Total Synthesis of Brevetoxin A: Part 1: First Generation Strategy and Construction of BCD Ring System

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Abstract: Discussed herein is our first generation strategy for the total synthesis of brevetoxin A. This approach relies upon dissection of the molecule at the nine-membered ring site (ring E). A Wittig coupling of requisite polycyclic fragments **3** and **4** followed by hydroxy dithioketal cyclization was expected to furnish the polycyclic framework of brevetoxin A (**1**). Intermediate **8** was anticipated to be a valid synthetic precursor to phosphonium salt **3**, and its synthesis was accomplished by a bis(lactonization)/ thionolactone formation/ functionalization sequence. In order to test our synthetic strategy, the synthesis of an advanced model system (**36**) was attempted. Aldehyde **38** and phosphonium salt **37** were successfully synthesized and coupled through a Wittig reaction. Unfortunately, the planned hydroxy dithioketal cyclization to form the crucial nonacene (ring E) did not proceed as anticipated and this synthetic approach was discontinued.

Keywords: brevetoxin A · synthetic methods · total synthesis

Introduction

The brevetoxins are extraordinary natural products by virtue of their unusual molecular architecture, biological activity, and association with the red tide phenomena.[1–3] The history and catastrophic effects of the red tides have been amply reviewed and it suffices to mention here their increasing frequency globally.[4] Scientific evidence points to certain species of dinoflagellates as some of the culprits for the poisoning of fish observed during these menacing events.[5] Specifically, it has been shown that some of these unicellular organisms secrete potent toxins such as the saxitoxins and brevetoxins. Amongst the latter, brevetoxin B (**2**)[6] and brevetoxin A (**1**)[7] enjoy special status within the class by being the first to be isolated and the most potent biotoxins isolated from the dinoflagellate species *Ptychodiscus brevis Davis* (*Gymnodium breve Davis*), (Figure 1). These substances have been shown to bind strongly with neuronal sodium channels,[8–12] causing them to open, thereby allowing sodium ion influx. This eventually leads to death of the parent organism by asphyxiation. The total synthesis of brevetoxin B (**2**) was accomplished in these laboratories and reported in 1995.[13–15] In this and the following articles[16–18] we report the details of the total synthesis of brevetoxin A (**1**).[19]

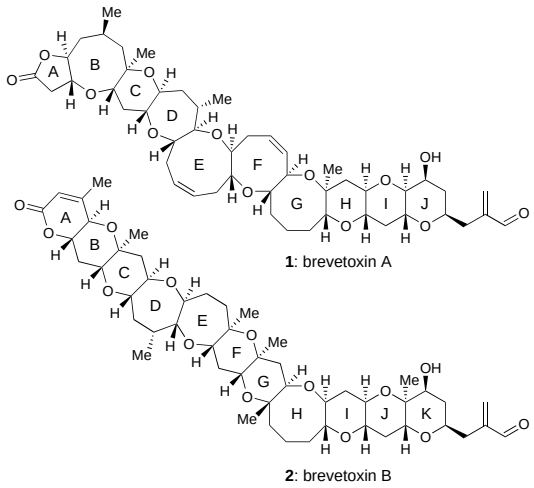

Figure 1. Structures of brevetoxins A (**1**) and B (**2**).

The molcular structure of brevetoxin A (**1**) was first elucidated by Shimizu et al. in 1986 by spectroscopic means[20] and X-ray crystallographic analysis,[7] and subsequently by Pawlak et al. through NMR spectroscopic and mass spectrometric techniques.[21] Despite possession of one less ring than brevetoxin B (**2**), the polycyclic framework of brevetoxin A

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comprises a longer main carbon chain (by two carbons) and has rings of all sizes from five- to nine-membered. Besides the 10 rings and 22 stereogenic centers, brevetoxin A (**1**) contains three carbon–carbon double bonds, a γ-lactone, a secondary hydroxyl group and an aldehyde function. Most notably, the X-ray crystallographic analysis revealed an approximate 90° twist at the ring G site of the molcule[7] and two distinct conformations of the aldehyde side chain and of the nine-membered ring (ring E).[22] The latter observation explains the difficulties in locating and assigning a number of the E ring NMR signals of **1** (slow conformational changes on NMR scale). The striking regularity by which the oxygen atoms bridge the polycyclic framework of brevetoxin A and its all-*trans* ring fusions are also remarkable features of this molecule, which, no doubt, have their origins in the biosynthetic pathway involved.[23, 24] In addition, all substituents flanking the oxygen atoms are *syn* to each other, except for those on ring J. The well known characteristics of medium-sized rings in terms of strain, unfavorable transannular interactions,[25] and difficulties associated with their construction, together with the complex stereochemistry and sheer size make the total synthesis of brevetoxin A (**1**) a special challenge.[26] As was the case with brevetoxin B (**2**), a number of new synthetic methods had to be developed and various strategies were attempted in order to face the challenge of brevetoxin A (**1**) before final success.[19]

Results and Discussion

Retrosynthetic analysis and first strategy

An attractive retrosynthetic analysis of brevetoxin A (**1**) is provided by the hypothetical biogenetic scheme shown in Figure 2.[27, 28] Daring and intriguing as this idea was, the lack of synthetic tools to effect the proposed epoxidations and ring

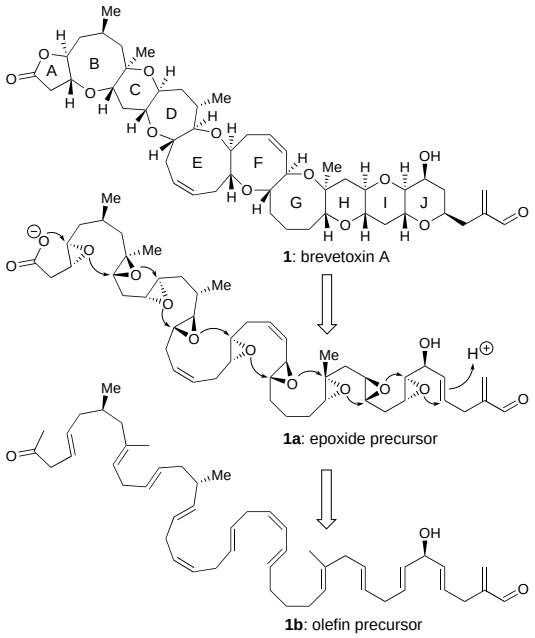
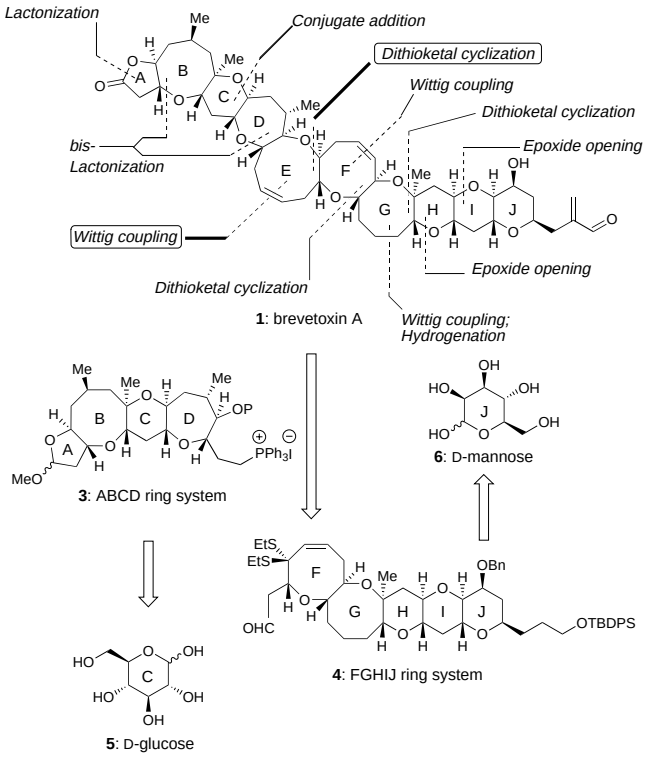


Figure 2. Hypothetical biosynthetic assembly of brevetoxin A (**1**).

closures in a selective manner steered us away from it and in search of more reasonable and stepwise approaches. Many of the strategic bond disconnections in our retrosynthetic analysis shown in Scheme 1 only became possible because of the development of new synthetic methods within these laboratories. We specifically relied on: a) the regio- and stereospecific hydroxyepoxide opening reaction[29] for the



Scheme 1. First generation strategic bond disconnections and retrosynthetic analysis of brevetoxin A (**1**). Bn = benzyl; TBDPS = *tert*-butyldiphenylsilyl; P = protecting group.

Abstract in Greek:

Στο αρθρο αυτο παραθετουμε την αρχικη στρατηγικη μας για την ολικη συνθεση της μπρεβετοξινης Α. Η προσεγγιση αυτη βασιζεται στην νοητη διχοτομιση του μοριου αυτου στον εννεαμελη δακτυλιο Ε. Μια αντιδραση Wittig των διακεκριμενων ενδιαμεσων **3** και **4**, ακολουθουμενη απο μια υδροξυ–θειοκεταλικη κυκλοποιηση, επιλεχθηκε για τη δημιουργια του πολυκυκλικου σκελετου της μπρεβετοξινης Α (**1**). Το ενδιαμεσο **8** αναμενοταν να ειναι ο πιο πιθανος συνθετικος προδρομος του φωσφωνιακου αλατος **3** και η συνθεση του επιτευχθηκε μεσω μιας ακολουθιας αντιδρασεων διπλης λακτονοποιησης/θειολακτονοποιησης/εισαγωγης χαρακτηριστικων ομαδων. Η συνθεση του αντιπροσωπευτικου μοντελου **36** σχεδιαστηκε με σκοπο τη μελετη της πιθανοτητας πρακτικης εφαρμογης της συνθετικης μας στρατηγικης. Η αλδευδη **38** και το φωσφωνιακο αλας **37** συντεθηκαν επιτυχως και στη συνεχεια συνδεθηκαν μεσω μιας αντιδρασης Wittig. Δυστυχως, η προσχεδιασμενη ενδομοριακη κυκλοποιηση υδροξυ–θειοκεταλης με σκοπο τη δημιουργια του εννεαμελους δακτυλιου Ε δεν απεδωσε τα αναμενομενα προιοντα με αποτελεσμα την διακοπη του συγκεκριμενου συνθετικου σχεδιου.

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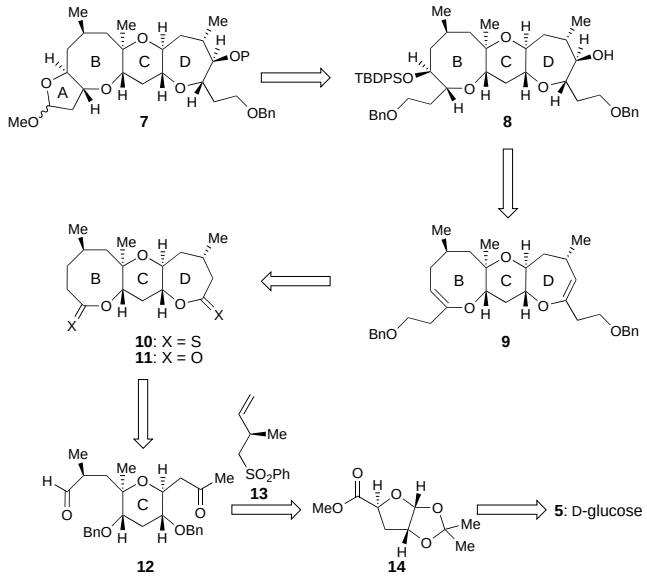
construction of rings H and I; b) the hydroxydithioketal cyclization reaction[30] to secure rings E, F, and G; and c) a bis(lactonization)/thionolactone formation/functionalization sequence[31] to form rings B and D. For optimum convergency, we elected to dissect the molecule at the nine-membered ring site (ring E), hoping for a successful hydroxydithioketal cyclization (see heavy line, structure **1**, Scheme 1) to deliver it in the synthetic direction. The resulting fragments **3** and **4** (Scheme 1) were to be coupled by a Wittig reaction and, after ring closure, the product was expected to lead to brevetoxin A (**1**) by appropriate elaboration. D-Glucose (**5**) and D-mannose (**6**) were recognized as potential starting materials for the construction of **3** and **4** respectively.

Scheme 2 outlines the retrosynthetic analysis of advanced intermediate **7** (a potential precursor of phosphonium salt **3**) relying on a bis-directional approach. Thus, **7** could be traced to bis(enol) ether **9** via **8**. The bis(enol) ether **9** was, in turn, expected to arise from the corresponding bis(lactone) **11** or bis(thionolactone) **10**. The latter compounds were traced back to the bis(carbonyl) compound **12** which was connected to D-glucose (**5**) via intermediate **14** and sulfone **13** (Scheme 2).



Scheme 2. Retrosynthetic analysis of ABCD ring system (**7**). First generation approach.

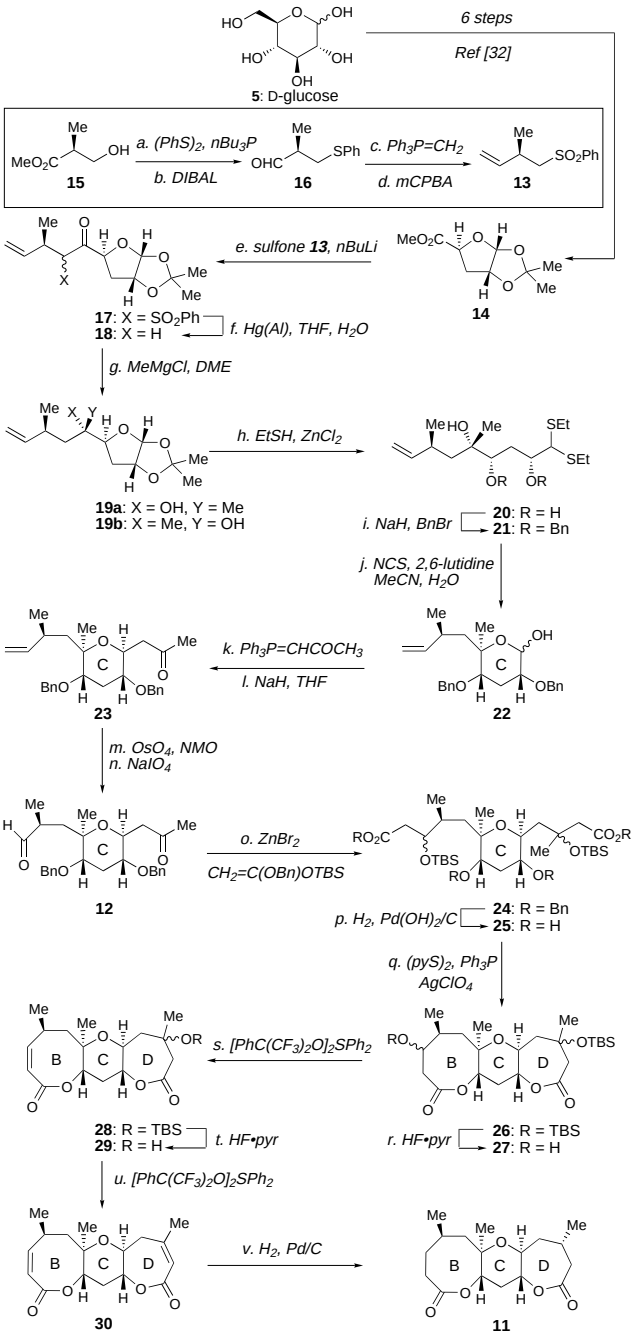
The strategy developed from the above analysis required the development of new synthetic technology. A number of methods were thus developed in conjunction with the total synthesis of brevetoxin A (**1**) [and brevetoxin B (**2**)] and applied at various stages of the program, as will become evident from the following sections.

