Studies directed toward the synthesis of the C(19)-C(32) carbon fragment of Scytophycin C
by William Richard Swain

A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science In Chemistry
Montana State University

Abstract:
The Scytophycins are a group of highly functionalized 22-membered macrolides isolated from the blue-green alga Scytonema pseudohofmanni. Scytophycin C exhibits potent cytotoxity against human cancer cells, and consequently, has been given attention from the synthetic community. The discovery of the direct bridgehead opening of oxabicyclo[3.2.1]octenes in concentrated solutions of lithium perchlorate-diethyl ether led to investigations for the conversion of the resulting cycloheptenones into building blocks containing the anti, anti stereotriad found in Scytophycin C. Methods have been developed for transforming an oxabicyclo[3.2.1]octene into the C(19)-C(26) carbon fragment of Scytophycin C.

STUDIES DIRECTED TOWARD THE SYNTHESIS OF THE C(19)-C(32) CARBON FRAGMENT OF SCYTOPHYCIN C

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APPROVAL

of a thesis submitted by

William Richard Swain

This thesis has been read by each member of the thesis committee and has been found to be satisfactory regarding content, English usage, format, citations, bibliographic style, and consistency, and is ready for submission to the College of Graduate Studies.

Paul A. Grieco _____ (Signature) 1-21-02 Date

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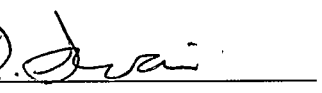
Signature 

Date 01/21/02

TABLE OF CONTENTS

LIST OF SCHEMES

Scheme Page

LIST OF ABBREVIATIONS

Bu	normal butyl
^{t}Bu	tertiary butyl
°C	degrees Celcius
CI	chemical ionization
DCC	dicyclohexylcarbodiimide
DIBALH	diisobutylaluminum hydride
DMAP	4-dimethylaminopyridine
ee	enantiomeric excess
equiv	equivalents
Et	ethyl
h	hour
Hz	Hertz
IR	infrared
J	coupling constant in Hertz
LDA	lithium diisopropylamide
M	molarity
m	*meta*
MCPBA	m-chloroperbenzoic acid
Me	methyl
mg	milligram
MHz	megaHertz

LIST OF ABBREVIATIONS – CONTINUED

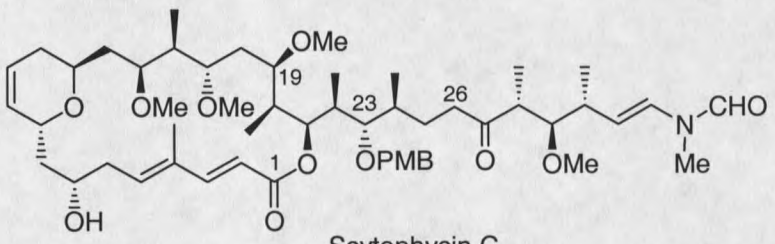
min	minutes
μL	microliter
mmol	millimole
mol. sieves	molecular sieves
mp	melting point
HRMS	high resolution mass spectrometry
NaHMDS	sodium hexamethyldisilazide
NMO	N-methylmorpholine-N-oxide
NMR	nuclear magnetic resonance
OAc	acetate
p	*para*
Ph	phenyl
ppm	parts per million
PPTS	pyridinium p-toluenesulfonate
pyr	pyridine
rt	room temperature
TBAF	tetrabutylammonium fluoride
TES	triethylsilyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TPAP	tetrapropylammonium perruthenate

ABSTRACT

The Scytophycins are a group of highly functionalized 22-membered macrolides isolated from the blue-green alga *Scytonema pseudohofmanni*. Scytophycin C exhibits potent cytotoxity against human cancer cells, and consequently, has been given attention from the synthetic community. The discovery of the direct bridgehead opening of oxabicyclo[3.2.1]octenes in concentrated solutions of lithium perchlorate-diethyl ether led to investigations for the conversion of the resulting cycloheptenones into building blocks containing the anti, anti stereotriad found in Scytophycin C. Methods have been developed for transforming an oxabicyclo[3.2.1]octene into the C(19)-C(26) carbon fragment of Scytophycin C.

INTRODUCTION

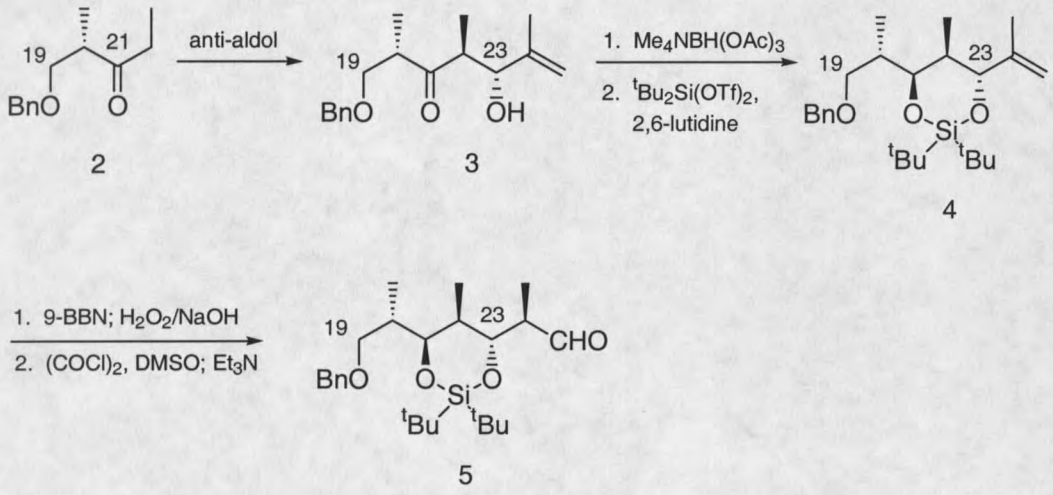
The Scytophycins are a group of highly functionalized 22-membered macrolides isolated from the blue-green alga *Scytonema pseudohofmanni*.[1] Scytophycin C **1** exhibits potent cytotoxicity against human cancer cells,[2] and consequently, has been given attention from the synthetic community.[3]



Scytophycin C

1

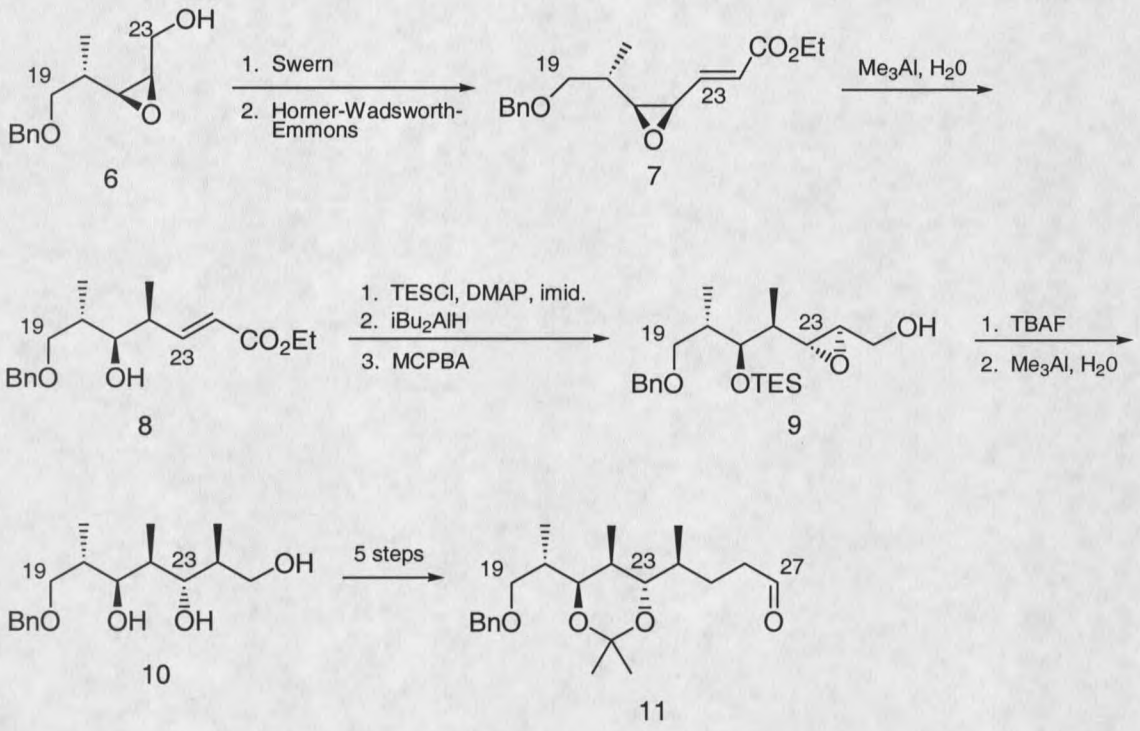
Several methods have been used to access the anti, anti stereotriad present in the C(22)-C(24) moiety of Scytophycin C. In the only total synthesis of Scytophycin C reported to date, Paterson utilized asymmetric aldol chemistry to build the C(19)-C(25) fragment (Scheme 1).[3a] Paterson employed ethyl ketone (*S*)-**2** in a key anti-aldol reaction with methacrolein to introduce the C(22) and C(23) stereocenters of β-hyroxy ketone **3**. The C(21) stereocenter was set using a stereoselective ketone reduction, followed by protection of the resulting diol which provided silylene **4**. The remaining C(24) stereocenter of the anti, anti stereotriad was set using an asymmetric hydroboration reaction. Oxidation of the resulting alcohol provided aldehyde **5** in nine steps from commercially available material.



2 3 4 5

Scheme 1

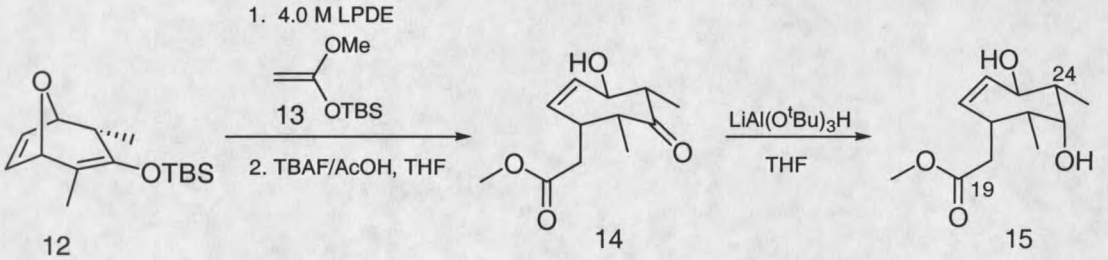
Grieco's approach to Scytophycin C centered around the C(19)-C(27) carbon fragment, and utilized an iterative, stereospecific methylation of epoxy acrylates (Scheme 2).[3b] Conversion of the known chiral epoxy alcohol **6** to its (*Z*)-epoxy acrylate, followed by treatment with trimethylaluminum and water established the C(21) and C(22) stereocenters of ester **8**. Functional group protection, hydride reduction, and a stereoselective epoxidation provided epoxy alcohol **9**. After deprotection of the C(21) hydroxyl group, the C(23) and C(24) stereocenters were set using stereospecific methylation to yield triol **10**, possessing the desired anti, anti stereotriad. The triol was converted to aldehyde **11** in five steps.



