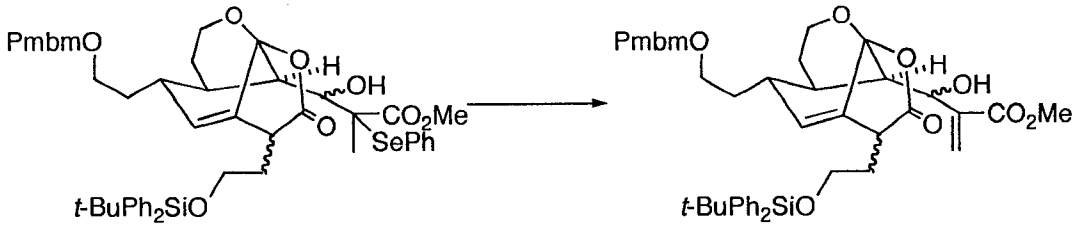


33.3 **35.1**

n-BuLi (2.5 M in hexane, 0.06 mL, 0.15 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of *i*-Pr_2NH (0.05 mL, 0.35 mmol) in THF (1 mL). Stirring was continued for 50 min and a solution of methyl 2-(phenylseleno)propionate (42 mg, 0.16 mmol) in THF (1 mL) was added over 5 min. Stirring was continued for 1 h and a solution of **33.3** (30 mg, 0.04 mmol) in THF (2 mL) was added dropwise. Stirring was continued for 4.5 h and the mixture

was quenched with saturated aqueous NH_4Cl (1 mL). The cooling bath was removed and stirring was continued for 10 min. The mixture was diluted with water (3 mL) and extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2.5 x 24 cm), using 1:6 to 1:1 EtOAc-hexane, gave **35.1** (29 mg, 70%) as a yellow oil, which was an inseparable mixture of isomers.

Compound 35.2.

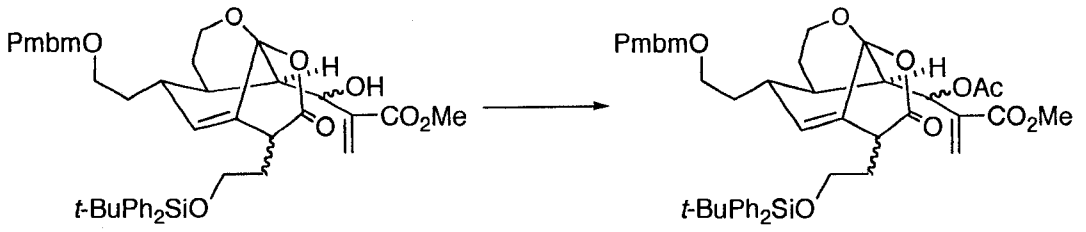


35.1 **35.2**

H_2O_2 (30%, 0.05 mL) was added to a stirred and cooled (0 °C) solution of **35.1** (33 mg, 0.04 mmol) in THF (2 mL) and water (0.2 mL). Stirring was continued for 1 h and the mixture was quenched with saturated aqueous $Na_2S_2O_3$ (1 mL). The ice bath was removed after 5 min and stirring was continued for 10 min. The mixture was diluted with water (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm),

using 1:1 EtOAc-hexane, gave **35.2** (23 mg, 85%) as a colorless oil, which was an inseparable mixture of isomers: FTIR (neat) 3478, 2933, 2859, 1791, 1714, 1613, 1514, 1249, 1111, 1036 cm^{-1}; exact mass (electrospray) *m/z* calculated for $C_{44}H_{54}NaO_{10}Si$ (M + Na) 793.33785, found 793.33735.

Compound 35.3.