First generation synthesis of BCD ring system

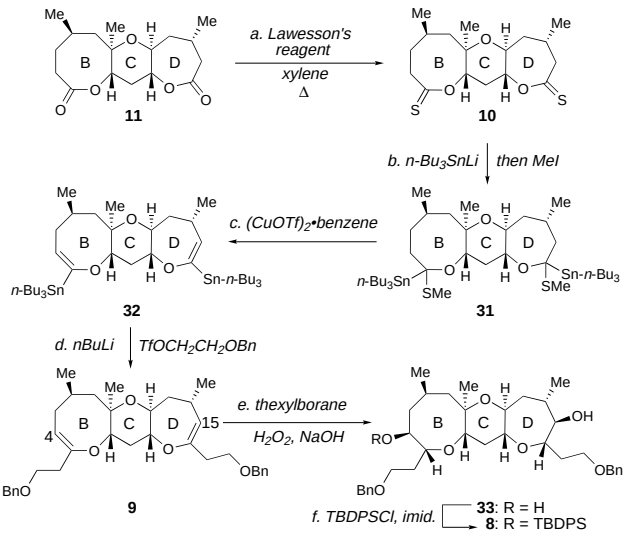
The first generation synthesis of the required BCD bis(lactone) **11** is shown in Scheme 3.[31] Thus, the required methyl ester **14** was prepared from D-glucose via a six-step literature procedure[32] and coupled with the lithio derivative of the easily accessible sulfone **13**[33] (from hydroxy methyl ester **15** via aldehyde sulfide **16**) to afford ketone **17**[34] (79% yield, mixture of diastereoisomers). The phenylsulfonyl group was reductively removed from **17** by the action of aluminum amalgam,[35] and the resulting compound (**18**, 86% yield) was treated with MeMgCl, leading to tertiary alcohols **19a, b** in 95% yield (**19a**:**19b** ca. 12.8:1) (chelation-controlled addition).[36] Rupturing both rings of **19a** with EtSH and $ZnCl_2$ allowed formation of trihydroxydithioketal **20** (92% yield).[37] The secondary alcohols of **20** were protected as benzyl ethers (NaH, BnBr, nBu$_4$NI, 86% yield) to afford **21**, which underwent ring closure and loss of both ethylthio groups on treatment with NCS (for abbreviations, see legends in Schemes) and 2,6-lutidine in acetonitrile: water (4:1), furnishing lactol **22** (80% yield).[38]

Wittig reaction of **22** with the appropriate stabilized ketophosphorane afforded the corresponding hydroxy-α,β-unsaturated ketone, which was induced to cyclize by Michael-type addition in the presence of NaH in THF at 25 °C, leading to the stereochemically defined tetrahydropyran system **23** (73% yield for two steps). Dihydroxylation of the double bond in **23** (OsO_4 cat., NMO) followed by cleavage of the resulting 1,2-diol with $NaIO_4$ gave the dicarbonyl compound **12** in 93% overall yield. The stage was now set for the bis-directional elaboration to more advanced intermediates. Thus, $ZnBr_2$-catalyzed Mukaiyama reaction of CH_2=C(OBn)OTBS with **12** furnished compound **24** as an inconsequential mixture of four diastereoisomers and in 81% total yield.[39] Removal of all four benzyl groups in **24** by hydrogenation with Pearlman's catalyst resulted in the formation of dihydroxy dicarboxylic acid **25** which underwent bis-lactonization on exposure to $(pyS)_2$-Ph_3P and subsequent heating in the presence of $AgClO_4$, furnishing bis(lactone) **26** in 76% overall yield.[40] The bis-desilylation of **26** and bis-dehydration of the resulting diol to afford the desired bis(lactone) **30** proceeded in low overall yield, and thus, a stepwise approach was adopted. Therefore, the secondary hydroxyl group was generated first in a clean fashion by controlled treatment of **26** with HF in pyridine (85% yield), and was eliminated by subsequent exposure to Martin's sulfurane ($[PhC(CF_3)_2O]_2SPh_2$) to afford the α,β-unsaturated lactone **28** (87% yield).[41] In a similar fashion, the tertiary alcohol in **28** was liberated (HF in pyridine) to afford **29** (92% yield) and thence eliminated once again by the action of Martin's sulfurane to afford the bis(unsaturated lactone) **30** (92% yield). Finally, reduction of **30** with H_2 in the presence of 10% Pd/C produced the saturated bis(lactone) **11** in 100% yield and with complete stereocontrol.

The completion of the synthesis of the intermediate **8** by bis-functionalization of **11** and final discrimination of diol **33** is shown in Scheme 4. At this juncture we should emphasize that, in order to attach the necessary appendages on rings B and D while maintaining the rings, it was necessary to develop new methodology. To this end, we developed two distinctly different methods, the first relying on the chemistry of thionolactones[42] and the second based on palladium-catalyzed coupling reactions of enol phosphates derived from lactones.[43] The application of the thionolactone method will be discussed here, whereas the phosphate-based approach will be presented in the third paper[17] of this series.



Scheme 3. Construction of BCD bis-lactone **11**. First generation approach. Reagents and conditions: a) 1.2 equiv of $(PhS)_2$, 1.2 equiv of nBu$_3$P, DMF, 0 → 25 °C, 5 h, 100 %; b) 1.02 equiv of DIBAL (1 M solution in hexanes), CH_2Cl_2, −78 °C, 0.5 h, 100 %; c) 1.2 equiv of $Br^-Ph_3P^+CH_3$, 1.2 equiv of NaHMDS, THF, 0 °C, 0.5 h; then aldehyde **16** in THF, 0 °C, 0.5 h, 91 %; d) 2.3 equiv of mCPBA, CH_2Cl_2, 0 °C, 1.5 h, 82 %; e) 2.2 equiv of sulfone **13**, 2.05 equiv of nBuLi (1.6 M in hexanes), THF, −78 °C, 4 h, 79 %; f) 8.8 equiv of Hg(Al), THF:H_2O (10:1), 65 °C, 2 h, 86 %; g) 1.3 equiv of MeMgCl (3 M in THF), DME, −78 → 25 °C, 3 h, 95 %, ca. **19a:19b** (12.8:1); h) 20 equiv of EtSH, 4.9 equiv of $ZnCl_2$, CH_2Cl_2, 0 °C, 1.5 h, 92 %; i) 3.0 equiv of NaH, THF, 25 °C, 1 h; 0.005 equiv of nBu$_4$NI, 2.05 equiv of BnBr, 0 → 25 °C, 11 h, 86 %; j) 6.0 equiv of NCS, 6.0 equiv of 2,6-lutidine, MeCN:H_2O (4:1), 0 °C, 5 min; 80 %; k) 1.5 equiv of $Ph_3P{=}CHCOCH_3$, $PhCH_3$, reflux, 4 h; l) 1.0 equiv of NaH, THF, 25 °C, 10 h, 73 % for two steps; m) 1.2 equiv of NMO, 0.02 equiv of OsO_4 (0.1 M in THF), THF:H_2O (20:1), 25 °C, 5 h; n) 1.2 equiv of $NaIO_4$, THF:H_2O (10:1), 25 °C, 2 h, 93 % for two steps; o) 3.0 equiv of $CH_2{=}C(OBn)OTBS$, 0.5 equiv of $ZnBr_2$, Et_2O, −78 °C, 20 min, 81 % (four diastereomers); p) H_2, 20 % Pd(OH)$_2$/C, THF, 25 °C, 3 h; q) 2.5 equiv of $(pyS)_2$, 2.5 equiv of Ph_3P, CH_2Cl_2, 25 °C, 1 h; 2.2 equiv of $AgClO_4$, $PhCH_3$, reflux, 4 h, 76 % for two steps (four diastereomers); r) HF · pyr (1 mL mmol^{-1}), THF, 0 → 25 °C, 3 h, 85 %; s) 1.2 equiv of $[PhC(CF_3)_2O]_2SPh_2$, CH_2Cl_2, 0 °C, 0.5 h, 87 %; t) HF · pyr (2 mL mmol^{-1}), THF, 0 → 25 °C, 4 h, 92 %; u) same as s), 92 %; v) H_2, 10 % Pd/C, EtOAc, CH_2Cl_2, 25 °C, 3.5 h, 100 %. DIBAL = diisobutylaluminum hydride; DME = 1,2-dimethoxyethane; DMF = *N*,*N*-dimethylformamide; mCPBA = *3*-chloroperbenzoic acid; NCS = *N*-chlorosuccinimide; $(pyS)_2$ = 2,2′-dipyridyl disulfide; NaHMDS = sodium bis(trimethylsilyl) amide; NMO = 4-methylmorpholine-*N*-oxide; TBS = *tert*-butyldimethylsilyl.



Scheme 4. Functionalization of BCD bis-lactone **11**. First generation approach. Reagents and conditions: a) 3.0 equiv of Lawesson's reagent, 1.0 equiv of tetramethylthiourea, xylene, 115 °C, 3 h, 63 %; b) 3.0 equiv of nBuLi (1.6 M in hexanes), 3.3 equiv of iPr$_2$NH, 3.0 equiv of nBu$_3$SnH, THF, −10 °C; then **10** in THF, −78 °C, 10 min; then 6.0 equiv of MeI, −78 °C, 15 min, 86 %; c) 4.0 equiv of $(CuOTf)_2 \cdot$benzene complex, 4.2 equiv of pentamethyl piperidine, PhH, 25 °C, 45 %; d) 3.0 equiv of nBuLi (1.6 M in hexanes), THF, −78 °C; then 25 equiv of HMPA, 5.0 equiv of $TfOCH_2CH_2OBn$ in hexanes, −78 → 25 °C, 45 min, 65 %; e) 4.0 equiv of thexylborane (0.5 M in THF), THF, 0 °C, 5 h; then 20 equiv of NaOH, 20 equiv of 50 % H_2O_2, 0 → 25 °C, 2 h, 73 %; f) 1.5 equiv of TBDPSCl, 3.0 equiv of imidazole, DMF, 25 °C, 24 h, 82 %. Tf = trifluoromethanesulfonate; HMPA = hexamethylphosphoramide.

Exposure of bis(lactone) **11** to Lawesson's reagent[44] and tetramethylthiourea in xylene solution at 115 °C resulted in the formation of bis(thionolactone) **10** in 63 % yield. Addition of nBu$_3$SnLi to **10**, followed by quenching with MeI furnished compounds **31** in 86 % yield (an inconsequential mixture of four diastereoisomers). Elimination of two equivalents of methanethiol from **31** was then accomplished by the action of $Cu(OTf)_2 \cdot PhH$ in the presence of PMP (pentamethyl piperidine), affording bis(stannane) derivative **32** in 45 % yield.[45] Tin to lithium exchange by treatment with nBuLi generated the dilithio derivative of **32**, which reacted with $TfOCH_2CH_2OBn$ in the presence of HMPA, affording the bis-substituted system **9** in 65 % yield. The next stage required installation of two hydroxy groups emanating from the top face of the molecule (as drawn), as well as establishment of the *syn* stereorelationships between the hydrogen atoms flanking the oxygen atoms of rings B and D. Model studies and molecular mechanics calculations (Figure 3) on **9** revealed a minimum energy conformation indicating the hydroboration reaction as a potential process to accomplish these goals. Indeed, it

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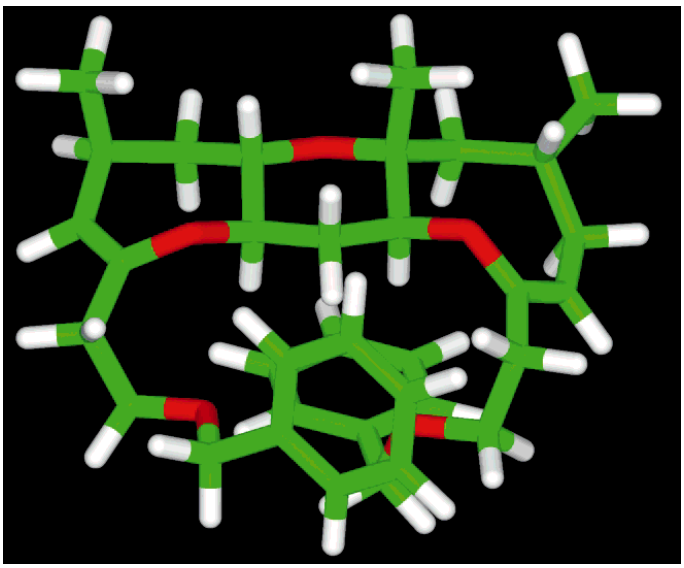
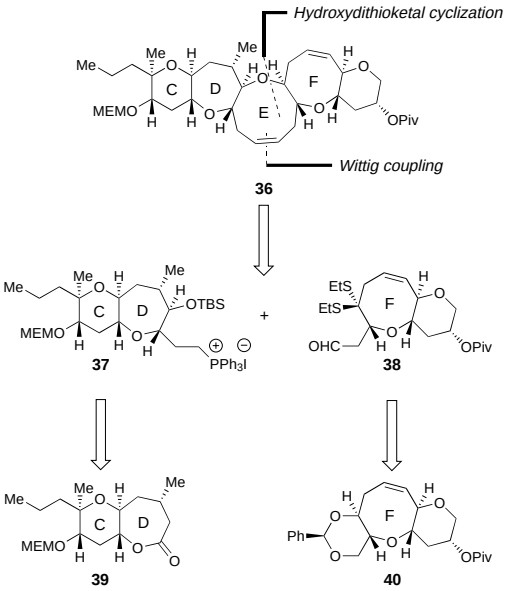


Figure 3. Computer-generated, minimized structure of **9**. The atoms are colored according to the following code: carbon, green; hydrogen, white; oxygen, red.



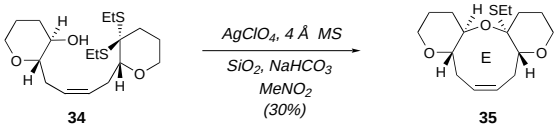
Scheme 6. Retrosynthetic analysis of CDEF model system **36**.

was found that thexylborane attacked both double bonds of **9** from the desired face, since, upon basic hydrogen peroxide workup, diol **33** was produced in 73% yield as a single stereoisomer.[46] In addition to spectroscopic evidence, the stereochemical assignments of **33** were confirmed by X-ray crystallographic analysis.[31a] Exploiting the substantially different steric environment of the two hydroxyl groups of **33**, the monosilyl ether **8** (TBDPS group on ring B) was prepared, in 82% yield, by treatment with TBDPSCl and imidazole under carefully controlled conditions.

Model studies for the construction of the CDEF ring system

Before proceeding with the synthesis of the final ABCD and FGHIJ ring systems, it was considered prudent to test the planned convergency by coupling and cyclizing to form ring E through a Wittig reaction and a hydroxydithioketal ring closure, respectively. To address this issue, a number of model studies were undertaken.

Having demonstrated amply the power of the hydroxydithioketal cyclization to form oxocene ring systems,[47] we attempted the formation of a nonacene ring system. Thus, the hydroxydithioketal **34** (Scheme 5) was synthesized by Wittig



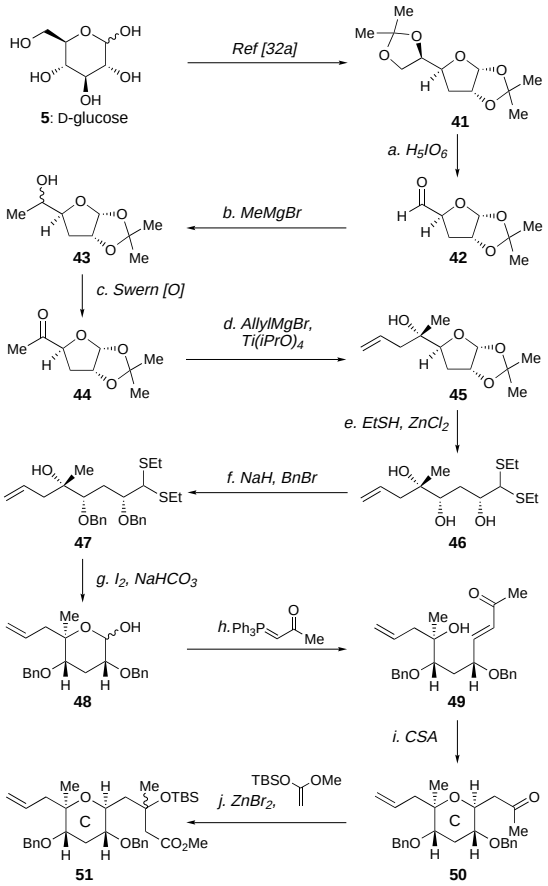
Scheme 5. Construction of didehydrooxanonacane **35** by hydroxydithioketal cyclization.

coupling of the appropriate fragments and subjected to the optimum ring closure conditions.[30b] Formation of the nine-membered ring **35** in 30% yield from this reaction was encouraging. On the basis of this result, we decided to proceed with the more advanced model system **36** (Scheme 6) in order to obtain more confidence in our convergent strategy.