Scheme 2

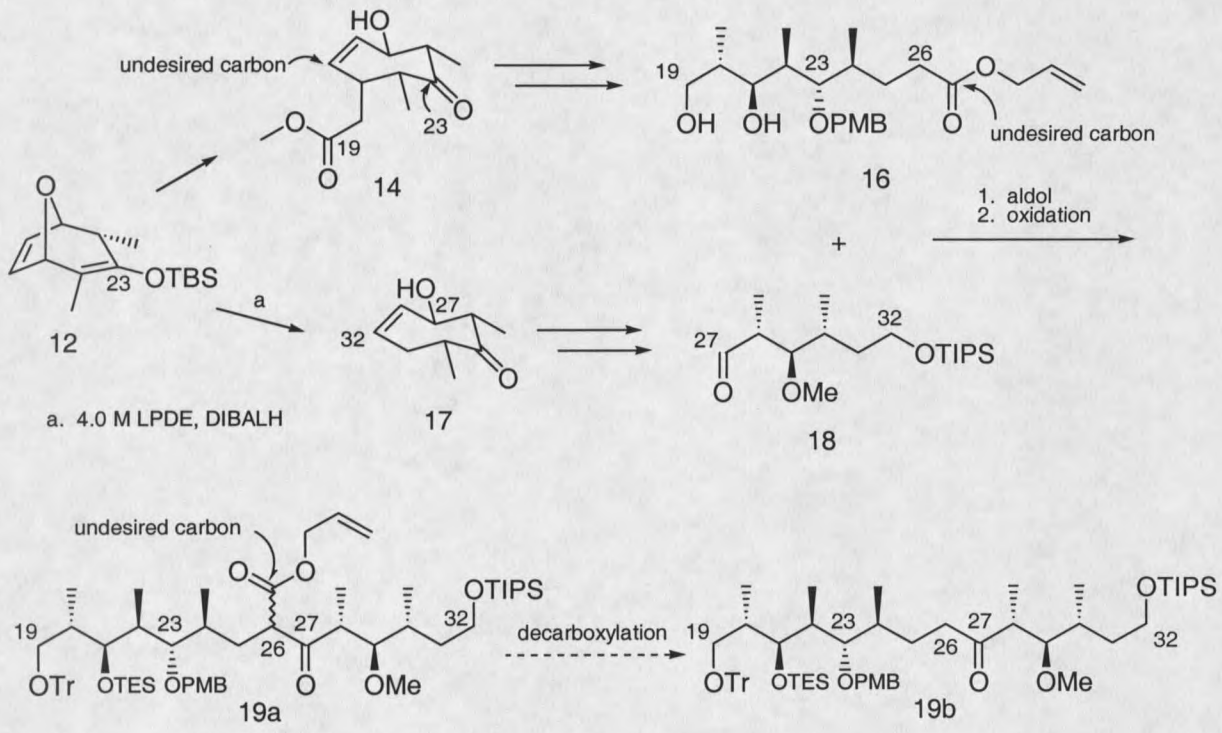
More recently, Grieco has explored the use of oxabicyclo[3.2.1]octenes as rigid templates for controlling acyclic stereochemistry. The discovery of the direct bridgehead opening of **12** in concentrated solutions of lithium perchlorate-diethyl ether led to investigations for the conversion of the resulting cycloheptenones into building blocks containing the anti, anti steriotriad found in Scytophycin C.[4,5] Treatment of **12**, available in 75% ee,[5] with silyl ketene acetal **13** in 4.0 M lithium perchlorate-diethyl ether, followed by exposure of the crude product to tetrabutylammonium fluoride and acetic acid[7] provided cycloheptenone **14** (Scheme 3). Stereoselective reduction of ketone **14** using lithium tri-*t*-butoxyaluminum hydride provided diol **15**. Examination of the

stereochemistry of **15** reveals the nascent anti, anti stereotriad found in the C(22)-C(24) moiety of Scytophycin C.



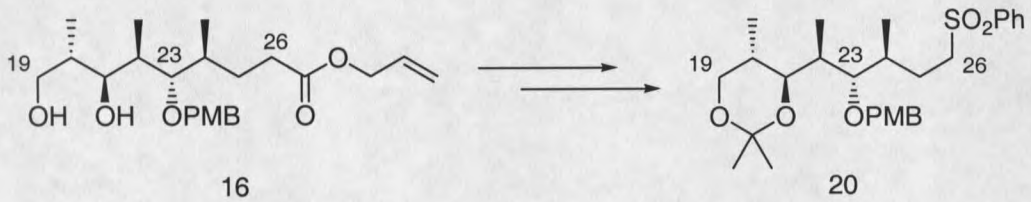
Scheme 3

Using the above methodology, the Grieco group has developed methods for transforming oxabicyclo[3.2.1]octene **12** into carbon fragments **16** and **18** of Scytophycin C (Scheme 4).[5] Aldol coupling followed by oxidation of the resulting C(27) hydroxyl group provided the C(19)-C(32) carbon fragment **19a**. Failed attempts to remove the C(26) carboallyloxy group of **19a** prevented the formation of the desired C(19)-C(32) fragment **19b** of Scytophycin C.



Scheme 4

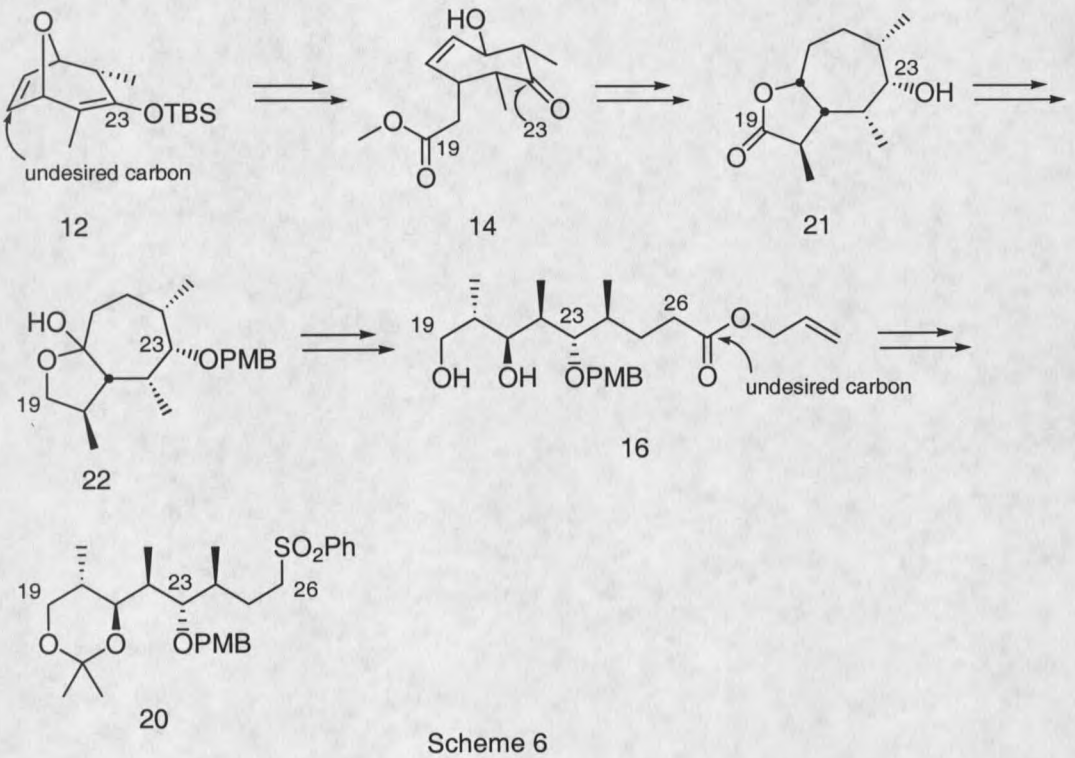
With this in mind, studies were directed toward the removal of the carboallyloxy group from carbon fragment **16** (Scheme 5). The goal was to arrive at sulfone **30** as a surrogate for allyl ester **16**.



Scheme 5

RESULTS AND DISCUSSION

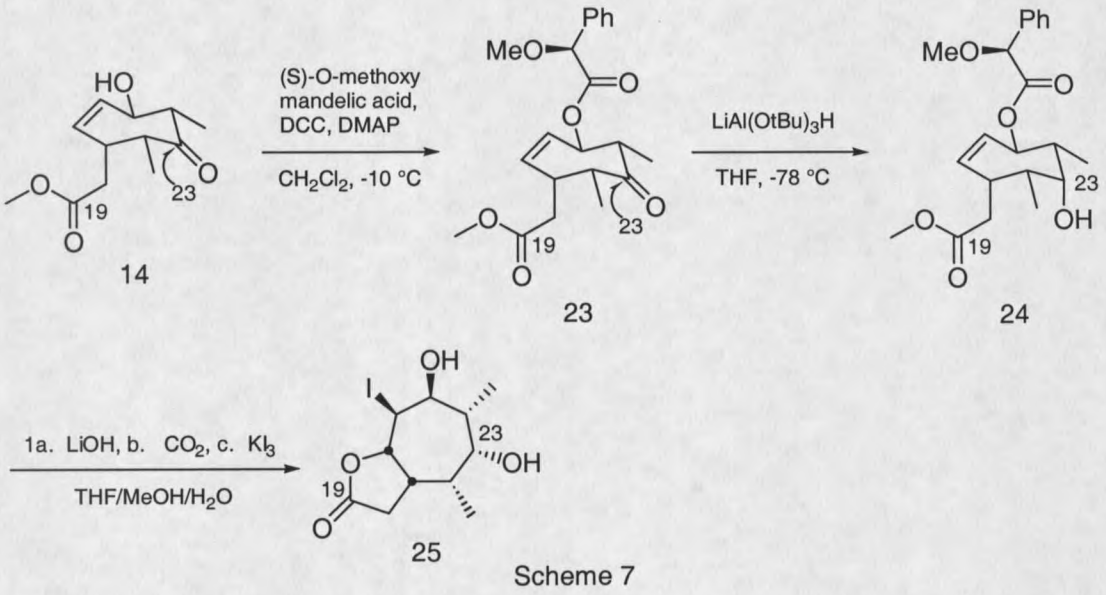
The strategy for the synthesis of the C(19)-C(26) carbon fragment of Scytophycin C is outlined in Scheme 6. Previous efforts by the Grieco group have demonstrated that allyl ester **16** is available in 16 steps from cycloheptenone **14** (Scheme 6).[5] This, in turn, is derived from oxabicyclo[3.2.1]octene **12**, available in 75% ee via asymmetric deprotonation of the parent ketone.[5,7]



Scheme 6

The synthesis of the of the C(19)-C(26) fragment of Scytophycin C began with cycloheptenone **14**.[5] In order to enhance the enantiomeric purity, **14** was derivatized as its mandelate ester **23** (Scheme 7).[5] To this end, **14** was treated with dicyclohexylcarbodiimide and 4-dimethylaminopyridine followed by the addition of (*S*)-

O-methylmandelic acid[8] to afford an inseparable 7:1 mixture of diastereomers. After stereoselective reduction of ketone **23** as a mixture of diastereomers using lithium tri-*t*-butoxyaluminum hydride, the diastereomeric mixture (96% yield) was separated by flash chromatography to provide a 64% isolated yield of alcohol **24** in 96% de. Alcohol **24** was submitted to a one-pot saponification/iodolactonization sequence giving rise to iodolactone **25** in 85% yield.