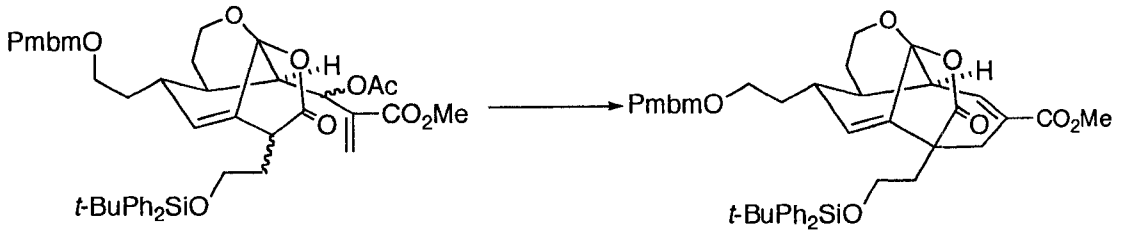


35.2 **35.3**

DMAP (1 mg, 0.008 mmol), pyridine (38 μL, 0.46 mmol) and AcCl (14 μL, 0.21 mmol) were added in that order to a stirred and cooled (0 °C) solution of **35.2** (23 mg, 0.03 mmol) in CH_2Cl_2 (1.5 mL). Stirring was continued for 1 h and the mixture was diluted with water (0.5 mL) and 10% HCl (0.2 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 21 cm), using 1:2 to 1:1 EtOAc-hexane, gave **35.3** (18 mg, 75%) as a viscous oil which was an inseparable mixture of isomers: FTIR (neat) 2933, 2859, 1793, 1741, 1718, 1670, 1540, 1465, 1246, 1110, 1029 cm^{-1}; exact mass

(electrospray) *m/z* calculated for $C_{46}H_{56}NaO_{11}Si$ (M + Na) 835.34841, found 835.34804. The NMR spectra were too complicated to be informative.

Compound 36.1.

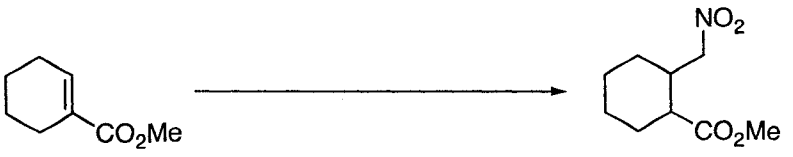


35.3 **36.1**

DBU (0.02 mL, 0.13 mmol) was added to a stirred solution of **35.3** (15 mg, 0.02 mmol) in MeCN (2 mL). The mixture was refluxed for 1.5 h, cooled to room temperature and then filtered through a pad of silica gel (1.5 x 2.5 cm), using 1:1 EtOAc-hexane. Evaporation of the filtrate and flash chromatography of the residue over silica gel (2 x 21 cm), using 1:1 EtOAc-hexane, gave **36.1** (9 mg, 69%) as a colorless oil: FTIR (CH_2Cl_2, cast) 2932, 2881, 2858, 1788, 1713, 1514, 1429, 1249, 1112, 1035 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.02 (s, 9 H), 1.08 (s, 2 H), 1.43-1.55 (m, 3 H), 1.62 (d, *J* = 11.7 Hz, 1 H), 1.87-1.92 (m, 1 H), 1.96-2.05 (m, 1 H), 2.33-2.37 (m, 2 H), 2.44-2.51 (m, 2 H), 2.91-2.97 (m, 1 H), 3.59 (dt, *J* = 6.0, 1.6 Hz, 2 H), 3.69 (s, 3 H), 3.79-3.86 [m, including a singlet at δ 3.80 (3 H), 4 H in all], 3.93-3.97 (m, 1 H), 4.52 (s, 2 H), 4.72 (s, 2 H),

5.58 (s, 1 H), 6.77-6.8 (m, 1 H), 6.88 (dd, J = 4.6, 2.0 Hz, 2 H), 7.25 (dd, J = 5.2, 2.1 Hz, 2 H), 7.36-7.44 (m, 6 H), 7.67-7.73 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.0 (s), 26.6 (q), 26.6 (q), 33.3 (t), 34.4 (t), 36.2 (t), 36.4 (d), 37.9 (d), 47.1 (d), 49.1 (t), 49.9 (s), 52.3 (q), 55.3 (q), 60.4 (t), 61.3 (t), 65.7 (t), 69.3 (t), 94.5 (t), 103.8 (s), 113.9 (d), 127.6 (d), 127.6 (d), 127.7 (d), 128.8 (s), 129.4 (d), 129.5 (d), 129.6 (d), 129.6 (d), 129.7 (s), 130.7 (d), 133.5 (s), 133.6 (s), 134.8 (d), 135.7 (d), 135.7 (d), 136.5 (s), 138.5 (d), 159.4 (s), 168.0 (s), 176.2 (s); exact mass (electrospray) m/z calculated for $C_{44}H_{52}NaO_9Si$ (M + Na) 775.32728, found 775.32784.