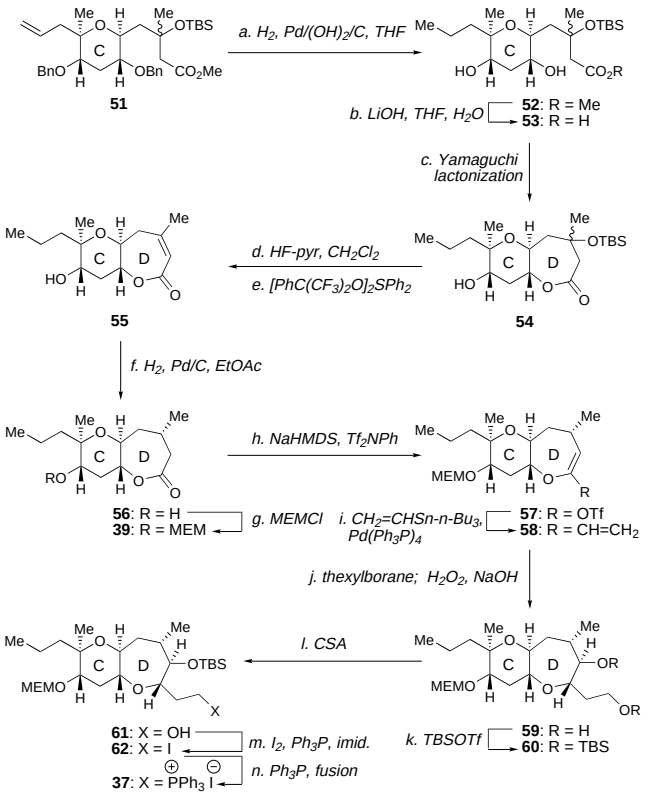
Model system **36** was targeted for synthesis according to the retrosynthetic analysis depicted in Scheme 6, which mimics the grand plan for brevetoxin A (**1**) (Scheme 1). The required fragments **39** and **40** were prepared by sequences based on the chemistry described for **8** above (Scheme 4) and for the synthesis of the FGHIJ ring system of brevetoxin A.[47]

D-Glucose (**5**) was expediently converted to bis(acetonide) **41** (Scheme 7) by a known procedure[32a] and thence selectively cleaved to aldehyde **42** by H_5IO_6.[48] Addition of MeMgBr to **42** (75% overall yield from **41**), followed by Swern oxidation[49] [$(COCl)_2$/DMSO, Et_3N, 80% yield] afforded methyl ketone **44** via alcohol **43** (mixture of diastereoisomers). Treatment of **44** with the reagent generated by mixing of allylmagnesium bromide with Ti(*i*PrO)$_4$ in THF at $-78\,^{\circ}C$ furnished tertiary alcohol **45** as a single stereoisomer in 94% yield (nonchelation-controlled addition). Opening of both rings of **45** with EtSH-$ZnCl_2$ afforded the open-chain trihydroxy dithioketal **46** in 89% yield. The secondary hydroxyl groups in **46** were protected as benzyl ethers by treatment with NaH–BnBr in the presence of catalytic amounts of nBu$_4$NI (81% yield), and the dithioketal was cleaved with I_2–$NaHCO_3$[50] (86% yield) leading to lactol **48** (mixture of anomers). Upon reaction of **48** with the stabilized phosphorane $Ph_3P{=}CHC(O)Me$ (toluene, $110\,^{\circ}C$), the α,β-unsaturated ketone **49** was obtained which was cyclized by treatment with CSA, furnishing C ring system **50** stereoselectively (73% yield for two steps). Ketone **50** reacted with $CH_2{=}C(OMe)OTBS$[39b] in the presence of $ZnBr_2$[39a] leading to methyl ester **51** (98% yield, an inconsequential mixture of diastereoisomers).

The conversion of **51** to **37** is summarized in Scheme 8. During the cleavage of the two benzyl ethers in **51** (H_2, $Pd(OH)_2$/C, 85% yield), the terminal olefin was concurrently reduced to the saturated propyl chain. Saponification of the methyl ester in **52** using LiOH led to the hydroxycarboxylic acid **53**, which was subsequently subjected to the standard Yamaguchi lactonization conditions[51] (90% yield, for two



Scheme 7. Synthesis of methyl ester **51**. Reagents and conditions: a) 1.1 equiv of H_5IO_6, EtOAc, 25 °C, 2 h; b) 4.0 equiv of MeMgBr, Et_2O, 0 →25 °C, 4 h, 75 % for two steps; c) 1.8 equiv of oxalyl chloride, 2.2 equiv of DMSO, 5.0 equiv of Et_3N, CH_2Cl_2, −78 → 0 °C, 1 h, 80 %; d) 1.5 equiv of AllylMgBr, 1.5 equiv of $Ti(iPrO)_4$, THF, −78 °C, 2 h, 94 %; e) 20.0 equiv of EtSH, 5.0 equiv of $ZnCl_2$, CH_2Cl_2, 0 °C, 1.5 h, 89 %; f) 3.0 equiv of NaH, 0.01 equiv of imidazole, 2.0 equiv of BnBr, $nBu_4NI_{cat.}$, 0 → 25 °C, 12 h, 81 %; g) 3.4 equiv of I_2, 6.7 equiv of $NaHCO_3$, acetone:H_2O (5:1), 25 °C, 1 h, 86 %; h) 1.7 equiv of Ph_3P=CHCOMe, toluene, 110 °C, 4 h; i) 0.1 equiv of CSA, CH_2Cl_2, 25 °C, 1 h, 73 % for two steps; j) 1.5 equiv of CH_2=C(OMe)OTBS, 0.5 equiv of $ZnBr_2$, Et_2O, −78 °C, 1 h, 98 %. CSA = 10-camphorsulfonic acid.

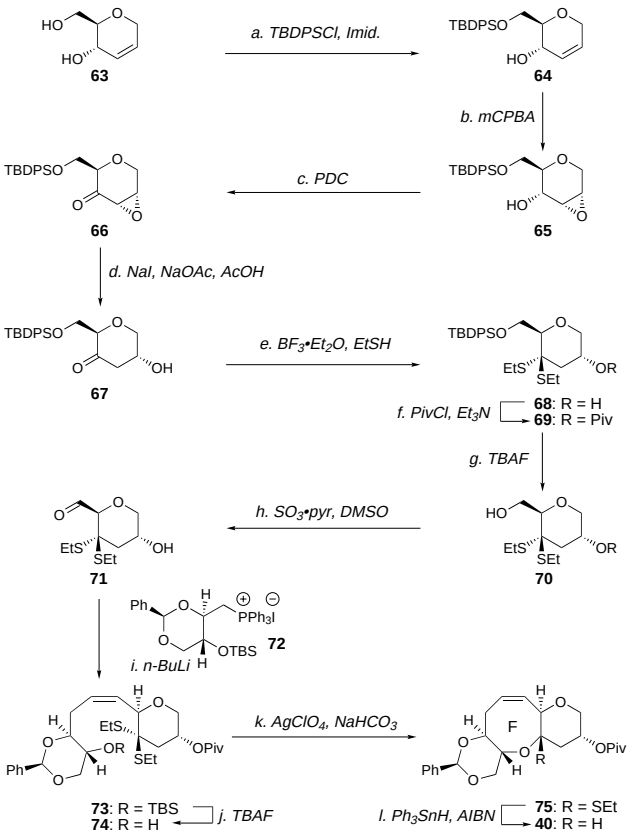


Scheme 8. Synthesis of model phosphonium salt **37**. Reagents and conditions: a) H_2, 20 % $Pd(OH)_2$/C, THF, 25 °C, 8 h, 85 %; b) 5.0 equiv of LiOH, THF:H_2O:MeOH (3:1:1), 25 °C, 12 h; c) 1.05 equiv of 2,4,6-trichlorobenzoyl chloride, 2.0 equiv of Et_3N, THF, 0 °C, 25 °C, 1.5 h; then 3.0 equiv of 4-DMAP, PhH, 25 °C, 2 h, 90 % for two steps; d) HF·pyr, CH_2Cl_2, 0 °C, 1 h; e) 2.1 equiv of $[PhC(CF_3)_2O]_2SPh_2$ (Martin's sulfurane), CH_2Cl_2, 0 °C, 15 min, 80 % for two steps; f) H_2, 10 % Pd/C, EtOAc, 25 °C, 12 h, 90 %; g) 4.0 equiv of Et_3N, 6.0 equiv of MEMCl, CH_2Cl_2, 25 °C, 24 h, 85 %; h) 6.0 equiv of NaHMDS, 4.0 equiv of Tf_2NPh, DME, −78 °C, 15 min; i) 6.0 equiv of CH_2=CHSnnBu$_3$, 0.1 equiv of $[Pd(Ph_3P)_4]$, 3.0 equiv of LiCl, THF, reflux, 2 h, 82 % for two steps; j) 1.5 equiv of thexylborane, THF, 0 °C, 24 h; then 30 % H_2O_2, aqueous NaOH, 25 °C, 2 h, 53 %; k) 2.6 equiv of TBSOTf, 3.0 equiv of 2,6-lutidine, CH_2Cl_2, 0 °C, 30 min, 94 %; l) 0.16 equiv of CSA, CH_2Cl_2:MeOH (1:1), 25 °C, 1.5 h, 91 %; m) 1.5 equiv of imidazole, 2.0 equiv of Ph_3P, 1.1 equiv of I_2, CH_2Cl_2, 25 °C, 15 min, 89 %; n) 10.0 equiv of Ph_3P, 85 °C (fusion), 2.5 h, 94 %. 4-DMAP = 4-*N*-dimethylaminopyridine; MEM = 2-methoxyethoxymethyl.

steps) to afford lactone **54**. The enone **55** was generated by removal of the TBS ether with HF in pyridine, followed by dehydration through controlled treatment with Martin's sulfurane (80 % yield for two steps). Enone **55** was hydrogenated exclusively from the α-face (H_2, Pd/C, 90 % yield), and the free hydroxyl group was protected as MEM ether **39** (77 % yield for two steps). Subsequently, lactone **39** was treated with NaHMDS and $PhNTf_2$ at −78 °C to afford cyclic ketene acetal triflate **57** in high yield. Palladium-catalyzed $[Pd(Ph_3P)_4]$ coupling of **57** with nBu$_3$SnCH=CH_2 in the presence of LiCl in refluxing THF, afforded diene **58** (81 % overall from **39**). Hydroboration of **58** with thexylborane, followed by basic H_2O_2 workup, resulted in the stereoselective formation of diol **59** in 53 % yield. The stereochemistry of the newly generated stereocenters in **59** was assigned based on NMR spectroscopic evidence and comparisons with diol **33** (Scheme 4), whose stereochemistry was unambiguously assigned by X-ray crystallographic analysis (vide supra, Figure 3). Silylation of both hydroxyl groups in **59** with TBSOTf-2,6-lutidine (94 %, yield), followed by selective mono-desilylation with CSA in CH_2Cl_2:MeOH (1:1) (91 % yield) gave primary alcohol **61**, which was converted to phosphonium salt **37**, via iodide **62**, by sequential reaction with I_2–Ph_3P and imidazole followed by excess Ph_3P (84 % for two steps).

Scheme 9 displays the synthesis of intermediate **40**. The synthesis commences with previously prepared[52] diol **63** which was selectively protected at the primary position as silyl ether **64** (TBDPSCl, imidazole, 94 % yield). Upon treatment with *m*CPBA, hydroxyl-directed epoxidation of **64** generated desired epoxide **65** (75 % yield). Hydroxy ketone **67** was produced by a PDC oxidation of alcohol **65**, followed by reductive opening of epoxide **66** (69 % yield, for two steps). This ketone (**67**) was transformed into the dithioketal **68** ($BF_3 \cdot Et_2O$, EtSH, 74 % yield), and protection of the secondary hydroxyl group as a pivaloate ester produced **69**. In preparation for the Wittig coupling, silyl ether **69** was

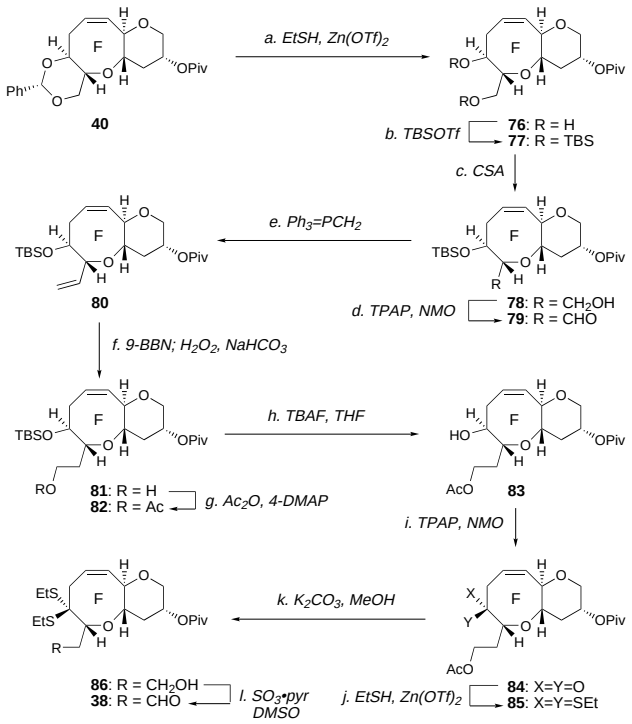
0947-6539/99/0502-0604 $ 17.50+.50/0 *Chem. Eur. J.* **1999**, *5*, No. 2



Scheme 9. Construction of model F ring system **40**. Reagents and conditions: a) 1.1 equiv of TBDPSCl, 2.0 equiv of imidazole, DMF, 0 °C, 1 h, 94 %; b) 1.2 equiv of *m*CPBA, CH_2Cl_2, 0 → 25 °C, 12 h, 75 %; c) 2.0 equiv of PDC, 3 Å MS, CH_2Cl_2, 25 °C, 6 h, 86 %; d) 3.6 equiv of NaI, 0.4 equiv of NaOAc, 3.6 equiv of AcOH, acetone, 25 °C, 10 min, 80 %; e) 2.5 equiv of $BF_3 \cdot Et_2O$, 10 equiv of EtSH, CH_2Cl_2, −78 °C, 1 h, 74 %; f) 1.5 equiv of PivCl, 2.0 equiv of Et_3N, 0.06 equiv of 4-DMAP, 25 °C, 2 h, 94 %; g) 1.5 equiv of TBAF, THF, 25 °C, 3 h, 95 %; h) 3.0 equiv of $SO_3 \cdot$ pyr, Et_3N:DMSO:CH_2Cl_2 (1:1:3), 0 °C, 1 h, 85 %; i) 1.02 equiv of phosphonium salt **72**, 0.9 equiv of *n*BuLi, THF, −78 °C, 1 h; then 3.7 equiv of HMPA, add aldehyde **71**, −78 → 25 °C, 12 h, 74 %; j) 1.5 equiv of TBAF, THF, 25 °C, 12 h, 98 %; k) 5.0 equiv of $NaHCO_3$, 4.0 equiv of $AgClO_4$, SiO_2, 3 Å MS, $MeNO_2$, 25 °C, 4 h, 74 %; l) 4.0 equiv of Ph_3SnH, 0.05 equiv of AIBN, 110 °C, 2 h, 95 %. AIBN = 2,2′-azobisisobutyronitrile; HMPA = hexamethylphosphoramide; MS = molecular sieves; PDC = pyridinium dichlorochromate; pyr = pyridine; TBAF = tetra-*n*-butylammonium fluoride.

deprotected by treatment with TBAF (95 % yield), and the resulting alcohol (**70**) was oxidized to aldehyde **71** ($SO_3 \cdot$ pyr. and DMSO, 85 % yield). Thus, **71** and **72** were coupled via the ylide of **72** (*n*BuLi, HMPA) to give *cis* olefin **73** in 74 % yield, while removal of the TBS group from the latter compound by the action of TBAF afforded the desired cyclization precursor **74** (98 % yield). Under the standard protocol ($AgClO_4$, $NaHCO_3$, SiO_2, 3 Å MS),[30b] hydroxy dithioketal **74** underwent cyclization to afford the mixed thioketal **75** (74 % yield), which was reduced under free radical conditions (Ph_3SnH, AIBN) to generate oxocene **40** (95 % yield).