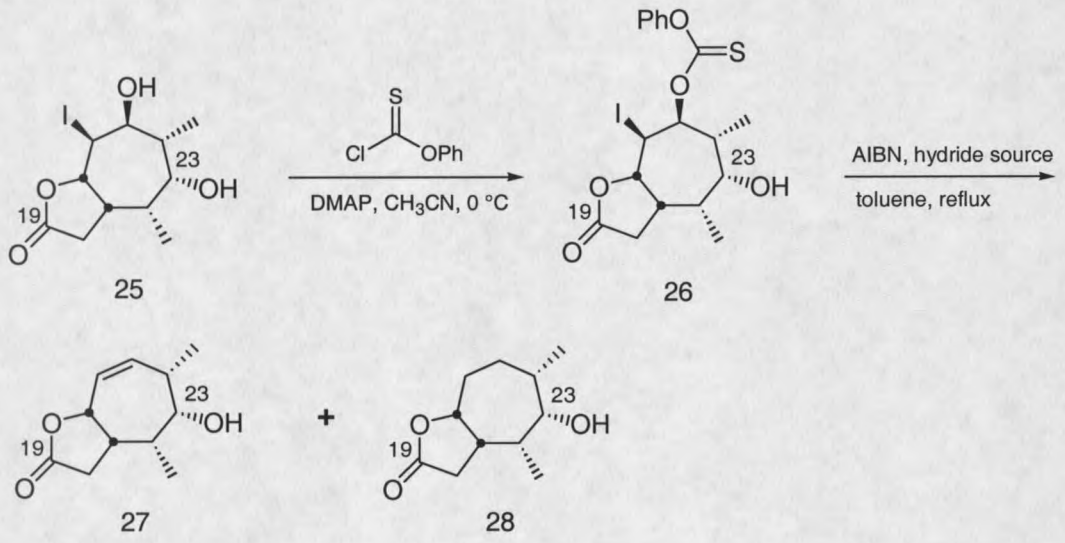


14 23 24 25

Scheme 7

At this point it became necessary to reductively remove the iodo group at C(26) and the hydroxyl group at C(25). Alcohol **25** was treated with phenyl chlorothionoformate and 4-dimethylaminopyridine, selectively converting the less hindered C(25) hydroxyl to thionocarbonate **26** in 87% yield (Scheme 8). With the installation of the thionocarbonate, the C(26) iodo group and C(25) hydroxyl group could be removed employing the Barton-McCombie deoxygenation protocol.[9] Initial studies

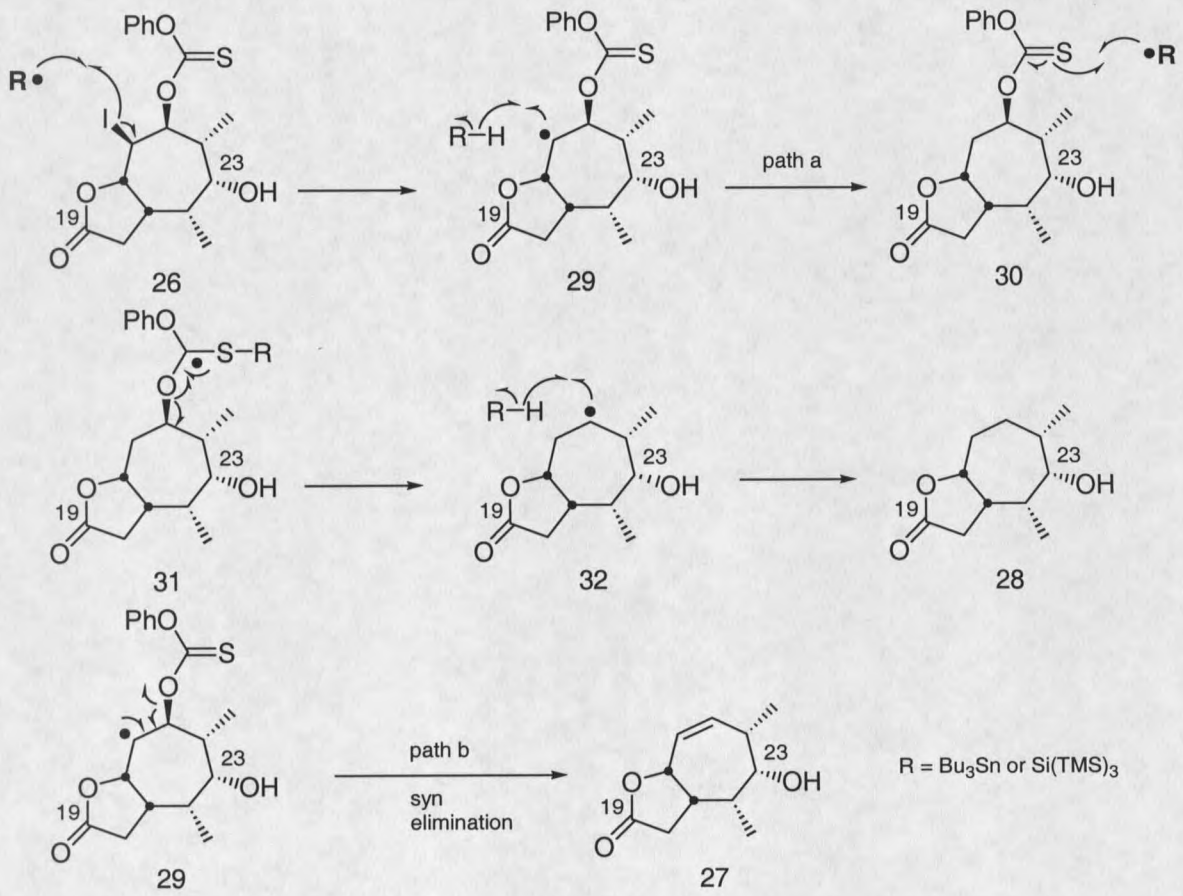
showed that treatment of lactone **26** with catalytic azobisisobutyronitrile and four equivalents of tris(trimethylsilyl)silane in deoxygenated toluene provided alkene **27** in a 61% yield along with a small amount (6%) of the fully saturated lactone **28**.[5] We later found that treatment of thionocarbonate **26** with catalytic azobisisobutyronitrile and two equivalents of tri-*n*-butylstannane provided 42% of **27** and 44% of **28**.



Scheme 8

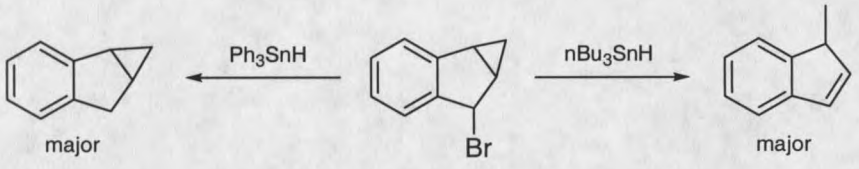
The results of the above radical reactions can be explained upon examination of the reaction mechanism (Scheme 9) and reactivity of hydride reagent. It is well established that alkyl iodides can react at ambient temperature with tri-*n*-butylstannane while secondary thionocarbonates require tri-*n*-butylstannane along with an initiator and elevated temperature.[10] Considering the facile reduction of alkyl iodides, it is probable that the C(26) iodo group of **26** is first reduced to radical intermediate **29**. If intermediate radical **29** abstracts a hydride to form **30**, the reaction will continue through path a to provide saturated lactone **28**. Syn elimination[11] of **29**, as shown in path b, yields **27**.

If the proposed reaction mechanism shown in Scheme 9 is correct, the more reactive hydride reagent should enable the rate of path a to compete with the rate of path b. The less reactive hydride source should favor syn elimination (path b). Giese showed that the rate of hydride abstraction of a secondary radical using tri-*n*-butylstannane is approximately eleven times that of tris(trimethylsilyl)silane.[12] With this in mind, the reaction conditions were altered to favor path a by increasing the concentration of the more reactive hydride donor. Treatment of thionocarbonate **26** with catalytic azobisisobutyronitrile and six equivalents of tri-*n*-butylstannane provided 25% of alkene **27** and 60% of lactone **28**.



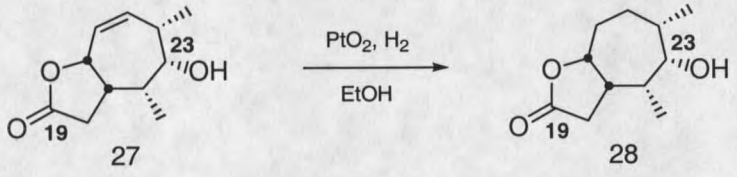
Scheme 9

The choice of hydride reagent has been used in other cases to influence the conversion of radical intermediates. Numerous tin hydride sources exist with varying degrees of reactivity. While tri-*n*-butylstannane is one of the most commonly used stannanes, it demonstrates the lowest reactivity of the following: $^{n}Bu_3SnH < {}^{n}Bu_2SnH_2 < Ph_3SnH < Ph_2SnH_2$.[10] The reactivity difference between tri-*n*-butylstannane and triphenylstannane was used to control product formation of the cyclopropyl carbinyl radical ring opening below (Scheme 10)[13]:



Scheme 10

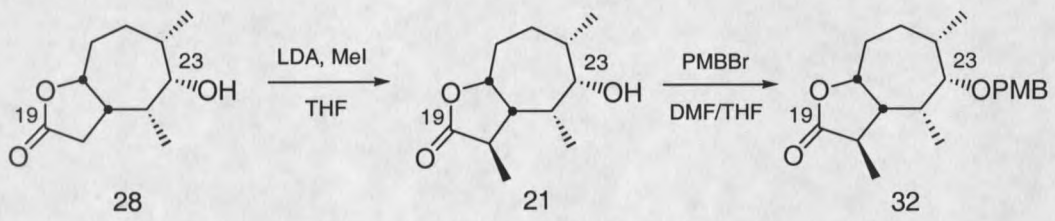
The above protocol for this dual deiodonation-deoxygenation provides predominately lactone **28**; however, the minor product could be converted to the fully saturated lactone via hydrogenation (Scheme 11). To this end, alkene **27** was treated with platinum(IV) oxide under an atmosphere of hydrogen to afford lactone **28** in 79% yield (Scheme 11).



27 28

Scheme 11

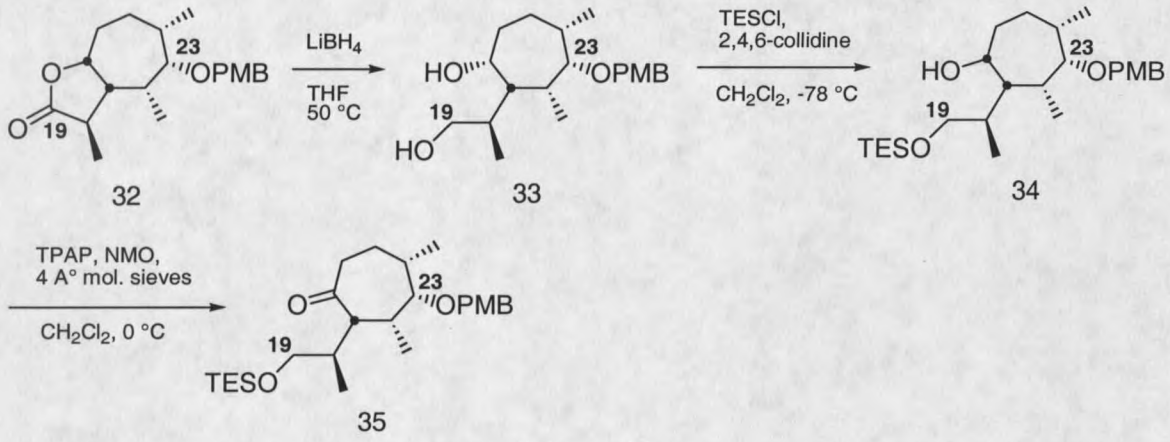
With **28** in hand, attention was focused on incorporation of the C(20) β-methyl group of **21** (Scheme 12). The dianion of lactone **28** was formed (2 equiv of LDA, –78 °C → 0 °C) and the reaction mixture was treated with eight equivalents of freshly distilled methyl iodide at –78 °C. The reaction was warmed to –36 °C and stirred for 9 h providing lactone **21** in 60% yield along with recovered starting material (21%). No alkylation product from the more hindered α-face was observed. Warming the reaction mixture to 0 °C, after the addition of methyl iodide, resulted in decomposition of the enolate. Protection of the C(23) hydroxyl as its *p*-methoxybenzyl ether provided **32** in quantitative yield.