2-(Nitromethyl)cyclohexanecarboxylic Acid Methyl Ester (37.2).



37.1 **37.2**

A catalytic amount of $Bu_4NF.3H_2O$ (2 mg) was added to a stirred solution of **37.1** (25.0 mg, 0.18 mmol) and $MeNO_2$ (16 μL, 0.31 mmol) in THF (1 mL). The solution was refluxed overnight, cooled and applied directly to a silica gel column (1.8 x 20 cm) made up with 1:5 EtOAc-hexane. Flash chromatography, using 1:5 EtOAc-hexane, gave **37.2** (15 mg,

43%) as a colorless oil: FTIR (neat) 2940, 2863, 1730, 1552, 1452, 1435, 1383, 1243, 1193, 1173, 1132, 1037 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.37-1.46 (m, 1 H), 1.46-1.53 (m, 2 H), 1.55-1.62 (m, 1 H), 1.64-1.78 (m, 3 H), 2.54-2.62 (m, 1 H), 2.76 (dd, *J* = 9.7, 4.6 Hz, 1 H), 3.70 (s, 3 H), 4.48 (dd, *J* = 12.5, 8.0 Hz, 1 H), 4.57 (dd, *J* = 12.5, 6.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.8 (t), 23.8 (t), 26.3 (t), 27.4 (t), 37.1 (d), 42.3 (d), 51.6 (q), 78.1 (t), 173.7 (s); exact mass (electrospray) *m/z* calculated for $C_9H_{15}NNaO_4$ (M + Na) 224.08933, found 224.08945.

2-Hydroxycyclohexanecarboxylic Acid Methyl Ester (38.2).

37.1 **38.2**

$Ni(cod)_2$ (3.3 mg, 0.01 mmol) and Cs_2CO_3 (114.0 mg, 0.35 mmol) were placed in flask under Ar. PhMe (1.5 mL) and $P(c\text{-}C_6H_{11})_3$ (0.50 M in PhMe, 24 μL, 0.01 mmol) were added dropwise. The suspension was stirred for 10 min at 0 °C. A solution of **37.1** (32.0 mg, 0.23 mmol) and bis(pinacolato)diboron (89.0 mg, 0.35 mmol) in PhMe (1 mL) was added. Finally, MeOH (0.12 mL) and water (1 drop) were added, and the ice bath was removed and stirring was continued for 21 h. The resulting mixture was diluted with

water (2 mL) and extracted with 1:4 EtOAc-hexane (5 mL x 3). The combined organic extracts were dried (Na_2SO_4) and evaporated.

The crude product was oxidized with aqueous NaOH (3.0 M, 0.5 mL) and aqueous H_2O_2 (30%, 0.5 mL) in THF/EtOH (1.0 mL : 0.5 mL) at room temperature for 30 min. The solution was quenched with aqueous $Na_2S_2O_3$ (10%, 2 mL) and extracted with 1:1 EtOAc:hexane (3 x 5 mL), dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 16 cm), using 1:4 EtOAc-hexane, gave **38.2** as a colorless oil (5.0 mg, 27% over 2 steps): FTIR (CH_2Cl_2, cast) 3473, 2936, 2855, 1723, 1437, 1250, 1206, 1174, 1037 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.25-1.38 (m, 1 H), 1.40-1.51 (m, 2 H), 1.65-1.73 (m, 3 H), 1.85-1.92 (m, 2 H), 2.50 (dt, J = 11.0, 3.7 Hz, 1 H), 3.08 (br s, 1 H), 3.71 (s, 3 H), 4.13-4.15 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.1 (t), 23.9 (t), 24.8 (t), 31.7 (t), 46.6 (d), 51.7 (q), 66.7 (d), 176.2 (s); exact mass m/z calculated for $C_8H_{14}O_3$ 158.09430, found 159.09400.

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