The synthesis of aldehyde **38** from intermediate **40** is summarized in Scheme 10. Thus, the benzylidene group in **40** was cleaved with EtSH – $Zn(OTf)_2$ and the resulting diol (**76**, 94 % yield) was silylated with TBSOTf-2,6-lutidine to afford compound **77** (92 % yield). Selective removal of the primary silyl group from bis(silylether) **77** was achieved by exposure to

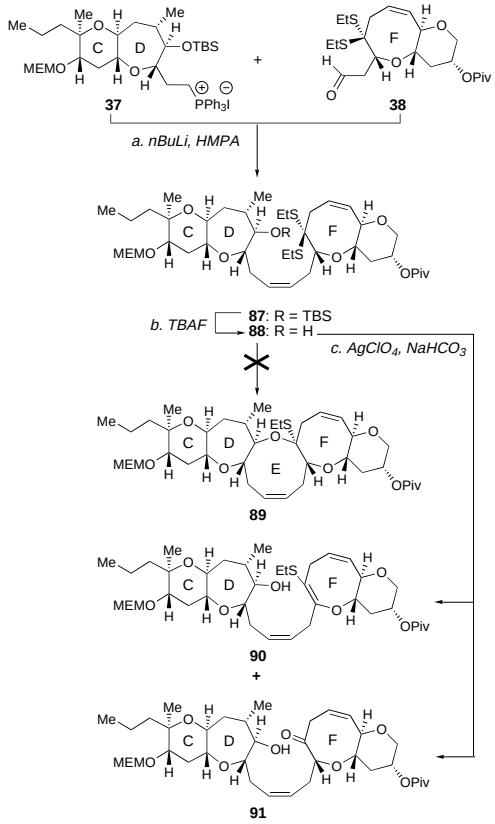


Scheme 10. Construction of model aldehyde **38**. Reagents and conditions: a) 14 equiv of EtSH, 0.2 equiv of $Zn(OTf)_2$, 25 °C, 4 h, 94 %; b) 2.1 equiv of TBSOTf, 3.0 equiv of 2,6-lutidine, 0 °C, 30 min, 92 %; c) 0.02 equiv of CSA, CH_2Cl_2:MeOH (1:1), 25 °C, 2 h, 92 %; d) 0.4 equiv of TPAP, 3.0 equiv of NMO, CH_2Cl_2, 25 °C, 1 h, 82 %; e) 1.2 equiv of $Ph_3P^+CH_3Br^-$, 1.2 equiv of NaHMDS, THF, 0 °C, 20 min; then add 1.0 equiv of **79**, 0 °C, 1 h, 78 %; f) 1.1 equiv of 9-BBN, 0 °C, 5 h; then 30 % H_2O_2, aq. $NaHCO_3$, 0 → 25 °C, 1.5 h, 88 %; g) 1.5 equiv of Et_3N, 1.1 equiv of Ac_2O, CH_2Cl_2, 25 °C, 40 min, 94 %; h) 1.6 equiv of TBAF, THF, 25 °C, 3 h, 94 %; i) 0.09 equiv of TPAP, 3.0 equiv of NMO, CH_2Cl_2, 25 °C, 30 min, 93 %; j) 15 equiv of EtSH, 0.1 equiv of $Zn(OTf)_2$, CH_2Cl_2, 25 °C, 16 h, 89 %; k) 0.2 equiv of K_2CO_3, MeOH, 25 °C, 2 h, 93 %; l) 3.0 equiv of $SO_3 \cdot$ pyr, DMSO:Et_3N:CH_2Cl_2 (1:1:2), 0 °C, 1 h, 83 %. 9-BBN = 9-borabicyclo[3. 3.1]nonane; NMO = 4-methylmorpholine-*N*-oxide; TBAF = tetra-*n*-butylammonium fluoride; TPAP = tetra-*n*-propylammonium perruthenate.

CSA in CH_2Cl_2:MeOH (1:1) leading to alcohol **78** (92 % yield), which was oxidized with TPAP/NMO[53] to afford aldehyde **79** (82 % yield). Wittig olefination of **79** resulted in the formation of olefin **80** (78 % yield), which was selectively hydroborated with 9-BBN, furnishing, after the usual basic H_2O_2 workup, primary alcohol **81** (88 % yield). Standard acetylation (**81** → **82**, 94% yield), desilylation (**82** → **83**, 94% yield) and oxidation (TPAP, NMO) gave ketone **84** (93% yield). Exposure of ketone **84** to $EtSHZn(OTf)_2$ in CH_2Cl_2 then afforded dithioketal **85** in 89% yield from **84**. Finally, deacetylation of **85** (K_2CO_3, 93% yield), followed by $SO_3 \cdot$ pyr. and DMSO oxidation led to the desired model aldehyde **38** (83% yield).

With fragments **37** and **38** at hand, the stage was then set to test the feasibility of constructing the CDEF ring system of brevetoxin A (**1**) by the hydroxy dithioketal technology[30] (Scheme 11). Thus, coupling of **37** and **38** through the ylide of **37** (*n*BuLi, HMPA) gave *cis* olefin **87** in 82 % yield, while removal of the TBS group from the latter compound by the action of TBAF afforded the desired cyclization precursor **88** (89 % yield). In spite of the success enjoyed in the simpler model (**34** → **35**, Scheme 5), many attempts to cyclize **88** by our previously developed conditions failed to provide the

nonacene system. For example, under the normal ring closure conditions ($AgClO_4$, $NaHCO_3$, SiO_2, 4 Å MS, $MeNO_2$), the conjugated elimination product **90** and hydrolysis product, ketone **91**, were obtained in 87% combined yield.



Scheme 11. Synthesis and attempted cyclization of precursor **88**. Reagents and conditions: a) 1.0 equiv of **37**, 1.2 equiv of *n*BuLi, −78 °C, 20 min; then add 10 equiv of HMPA, 1.2 equiv of aldehyde **38**, −78 (20 min) → 25 °C (1.5 h), 82%; b) 2.0 equiv of TBAF, THF, 25 °C, 36 h, 89%; c) 3.0 equiv of $AgClO_4$, 10 equiv of $NaHCO_3$, SiO_2, 4 Å MS, $MeNO_2$, 25 °C, 3 h, 56% of **90** and 31% of **91**. HMPA = hexamethylphosphoramide; Piv = pivaloyl.

Conclusion

It became clear from these studies that the first strategy towards brevetoxin A (**1**), in which the nine-membered ring (ring E) was to be constructed last by the hydroxydithioketal method would, perhaps, be problematic. Given the well-known resistance to nine-membered ring formation supported by entropic, strain and other factors intrinsic to the particular structure of brevetoxin A (**1**), this observation was not entirely surprising although highly disappointing. This failure, however, like many others in total synthesis, was perhaps a blessing in disguise, for having regrouped, we set out in search of a new strategy and a new method for the construction of medium-sized rings. As it turned out, such a method was found.[43] Its application to the problem of brevetoxin A (**1**) is described in the following articles.[16–18]

Experimental Section

General techniques: All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. Tetrahydrofuran (THF), toluene, and diethyl ether (ether) were distilled from sodium benzophenone, and methylene chloride (CH_2Cl_2) from calcium hydride. Anhydrous solvents were also obtained by passing them through commercially available alumina column. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at highest commercial quality and used without further purification unless otherwise stated. Reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica gel plates (60 G-254) using UV light as visualizing agent and 7% ethanol phosphomolybdic acid or *p*-anisaldehyde solution and heat as developing agents. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography (PTLC) separations were carried out on 0.25, 0.50, or 1 mm E. Merck silica gel plates (60 F-254). NMR spectra were recorded on Bruker DRX-600, AMX-500, AMX-400, or AC-250 instruments and calibrated with residual undeuterated solvent as an internal reference. The following abbreviations were used to designate the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. IR spectra were recorded on a Perkin-Elmer 241 polarimeter. High-resolution mass spectra (HRMS) were recorded on a VG ZAB-SE mass spectrometer under fast atom bombardment (FAB) conditions with nitrobenzyl alcohol (NBA) as the matrix. Melting points (m.p.) are uncorrected and were recorded on a Thomas Hoover Unimelt capillary melting point apparatus.

Aldehyde 16: A solution of (*S*)-(+)-methyl 3-hydroxy-2-methyl propionate **15** (47 g, 400 mmol) and PhSSPh (104 g, 480 mmol) in DMF (380 mL) was treated with nBu$_3$P (97 g, 480 mmol) at 0 °C and was allowed to warm to 25 °C over 5 h. The reaction mixture was diluted with ether (1.5 L), washed with H_2O (3 × 200 mL), and dried ($MgSO_4$). The concentrated residue was purified by flash column chromatography (silica gel, 1:9, ether:hexanes) to afford the desired sulfide. A solution of the sulfide (84 g, 400 mmol) in CH_2Cl_2 (1.2 L) was treated with DIBAL (410 mL of 1M in hexanes, 410 mmol) at −78 °C for 30 min. The reaction mixture was quenched by pouring into a saturated aqueous sodium potassium tartrate solution (300 mL) and was diluted with ether (1.5 L). The organic phase was dried ($MgSO_4$) and concentrated to afford aldehyde **16** (72 g, 100%). **16**: R_f = 0.44 (silica gel, 3:7, ether:hexanes); $[\alpha]_D^{25} = +2.3$ (c = 2.4, CCl_4); IR (thin film): $\tilde{\nu}_{max}$ = 3055, 2962, 2925, 2805, 2720, 1720, 1584, 1481, 1455, 1439, 1390, 1372, 1290, 1090, 1021, 928, 738, 690 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 9.67 (d, J = 1.0 Hz, 1H, HC(O)), 7.38–7.17 (m, 5H, ArH), 3.30 (dd, J = 13.5, 7.0 Hz, 1H, C*H*H), 2.91 (dd, J = 13.5, 7.0 Hz, 1H, C*H*H), 2.62 (dddd, J = 7.0, 7.0, 7.0, 1.0 Hz, 1H, CH), 1.23 (d, J = 7.0 Hz, 3H, CH_3); HRMS calcd for $C_{10}H_{12}OS$ ([M^+]) 180.061, found 180.063.

Sulfone 13: A solution of aldehyde **16** (72 g, 400 mmol) in THF (100 mL) was added to a slurry of methyltriphenylphosphonium bromide (171 g, 480 mmol) and NaN(SiMe$_3$)$_2$ (460 mL of 1M in THF, 460 mmol) in THF (1.2 L) at 0 °C and was stirred for 30 min. The reaction mixture was quenched by pouring into a saturated aqueous ammonium chloride solution (200 mL) and diluted with ether (1.5 L). The organic phase was washed with water (2 × 200 mL), dried ($MgSO_4$), and concentrated. The residue was purified by flash column chromatography (silica gel, 1:19, ether:hexanes) to afford the desired olefin (64.8 g, 91%). A solution of the olefin (64.8 g, 364 mmol) in CH_2Cl_2 (1 L) was treated portionwise with *m*CPBA (180 g of 80-85%, 837 mmol) at 0 °C over 1.5 h. The reaction mixture was quenched by treating with dimethyl sulfide (4 mL) and diluted with ether (1.5 L). The organic solution was washed with a saturated aqueous sodium bicarbonate solution (4 × 200 mL) and dried ($MgSO_4$). After concentration, the residue was purified by flash column chromatography (silica gel, 3:7, ether:hexanes) to afford sulfone **13** (63.5 g, 82%). **13**: R_f = 0.25 (silica gel, 3:7, ether:hexanes); $[\alpha]_D^{25} = +3.84$ (c = 3.85, CCl_4); IR (thin film): $\tilde{\nu}_{max}$ = 3070, 2975, 2937, 2880, 1644, 1580, 1482, 1450, 1408, 1310, 1259, 1205, 1150, 1090, 1001, 920, 880, 858, 814, 787, 740, 691, 650 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.04–7.23 (m, 5H, ArH), 5.88 (ddd, J = 17.0, 10.0, 7.0 Hz, 1H, =CH), 4.99–4.90 (m, 2H, =CH_2), 3.14 (dd, J = 14.0, 6.0 Hz, 1H, C*H*H), 3.00 (dd, J = 14.0, 6.0 Hz, 1H, C*H*H), 2.82-2.71 (m, 1H, CH), 1.15 (d, J = 7.0 Hz, 3H, CH_3); HRMS calcd for $C_{11}H_{14}O_2S$ ([$M+H^+$]) 211.079, found 211.077.

***β*-Keto sulfone 17**: A solution of sulfone **13** (95 g, 450 mmol) in THF (1 L) was treated with *n*BuLi (262 mL of 1.6M in hexanes, 429 mmol) at −78 °C for 40 min before addition of methyl ester **14** (41 g, 205 mmol) in THF (30 mL). After 4 h, acetic acid (50 mL) in THF (20 mL) was added, and the reaction mixture was diluted with EtOAc (1 L), washed with water

0947-6539/99/0502-0606 $ 17.50+.50/0 *Chem. Eur. J.* **1999**, *5*, No. 2

(200 mL), brine (200 mL), and dried ($MgSO_4$). After concentration, the residue was purified by flash column chromatography (silica gel, 4:6, ether:hexanes) to afford a diastereomeric mixture of β-keto sulfones **17** (62 g, 79%). **17** (major diastereomer): white solid, m.p. = 134–135 °C; R_f = 0.25 (silica gel, 1:1, ether:hexanes); $[\alpha]_D^{25} = -91.1$ (c = 6.3, CH_2Cl_2); IR (thin film): $\tilde{\nu}_{max}$ = 3040, 2980, 2920, 1719, 1441, 1380, 1370, 1317, 1305, 1212, 1148, 1079, 1020, 928, 841, 790, 682 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.88 (d, J = 7.6 Hz, 2H, ArH), 7.66 (t, J = 7.5 Hz, 1H, ArH), 7.55 (t, J = 8.0 Hz, 2H, ArH), 5.78 (d, J = 3.0 Hz, 1H, anomeric CH), 5.58–5.50 (m, 1H), 4.97-4.94 (m, 2H), 4.85 (d, J = 10.0 Hz, 1H), 4.64 (dd, J = 4.0, 4.0 Hz, 1H, OCH), 4.13 (dd, J = 10.5, 5.5 Hz, 1H, OCH), 3.04-2.96 (m, 1H, CH), 2.21 (dd, J = 14.0, 5.5 Hz, 1H, C*H*H), 1.77-1.65 (m, 1H, C*H*H), 1.40 (s, 3H, CH_3), 1.32 (d, J = 6.5 Hz, 3H, CH_3), 1.29 (s, 3H, CH_3); HRMS calcd for $C_{19}H_{24}O_6S$ ($[M+NH_4^+]$) 398.163, found 398.163.

Ketone 18: A solution of sulfone **17** (31.9 g, 84 mmol) in THF (440 mL) and water (44 mL) was treated portionwise with freshly prepared strips of Al(Hg) (20 g, 740 g-atom) at 65 °C over 2 h. After 1 h, the reaction mixture was cooled and filtered through a pad of celite. After concentration, the residue was purified by flash column chromatography (silica gel, 3:7, ether:hexanes) to afford ketone **18** (17.3 g, 86%). **18**: R_f = 0.38 (silica gel, 3:7, ether:hexanes); $[\alpha]_D^{25} = -61.3$ (c = 0.7, CH_2Cl_2); IR (thin film): $\tilde{\nu}_{max}$ = 2880, 2855, 2830, 1717, 1641, 1459, 1435, 1384, 1374, 1260, 1240, 1213, 1171, 1060, 1025, 914, 850, 680 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 5.84 (d, J = 3.5 Hz, 1H, anomeric CH), 5.68 (ddd, J = 17.5, 10.5, 7.0 Hz, 1H, =CH), 4.93 (dd, J = 17.5, 1.5 Hz, 1H, =C*H*H), 4.88 (dd, J = 10.5, 1.5 Hz, 1H, =C*H*H), 4.66 (dd, J = 4.0, 4.0 Hz, 1H, OCH), 4.51 (dd, J = 11.0, 5.0 Hz, 1H, OCH), 2.73–2.67 (m, 1H, CH), 2.57 (dd, J = 17.0, 7.0 Hz, 1H, C*H*H), 2.46 (dd, J = 17.0, 7.0 Hz, 1H, C*H*H), 2.27 (dd, J = 13.5, 5.0 Hz, 1H, C*H*H), 1.71–1.65 (m, 1H, C*H*H), 1.44 (s, 3H, CH_3), 1.26 (s, 3H, CH_3), 0.95 (d, J = 6.5 Hz, 3H, CH_3); HRMS calcd for $C_{13}H_{20}O_4$ ($[M+H^+]$) 241.144, found 241.143.

Tertiary alcohol 19a,b: A solution of ketone **18** (29.0 g, 122 mmol) in DME (50 mL) was added to a solution of methylmagnesium chloride (54 mL of 3 M in THF, 162 mmol) in DME (750 mL) at −78 °C over 15 min. The resulting solution was stirred at −78 °C for 1 h, warmed to −30 °C over 1.5 h, stirred at 25 °C for 15 min, and quenched by addition of a saturated aqueous ammonium chloride solution (50 mL). The reaction mixture was diluted with ether (1 L), washed with additional saturated aqueous ammonium chloride solution (2 × 100 mL), and dried ($MgSO_4$). The solution was concentrated to afford a mixture of the epimeric tertiary alcohols **19a, b** (29.8 g, 95%, ca. **19a**:**19b** = 12.8:1). **19a, b**: R_f = 0.25 (silica gel, 4:6, ether:hexanes); $[\alpha]_D^{25} = -2.1$ (c = 1.3, CH_2Cl_2); IR (thin film): $\tilde{\nu}_{max}$ = 3580, 2980, 2937, 1642, 1455, 1450, 1390, 1378, 1318, 1220, 1169, 1060, 1021, 962, 919, 855 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 5.77 (d, J = 3.5 Hz, 1H, anomeric CH), 5.70 (ddd, J = 17.5, 10.0, 8.0 Hz, 1H, =CH), 4.99 (dd, J = 17.5, 1.5 Hz, 1H, =CH), 4.89 (dd, J = 10.0, 1.5 Hz, 1H, =CH), 4.69 (dd, J = 4.0, 4.0 Hz, 1H, OCH), 4.10 (dd, J = 10.5, 4.5 Hz, 1H, OCH), 2.46–2.41 (m, 1H, CH), 1.95 (dd, J = 13.5, 4.5 Hz, 1H, C*H*H), 1.83–1.77 (m, 1H, C*H*H), 1.48 (s, 3H, CH_3), 1.42-1.39 (m, 2H, C*H*H), 1.29 (s, 3H, CH_3), 1.26 (s, 3H, CH_3), 1.04 (d, J = 6.5 Hz, 3H, CH_3); HRMS calcd for $C_{14}H_{24}O_4$ ($[M+NH_4^+]$) 274.202, found 274.203.