28 21 32

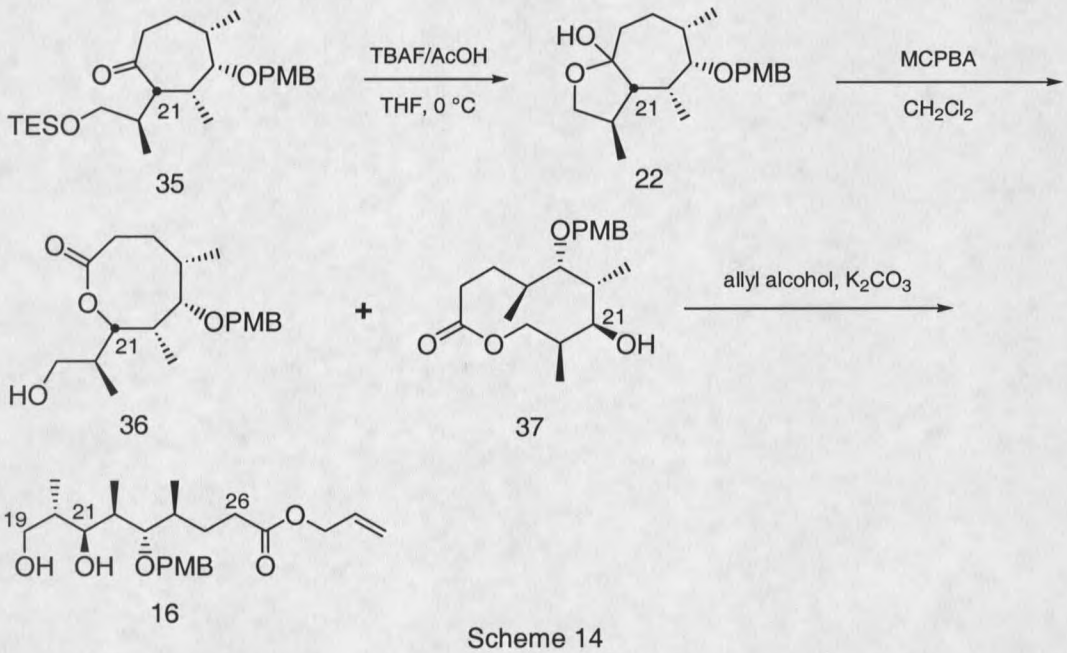
Scheme 12

Reduction of lactone **32** to diol **33** using lithium borohydride, followed by protection of the resulting primary alcohol using triethylchlorosilane and 2,4,6-collidine provided **34** in 88% yield for the two steps (Scheme 13). The secondary alcohol was oxidized using Ley conditions[14] to provide ketone **35** in an 88% yield.



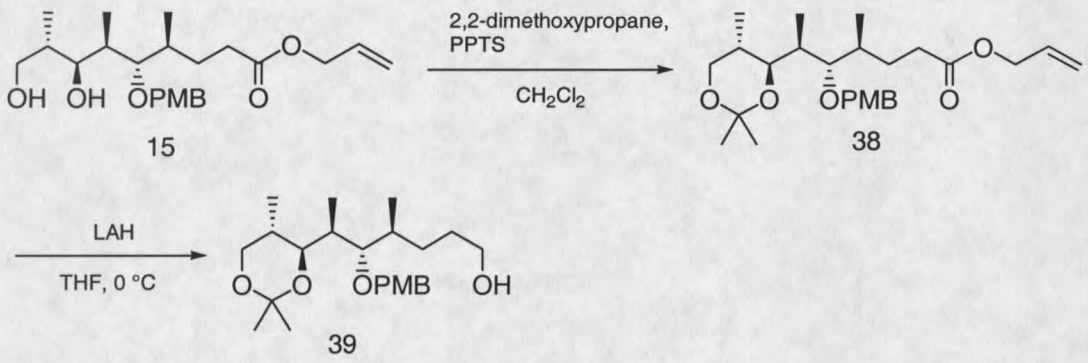
Scheme 13

Earlier studies showed that ketone **35** will not undergo Baeyer-Villiger oxidation. However, it was discovered that internal hemiketal **22**, formed via deprotection of **35**, will readily undergo Baeyer-Villiger oxidation to insert an oxygen atom at C(21) (Scheme 14).[5, 15] Deprotection of **35** using tetrabutylammonium fluoride and acetic acid furnished hemiketal **22**. The crude product was treated with *m*-chloroperbenzoic acid to afford a mixture of lactones **36** and **37**. Exposure of the crude lactones to potassium carbonate and allyl alcohol afforded allyl ester **16** in 68% overall yield.



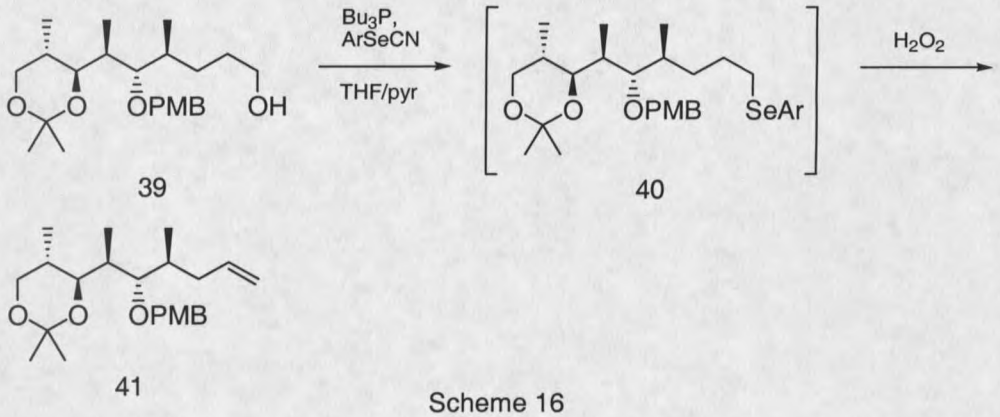
Scheme 14

With allyl ester **16** in hand, efforts were directed at the removal of the C(27) carbon of the C(19)-C(27) fragment. The 1,3-diol functionality of ester **16** was first protected as an acetonide employing pyridinium *p*-toluenesulfonate and 2,2-dimethoxypropane (Scheme 15). The reaction mixture was exhaustively washed with saturated aqueous sodium bicarbonate and purified by column chromatography to afford acetonide **38** in a 97% yield. If exhaustive workup conditions were not employed, acetonide **38** decomposed to ester **16** and other unidentified products upon concentration. Base washed glassware was essential, otherwise the labile acetonide **38** would decompose. Treatment of acetonide **38** with lithium aluminum hydride provided alcohol **39** in a 88% yield.



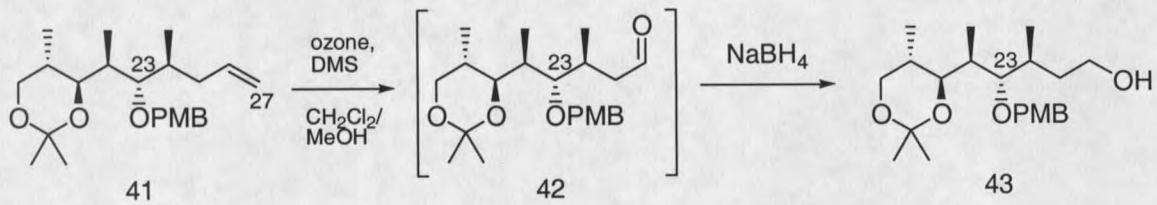
Scheme 15

Attempts were next directed at converting **39** to alkene **41** employing the Grieco protocol (Scheme 16).[16] Treatment of alcohol **39**, azeotropically dried with benzene, with 2-nitrophenylselenocyanate and tri-*n*-butylphosphine in tetrahydrofuran afforded recovered starting material (30%) and an inseparable mixture of selenide **40** and 2-nitrophenylselenocyanate. The mixture of selenide and 2-nitrophenylselenocyanate was exposed to hydrogen peroxide to provide **41** in a 35% yield for two steps. In order to improve the yield of the reaction, alcohol **39** was treated with 2-nitrophenylselenocyanate and tri-*n*-butylphosphine in a 1:1 mixture of tetrahydrofuran/pyridine.[17] TLC analysis showed complete conversion to selenide **40** after 1 h. The reaction mixture was treated with hydrogen peroxide to provide alkene **41** in 85% yield.



Scheme 16

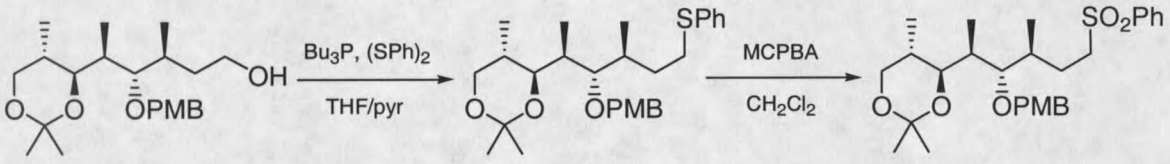
With the double bond in place, the stage was set for removing the C(27) carbon of **41** (Scheme 17). To this effort, olefin **41** was added to a saturated solution of ozone in methylene chloride. The reaction mixture was treated with methylsulfide to provide aldehyde **42** in situ. Sodium borohydride was then added to give 66% of alcohol **43** and 26% of recovered starting material. Attempts to improve the reaction yield using excess ozone appeared to cleave the *p*-methoxybenzyl protected hydroxy group at C(23). Additionally, attempts to directly reduce the ozonide with sodium borohydride resulted in lower yields.



Scheme 17

Having cleaved the extra carbon, all that remained to complete the synthesis of the C(19)-C(26) fragment of Scytophycin C was the transformation of alcohol **43** into

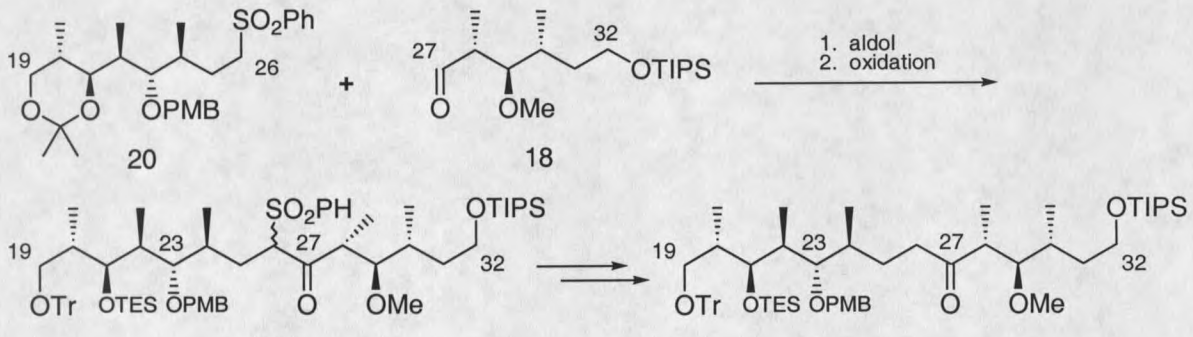
sulfone **20** (Scheme 18). Exposure of alcohol **43** to tri-*n*-butylphosphine and phenyl disulfide in tetrahydrofuran resulted in decomposition of starting material. Changing the solvent system to a 2:1 mixture of tetrahydrofuran/pyridine provided sulfide **44** in a 48% yield along with 35% recovered starting material. Sulfide **44** was treated with *m*-chloroperbenzoic acid in a solution of methylene chloride buffered with potassium carbonate to afford sulfone **20**, the desired C(19)-C(26) fragment, in 94% yield.



43 44 20

Scheme 18

Future efforts will involve investigating the coupling of sulfone **20** and aldehyde **18** (Scheme 19). Addition of the anion of sulfone **20** to aldehyde **18** followed by oxidation of the resulting alcohol will provide ketone **45**. Desulfurization of **45** will complete the synthesis of the C(19)-C(32) fragment **19b** of Scytophycin C.

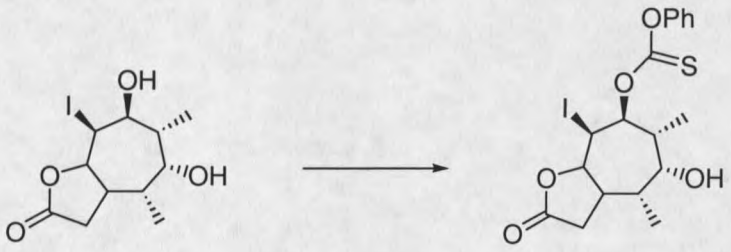


20 18 45 19b

Scheme 19

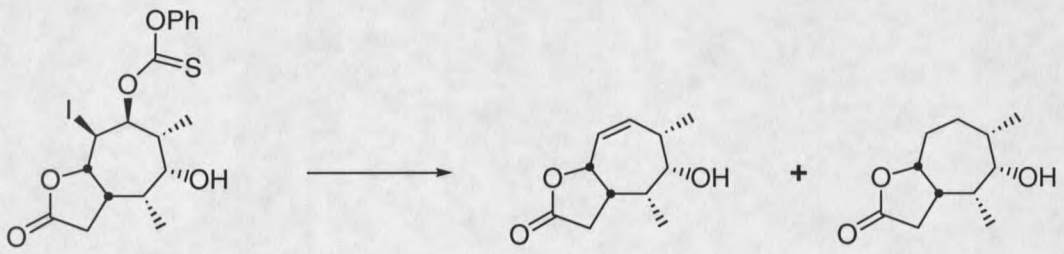
EXPERIMENTAL

Proton (^{1}H) and carbon (^{13}C) nuclear magnetic resonance (NMR) spectra were recorded on a Varian VXR-500 MHz or Bruker DPX-300 MHz spectrometer as indicated. Chemical shifts are reported in parts per million (δ) and peaks are reported as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and apparent (app). Singlets may be described as broad (br). Infrared (IR) spectra were taken on a Perkin-Elmer 1600 series FTIR spectrometer as thin films (chloroform) on NaCl plates. Signals are described as broad (br), weak (w), medium (m) and strong (s). Melting points were taken on a Fisher-Johns hot-stage melting point apparatus and are uncorrected. High resolution mass spectra were obtained using a Kratos MS 80/RFAQ spectrometer or a Bruker Biflex-III spectrometer. Reactions were monitored by thin layer chromatography (TLC) using E. Merck precoated silica gel 60 F-254 (0.25 mm thickness) plates. Visualization of TLC plates was effected by either: ultraviolet illumination, potassium permanganate oxidation, or *p*-anisaldehyde derivitization. Potassium permanganate indicator was prepared using 1.5 g potassium permanganate, 10 g potassium carbonate, 2.5 mL 5% sodium hydroxide and 150 mL water. The *p*-anisaldehyde stain was prepared using 3 L ethanol, 93 ml sulfuric acid, 8 mL *p*-anisaldehyde and 3.5 mL acetic acid. E. Merck silica gel 60 (230-400 mesh) or Davisil silica gel (Grade 643, pH = 7) were used for flash chromatography. All solvents were reagent grade unless noted otherwise. Methylene chloride, tetrahydrofuran, ether and toluene were distilled from sodium and benzophenone. Other anhydrous solvents were distilled from calcium hydride immediately before use. Methyl iodide was distilled from $CaCl_2$.



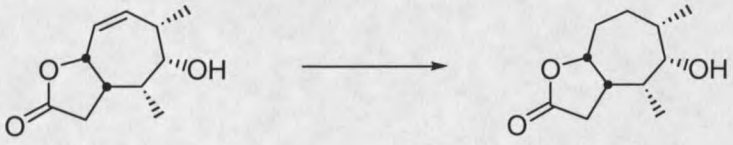
(3a*S*, 4*R*, 5*R*, 6*R*, 7*S*, 8*S*, 8a*S*)-Thiocarbonic acid O-(5-hydroxy-8-iodo-4,6-dimethyl-2-oxo-octahydro-cyclohepta[b]furan-7-yl) ester O-phenyl ester (**26**). A solution of iodolactone **25** (3.40 g, 10.0 mmol) in CH_3CN (50 mL, 0.20 M) was treated with DMAP and cooled to 0 °C under argon. After stirring 30 min, phenyl chlorothioformate (1.66 ml, 12.00 mmol) was added via syringe and the reaction mixture was stirred for 28 h at 0 °C before quenching with saturated aqueous $NaHCO_3$ (65 mL). The solution was diluted with ether, the layers separated, and the aqueous layer was extracted with ether (3x70 mL). The combined organic layers were dried, filtered and concentrated in vacuo. The crude white solid was purified on silica gel (7:3 Et_20-pentane) to provide 0.33 g (9.5%) of recovered starting material and 4.12 g (87%) of lactone **26** as a white solid, mp 80 °C (dec): $[\alpha]^{25}_D$ –61.0 (c 1.5 $CHCl_3$), R_f 0.35 (1:1 EtOAc-hexanes), IR (thin film, $CHCl_3$) 3484 (br m), 2965 (m), 2933 (m), 2880 (m), 2251 (w), 1773 (s), 1591 (m), 1489 (m), 1455 (m), 1413 (w), 1374 (m), 1340 (m), 1274 (s), 1200 (s), 1118 (w), 1102 (w), 1069 (w), 1012 (m), 965 (m), 912 (s), 865 (m), 772 (m), 740 (s), 689 (m) cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 6.95-7.05 (m, 4H), 6.93-6.83 (m, 1H), 5.32 (d, J = 10.35 Hz, 1H), 5.23 (dd, J = 5.79, 2.40 Hz, 1H), 4.44 (app t, J = 3.73 Hz, 1H), 3.24 (AB quartet, J_{AB} = 6.85 Hz, Δν = 12.15 Hz, 1H), 2.99 (d, J = 3.73 Hz, 1H), 2.73 (d, J = 17.41 Hz, 1H), 2.28-2.42 (m, 1H), 2.14-2.24 (m, 1H), 2.08-1.90 (m, 2H), 1.12 (d, J = 6.38 Hz, 3H), 0.75 (d, J

= 7.02 Hz, 3H); ^{13}C NMR (300 MHz) δ 193.82, 177.26, 153.81, 129.67 (2C), 126.49, 122.31 (2C), 82.74, 81.71, 77.54, 44.41, 40.70, 36.07, 32.80, 31.58, 19.64, 16.21; HRMS (CI) calcd. for $C_{18}H_{21}O_5S$ $(M+NH_4)^+$ m/e 494.0483, found 494.0498.



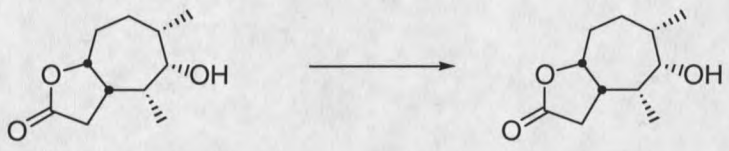
(3a*S*, 4*R*, 5*S*, 6*S*, 8a*R*)-5-Hydroxy-4,6-dimethyl-3,3a,4,5,6,8a-hexahydro-cyclohepta[b]furan-2-one (**27**). Iodolactone **26** (47 mg, 0.099 mmol) was dissolved in toluene (4.0 ml, 0.025 M) and the solution was sparged with argon for 45 min. Bu_3SnH (106 μL, 0.395 mmol) was added via syringe and the solution was sparged for 15 minutes followed by addition of AIBN (5 mg, 0.030 mmol). The reaction mixture was brought to reflux for 2 h and the solution was cooled to ambient temperature and concentrated in vacuo. The residue was purified on silica gel (4:6 EtOAc-hexanes → 0.5:9.5 MeOH-$CHCl_3$) to afford 9 mg (48%) of saturated lactone **28** as a yellow oil and 7 mg (34%) of unsaturated lactone **27** as a white solid, mp 124-125 °C: $[\alpha]^{25}_D$ +40.0 (c 0.8, $CHCl_3$); R_f 0.13 (1:1 EtOAc-hexanes); IR (thin film, $CHCl_3$) 3416 (br s), 3026 (w), 2965 (m), 2934 (m), 2879 (m), 2246 (w), 1704 (s), 1458 (m), 1392 (m), 1336 (m), 1264 (m), 1192 (s), 1156 (m), 1125 (m), 1074 (s), 1042 (m), 995 (m), 964 (m), 921 (m), 864 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.68 (dm, J = 11.59 Hz, 1H), 5.26 (app dt, J = 11.57, 2.71 Hz, 1H), 4.46 (m, 1H), 4.183 (s, 1H), 2.67-2.35 (m, 3H), 2.08-1.92 (m, 2H), 1.85 (s, 1H),

1.29 (d, J = 7.59, 3H), 1.26 (d, J = 7.30, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 170.4, 135.9, 132.1, 84.9, 74.0, 40.5, 39.8, 34.7, 26.6, 20.8, 20.2; HRMS (EI) calcd. for $C_{11}H_{16}O_3$ (M^+) *m/e* 196.1108, found 196.1099.



(3a*S*, 4*R*, 5*S*, 6*S*, 8a*R*)-5-Hydroxy-4,6-dimethyl-octahydro-cyclohepa[b]furan-2-one (**28**). A solution of olefin **27** in absolute EtOH (25 mL, 0.15 M) was treated with PtO_2 (0.17 mg, 0.75 mmol). The reaction vessel was purged with hydrogen gas and the mixture was stirred at ambient temperature for 4 h. The reaction mixture was filtered through a pad of Celite, dried with $MgSO_4$, filtered and concentrated in vacuo. The crude oil was purified using silica gel (3.5:6.5 → 4.5:5.5 EtOAc—hexanes) to provide 0.58 g (78%) of saturated lactone **28** as a white solid, mp 89-90 °C: $[\alpha]^{25}_D$ –4.3° (c 1.1, $CHCl_3$); R_f 0.42 (1:1 EtOAc-hexanes); IR (thin film, $CHCl_3$) 3494 (br s), 2958 (s), 2929 (s), 2874 (s), 1752 (s), 1456 (m), 1413 (w), 1372 (m), 1298 (w), 1207 (s), 1094 (s), 1039 (w), 1005 (s), 969 (s), 954 (s), 917 (w), 868 (w), 830 (w), 801 (w), 775, (w), 727 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.86 (app t, J = 7.20 Hz, 1H), 3.66 (s, 1H), 2.98 (dd, J = 17.4, 2.2 Hz, 1H), 2.71-2.59 (m, 1H), 2.49 (dd, J = 17.4, 11.3 Hz, 1H), 2.24 (app dt, J = 14.8 Hz, 1H), 1.97 (m, 1H), 1.84 (app t, J = 13.0 Hz, 1H), 1.71 (d, J = 14.8 Hz, 1H) 1.65-1.54 (m, 1H), 1.53 (d, J = 3.1 Hz, 1H), 1.37-1.23 (m, 1H), 1.12 (d, J = 7.2 Hz, 3H), 0.95 (d, J = 6.9

Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 178.3, 81.2, 80.6, 42.1, 41.8, 37.7, 32.6, 28.9, 23.7, 20.6, 19.9); HRMS (EI) calcd. for $C_{11}H_{18}O_3$ (M^+) *m/e* 198.1256, found 198.1265.



(3*R*, 3a*R*, 4*R*, 5*S*, 6*S*, 8a*R*)-5-Hydroxy-3,4,6-trimethyl-octahydro-cyclohept[b]furan-2-one (**21**). Diisopropylamine (2.90 ml, 20.3 mmol) in THF (12.1 ml), cooled to 0 °C under argon, was treated with ^{n}BuLi (7.6 ml, 2.5 M solution hexanes). After 30 min, the solution was cooled to -78 °C. Saturated lactone **28** (1.34 g, 6.77 mmol) in THF (30 ml + 2x7 ml washings) was added via syringe and the reaction was warmed to 0 °C and stirred for 2 h. The reaction mixture was cooled to -78 °C and methyl iodide (3.4 ml, 54 mmol) was added via syringe. The reaction mixture was warmed to -45 °C, stirred for 2 h, and placed in a -36 °C freezer. After 7 h, the mixture was quenched with saturated aqueous NH_4Cl. The layers were separated and the aqueous layer was extracted with EtOAc (2x50 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The crude oil was purified on silica gel (3:7 EtOAc-hexanes) to provide 0.29 g (21%) recovered **28** and 0.87 g (60%) of product **21** as a colorless oil: $[\alpha]^{25}_D$ +17.8° (c 0.45, $CHCl_3$); R_f 0.50 (1:1 EtOAc-hexanes); IR (thin film, $CHCl_3$) 3493 (br m), 2959 (s), 2930 (s), 2874 (s), 1749 (s), 1456 (m), 1383 (m), 1301 (w), 1280 (w), 1212 (m), 1129 (w), 1087 (m), 1030 (w), 1001 (s), 975 (m), 957 (s), 915 (m), 841 (w), 725 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.89 (app t , J = 7.19 Hz,

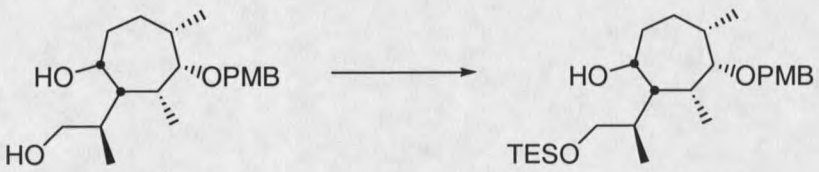
1H), 3.65 (s, 1H), 3.16 (ddd, J = 15.27, 7.62, 2.73 Hz, 1H), 2.33-2.17 (m, 2H), 2.10-1.93 (m, 1H), 1.92-1.76 (m, 1H), 1.75-1.49 (m, 3H), 1.45-1.25 (m, 1H), 1.27 (d, J = 7.72 Hz, 3H), 1.14 (d, J = 7.17 Hz, 3H), 0.95 (d, J = 6.87, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 181.77, 79.97, 79.333, 50.69, 41.76, 38.79, 37.91, 28.92, 23.66, 20.05, 19.80, 19.13; HRMS (EI) calcd. for $C_{12}H_{20}O_3$ (M^+) *m/e* 212.1412, found 212.1412.