Triol 20: A solution of alcohol **19a, b** (25.6 g, 100 mmol) in CH_2Cl_2 (400 mL) was treated with EtSH (148 mL, 2 mol) and $ZnCl_2$ (67 g, 492 mmol) at 0 °C for 1.5 h. The reaction mixture was concentrated, and the resulting oil was dissolved in ether (500 mL), washed with 5% aqueous ammonium hydroxide solution (2 × 100 mL), and dried ($MgSO_4$). After concentration, the residue was purified by flash column chromatography (silica gel, 8:2, ether:hexanes) to afford triol **20** (26.6 g, 92%). **20**: R_f = 0.33 (silica gel, 8:2, ether:hexanes); $[\alpha]_D^{25} = +76.7$ (c = 1.2, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max}$ = 3500, 2995, 2950, 2885, 1650, 1450, 1388, 1126, 1079, 1040, 988, 918, 740 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 5.68 (ddd, J = 18.0, 10.0, 8.0 Hz, 1H, =CH), 4.99 (dd, J = 18.0, 1.5 Hz, 1H, =CH), 4.92 (dd, J = 10.0, 1.5 Hz, 1H, =CH), 4.87 (d, J = 1.5 Hz, 1H, $CH(SEt)_2$), 3.87 (d, J = 3.0 Hz, 1H), 3.64 (d, J = 8.6 Hz, 1H), 3.51–3.48 (m, 1H), 3.38 (d, J = 4.5 Hz, 1H), 2.72 (dd, J = 7.5, 7.5 Hz, 4H, CH_2S), 2.45–2.40 (m, 1H, C*H*H), 2.20 (ddd, J = 15.0, 3.0, 3.0 Hz, 1H, C*H*H), 2.04 (ddd, J = 15.0, 3.0, 3.0 Hz, 1H, C*H*H), 1.67 (dd, J = 14.5, 4.5 Hz, 1H), 1.51 (dd, 14.5, 7.6 Hz, 1H), 1.34 (s, 3H, CH_3), 1.31 (dd, J = 7.0 Hz, 6H, CH_3), 1.09 (d, J = 7.0 Hz, 3H, CH_3); HRMS calcd for $C_{15}H_{30}O_3S_2$ ($[M+H^+]$) 323.172, found 323.170.

Dibenzyl ether 21: A solution of triol **20** (29.6 g, 92 mmol) in THF (50 mL) was added to a suspension of NaH (12 g of 60% in oil, 276 mmol) in THF (500 mL) at 0 °C. The reaction mixture was stirred at 25 °C for 1 h, and then recooled to 0 °C before the addition of BnBr (24.5 mL, 118.6 mmol) and nBu$_4$NI (170 mg, 0.46 mmol). The reaction mixture was allowed to warm to 25 °C and stirred for 11 h. After the excess NaH was quenched by the addition of MeOH (25 mL), the reaction mixture was diluted with ether (1 L), washed with saturated aqueous ammonium chloride solution (2 × 200 mL), dried ($MgSO_4$), and concentrated. The residue was purified by flash column chromatography (silica gel, 2:8, ether:hexanes) to afford dibenzyl ether **21** (39.7 g, 86%). **21**: R_f = 0.38 (silica gel, 2:8, ether:hexanes); $[\alpha]_D^{25} = +56.6$ (c = 1.6, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max}$ = 3590, 3500, 1652, 1510, 1467, 1389, 1278, 1220, 1100, 1040, 921, 745, 710 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 7.38–7.24 (m, 10H, ArH), 5.78–5.68 (m, 1H, =CH), 4.93–4.83 (m, 2H, =CH), 4.71 (d, J = 11.5 Hz, 1H, C*H*HPh), 4.69 (d, J = 11.5 Hz, 1H, C*H*HPh), 4.56 (d, J = 11.5 Hz, 1H, C*H*HPh), 4.46 (d, J = 11.5 Hz, 1H, C*H*HPh), 4.03 (d, J = 3.5 Hz, 1H, SCH), 3.96–3.87 (m, 1H, OCH), 3.35 (dd, J = 5.0 Hz, 1H, OCH), 2.72–2.60 (m, 4H, 2 CH_2), 2.45–2.30 (m, 1H), 2.36 (s, 1H, OH), 2.27–2.15 (m, 1H), 2.04–1.92 (m, 1H), 1.66–1.41 (m, 2H), 1.24 (dd, J = 7.0 Hz, 6H, CH_3), 1.15 (s, 3H, CH_3), 0.96 (d, J = 7.0 Hz, 3H, CH_3); HRMS calcd for $C_{29}H_{42}O_3S_2$ ($[M+H^+]$) 503.266, found 503.263.

Lactol 22: A solution of alcohol **21** (15.5 g, 30.0 mmol) in acetonitrile (75 mL) was added to a solution of *N*-chlorosuccinimide (24.0 g, 180 mmol) and 2,6-lutidine (21 mL, 180 mmol) in acetonitrile (480 mL) and water (120 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 5 min, then quenched by the addition of 10% aqueous sodium sulfate solution (150 mL) and diluted with ether (1 L). The organic layer was separated and washed successively with 10% aqueous sodium sulfate solution (100 mL) and saturated aqueous copper sulfate solution (3 × 75 mL). The organic phase was dried ($MgSO_4$), filtered, concentrated, and purified by flash column chromatography (silica gel, 3:7, ether:hexanes) to afford lactol **22** (9.48 g, 80%). **22**: R_f = 0.40 (silica gel, 3:7, ether:hexanes); $[\alpha]_D^{25} = +37.6$ (c = 1.8, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max}$ = 3400, 3035, 3010, 2920, 2860, 1639, 1495, 1451, 1350, 1264, 1202, 1100, 908, 732, 698 cm^{-1}; ^1H NMR (250 MHz, C_6D_6): δ = 7.45–7.06 (m, 10H, ArH), 5.90 (ddd, J = 17.5, 10.0, 7.5 Hz, 1H, =CH), 5.07–4.91 (m, 2H, =CH), 4.88 (d, J = 12.0 Hz, 1H, C*H*HPh), 4.78 (dd, J = 7.5, 5.5 Hz, 1H, anomeric CH), 4.64 (d, J = 12.0 Hz, 1H, C*H*HPh), 4.30 (d, J = 11.5 Hz, 1H, C*H*HPh), 4.05 (d, J = 11.5 Hz, 1H, C*H*HPh), 3.18–3.05 (m, 2H, OCH), 2.62–2.55 (m, 1H), 2.34 (d, J = 5.5 Hz, 1H), 2.25 (ddd, J = 12.5, 5.0, 5.0 Hz, 1H), 1.95 (dd, J = 14.0, 6.5 Hz, 1H), 1.75–1.60 (m, 1H), 1.49 (dd, J = 14.0, 5.5 Hz, 1H), 1.23 (s, 3H, CH_3), 1.14 (d, J = 7.0 Hz, 3H, CH_3); HRMS calcd for $C_{25}H_{32}O_4$ ($[M-OH^-]$) 379.227, found 379.224.

Ketone 23: A solution of lactol **22** (18 g, 47 mmol) in toluene (70 mL) was treated with 1-triphenylphosphoranylidene-2-propanone (22.8 g, 71.4 mmol) at 110 °C for 4 h. The reaction mixture was cooled to room temperature, diluted with ether:hexanes (1:1), filtered through silica gel, concentrated, and azeotroped with benzene. The resulting oil was taken up in THF (1.2 L) and treated with NaH (1.88 g of 60% in mineral oil, 47.0 mmol) at 25 °C for 10 h. The reaction mixture was quenched by the addition of methanol (5 mL) and diluted with ether (1 L). The organic phase was washed with saturated aqueous ammonium chloride solution (2 × 100 mL), brine (100 mL), dried ($MgSO_4$), and concentrated. The residue was purified by flash column chromatography (silica gel, 1:3, ether:hexanes) to afford ketone **23** (14.9 g, 73%). **23**: R_f = 0.37 (silica gel, 2:8, ether:hexanes); $[\alpha]_D^{25} = -22.2$ (c = 2.0, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max}$ = 2975, 2895, 1729, 1651, 1510, 1468, 1390, 1365, 1320, 1250, 1195, 1100, 1041, 921, 747, 710 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 7.38–7.24 (m, 10H, ArH), 5.74 (ddd, J = 17.5, 10.0, 7.5 Hz, 1H, =CH), 4.92–4.78 (m, 2H, =CH), 4.60 (d, J = 11.5 Hz, 1H, C*H*HPh), 4.60 (d, J = 11.5 Hz, 1H, C*H*HPh), 4.43 (d, J = 11.5 Hz, 1H, C*H*HPh), 4.40 (d, J = 11.5 Hz, 1H, C*H*HPh), 3.90 (ddd, J = 9.5, 9.5, 3.5 Hz, 1H, OCH), 3.19 (dd, J = 10.5, 3.5 Hz, 1H, OCH), 3.15-3.03 (m, 1H, OCH), 2.77 (dd, J = 15.0, 3.5 Hz, 1H), 2.52-2.31 (m, 3H), 2.13 (s, 3H, CH_3), 1.81 (dd, J = 14.5, 6.5 Hz, 1H), 1.54 (ddd, J = 11.5, 11.5, 11.5 Hz, 1H), 1.33–1.20 (m, 1H), 1.23 (s, 3H, CH_3), 0.93 (d, J = 7.0 Hz, 3H, CH_3); HRMS calcd for $C_{28}H_{36}O_4$ ($[M+H^+]$) 379.227, found 379.224.

Aldehyde 12: A solution of ketone **23** (9.3 g, 21 mmol) in THF (100 mL) and water (5 mL) was treated with a 60% aqueous solution of *N*-methylmorpholine-*N*-oxide (4.87 mL, 25.7 mmol) and osmium tetroxide (4.34 mL of 0.1 M in THF, 0.42 mmol) at 25 °C for 5 h. The reaction mixture was quenched by the addition of saturated aqueous sodium dithionate solution (10 mL), followed by vigorous stirring for 2 h. The reaction

mixture was diluted with EtOAc (200 mL) and washed with water (2 × 25 mL). The aqueous washings were back extracted with EtOAc (25 mL), and the combined organic layers were dried ($MgSO_4$), and concentrated. The residue was dissolved in THF (200 mL) and water (20 mL), treated portionwise with $NaIO_4$ (5.5 g, 25.7 mmol) over 30 min, and stirred at 25 °C for 2 h. The reaction mixture was diluted with ether (500 mL) and then washed with water (2 × 100 mL) and brine (100 mL). The organic layer was dried ($MgSO_4$) and concentrated to afford aldehyde **12** (8.7 g, 93 %). **12**: $R_f = 0.12$ (silica gel, 3:7, ether:hexanes); $[\alpha]_D^{25} = -52.1$ ($c = 0.85$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 2935$, 2850, 1720, 1710, 1491, 1479, 1450, 1352, 1307, 1201, 1180, 1100, 1024, 732, 697, 678 cm^{-1}; ^1H NMR (250 MHz, C_6D_6): $\delta =$ 9.24 (d, $J = 4.0$ Hz, 1H), 7.33-7.02 (m, 10H, ArH), 4.37 (d, $J = 11.5$ Hz, 1H, C*H*HPh), 4.35 (d, $J = 12.0$ Hz, 1H, C*H*HPh), 4.12 (d, $J = 11.5$ Hz, 1H, C*H*HPh), 4.07 (d, $J = 12.0$ Hz, 1H, C*H*HPh), 4.06 – 4.01 (m, 1H, OCH), 3.22 (dd, $J = 12.5$, 4.5 Hz, 1H, OCH), 2.94 – 2.84 (m, 1H), 2.64 (dd, $J = 15.5$, 3.0 Hz, 1H), 2.39 – 2.27 (m, 2H), 2.16-2.11 (m, 1H), 1.87 – 1.77 (m, 1H), 1.82 (s, 3H, CH_3), 1.52-1.44 (m, 2H), 1.18 (s, 3H, CH_3), 0.70 (d, $J = 7.0$ Hz, 3H, CH_3); HRMS calcd for $C_{27}H_{34}O_5$ ($[M+H^+]$) 439.248, found 439.248.

Bis-lactone 26: A solution of ketoaldehyde **12** (16.95 g, 38.7 mmol) in ether (100 mL) was transferred to a solution of zinc bromide (4.35 mL, 19.3 mmol) in ether (250 mL) at −78 °C, followed by the addition of CH_2=C(OBn)OTBS (30.0 g, 116 mmol) in ether (100 mL). The reaction mixture was quenched after 20 min at −78 °C with a saturated aqueous sodium bicarbonate solution (100 mL). The organic layer was separated, washed with water (2 × 75 mL) and brine (75 mL), and dried ($MgSO_4$). The organic solution was concentrated, and the residue was purified by flash column chromatography (silica gel, 3:17, ether:hexanes) to afford a mixture of four diastereomeric dibenzyl esters **24** (30.2 g, 81 %). A solution of dibenzyl esters **24** (all four diastereomers) (30.2 g, 31.3 mmol) in THF (400 mL) was stirred with 20 % $Pd(OH)_2$/C (6 g) under hydrogen atmosphere at 25 °C for 3 h. The reaction mixture was filtered through a pad of celite, and the filtrate was concentrated and azeotroped with benzene. The resulting solid was dissolved in CH_2Cl_2 (175 mL) and treated with 2,2′-dipyridyl disulfide (17.2 g, 78.3 mmol) and triphenylphosphane (20.5 g, 78.3 mmol) at 25 °C for 1 h. The resulting mixture was concentrated, taken up in toluene (375 mL), and added to $AgClO_4$ (14.4 g, 69.5 mmol) in toluene (3 L) at 110 °C over 2 h. The reaction mixture was refluxed for 2 h and then concentrated and purified by flash column chromatography (silica gel, 3:7, EtOAc:hexanes) to afford a diastereomeric mixture of bis-lactones **26** (13.5 g, 76 % for two steps). Data for each of the four diastereoisomers separately:

26a: $R_f = 0.51$ (silica gel, 1:1, ether:hexanes); $[\alpha]_D^{25} = -7.7$ ($c = 0.9$, CCl_4); IR (thin film): $\tilde{\nu}_{max} = 2960$, 2940, 2865, 1740, 1580, 1478, 1469, 1420, 1389, 1368, 1307, 1290, 1252, 1170, 1140, 1092, 1050, 1010, 940, 900, 882, 840, 779, 740, 703, 660, 649, 631, 613 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): $\delta = 4.38$ (dd, $J = 12.0$, 4.5 Hz, 1H), 4.23 – 4.13 (m, 1H), 4.00 (dd, $J = 7.0$, 7.0 Hz, 1H), 3.60 – 3.50 (m, 1H), 3.01 (d, $J = 13.5$ Hz, 1H), 2.87-2.64 (m, 3H), 2.34 – 2.00 (m, 5H), 1.86 (dd, $J = 13.0$, 11.5 Hz, 1H), 1.70 – 1.60 (m, 1H), 1.37 (s, 3H), 1.28 (s, 3H), 1.00 (d, $J = 7.0$ Hz, 3H), 0.90 (s, 9H), 0.84 (s, 9H), 0.12 (s, 6H), 0.08 (s, 3H), 0.06 (s, 3H); HRMS calcd for $C_{29}H_{54}O_7Si_2$ ($[M+H^+]$) 571.349, found 571.347.

26b: $R_f = 0.44$ (silica gel, 1:1, ether:hexanes); $[\alpha]_D^{25} = +53.8$ ($c = 0.6$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 2960$, 2937, 2900, 2865, 1740, 1468, 1382, 1368, 1313, 1270, 1230, 1178, 1100, 1109, 971, 942, 910, 897, 840, 780, 700, 670, 658, 639, 615 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): $\delta = 4.21$ (dd, $J = 12.0$, 4.5 Hz, 1H), 4.16 – 4.08 (m, 1H), 3.60-3.50 (m, 2H), 3.13 (dd, $J = 13.0$, 4.0 Hz, 1H), 3.00 (d, $J = 13.5$ Hz, 1H), 2.74 (dd, $J = 13.5$, 2.5 Hz, 1H), 2.48 (dd, $J = 13.0$, 3.0 Hz, 1H), 2.34 – 2.01 (m, 3H), 1.80 (dd, $J = 12.0$, 12.0 Hz, 1H), 1.70 – 1.40 (m, 3H), 1.37 (s, 3H), 1.32 (s, 3H), 1.05 (d, $J = 6.5$ Hz, 3H), 0.93 (s, 9H), 0.85 (s, 9H), 0.14 (s, 3H), 0.12 (s, 3H), 0.12 (s, 3H), 0.07 (s, 3H); HRMS calcd for $C_{29}H_{54}O_7Si_2$ ($[M+H^+]$) 571.349, found 571.345.

26c: $R_f = 0.18$ (silica gel, 6:4, ether:hexanes); $[\alpha]_D^{25} = +71.6$ ($c = 0.7$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 2960$, 2935, 2882, 2860, 1740, 1467, 1380, 1309, 1285, 1234, 1190, 1162, 1125, 1080, 1047, 1001, 971, 940, 917, 902, 879, 844, 810, 781, 672, 631 cm^{-1}; ^1H NMR (250 MHz, C_6D_6): $\delta = 4.16$ (dd, $J = 11.5$, 4.5 Hz, 1H), 4.07 – 3.92 (m, 2H), 3.74 – 3.64 (m, 1H), 2.74 – 2.68 (m, 3H), 2.45 (d, $J = 14.0$ Hz, 1H), 2.30 – 2.04 (m, 4H), 1.66 (dd, $J = 8.0$, 8.0 Hz, 1H), 1.32 – 1.19 (m, 2H), 1.16 (s, 3H), 1.07 (s, 3H), 1.04 (s, 9H), 0.95 (s, 9H), 0.85 (d, $J = 7.0$ Hz, 3H), 0.21 (s, 3H), 0.10 (s, 3H), 0.06 (s, 3H), 0.00 (s, 3H); HRMS calcd for $C_{29}H_{54}O_7Si_2$ ($[M+H^+]$) 571.349, found 571.342.

26d: $R_f = 0.21$ (silica gel, 8:2, ether:hexanes); $[\alpha]_D^{25} = +60.2$ ($c = 1.4$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 2965$, 2940, 2900, 2875, 1760, 1470, 1382, 1316, 1263, 1240, 1200, 1170, 1140, 1130, 1011, 1084, 1056, 988, 960, 941, 843 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): $\delta = 4.21$ (dd, $J = 12.0$, 4.5 Hz, 1H), 4.16 – 4.05 (m, 1H), 3.92 (ddd, $J = 10.0$, 10.0, 4.0 Hz, 1H), 3.60 – 3.55 (m, 1H), 3.14 (dd, $J = 13.0$, 4.0 Hz, 1H), 2.80 (s, 2H), 2.47 (dd, $J = 13.0$, 3.0 Hz, 1H), 2.35 – 2.26 (m, 1H), 2.21 – 2.00 (m, 2H), 1.67 – 1.44 (m, 4H), 1.40 (s, 3H), 1.30 (s, 3H), 1.05 (d, $J = 6.5$ Hz, 3H), 0.93 (s, 9H), 0.87 (s, 9H), 0.15 (s, 3H), 0.14 (s, 3H), 0.12 (s, 3H), 0.07 (s, 3H); HRMS calcd for $C_{29}H_{54}O_7Si_2$ ($[M+H^+]$) 571.349, found 571.351.

Alcohol 27c: A solution of bis-lactone **26c** (6.3 g, 11.0 mmol) in THF (36 mL) was treated with HF · pyr. (11.0 mL) at 0 °C. The reaction mixture was warmed to 25 °C and stirred for 3 h. The reaction mixture was quenched by dilution with EtOAc (40 mL), followed by pouring into a saturated aqueous sodium carbonate solution (156 mL) and EtOAc (400 mL). The separated organic layer was washed with saturated aqueous sodium carbonate solution (3 × 200 mL), dried ($MgSO_4$), and concentrated. The residue was purified by flash column chromatography (silica gel, EtOAc) to afford alcohol **27** (4.26 g, 85 %). **27**: $R_f = 0.40$ (silica gel, EtOAc); IR (thin film): $\tilde{\nu}_{max} = 3610$, 3460, 2950, 2924, 2850, 1738, 1462, 1378, 1309, 1233, 1190, 1156, 1120, 1079, 1044, 1000, 838, 809, 776, 690, 665, 620 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 4.37$ (dd, $J = 12.0$, 5.0 Hz, 1H), 4.15 – 4.04 (m, 2H), 3.93 (ddd, $J = 10.5$, 10.5, 4.0 Hz, 1H), 2.89 – 2.78 (m, 2H), 2.81 (s, 2H), 2.33 (ddd, $J = 13.5$, 5.3, 5.3 Hz, 1H), 2.19 (dd, $J = 13.5$, 4.0 Hz, 1H), 2.12 (ddd, $J = 12.0$, 12.0, 12.0 Hz, 1H), 2.02 (dd, $J = 15.0$, 7.5 Hz, 1H), 1.86 (d, $J = 4.0$ Hz, 1H), 1.75 – 1.73 (m, 1H), 1.58 (dd, $J = 13.5$, 10.5 Hz, 1H), 1.41 (s, 3H), 1.30 – 1.25 (m, 1H), 1.29 (s, 3H), 1.08 (d, $J = 7.0$ Hz, 3H), 0.87 (s, 9H), 0.16 (s, 3H), 0.12 (s, 3H); HRMS calcd for $C_{23}H_{40}O_7Si$ ($[M+H^+]$) 474.288, found 474.286.

Olefin 28: A solution of alcohol **27** (4.26 g, 9.35 mmol) in methylene chloride (47 mL) was treated with Martin's sulfurane (7.54 g, 11.2 mmol) at 0 °C for 30 min. The reaction mixture was concentrated and purified by flash column chromatography (silica gel, 1:1, EtOAc:hexanes) to afford α,β-unsaturated lactone **28** (3.56 g, 87 %). **28**: $R_f = 0.18$ (silica gel, 4:6, EtOAc:hexanes); $[\alpha]_D^{25} = -8.95$ ($c = 2.0$, CH_2Cl_2); IR (thin film): $\tilde{\nu}_{max} =$ 2970, 2940, 2870, 1742, 1480, 1472, 1388, 1342, 1317, 1244, 1218, 1162, 1149, 1131, 1116, 1085, 1060, 1040, 1010, 910, 890, 846, 833, 819, 784, 682, 655 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 5.98$ (dd, $J = 11.5$, 8.0 Hz, 1H), 5.79 (d, $J = 11.5$ Hz, 1H), 4.61 (dd, $J = 11.0$, 5.5 Hz, 1H), 4.06 – 4.00 (m, 1H), 3.85 (ddd, $J = 10.0$, 10.0, 4.0 Hz, 1H), 2.79 (br s, 2H), 2.54-2.49 (m, 1H), 2.31 (ddd, $J = 13.5$, 5.5, 5.5 Hz, 1H), 2.18 (dd, $J = 13.5$, 4.0 Hz, 1H), 2.12 (ddd, $J = 13.0$, 12.0, 12.0 Hz, 1H), 1.66 – 1.60 (m, 1H), 1.53 (dd, $J = 13.5$, 10.5 Hz, 1H), 1.53 – 1.45 (m, 1H), 1.39 (s, 3H), 1.33 (s, 3H), 1.11 (d, $J = 7.0$ Hz, 3H), 0.87 (s, 9H), 0.15 (s, 3H), 0.12 (s, 3H); HRMS calcd for $C_{23}H_{38}O_6Si$ ($[M+H^+]$) 439.251, found 439.243.

Alcohol 29: A solution of α,β-unsaturated lactone **28** (3.56 g, 8.13 mmol) in THF (25 mL) was treated with HF · pyr. (16.5 mL) at 0 °C. The reaction mixture was warmed to 25 °C and stirred for 4 h. The reaction mixture was quenched by dilution with EtOAc (30 mL) followed by pouring into saturated aqueous sodium carbonate solution (250 mL) and EtOAc (450 mL). The separated organic layer was washed with saturated aqueous sodium carbonate solution (3 × 200 mL), dried ($MgSO_4$), and concentrated. The residue was purified by flash column chromatography (silica gel, 8:2, EtOAc:hexanes) to afford α,β-unsaturated lactone **29** (2.42 g, 92 %). **29**: $R_f = 0.34$ (silica gel, 8:2, EtOAc:hexanes); $[\alpha]_D^{25} = -24.3$ ($c = 3.7$, CH_2Cl_2); IR (thin film): $\tilde{\nu}_{max} = 3605$, 3500, 2985, 2950, 2895, 1738, 1470, 1388, 1335, 1320, 1251, 1217, 1168, 1147, 1100, 1081, 1060, 1040, 983, 966, 954, 919, 900, 867, 801, 684, 660 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 5.95$ (dd, $J = 11.5$, 8.0 Hz, 1H), 5.75 (d, $J = 11.5$ Hz, 1H), 4.58 (dd, $J = 12.0$, 4.5 Hz, 1H), 4.04 (ddd, $J = 11.0$, 9.5, 6.0 Hz, 1H), 3.80 (ddd, $J = 10.5$, 10.5, 4.5 Hz, 1H), 2.88 (d, $J = 14.0$ Hz, 1H), 2.73 (dd, $J = 14.0$, 2.0 Hz, 1H), 2.57 (br s, 1H), 2.50 – 2.42 (m, 1H), 2.27 (ddd, $J = 13.0$, 5.5, 5.5 Hz, 1H), 2.17 (ddd, $J = 14.0$, 4.0, 2.0 Hz, 1H), 2.10 (ddd, $J = 12.0$, 12.0, 12.0 Hz, 1H), 1.58 (br d, $J = 14.0$ Hz, 1H), 1.50 (dd, $J = 14.0$, 10.5 Hz, 1H), 1.43 (br d, $J = 12.0$ Hz, 1H), 1.36 (s, 3H), 1.30 (s, 3H), 1.07 (d, $J = 7.0$ Hz, 3H); HRMS calcd for $C_{17}H_{24}O_6$ ($[M+H^+]$) 325.165, found 325.169.

Bis-olefin 30: A solution of alcohol **29** (2.42 g, 7.48 mmol) in methylene chloride (37 mL) was treated with Martin's sulfurane (5.54 g, 8.96 mmol) at 0 °C for 30 min. The reaction mixture was concentrated, and the residue was purified by flash column chromatography (silica gel, ether) to afford bis-olefin **30** (2.1 g, 92 %). **30**: $R_f = 0.27$ (silica gel, ether); $[\alpha]_D^{25} = +2.6$

0947-6539/99/0502-0608 $ 17.50+.50/0 *Chem. Eur. J.* **1999**, *5*, No. 2

($c = 3.4$, CH_2Cl_2); IR (thin film): $\tilde{\nu}_{max} = 2964$, 2910, 1730, 1720, 1700, 1640, 1460, 1382, 1317, 1310, 1240, 1210, 1160, 1133, 1072, 1056, 1034, 880, 852, 850, 822, 791, 670 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 5.95$ (dd, $J = 11.5$, 8.0 Hz, 1H), 5.79 (br s, 1H), 5.75 (dd, $J = 11.5$, 1.0 Hz, 1H), 4.60 (dd, $J =$ 12.0, 5.5 Hz, 1H), 4.15–4.05 (m, 1H), 3.88–3.79 (m, 1H), 2.83 (dd, $J = 19.0$, 7.0 Hz, 1H), 2.51–2.41 (m, 1H), 2.38–2.06 (m, 4H), 1.91 (s, 3H), 1.55–1.42 (m, 1H), 1.30 (s, 3H), 1.07 (d, $J = 7.0$ Hz, 3H); HRMS calcd for $C_{17}H_{22}O_5$ ($[M + H^+]$) 307.154, found 307.154.

Bis-lactone 11: A solution of bis-olefin **30** (370 mg, 1.2 mmol) in EtOAc (5 mL) was treated with 10% Pd/C (30 mg) and stirred under a hydrogen atmosphere. After 1.5 h, CH_2Cl_2 (4 mL) was added, and the stirring was continued for an additional 2 h. The reaction mixture was filtered through a pad of celite and concentrated to afford bis-lactone **11** (370 mg, 100%). **11**: white solid, m.p. = 179–180 °C; $R_f = 0.37$ (silica gel, 8:2, CH_2Cl_2:EtOAc); $[\alpha]_D^{25} = +22.1$ ($c = 1.4$, CH_2Cl_2); IR (thin film): $\tilde{\nu}_{max} = 2963$, 2930, 2870, 1745, 1730, 1462, 1390, 1359, 1330, 1251, 1230, 1193, 1172, 1142, 1123, 1100, 1081, 1047, 1011, 980, 950, 920, 852, 641, 609 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 4.31$ (dd, $J = 12.0$, 4.5 Hz, 1H), 4.05 (ddd, $J = 11.0$, 11.0, 6.0 Hz, 1H), 3.68 (ddd, $J = 10.5$, 10.5, 4.0 Hz, 1H), 2.84 (ddd, $J = 12.5$, 12.5, 7.0 Hz, 1H), 2.77 (dd, $J = 14.0$, 2.0 Hz, 1H), 2.60 (ddd, $J = 14.0$, 6.5, 1.0 Hz, 1H), 2.40 (ddd, $J = 12.5$, 6.5, 2.0 Hz, 1H), 2.29–2.24 (m, 2H), 2.08 (ddd, $J = 12.0$, 12.0, 12.0 Hz, 1H), 1.98–1.91 (m, 2H), 1.66–1.37 (m, 5H), 1.27 (s, 3H), 1.06 (d, $J = 7.5$ Hz, 3H), 0.98 (d, $J = 7.0$ Hz, 3H); HRMS calcd for $C_{17}H_{26}O_5$ ($[M + H^+]$) 311.185, found 311.186.

Bis-thionolactone 10: A solution of bis-lactone **11** (267 mg, 0.86 mmol) in degassed xylene (5 mL) was treated with recrystallized Lawesson's reagent (1.04 g, 2.58 mmol) and tetramethylthiourea (113 mg, 0.86 mmol) at 115 °C for 3 h. The reaction mixture was concentrated and purified by flash column chromatography (silica gel, 8:2, CH_2Cl_2:hexanes, then ether) to afford bis-thionolactone **10** (126 mg, 43%) and mono-thionated products (93 mg, 33%). The mono-thionated products were resubjected to the same conditions as described above for 5 h. Silica gel chromatography gave additional **10** (58 mg, 20%). **10**: $R_f = 0.17$ (silica gel, 4:6, ether:hexanes); $[\alpha]_D^{25} = +35.3$ ($c = 1.5$, CH_2Cl_2); IR (thin film): $\tilde{\nu}_{max} = 2960$, 2923, 2865, 1461, 1390, 1339, 1312, 1290, 1243, 1228, 1207, 1179, 1168, 1106, 1090, 1074, 1060, 1035, 1000, 970, 886, 618 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 4.62$ (dd, $J = 11.5$, 5.5 Hz, 1H), 4.34 (ddd, $J = 10.0$, 10.0, 7.0 Hz, 1H), 3.76 (ddd, $J = 9.5$, 9.5, 3.0 Hz, 1H), 3.50 (dd, $J = 14.5$, 6.5 Hz, 1H), 3.18 (ddd, $J = 12.0$, 12.0, 6.5 Hz, 1H), 3.14–3.07 (m, 1H), 3.04 (dd, $J = 14.0$, 1.5 Hz, 1H), 2.49–2.39 (m, 2H), 2.23 (br s, 1H), 2.10–1.98 (m, 2H), 1.72-1.48 (m, 5H), 1.34 (s, 3H), 1.13 (d, $J = 7.5$ Hz, 3H), 0.99 (d, $J = 6.5$ Hz, 3H); HRMS calcd for $C_{17}H_{26}O_3S_2$ ($[M^+]$) 342.132, found 342.134.

Bis-stannane 31: A solution of *n*-butyllithium (0.71 mL of 1.6 M in hexanes, 1.13 mmol) was added to diisopropylamine (175 μL, 1.25 mmol) in THF (1.4 mL) at −10 °C. After 15 min, a solution of tributyltin hydride (306 μL, 1.13 mmol) in THF (1.4 mL) was added, and the reaction mixture was stirred an additional 10 min at −10 °C. The reaction mixture was cooled to −78 °C before a solution of bis-thionolactone **10** (130 mg, 0.38 mmol) in THF (0.5 mL) was added. After stirring for 10 min, iodomethane (150 μL, 2.28 mmol) was added, and the reaction mixture was stirred at −78 °C for an additional 15 min. The reaction mixture was diluted with ether, washed with water (5 mL), dried ($MgSO_4$), and concentrated. The residue was purified by flash column chromatography (silica gel, 1:19 ether:hexanes) to afford bis-stannane **31** (300 mg, 86%). **31**: $R_f = 0.37$ (silica gel, 1:19, ether:hexanes); $[\alpha]_D^{25} = +17.0$ ($c = 0.9$, CH_2Cl_2); IR (thin film): $\tilde{\nu}_{max} = 2960$, 2925, 2870, 2855, 1460, 1380, 1348, 1295, 1270, 1252, 1228, 1127, 1075, 1032, 964, 867, 742, 690, 668 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 4.04$ (dd, $J =$ 16.0, 8.5 Hz, 1H), 3.66–3.55 (m, 2H), 2.74 (ddd, $J = 16.0$, 12.0, 4.5 Hz, 1H), 2.46–2.37 (m, 1H), 2.24-2.09 (m, 7H), 2.13 (s, 3H), 2.07 (s, 3H), 1.95–1.90 (m, 2H), 1.86–1.60 (m, 16H), 1.55–1.40 (m, 11H), 1.37 (s, 3H), 1.35–1.11 (m, 11H), 1.10–0.96 (m, 17H), 0.95–0.82 (m, 2H), 0.91 (d, $J = 6.0$ Hz, 3H), 0.88 (d, $J = 7.0$ Hz, 3H); HRMS calcd for $C_{43}H_{86}O_3S_2Sn_2$ ($[M + H^+]$) 959.446, found 959.448.