(3*R*, 3a*R*, 4*R*, 5*S*, 6*S*, 8a*R*)-5-(4-Methoxy-benzyloxy)-3,4,6-trimethyl-octahydro-cyclohepta[b]furan-2-one (**32**). A solution of alcohol **21** (0.87 g, 4.1 mmol) in DMF (13.6 mL, 0.15 M) was treated with 18-C-6 (1.08 g, 4.09 mmol), followed by Bu_4NI (1.51 g, 4.09 mmol) at ambient temperature under argon. THF (13.6 mL) was added and the solution was cooled to 0 °C. After stirring 20 min, PMBBr (4.13 mL, 28.6 mmol) was added, followed by a slurry of KH in mineral oil (30%, 1.63 g, 12.3 mmol). The reaction mixture was stirred 3 h and quenched with saturated aqueous NH_4Cl. The layers were separated, the aqueous layer was extracted with ether (3x20ml), and the combined organic layers were concentrated, filtered and dried using $MgSO_4$. Purification on silica gel (3:7 EtOAc-hexanes) gave 1.35 g (99%) of protected alcohol **32** as a white solid, mp 99-102 °C: $[\alpha]^{25}_D$ +14.4° (c 1.0, $CHCl_3$); R_f 0.30 (3:7 EtOAc-hexanes); IR (thin film, $CHCl_3$) 2958 (s), 2930 (s), 2874 (s), 1761 (s), 1611 (m), 1585 (w), 1514 (s), 1454 (m), 1379 (m), 1361 (w), 1345 (w), 1303 (m), 1247 (s), 1200 (s), 1176 (m), 1085 (m), 1035

(s), 1000 (m), 974 (w), 942 (w), 908 (w), 819 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25 (dm, J = 6.82 Hz, 2H), 6.87 (dm, J = 8.65 Hz, 2H), 4.83 (tm, J = 6.36 Hz, 1H), 4.52 (AB quartet, J_{AB} = 11.58 Hz, $\Delta\nu_{AB}$ = 14.41 Hz, 2H), 3.81 (s, 3H), 3.45 (s, 1H), 3.02 (app dq, J = 15.14, 3.78 Hz, 1H), 2.30-2.11 (m, 2H), 2.00-1.78 (m, 2H), 1.71-1.50 (m, 2H), 1.33-1.26 (m, 1H), 1.23 (d, J = 7.63 Hz, 3H), 0.97 (d, J = 7.30 Hz, 3H), 0.94 (d, J = 6.90 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 180.82, 159.17, 130.94, 129.82 (2C), 113.62 (2C), 88.03, 79.31, 76.02, 55.24, 50.57, 42.69, 38.58, 38.40, 29.66, 24.71, 20.69, 20.53, 19.07; HRMS (CI) calcd. for $C_{20}H_{32}NO_4$ $(M+NH_4)^+$ m/e 350.2328, found 350.2331.

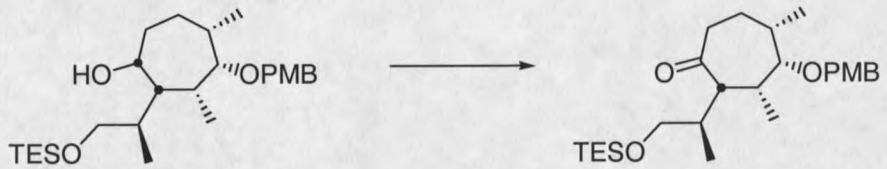
(1*R*, 2*S*, 3*R*, 4*S*, 5*S*)-2-((S)-2-Hydroxy-1-methyl-ethyl)-4-(4-methoxy-benzyloxy)-3,5-dimethyl-cycloheptanol (**33**). Lactone **32** (1.35 g, 4.05 mmol) in THF (27 mL, 0.15 M) was treated with $LiBH_4$ (0.53 g, 24 mmol) and heated to 50 °C. After heating for 65 h, the reaction mixture was quenched with H_20 (15 mL), diluted with Et_2O (20 mL), and treated with a 20% aqueous K_2CO_3 (5 mL). The solution was diluted with EtOAc (15 mL), the layers were separated, and the aqueous layer was extracted with EtOAc (2x20 mL). The combined organic washes were dried with Na_2SO_4, filtered and concentrated in vacuo. Purification of the residue on silica gel (6:4 EtOAc-hexanes) provided 1.18 g (87%) of diol **33** as a white, amorphous solid, mp 72-75 °C: $[\alpha]^{25}_D$ +19.2 ° (c 1.2 $CHCl_3$); R_f 0.25 (1:1 EtOAc-hexanes); IR (thin film, $CHCl_3$); 3374 (br s), 2953 (s), 2918 (s), 2876

(s), 1613 (m), 1514 (s), 1456 (m), 1301 (w), 1248 (s), 1173 (w), 1082 (m), 1035 (s), 862 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27 (dm, J = 8.64 Hz, 2H), 6.88 (dm, J = 8.69 Hz, 2H), 4.59 (AB quartet, J_{AB} = 11.03 Hz, Δν = 5.65 Hz, 2H), 4.15 (m, 2H), 3.80 (s, 3H), 3.69 (m, 2H), 3.56 (dd, J = 4.57, 2.17 Hz, 1H), 2.65 (br s, 1H), 2.19 (m, 1H), 2.09-1.78 (m, 4H), 1.62 (app t, J = 6.55 Hz, 1H), 1.56-1.37 (m, 2H), 1.20 (d, J = 7.51 Hz, 3H), 1.11 (d, J = 7.00 Hz, 3H), 0.99 (d, J = 6.90 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 160.11, 131.57, 129.62 (2C), 114.54 (2C), 86.99, 74.09, 70.49, 67.11, 55.14, 49.64, 40.56, 36.98, 36.38, 34.71, 26.40, 20.74, 18.20, 14.86; HRMS (CI) calcd. for $C_{20}H_{32}O_4$ $(M+H)^+$ m/e 337.2379, found 337.2365.



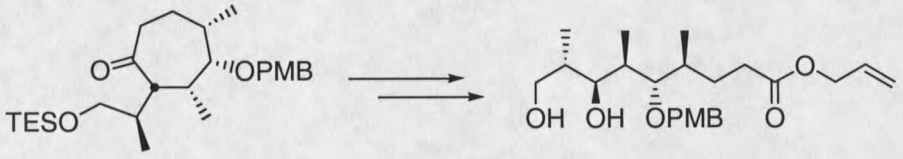
(1*R*, 2*S*, 3*R*, 4*S*, 5*S*)-4-(4-Methoxy-benzyloxy)-3,5-dimethyl-2-[1-(*R*)-methyl-2-(triethyl-silanyloxy)-ethyl]-cycloheptanol (**34**). Diol **33** (1.18 g, 3.50 mmol) was dissolved in CH_2Cl_2 (35 mL) and treated with 2,4,6-collidine (1.40 mL, 10.5 mmol) and cooled to –78 °C under argon. The reaction mixture was stirred for 30 min and treated with TESCl (0.76 mL, 4.6 mmol). After 4 h, the reaction was quenched with saturated aqueous NH_4Cl, diluted with Et_2O and warmed to rt. The layers were separated, the aqueous layer was extracted with EtOAc (2x50 mL), and the combined organic washes were dried with $MgSO_4$, filtered and concentrated. Purification of the crude oil on silica gel (1:9→2:8 EtOAc-hexanes) gave 1.47 g (93%) of alcohol **34** as a yellow oil: $[\alpha]^{25}_D$

+13.8° (c 0.68, EtOAc); R_f 0.79 (1:1 EtOAc-hexanes); IR (thin film, $CHCl_3$) 3445 (s), 2954 (s), 2874 (s), 2731 (m), 2071 (w), 1873 (w), 1615 (s), 1585 (m), 1515 (s), 1459 (s), 1412 (s), 1370 (s), 1302 (s), 1247 (s), 1165 (s), 1083 (s), 1013 (s), 956 (s), 914 (m), 893 (m), 814 (s), 744 (s), 667 (m) cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 7.24 (d, J = 7.67 Hz, 2H), 6.78 (d, J = 7.34 Hz, 2H) 4.41 (s, 2H), 4.23 (m, 1H), 3.72-3.49 (m, 3H), 3.53 (m, 1H), 3.30 (s, 3H), 2.17 (m, 1H), 2.11-1.93 (m, 4H), 1.54 (m, 1H), 1.42 (m, 2H), 1.37 (d, J = 7.49 Hz, 3H), 1.13 (d, J = 5.28 Hz, 3H), 1.00 (m, 12H), 0.59 (m, 6H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 159.66, 131.40, 129.13 (2C), 114.10 (2C), 86.31, 73.37, 70.17, 67.36, 54.72, 49.08, 39.84, 36.58, 35.87, 34.31, 26.06, 20.05, 17.57, 13.93, 7.05 (3C), 4.68 (3C); HRMS (CI) calcd. for $C_{26}H_{46}O_4Si$ $(M+H)^+$ m/e 451.3244, found 451.3238.



(2*S*, 3*R*, 4*S*, 5*S*)-4-(4-Methoxy-benzyloxy)-3,5-dimethyl-2-[1-(*R*)-methyl-2-(triethyl-silanyloxy)-ethyl]-cycloheptanone (**35**). Alcohol **34** (1.34 g, 2.96 mmol) in CH_2Cl_2 (20 mL, 0.15M) was treated with NMO (0.69 g, 5.9 mmol) followed by 4 A° molecular sieves (1.98 g). The reaction mixture was stirred for 5 min, cooled to 0 °C, treated with TPAP (78 mg, 0.22 mmol) and allowed to warm to ambient temperature. After stirring 6 h, the reaction mixture was filtered through Davisil, concentrated, and applied to silica gel. Elution with Et_2O-pentane (1:9) provided 1.17 g (88%) of **35** as a clear, colorless oil: $[\alpha]^{25}_D$ +61.2° (c 0.6, $CHCl_3$); R_f 0.50 (1:4 Et_2O-pentane); IR (thin

film, $CHCl_3$) 2954 (s), 2913 (s), 2875 (s), 1699 (s), 1614 (m), 1590 (w), 1515 (s), 1456 (s), 1413 (m), 1381 (m), 1343 (w), 1299 (m), 1248 (s), 1205 (m), 1171 (m), 1080 (s), 1038 (s), 1011 (s), 963 (m), 819 (s), 798 (m), 745 (s), 670 (w) cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 7.24 (dm, J = 8.63 Hz, 2H), 6.82 (dm, J = 6.86 Hz, 2H), 4.33 (s, 2H), 3.55 (dd, J = 9.58, 4.92 Hz, 1H), 3.40 (dd, J = 9.58, 3.64 Hz, 1H), 3.33 (s, 3H), 3.32-3.28 (m, 1H), 2.72 (dd, J = 10.11, 2.34 Hz, 1H), 2.62-2.32 (m, 3H), 2.29-2.14 (m, 2H), 1.69 (app tdd, J = 12.32, 5.77, 1.83 Hz, 1H), 1.49-1.36 (m, 1H), 1.06-0.89 (m, 18 H), 0.58 (m, 6H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 211.67, 160.02, 131.98, 129.39 (2C), 114.45 (2C), 85.57, 71.14, 67.32, 55.15, 51.97, 41.70, 36.42, 34.68, 33.99, 26.35, 15.35, 13.46, 10.65, 7.47 (3C), 5.14 (3C); HRMS (CI) calcd. for $C_{26}H_{44}O_4Si$ $(M+H)^+$ m/e 449.3087, found 449.3080.