Bis-vinylstannane 32: A solution of bis-stannane **31** (300 mg, 0.30 mmol) and pentamethyl piperidine (444 μL, 1.26 mmol) in benzene (1.2 mL) was added to $(CuOTf)_2 \cdot$benzene complex (606 mg, 1.20 mmol) at 25 °C. The resulting dark brown mixture was diluted with 2:8 ether:hexanes (25 mL), and was stirred until a granular precipitate formed. The mixture was filtered through a pad of silica gel, washed with 2:8 ether:hexanes, and the filtrate was concentrated. The residue was purified by flash column chromatography (silica gel, 1:19 ether:hexanes) to afford bis-vinylstannane **32** (115 mg, 45%). **32**: $R_f = 0.36$ (silica gel, 1:39, ether:hexanes); $[\alpha]_D^{25} = +19.9$ ($c = 0.4$, CH_2Cl_2); IR (thin film): $\tilde{\nu}_{max} = 2965$, 2930, 2880, 2864, 1615, 1470, 1460, 1422, 1383, 1348, 1329, 1300, 1277, 1259, 1236, 1122, 1060, 1024, 1010, 968, 880, 870, 845, 820, 786, 750, 693, 670 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 5.06$ (dd, $J = 8.5$, 6.0 Hz, 1H), 4.63 (d, $J = 4.5$ Hz, 1H), 3.73 (ddd, $J = 10.0$, 5.5, 5.5 Hz, 1H), 3.53 (ddd, $J = 11.5$, 11.5, 5.0 Hz, 1H), 3.26 (dd, $J = 12.0$, 4.5 Hz, 1H), 2.74–2.53 (m, 2H), 2.10–1.58 (m, 6H), 1.55–1.41 (m, 13H), 1.38–1.21 (m, 17H), 1.09–0.62 (m, 35H); HRMS calcd for $C_{41}H_{78}O_3Sn_2$ ($[M + H^+]$) 859.407, found 859.410.

Bis-enol ether 9: A solution of bis-vinylstannane **32** (30 mg, 0.035 mmol) in THF (2.1 mL) was treated with *n*-butyllithium (0.09 mL of 1.6 M in hexanes, 0.105 mmol) at −78 °C. After 5 min, the reaction mixture was treated with HMPA (0.15 mL, 0.87 mmol) and a solution of the triflate of 2-benzyloxyethanol (60 mg, 0.175 mmol) in hexanes (1.05 mL). To the reaction mixture was then added Et_3N (0.05 mL, 0.35 mmol) at 25 °C and stirring was continued for 45 min. Following dilution with ether (40 mL), the organic solution was washed with water (5 × 10 mL), brine (10 mL), dried ($MgSO_4$), and concentrated. The residue was purified by flash column chromatography (silica gel, 3:17 ether:hexanes) to afford bis-enol ether **9** (12.4 mg, 65%). **9**: $R_f = 0.40$ (silica gel, 2:8, ether:hexanes); $[\alpha]_D^{25} = +15.6$ ($c = 1.8$, CH_2Cl_2); IR (film thin): $\tilde{\nu}_{max} = 2950$, 2920, 2845, 1680, 1660, 1452, 1380, 1361, 1330, 1308, 1207, 1170, 1100, 1072, 1040, 690 cm^{-1}; ^1H NMR (500 MHz, C_6D_6): $\delta = 7.37$-7.14 (m, 10H), 4.77 (dd, $J = 8.0$, 5.0 Hz, 1H), 4.59 (d, $J = 4.0$ Hz, 1H), 4.45 (d, $J = 12.0$ Hz, 1H), 4.41 (s, 2H), 4.40 (d, $J =$ 12.0 Hz, 1H), 3.90–3.78 (m, 2H), 3.71–3.54 (m, 5H), 2.69 (br s, 1H), 2.45 (dd, $J = 6.5$, 6.5 Hz, 2H), 2.42 (dd, $J = 6.5$, 6.5 Hz, 2H), 2.38–2.32 (m, 1H), 2.25 (ddd, $J = 12.0$, 4.5, 4.5 Hz, 1H), 2.15–2.01 (m, 3H), 1.89 (dd, $J = 14.0$, 3.0 Hz, 1H), 1.85–1.74 (m, 2H), 1.64 (dd, $J = 14.0$, 10.5 Hz, 1H), 1.34 (s, 3H), 1.02 (d, $J = 7.0$ Hz, 3H), 0.90 (d, $J = 7.0$ Hz, 3H); HRMS calcd for $C_{35}H_{46}O_5$ ($[M + H^+]$) 547.343, found 547.343.

Diol 33: A solution of bis-enol ether **9** (30 mg, 0.05 mmol) in THF (0.5 mL) was treated with thexylborane (0.4 mL of 0.5 M in THF, 0.2 mmol) at 0 °C for 5 h. Then the reaction mixture was treated with 3 M NaOH (0.33 mL, 1.0 mmol) and 50% hydrogen peroxide (0.7 mL, 1.0 mmol) and stirred (0 → 25 °C) for 2 h. The reaction mixture was diluted with ether (20 mL), washed with water (2 × 5 mL), brine (5 mL), dried ($MgSO_4$) and concentrated. The residue was purified by flash column chromatography (silica gel, 9:1 ether:hexanes) to afford diol **33** (23.2 mg, 73%). **33**: $R_f = 0.22$ (silica gel, 9:1, ether:hexanes); $[\alpha]_D^{25} = -25.5$ ($c = 1.3$, CH_2Cl_2); IR (thin film): $\tilde{\nu}_{max} = 3460$, 2955, 2920, 2860, 1452, 1365, 1262, 1100, 1072, 1028, 731, 699, 670 cm^{-1}; ^1H NMR (500 MHz, C_6D_6): $\delta = 7.33–7.08$ (m, 10H), 4.33-4.30 (m, 3H), 4.25 (d, $J = 12.0$ Hz, 1H), 3.69–3.47 (m, 6H), 3.31 (dd, $J = 11.5$, 5.0 Hz, 1H), 3.28–3.15 (m, 3H), 3.01–2.93 (m, 1H), 2.29–2.15 (m, 2H), 2.09–2.00 (m, 2H), 1.95–1.93 (m, 2H), 1.84–1.80 (m, 2H), 1.74–1.57 (m, 6H), 1.23 (s, 3H), 1.14 (d, $J = 7.0$ Hz, 3H), 0.92 (d, $J = 7.0$ Hz, 3H); HRMS calcd for $C_{35}H_{50}O_7$ ($[M + H^+]$) 583.364, found 583.368.

Silyl ether 8: A solution of diol **33** (10 mg, 0.016 mmol) in DMF (0.2 mL) was treated with imidazole (3.3 mg, 0.048 mmol) and TBDPSCl (6 μL, 0.024 mmol) at 25 °C for 24 h. The reaction mixture was diluted with ether (15 mL), washed with water (2 × 5 mL) and brine (5 mL). The separated organic layer was dried ($MgSO_4$) and concentrated. The residue was purified by flash column chromatography (silica gel, 4:6, ether:hexanes) to afford silyl ether **8** (11 mg, 80%). **8**: $R_f = 0.24$ (silica gel, 1:1, ether:hexanes); $[\alpha]_D^{25} = -37.2$ ($c = 0.9$, CH_2Cl_2); IR (thin film): $\tilde{\nu}_{max} = 3500$, 2960, 2920, 2860, 1450, 1428, 1390, 1360, 1100, 1090, 820, 738, 700 cm^{-1}; ^1H NMR (500 MHz, C_6D_6): $\delta = 7.76–7.72$ (m, 4H), 7.35–7.02 (m, 16H), 4.37 (d, $J =$ 12.0 Hz, 1H), 4.32 (d, $J = 12.0$ Hz, 1H), 4.26 (d, $J = 12.0$ Hz, 1H), 4.19 (d, $J = 12.0$ Hz, 1H), 3.65–3.58 (m, 4H), 3.49–3.40 (m, 5H), 3.08 (dd, $J = 11.0$, 7.0 Hz, 1H), 2.90 (ddd, $J = 11.5$, 9.5, 4.0 Hz, 1H), 2.55–2.45 (m, 1H), 2.22–2.19 (m, 1H), 1.99–1.42 (m, 12H), 1.13 (s, 9H), 1.05 (s, 3H), 1.00 (d, $J =$ 7.0 Hz, 3H), 0.05 (d, $J = 7.0$ Hz, 3H); HRMS calcd for $C_{51}H_{68}O_7Si$ ($[M + NH_4^+]$) 838.507, found 838.502.

Tertiary alcohol 45: The bis-acetonide (**41**) (73.7 g, 0.302 mol) was dissolved in EtOAc (1.5 L), and the solution was treated with periodic acid (75.7 g, 0.332 mol). The reaction mixture was mechanically stirred at 25 °C until TLC showed completion of the reaction (ca. 2 h). Following concentration under reduced pressure, the residue was treated with benzene (3 × 100 mL) to remove residual EtOAc. The crude aldehyde **42** was dissolved in Et_2O (750 mL), and the solution was transferred by cannula to MeMgBr (403 mL of 3 M in ether, 1.21 mol) at 0 °C over a period of 1 h. The reaction mixture was allowed to warm to room temperature and

quenched by addition of saturated aqueous ammonium chloride solution (500 mL). The layers were separated, and the aqueous layer was extracted with ether (3 × 500 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide alcohol **43** (42.3 g, 75% for two steps). Oxalyl chloride (28.4 mL, 0.325 mol) was dissolved in CH_2Cl_2 (750 mL) and cooled to −78 °C. The solution was treated dropwise with DMSO (28.2 mL, 0.397 mol) and stirred at −78 °C for 15 min before a solution of alcohol **43** (34.0 g, 0.181 mol) in CH_2Cl_2 (600 mL) was added dropwise through an addition funnel at −78 °C over a period of 1 h. The stirring was continued for 30 min and then Et_3N (126 mL, 0.903 mol) was added over a period of 30 min. The reaction mixture was allowed to warm to 0 °C and quenched by pouring into aqueous ammonium chloride solution (750 mL). The aqueous layer was back extracted with CH_2Cl_2 (750 mL), and the combined organic extracts were washed with saturated aqueous ammonium chloride solution (2 × 500 mL) and brine (500 mL). The separated organic phase was dried ($MgSO_4$), filtered, and concentrated. The residue was purifed by flash column chromatography (silica gel, hexanes →2:1, hexanes:ether) to afford pure ketone **44** (33.8 g, 80%). A solution of titanium isopropoxide (188.8 mL, 0.634 mol) in THF (1.85 L) was treated with allylmagnesium bromide (635 mL, 1.0 M solution in ether, 0.635 mol) at −78 °C and the resulting orange-brown reaction mixture was stirred for 45 min. A solution of ketone **44** (79.2 g, 0.423 mol) in THF (550 mL) was added dropwise, and the resulting mixture was stirred at −78 °C until completion of the reaction was verified by TLC (ca. 2 h). After pouring into a saturated aqueous NH_4Cl solution (2.0 L), ether (0.5 L) was added, and the layers were separated with the addition of a 2% aqueous HCl solution. The aqueous layer was extracted with $CHCl_3$ (1.0 L), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Filtration (silica gel, 1:1, ether:hexanes, 2% Et_3N) provided pure alcohol **45** (90.7 g, 94%). **45**: R_f = 0.51 (silica gel, 1:1, EtOAc:hexanes); $[\alpha]_D^{25}$ = +5.3 (c = 1.0, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max}$ = 3488, 2983, 1641, 1377, 1217, 1165, 1062, 1022, 919, 851 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 5.89 – 5.81 (m, 1H, =CH), 5.79 (d, J = 3.5 Hz, 1H, OCHO), 5.14 – 5.10 (m, 1H, C*H*H=), 5.09 (br m, 1H, CH*H*=), 4.73 (t, J = 4.5 Hz, 1H, C(OH)CHO), 4.06 (dd, J = 11.0, 5.0 Hz, 1H, CHO), 2.25 (dd, J = 14.0, 7.0 Hz, 1H, =CHC*H*H), 2.10 (dd, J = 13.5, 8.0 Hz, 1H, =CHCH*H*), 1.99 (dd, J = 13.5, 4.5 Hz, 1H, C*H*H), 1.87 (ddd, J = 13.5, 11.0, 5.0 Hz, 1H, CH*H*), 1.50 (s, 3H, CH_3), 1.31 (s, 3H, 1 $C(CH_3)$), 1.26 (s, 3H, 1 $C(CH_3)$); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 133.0, 118.6, 111.1, 105.2, 83.6, 80.6, 71.7, 42.6, 32.6, 26.8, 26.2, 24.7; HRMS calcd for $C_{12}H_{20}O_4$ ([M + H^+]) 229.1440, found 229.1446.

Triol 46: Tertiary alcohol **45** (87.6 g, 0.384 mol) was dissolved in CH_2Cl_2 (1.6 L). EtSH (568.5 mL, 7.68 mol) was added and the solution was cooled to 0 °C. Subsequently, $ZnCl_2$ (261.3 g, 1.92 mol) was added in three portions at 0 °C, and the reaction mixture was stirred at this temperature until completion of the reaction was confirmed by TLC (ca. 90 min). The reaction mixture was quenched by pouring into a 10% aqueous HCl solution (1.0 L). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (0.5 L). The combined organic extracts were washed with brine (1.0 L), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Flash chromatography (silica gel, hexanes →1:2, ether:hexanes →4:1, ether:hexanes →ether) provided pure triol **46** (100.8 g, 89%). **46**: R_f = 0.30 (silica gel, 1:1, EtOAc:hexanes); $[\alpha]_D^{25}$ = +31.3 (c = 1.0, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ = 5.96 – 5.83 (m, 1H, =CH), 5.18 – 5.06 (m, 2H, =CH_2), 3.88 (ddd, J = 10.0, 6.5, 2.5 Hz, 1H, C(OH)C*H*OH), 3.78 (d, J = 6.5 Hz, 1H, $CH(SEt)_2$), 3.65 (dd, J = 10.0, 1.5 Hz, 1H, C*H*OH), 2.76 – 2.60 (m, 4H, 2 SCH_2), 2.43 (dd, J = 14.0, 7.0 Hz, 1H, C*H*HCHOH), 2.19-2.11 (m, 2H, =CHCH_2), 1.62 (ddd, J = 14.5, 10.0, 10.0 Hz, 1H, CH*H*CHOH), 1.27 (t, J = 7.5 Hz, 3H, CH_3CH_2S), 1.27 (t, J = 7.5 Hz, 3H, CH_3CH_2S), 1.16 (s, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 133.8, 118.9, 77.6, 76.4, 73.6, 58.7, 41.7, 34.3, 25.8, 24.6, 22.9, 14.7, 14.5; HRMS calcd for $C_{13}H_{26}O4_3S_2$ ([M + Na^+]) 317.1221, found 317.1227.

Dibenzyl ether 47: The triol **46** (100.8 g, 0.342 mol) was dissolved in THF (1.84 L) and treated with imidazole (0.24 g, 3.53 mmol) and NaH (41.1 g, 60% in mineral oil, 1.03 mol). The reaction mixture was stirred at 25 °C for 1 h and cooled to 0 °C. $n$$Bu_4NI$ (0.64 g, 1.73 mol) was added followed by the dropwise addition of BnBr (81.4 mL, 0.684 mol) at 0 °C. The reaction mixture was allowed to warm up to room temperature, stirred for 12 h and then quenched by successive addition of CH_3OH (10 mL), CH_3CO_2H (1 mL) and ether (2 L). After washing with a saturated aqueous NH_4Cl solution (2 × 500 mL), the organic phase was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Flash chromatography (silica gel, hexanes, hexanes:EtOAc, 25:1 →3:1) provided pure dibenzyl ether **47** (131.3 g, 81%). **41**: R_f = 0.50 (silica gel, 1:2, EtOAc:hexanes); $[\alpha]_D^{25}$ = +40.6 (c = 1.0, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$): δ = 7.41 – 7.23 (m, 10H, ArH), 5.88 – 5.78 (m, 1H, =CH), 5.15 – 5.03 (m, 2H, =CH_2), 4.71 (d, J = 11.5 Hz, 1H, C*H*HPh), 4.70 (d, J = 11.5 Hz, 1H, C*H*HPh), 4.58 (d, J = 11.5 Hz, 1H, C*H*HPh), 4.46 (d, J = 11.5 Hz, 1H, C*H*HPh), 4.04 (d, J = 4.0 Hz, 1H, $CH(SEt)_2$), 3.93 (ddd, J = 8.0, 8.0, 4.0 Hz, 1H, CHO), 3.34 (dd, J = 6.0, 4.5 Hz, 1H, CHO), 2.78 – 2.59 (m, 4H, 2 SCH_2), 2.38 (dd, J = 13.5, 7.0 Hz, 1H, C*H*HCHO), 2.32 – 2.17 (m, 2H, CH_2), 2.00 (ddd, J = 15.0, 8.0, 4.5 Hz, 1H, CH*H*CHO), 1.27, 1.24 (2 t, J = 7.5 Hz, 6H, 2 × CH_3CH_2), 1.17 (s, 3H, CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 134.0, 128.4, 128.3, 128.2, 127.8, 127.6, 127.4, 118.4, 82.0, 80.2, 74.8, 72.3, 72.1, 54.5, 42.7, 32.5, 26.1, 26.0, 23.0, 14.54, 14.50. HRMS calcd for $C_{27}H_{38}O_3S_2$ ([M + Cs^+]) 607.1317, found 607.1295.