(4*S*, 5*S*, 6*R*, 7*S*, 8*S*)-7,9-Dihydroxy- 5-(4-methoxy-benzyloxy)-4,6,8-trimethyl-nonanoic acid allyl ester (**16**). Cycloheptanone **35** (107 mg, 0.238 mmol) was dissolved in THF (2.4 ml, 0.1 M) and cooled to 0 °C under argon. After stirring for 15 min, the reaction mixture was treated with a 1:1 solution of TBAF/AcOH in THF (0.48 ml 1.0 M TBAF in THF, 27 μL AcOH). The reaction mixture was stirred for 8 h, quenched with saturated aqueous $NaHCO_3$ (3 mL) and diluted with EtOAc (3 mL). The layers were separated and the organic layer was washed with saturated aqueous $NaHCO_3$ (3 mL).

The combined aqueous layers were extracted with EtOAc (3x5 mL), dried with $MgSO_4$, and filtered through a plug of Davisil. The filtrate was concentrated in vacuo to provide 118 mg of crude hemiketal **22**.

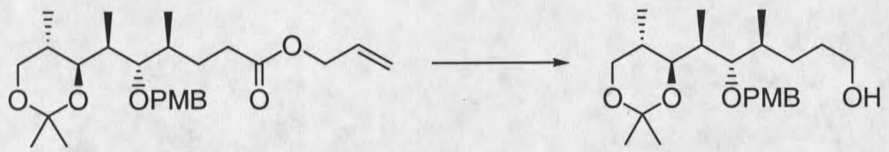
Crude hemiketal **22** prepared in the first step was dissolved in CH_2Cl_2 (2.4 mL, 0.1 M) and the reaction mixture was purged with argon and treated with MCPBA (58 mg, 0.33 mmol). The reaction vessel was immediately wrapped in aluminum foil. After stirring 3 h, the reaction was quenched with 10% aqueous Na_2SO_3 (2 mL), followed by saturated aqueous $NaHCO_3$ (2 mL) and EtOAc (4 mL). The layers were separated and the organic layer was washed with of 20% aqueous K_2CO_3 (2 mL). The combined aqueous washes were washed with EtOAc (2x5 mL) and the combined organic washes were dried with Na_2SO_4 and filtered through a plug of Davisil. The filtrate was concentrated in vacuo and crude **36** and **37** were submitted to the next step without further purification.

A solution of the crude oil from the previous step and allyl alcohol (2.4 mL, 0.1 M) was treated with K_2CO_3 (46 mg, 0.33 mmol) and warmed to 50 °C. The reaction was stirred for 2 h, quenched with saturated aqueous NH_4Cl, (4 mL) and diluted with EtOAc (4 mL). The layers were separated and the organic layer was washed with brine (2 mL). The combined aqueous washes were extracted with EtOAc (2x5 mL), and the combined organic washes were dried with Na_2SO_4, filtered, concentrated in vacuo and applied to silica gel. Elution with EtOAc/hexanes (4:6→1:1) yielded 66 mg (68% for 3 steps) of allyl ester **16** as a light yellow oil: $[\alpha]^{25}_D$ –14.5° (c 0.6, $CHCl_3$); R_f 0.26 (1:1 EtOAc-hexanes); IR (thin film, $CHCl_3$) 3419 (br, m), 2964 (m), 2934 (m), 2873 (m), 1732 (s),

1614 (m), 1515 (s), 1455 (m), 1381 (m), 1303 (m), 1249 (s), 1173 (s) 1032 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.23 (dm, J = 8.56 Hz, 2H), 6.76 (dm, J = 8.60 Hz, 2H), 5.83-5.68 (m, 1H), 5.13 (dm, J = 17.20 Hz, 1H), 4.99 (dm, J = 10.39 Hz, 1H), 4.47 (dm, J = 5.65 Hz, 2H), 4.38 (s, 2H), 4.07 (s, 1H), 3.85 (d, J = 9.63 Hz, 1H), 3.74-3.66 (m, 2H), 3.43-3.37 (m, 1H), 3.28 (s, 3H), 3.01 (dd, J = 7.59, 3.53 Hz, 1H), 2.32-2.00 (m, 3H), 1.93-1.80 (m, 1H), 1.78-1.65 (m, 2H), 1.53-1.37 (m, 1H), 1.01 (d, J = 7.08 Hz, 3H), 0.65 (d, J = 6.78 Hz, 3H), 0.54 (d, J = 6.90 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 173.20, 160.39, 133.25, 130.89, 130.14 (2C), 118.17, 114.68 (2C), 90.01, 77.14, 76.46, 69.61, 65.31, 55.12, 38.31, 36.21, 35.98, 32.52, 28.35, 16.45, 13.83, 12.13; HRMS (CI) calcd. for $C_{23}H_{36}O_6$ $(M+H-H_20)^+$ m/e 391.2481, found 391.2485.

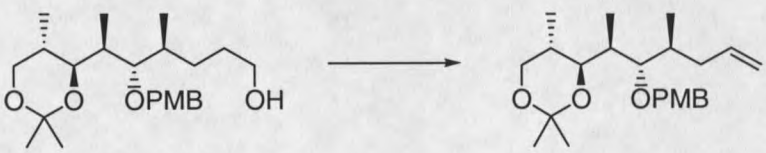
(4*S*, 5*S*, 6*S*)-5-(4-Methoxy-benzyloxy)-4-methyl-6-((4*S*, 5*S*)-2,2,5-trimethyl-[1,3]dioxan-4-yl)-heptanoic acid allyl ester (**38**). A solution of ester **16** (142 mg, 0.348 mmol) in CH_2Cl_2 (2.4 mL, 0.12 M) was treated with 2,2-dimethoxypropane (1.7 mL). The mixture was purged with argon and treated with a solution PPTS (9 mg, 0.035 mmol) in CH_2Cl_2 (0.5 mL). The reaction mixture was stirred for 30 min and quenched with $NaHCO_3$ (4 mg, 0.042 mmol). The mixture was washed with saturated $NaHCO_3$ (2x3 mL). The combined aqueous layers were washed with EtOAc (2x4 mL) and the combined organic washes were washed with brine, dried with Na_2SO_4, and concentrated

in vacuo to provide 152 mg (97%) of crude acetonide **38** as a yellow oil. An analytical sample was prepared on Davisil (0.5:9.5→1:10 EtOAc-hexanes): R_f 0.75 (1:1 EtOAc-hexanes); IR (thin film, $CHCl_3$) 3005 (s), 2959 (s), 2880 (m), 1737 (s), 1612 (m), 1514 (s), 1462 (m), 1382 (s), 1300 (m), 1248 (s), 1180 (s), 1173 (s), 1082 (s), 1061 (s), 1007 (m), 928 (m), 868 (m), 821 (m) cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.33 (d, J = 8.49 Hz, 2H), 6.85 (d, J = 8.55 Hz, 2H), 5.73 (m, 1H), 5.10 (dd, J = 17.19, 1.38 Hz, 1H), 4.95 (dm, J = 10.41 Hz, 1H), 4.63 (AB quartet, J_{AB} = 11.24, Δν = 18.43 Hz, 2H), 4.44 (m, 2H), 3.98 (d, J = 10.38 Hz, 1H), 3.58 (dd, J = 11.40, 5.01 Hz, 1H), 3.44 (dm, J = 8.88 Hz, 1H), 3.32 (m, 4H), 2.34 (app dq, J = 15.72, 5.01 Hz, 1H), 2.21 (m, 1H), 2.00 (m, 2H), 1.87-1.67 (m, 3H), 1.55 (s, 3H), 1.37 (s, 3H), 0.98 (d, J = 6.58 Hz, 3H), 0.96 (d, J = 6.99 Hzm, 3H), 0.42 (d, J = 6.65 Hz, 3H); ^{13}C NMR (300 MHz) δ 175.83, 159.01, 131.71, 128.64 (2C), 128.46, 113.85 (2C), 98.21, 84.17, 74.64, 73.69, 66.42, 63.36, 55.39, 36.85, 35.26, 30.96, 30.45, 29.99, 25.67, 20.86, 19.73, 18.17, 12.62, 9.84; HRMS (CI) calcd. for $C_{26}H_{41}O_6$ $(M+H)^+$ m/e 449.2899, found 449.2903.



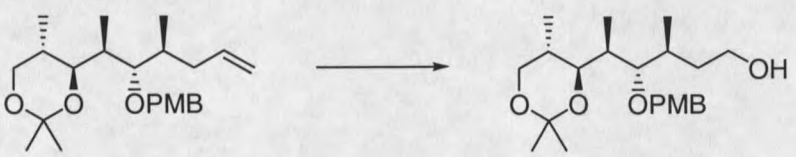
(4*S*, 5*S*, 6*S*)-5-(4-Methoxy-benzyloxy)-4-4methyl-6-((4*S*, 5*S*)-2,2,5-trimethyl-[1,3]dioxan-4-yl)-heptan-1-ol (**39**). A solution of allyl ester **38** (13 mg, 0.029 mmol) in THF (1.0 mL, 0.029 M) was treated with LAH (58 μL 1 M LAH in THF) at 0 °C. The solution was stirred for 10 min and successively treated with H_2O (3 μL), aqueous 1.0 M

NaOH (3 μL), and H_2O (7 μL). The slurry was diluted with EtOAc (1 mL), filtered, dried with Na_2SO_4, filtered, concentrated in vacuo and purified on Davisil (4:6 EtOAc-hexanes) to afford 10 mg (88%) of alcohol **39** as a clear, colorless oil: $[\alpha]^{25}_D$ -41.0 ° (c 0.48, $CHCl_3$); R_f 0.27 (1:1 EtOAc-hexanes); IR (thin film, CHCl3) 3425 (br, m), 2934 (s), 2875 (m), 1613 (m), 1514 (s), 1462 (m), 1384 (m), 1299 (w), 1248 (s), 1198 (m), 1172 (m), 1060 (s), 1008 (m), 949 (w), 873 (m), 821 (w) cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.36 (d, J = 8.43 Hz, 2H), 6.86 (d, J = 8.53 Hz, 2H), 4.65 (app t, J = 11.50 Hz, 2H), 4.01 (d, J = 10.37 Hz, 1H), 3.60 (dd, J = 11.38, 5.00 Hz, 1H), 3.47 (dm, J = 9.82 Hz, 1H), 3.38-3.27 (m, 3H), 3.31 (s, 3H), 1.99 (m, 1H), 1.84 (m, 1H), 1.72 (m, 1H), 1.65-1.51 (m, 2H), 1.57 (s, 3H), 1.44-1.26 (m, 2H), 1.39 (s, 3H), 1.07 (d, J = 6.87 Hz, 3H), 0.95 (d, J = 6.98 Hz, 3H), 0.60 (s, 1H), 0.45 (d, J = 6.65 Hz, 3H); ^{13}C NMR (300 MHz) δ; HRMS (CI) calcd. for $C_{23}H_{38}O_5$ $(M + H)^+$ m/e 395.2798, found 395.2803.



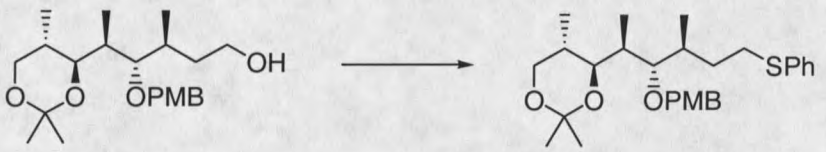
(4S, 5S)-4-[(1*S*, 2*S*, 3*S*)-2-4-Methoxy-benzyloxy)-1,3-dimethyl-hex-5-enyl]-2,2,5-trimethyl-[1,3]dioxane (**41**). To a solution of alcohol **39** (103 mg, 0.261 mmol) in THF/pyr (2.6 mL, 1:1) was added 2-nitrosophenylselenocyanate (130 mg, 0.572 mmol). The reaction mixture was cooled to 0 °C, stirred for 5 min, and treated with Bu_3P (194 μL, 0.572 mmol). After 1 h, the reaction mixture was treated with H_2O_2 (1.2 mL 30% H_2O_2), stirred for 10 h, quenched with saturated aqueous $NaHCO_3$ (3 mL), and diluted

with EtOAc (3 mL). The aqueous layer was washed with EtOAc (3x4 mL) and the combined organic washes were dried with Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified on Davisil (1:9 EtOAc-hexanes) to give 84 mg (85%) of olefin **41** as a clear, colorless oil: $[\alpha]^{25}_D$ +40.1° (c 1.45, $CHCl_3$); R_f 0.75 (1:1 EtOAc-hexanes); IR (thin film, CHCl3) 3072 (w), 2961 (s), 2931 (s), 2875 (m), 1640 (s), 1613 (m), 1586 (w), 1514 (s), 1459 (m), 1383 (s), 1201 (m), 1247 (s), 1198 (s), 1172 (s), 1148 (m), 1108 (s), 1060 (s), 1038 (s), 1006 (s), 955 (m), 909 (m), 869 (m), 820 (m), 765 (w) cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.35 (d, J = 8.46 Hz, 2H), 6.85 (d, J = 8.54, 2H), 5.87-5.77 (m, 1H), 5.08 (d, J = 17.05 Hz, 1H), 5.04 (d, J = 10.05 Hz, 1H), 4.65 (s, 2H), 3.99 (d, J = 10.36 Hz, 1H), 3.60 (dd, J = 11.40, 5.02 Hz, 1H), 3.47 (dd, J = 9.73, 1.62 Hz, 1H), 3.37-3.29 (m, 1H), 3.31 (s, 3H), 2.37 (d, J = 13.88 Hz, 1H), 2.15 (app dt, J = 13.80, 9.14 Hz, 1H), 1.96 (m, 1H), 1.83 (m, 2H), 1.56 (s, 3H), 1.38 (s, 3H), 1.10 (d, J = 6.90 Hz, 3H), 0.92 (d, J = 6.99 Hz, 3H), 0.43 (d, J = 6.62, 3H); ^{13}C NMR (300 MHz) δ 159.07, 138.58, 131.85, 128.58 (2C), 115.51, 113.89 (2C), 98.12, 83.80, 74.67, 73.73, 66.52, 55.44, 37.06, 35.55, 34.52, 30.54, 30.09, 19.77, 18.20, 12.67, 9.86; HRMS (CI) calcd. for $C_{23}H_{36}O_4$ $(M+Na)^+$ m/e 399.2561, found 399.2511.



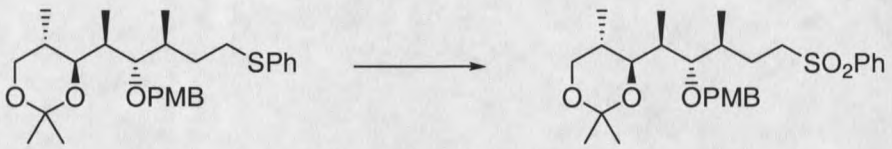
(3*S*, 4*S*, 5*S*)-4-(4-Methoxy-benzyloxy)-3-methyl-5-((4*S*, 5*S*)-2,2,5-trimethyl-[1,3]dioxan-4-yl)-hexan-1-ol (**43**). Ozone was bubbled through CH_2Cl_2 (9.4 mL, 0.040

M) at –78 °C until a blue color persisted for five minutes. A solution of alkene **41** (141 mg, 0.374 mmol) in MeOH (2.9 mL) was then added. Upon addition of substrate, the blue color immediately dissipated. The solution was stirred 5 min before adding DMS (0.61 mL). The solution was stirred for 10 minutes and treated with solid $NaBH_4$ (28 mg, 0.75 mmol). The reaction mixture was warmed to ambient temperature and stirred for 30 min before the reaction was quenched with Rochelle's Salt (10 mL). The reaction mixture was diluted with EtOAc (12 ml) and the layers were separated. The aqueous layer was extracted with EtOAc (3x15 mL), dried with Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified on Davisil (3.5:6.5 EtOAc-hexanes) to afford 94 mg (66%) of alcohol **43** as a yellow oil, along with 37 mg (26%) recovered starting material: $[\alpha]^{25}_D$ +35.9° (c 1.08, $CHCl_3$); R_f 0.38 (1:1 EtOAc-hexanes), IR (thin film, $CHCl_3$) 3421 (br, m), 2934 (s), 2845 (s), 1613 (m), 1514 (s), 1457 (s), 1384 (s), 1301 (m), 1248 (s), 1198 (s), 1172 (s), 1060 (s), 1007 (m), 947 (w), 868 (w), 821 (m), 763 (w) cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.32 (d, J = 8.46 Hz, 2H), 6.84 (d, J = 8.51 Hz, 2H), 4.63 (AB quartet, J_{AB} = 11.09 Hz, Δν = 27.09 Hz), 3.99 (d, J = 10.36 Hz, 2H), 3.67-3.57 (m, 2H), 3.52-3.42 (m, 2H), 3.33 (at, J = 11.27 Hz, 1H), 3.30 (s, 3H), 2.11-2.01 (m, 1H), 1.95-1.87 (m, 1H), 1.86-1.77 (m, 2H), 1.70-1.60 (m, 2H), 1.56 (s, 3H), 1.38 (s, 3H), 1.01 (d, J = 7.03 Hz, 3H), 0.92 (d, J = 6.96 Hz, 3H), 0.46 (d, J = 6.65, 3H); ^{13}C NMR (300 MHz) δ 159.19, 131.00, 128.60 (2C), 113.99 (2C), 98.15, 83.78, 75.04, 73.57, 66.41, 59.44, 55.38, 37.07, 32.61, 32.47, 30.40, 30.04, 19.78, 17.80, 12.60, 9.69; HRMS (CI) calcd. for $C_{22}H_{36}O_5$ $(M+Na)^+$ m/e 403.2449, found 403.2460.



(4*S*, 5*S*)-4-[(1*S*, 2*S*, 3*S*)-2-(4-Methoxy-phenoxymethyl)-1,3-dimethyl-5-phenylsulfanyl-pentyl]-2,2,5-trimethyl-[1,3]dioxane (**44**). Alcohol **43** (55 mg, 0.15 mmol) was dissolved in THF:pyr (0.9 mL, 1:1) and cooled to 0 °C under argon. A solution of $(PhS)_2$ (31 mg, 0.14 mmol), Bu_3P (36 μL) in THF (0.5 mL) was added to the above solution of alcohol **43** over a 1 h period. The mixture was allowed to warm to ambient temperature and stirred for 29 h before quenching with saturated aqueous $NaHCO_3$ (1 mL). The layers were separated, the organic layer was washed with brine (1 mL), and the combined aqueous washes were extracted with EtOAc (3x3 mL). The combined organic washes were dried with Na_2SO_4, filtered, concentrated in vacuo, and the crude oil was purified on Davisil. Elution with EtOAc-hexanes (2:8) provided 19 mg (35%) of recovered starting material and 33 mg (48%) of sulfide **44** as a light yellow oil: $[\alpha]^{25}_D$ +29.2° (c 1.3, $CHCl_3$); R_f 0.68 (1:1 EtOAc-hexanes), IR (thin film, $CHCl_3$) 3071 (w), 2955 (s), 2991 (s), 2874 (m), 1612 (m), 1584 (m), 1515 (s), 1458 (s), 1438 (m), 1383 (s), 1300 (m), 1269 (m), 1247 (s), 1197 (s), 1171 (s), 1148 (m), 1109 (s), 1084 (s), 1060 (s), 1036 (s), 1006 (m), 947 (w), 870 (m), 819 (m), 737 (s), 692 (s) cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.32 (app t, J = 1.41, 1H), 7.30 (m, 1H), 7.28-7.22 (m, 4H), 7.17-7.12 (app tt, J = 7.13, 1.21 Hz, 1H), 6.87 (app dt, J = 8.64, 2.52 Hz, 2H), 4.54 (AB quartet, J_{AB} = 11.11, Δν = 8.41 Hz, 2H), 3.87 (dd, J = 10.41, 1.49 Hz, 1H), 3.81 (s, 3H), 3.67 (dd, J =

11.49, 5.06 Hz, 1H), 3.49 (app t, J = 11.31 Hz, 1H), 3.34 (dd, J = 9.93, 1.77 Hz, 1H), 2.12 (m, 1H), 2.85 (app dt, J = 12.64, 8.38 Hz, 1H), 1.98-1.90 (m, 1H), 1.89-1.72 (m, 3H), 1.69-1.59 (m, 1H), 1.40 (s, 3H), 1.38 (s, 3H), 1.10 (d, J = 6.92 Hz, 3H), 0.79 (d, J = 6.98 Hz, 3H), 0.65 (d, J = 6.69 Hz, 3H); ^{13}C NMR (300 MHz) δ 158.85, 136.92, 131.53, 128.76 (2C), 128.69 (2C), 128.35 (2C), 125.56, 113.68 (2C), 97.97, 83.89, 74.49, 73.43, 66.28, 55.24, 36.72, 34.26, 31.78, 30.29, 29.88, 28.91, 19.57, 17.83, 12.40, 9.59; HRMS (EI) calcd. for $C_{22}H_{36}O_5$ $(M-CH_3)^+$ m/e 457.2413, found 457.2409.



(4*S*, 5*S*)-4-[(1*S*, 2*S*, 3*S*)-5-Benzenesulfonyl-2-(4-methoxy-phenoxymethyl-1,3-dimethyl-pentyl]-2,2,5-trimethyl-[1,3]dioxane (**20**). A solution of thioether **44** (6 mg, 0.013 mmol) in CH_2Cl_2 (0.6mL, 0.02 M) was treated with K_2CO_3 (10 mg, 0.072 mmol), followed by MCPBA (6 mg, 0.034 mmol) at 0 °C under argon. The reaction mixture was stirred for 15 min, quenched with $Na_2S_2O_3$ (1 mL), and diluted with EtOAc (2 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (1 mL) and the combined aqueous washes were extracted with EtOAc (3x2mL). The combined organic washes were dried with Na_2SO_4, filtered, concentrated in vacuo and purified using Davisil (3:7 EtOAc-hexanes) to provide 6 mg (94%) of sulfone **20** as a clear, colorless oil: $[\alpha]^{25}_D$ +27° (c 0.51 , $CHCl_3$); R_f 0.55 (1:1 EtOAc-hexanes), IR (thin film, $CHCl_3$) 3060 (w), 2958 (m), 2939 (m), 2874 (m), 1612 (m), 1584 (w), 1513 (s), 1458 (m), 1440 (m), 1384

(m), 1304 (s), 1247 (s), 1197 (m), 1172 (m), 1147 (s), 1109 (m), 1076 (s), 1060 (s), 1034 (m), 1007 (m), 954 (w), 865 (w), 748 (m), 690 (m) cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.89 (m, 2H), 7.64 (app t, J = 7.45 Hz, 1H), 7.55 (app t, J = 7.92, 2H, 7.17 (dm, J = 8.57 Hz, 2H), 6.85 (dm, J = 8.62 Hz, 2H), 4.49 (AB quartet, J_{AB} = 11.11, $\Delta\nu_{AB}$ = 16.40 Hz, 2H), 3.85-3.78 (m, 1H), 3.81 (s, 3H), 3.68 (dd, J = 11.51, 5.05 Hz, 1H), 3.49 (at, J = 11.33 Hz, 1H), 3.32-3.23 (m, 2H), 3.04 (m, 1H), 1.89-1.79 (m, 3H), 1.78-1.67 (m, 2H)k, 1.37 (s, 3H), 1.36 (s, 3H), 0.99 (d, J = 6.81 Hz, 3H), 0.77 (d, J = 6.98 Hz, 3H), 0.66 (d, J = 6.68 Hz, 3H); ^{13}C NMR (300 MHz) δ 158.90, 139.35, 133.48, 131,22, 129.18 (2C), 128.22 (2C), 127.98 (2C), 113.72 (2C), 97.80, 83.57, 74.58, 73.37, 66.22, 55.27, 54.50, 36.91, 33.96, 30.25, 29.86, 22.65, 19.55, 17.69, 12.45, 9.59; HRMS (MALDI) calcd. for $C_{22}H_{36}O_5$ $(M+Na)^+$ m/e 527.2443, found 527.2464.

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