Lactol 48: Dibenzyl ether **47** (130.9 g, 0.276 mol) was dissolved in acetone (2.0 L) and H_2O (0.4 L) and cooled to 0 °C. To that solution, powdered $NaHCO_3$ (156.5 g, 1.86 mol) and solid I_2 (236.5 g, 0.932 mol) were successively added at 0 °C. The reaction mixture was stirred at this temperature until TLC showed completion of the reaction (ca. 1 h), and then it was quenched with an aqueous sodium thiosulfate solution (1 L). After concentration under reduced pressure, the residue was extracted with EtOAc (5 × 400 mL). The organic extracts were washed with brine (500 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Flash chromatography (silica gel, hexanes →25:1, hexanes:EtOAc →2:1, hexanes:EtOAc) furnished pure lactol **48** (87.4 g, 86%). **48**: R_f = 0.44 (silica gel, 1:2, EtOAc:hexanes); $[\alpha]_D^{25}$ = +0.5 (c = 1.0, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max}$ = 3410, 3068, 2938, 1713, 1451, 1274, 1073, 1025, 920, 748, 703 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.40 – 7.29 (m, 10H, ArH), 5.99 – 5.89 (m, 1H, =CH), 5.12 – 5.03 (m, 2H, =CH_2), 4.91 (d, J = 7.5 Hz, 1H, C*H*OH), 4.81 (d, J = 11.5 Hz, 1H, C*H*HPh), 4.68 (d, J = 11.5 Hz, 1H, C*H*HPh), 4.61 (d, J = 11.5 Hz, 1H, C*H*HPh), 4.61 (d, J = 11.5 Hz, 1H, C*H*HPh), 3.41 (dd, J = 12.0, 5.0 Hz, 1H), 3.20 (ddd, J = 12.0, 7.5, 5.0 Hz, 1H), 2.44 (dd, J = 14.0, 7.0 Hz, 1H), 2.42-2.32 (m, 2H), 1.66 (ddd, J = 12.0, 12.0, 12.0 Hz, 1H), 1.26 (s, 3H, CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 138.1, 138.0, 133.4, 128.1, 128.0, 127.5, 127.4, 127.3, 127.2, 117.4, 93.5, 76.9, 76.5, 73.9, 71.9, 70.8, 44.2, 29.9, 16.4; HRMS calcd for $C_{23}H_{28}O_4$ ([M + Na^+]) 391.1885, found 391.1889.

Ketone 50: A mixture of the lactol **48** (87.4 g, 0.237 mol) and 1-triphenylphosphoranylidene-2-propanone (124.9 g, 0.392 mol) in toluene (560 mL) was stirred under reflux for 4 h. Following concentration under reduced pressure, the residue was diluted with ether:hexanes (1:1) and filtered through silica gel (1:1, ether:hexanes). The filtrate was concentrated under reduced pressure, and the residue (α,β-unsaturated ketone) was dissolved in CH_2Cl_2. To that solution, CSA (5.56 g, 0.024 mol, 0.1 equiv) was added, and the reaction mixture was stirred until TLC showed completion of the reaction (ca. 1 h). The resulting solution was washed with a saturated aqueous $NaHCO_3$ solution (300 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Flash chromatography (silica gel, hexanes →1:20, EtOAc:hexanes →1:2, EtOAc:hexanes) furnished pure ketone **50** (70.8 g, 73%). **50**: R_f = 0.44 (silica gel, 1:4, EtOAc:hexanes); IR (thin film): $\tilde{\nu}_{max}$ = 3031, 2869, 1713, 1456, 1352, 1098, 740, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.39 – 7.28 (m, 10H, ArH), 5.87 – 5.77 (m, 1H, =CH), 5.06 – 4.96 (m, 2H, =CH_2), 4.62, 4.61 (2 d, J = 11.5 and 12.0 Hz, 2H, C*H*HPh), 4.44, 4.42 (2 d, J = 12.0 Hz, 2H, C*H*HPh), 3.90 (ddd, J = 9.0, 9.0, 3.5 Hz, 1H), 3.29 (dd, J = 12.0, 4.5 Hz, 1H), 3.11 (ddd, J = 11.0, 9.5, 4.5 Hz, 1H), 2.80 (dd, J = 14.5, 3.5 Hz, 1H), 2.50 (ddd, J = 12.0, 4.5, 4.5 Hz, 1H), 2.42, 2.37 (2 dd, J = 14.5, 9.0 and 14.0, 7.0 Hz, 2H), 2.25 (dd, J = 14.0, 7.5 Hz, 1H), 2.15 (s, 3H, $CH_3C(O)$), 1.55 (ddd, J = 12.0, 12.0, 12.0 Hz, 1H), 1.21 (s, 3H, CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 207.7, 138.4, 137.9, 134.0, 128.4, 128.3, 127.8, 127.6, 127.5, 77.4, 76.5, 76.3, 71.0, 70.7, 69.9, 46.8, 44.5, 30.7, 30.2, 15.8; HRMS calcd for $C_{26}H_{32}O_4$ ([M + Na^+]) 431.2198, found 431.2188.

Methyl ester 51: A suspension of flame-dried $ZnBr_2$ (19.51 g, 0.087 mol) in ether (1.2 L) was cooled to −78 °C. A solution of the ketone **50** (70.8 g, 0.173 mol) in ether (200 mL) was added by cannula, followed by the dropwise addition of a solution of CH_2=C(OMe)OTBS (49.29 g, 0.262 mol) in ether (100 mL). The reaction mixture was stirred at −78 °C until TLC showed completion of the reaction (ca. 1 h). The reaction mixture was poured into a saturated aqueous $NaHCO_3$ solution (1.5 L), the layers were separated, and the ether layer was washed with brine (100 mL), dried

0947-6539/99/0502-0610 $ 17.50+.50/0 *Chem. Eur. J.* **1999**, *5*, No. 2

($MgSO_4$), filtered, and concentrated under reduced pressure. Flash chromatography (silica gel, hexanes →1:20, EtOAc:hexanes) provided pure methyl ester **51** as a mixture of two diastereomers (100.8 g, 98 %). **51**: $R_f = 0.68$ (silica gel, 2:8, EtOAc:hexanes); $[\alpha]_D^{25} = -55.9$ ($c = 1.0$, CH_2Cl_2); IR (thin film): $\tilde{\nu}_{max} = 2947, 2854, 1742, 1455, 1436, 1349, 1251, 1212, 1124, 1093, 1027, 1005, 913, 834, 773, 734, 696\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.36$-7.26 (m, 10H, ArH), 5.88-5.77 (m, 1H, =CH), 5.01 (d, $J = 10.5$ Hz, 1H, =CH), 4.98 (d, $J = 17.0$ Hz, 1H, =CH), 4.62 (d, $J = 11.5$ Hz, 1H, C*H*HPh), 4.58 (d, $J = 11.5$ Hz, 1H, C*H*HPh), 4.42 (d, $J = 11.5$ Hz, 1H, C*H*HPh), 4.41 (d, $J = 11.5$ Hz, 1H, C*H*HPh), 3.75 (dd, $J = 9.5$, 9.5 Hz, 1H, OCH), 3.59 (s, 3H, CO_2CH_3), 3.27 (dd, $J = 11.5$, 4.5 Hz, 1H, OCH), 2.97 (ddd, $J = 11.0$, 9.5, 5.0 Hz, 1H, OCH), 2.68 (d, $J = 15.0$ Hz, 1H, C*H*HCO_2CH_3), 2.57 (d, $J = 15.0$ Hz, 1H, C*H*HCO_2CH_3), 2.47 (ddd, $J =$ 12.0, 4.5, 4.5 Hz, 1H, C*H*H), 2.33 (dd, $J = 14.0$, 6.0 Hz, 1H, C*H*H), 2.26 (dd, $J = 14.0$, 7.5 Hz, 1H, C*H*H), 2.12 (d, $J = 14.0$ Hz, 1H, C*H*H), 1.67 (dd, $J =$ 14.5, 9.5 Hz, 1H, C*H*H), 1.51 (ddd, $J = 12.0$, 12.0, 12.0 Hz, 1H, C*H*H), 1.43 (s, 3H, CH_3), 1.21 (s, 3H, CH_3), 085 (s, 9H, *t*BuSi), 0.06 (s, 3H, CH_3Si), 0.05 (s, 3H, CH_3Si); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 171.9$, 138.7, 138.5, 134.6, 128.3, 128.2, 127.6, 127.5, 117.2, 77.1, 76.7, 76.0, 73.7, 70.9, 70.6, 69.5, 50.9, 46.0, 44.6, 43.8, 30.5, 29.7, 25.8, 18.1, 16.3, -1.97, -2.11; HRMS calcd for $C_{35}H_{52}O_6Si$ ($[M + Cs^+]$) 729.2588, found 729.2566.

Lactone 54a,b: A solution of ester **51** (3.19 g, 5.34 mmol) in THF (60 mL) was treated wtih 20 % $Pd(OH)_2$/C (0.51 g). The reaction mixture was stirred under H_2 atmosphere overnight, and then filtered through a pad of silica gel eluting with EtOAc. The filtrate was concentrated and purified by flash column chromatography (silica gel, 2:1 →1:2, EtOAc:hexanes) to provide pure diol **52** (1.90 g, 85 %). A solution of diol **52** (1.80 g, 4.32 mmol) in THF (60 mL) and methanol (20 mL) was added to a solution of $LiOH \cdot H_2O$ (0.91 g, 21.6 mmol) in water (20 mL). The reaction mixture was stirred at 25 °C for 12 h. Following concentration under reduced pressure, the residue was diluted with water (30 mL) and acidified with acetic acid until pH = 3.0. The solution was saturated with sodium chloride (solid) and extracted with ether (2 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated to afford crude dihydroxy acid **53** (1.73 g, 99 %). Dihydroxy acid **53** (1.53 g, 3.80 mmol) was dissolved in THF (20 mL), cooled to 0 °C, and treated with Et_3N (1.06 mL, 7.60 mmol) and 2,4,6-trichlorobenzoyl chloride (0.62 mL, 3.99 mmol) at 0 °C for 1 h and at 25 °C for 30 min. The reaction mixture was diluted with benzene (120 mL) and was transferred by cannula over a period of 30 min to a solution of 4-DMAP (1.39 g, 11.4 mmol) in benzene (60 mL) at 25 °C. The reaction mixture was stirred at 25 °C until TLC showed completion of the reaction (ca. 2 h). After concentration under reduced pressure, the residue was diluted with EtOAc and filtered. The filtrate was concentrated and purified by flash column chromatography (silica gel, 1:2 →4:1, EtOAc:hexanes) to afford two diastereomeric lactones: Minor diastereomer **54a** (0.47 g, 32 %): $R_f = 0.47$ (silica gel, 1:1, EtOAc:hexanes); $[\alpha]_D^{25} = +6.3$ ($c = 1.0$, CH_2Cl_2), IR (thin film): $\tilde{\nu}_{max} = 3456, 2956, 2933, 2858, 1723, 1465, 1382, 1303, 1252, 1137, 1073, 1046, 938, 834, 775\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 4.08$ (ddd, $J =$ 11.0, 9.5, 6.0 Hz, 1H), 3.55 (br d, $J = 9.5$ Hz, 1H), 3.42 (ddd, $J = 11.0$, 9.5, 4.0 Hz, 1H), 2.97 (d, $J = 13.5$ Hz, 1H), 2.70 (dd, $J = 13.5$, 2.5 Hz, 1H), 2.25 (ddd, $J = 12.5$, 5.5, 5.5 Hz, 1H), 2.17 (ddd, $J = 13.0$, 4.0, 3.0 Hz, 1H), 1.84 (ddd, $J = 12.0$, 12.0, 11.5 Hz, 1H), 1.82 – 1.75 (m, 2H), 1.65 – 1.58 (m, 1H), 1.46 – 1.37 (m, 3H), 1.35 (s, 3H, CH_3), 1.15 (s, 3H, CH_3), 0.91 (dd, $J = 6.0$, 6.0 Hz, 3H, CH_3), 0.83 (s, 9H, *t*BuSi), 0.11 (s, 3H, CH_3Si), 0.11 (s, 3H, CH_3Si); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 170.9, 76.9, 76.0, 70.9, 70.3, 67.6, 51.5, 49.4, 42.1, 34.1, 26.9, 25.5, 17.8, 15.8, 14.6, 14.4, -2.1, -2.1$; HRMS calcd for $C_{20}H_{38}O_5Si$ ($[M + Na^+]$) 409.2386, found 409.2374. Major diastereomer **54b** (0.85 g, 58 %): $R_f = 0.30$ (silica gel, 1:1, EtOAc:hexanes), $[\alpha]_D^{25} = +17.8$ ($c = 1.0$, CH_2Cl_2); IR (thin film): $\tilde{\nu}_{max} = 3442, 2955, 2932, 2858, 1731, 1463, 1377, 1313, 1241, 1191, 1081, 1048, 1003, 888, 836, 774\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 4.05$ (ddd, $J = 11.0$, 9.5, 6.0 Hz, 1H), 3.79 (ddd, $J = 10.0$, 10.0, 4.0 Hz, 1H), 3.53 (br d, $J = 9.0$ Hz, 1H), 2.82-2.74 (m, 2H), 2.28 (ddd, $J = 13.0$, 5.5, 5.5 Hz, 1H), 2.15 (dd, $J = 14.0$, 2.5 Hz, 1H), 2.08 (br m, 1H), 1.90 (ddd, $J = 12.5$, 12.5, 11.0 Hz, 1H), 1.66 – 1.59 (m, 1H), 1.55 (dd, $J = 13.5$, 10.5 Hz, 1H), 1.45 – 1.38 (m, 3H), 1.37 (s, 3H, CH_3), 1.14 (s, 3H, CH_3), 0.89 (dd, $J = 7.0$, 7.0 Hz, 3H, CH_3), 0.85 (s, 9H, *t*BuSi), 0.13 (s, 3H, CH_3Si), 0.11 (s, 3H, CH_3Si); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 170.8$, 76.6, 75.9, 71.3, 70.3, 67.0, 49.9, 48.8, 42.1, 34.4, 32.0, 25.7, 18.2, 15.8, 14.6, 14.4, -2.2, -2.3; HRMS calcd for $C_{20}H_{38}O_5Si$ ($[M + H^+]$) 387.2567, found 387.2557.

Olefin 55: A solution of lactone **54a** (0.470 g, 1.22 mmol) in CH_2Cl_2 (25 mL) was treated with HF · pyr (2.5 mL) at 0 °C until TLC showed completion of the reaction (ca. 1 h). The reaction mixture was diluted with CH_2Cl_2 (10 mL) and poured into an aqueous sodium bicarbonate solution (20 mL) at 0 °C. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (20 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated to provide the crude hydroxy lactone. A solution of the crude hydroxy lactone in CH_2Cl_2 (45 mL) was cooled to 0 °C, and a solution of Martin's sulfurane (1.72 g, 2.56 mmol) in CH_2Cl_2 (15 mL) was added by cannula. The reaction mixture was stirred at this temperature until TLC showed completion of the reaction (ca. 15 min). After concentration, the residue was purified by flash column chromatography (silica gel, 1:5, EtOAc:hexanes →EtOAc) to provide pure olefin **55** (0.246 g, 80 % for two steps). **55**: $R_f = 0.30$ (silica gel, 1:1, EtOAc:hexanes); $[\alpha]_D^{25} = +64.0$ ($c = 1.0$, CH_2Cl_2); IR (thin film): $\tilde{\nu}_{max} = 3436, 2958, 2873, 1696, 1642, 1450, 1420, 1380, 1317, 1278, 1157, 1127, 1052, 950, 866, 841\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 5.78$ (br s, 1H, =CH), 4.15 (ddd, $J = 10.5$, 9.0, 6.0 Hz, 1H), 3.79 (ddd, $J = 9.0$, 7.0, 7.0 Hz, 1H), 3.54 (br d, $J = 10.5$ Hz, 1H), 2.79 (dd, $J = 19.0$, 7.0 Hz, 1H), 2.41 (br m, 1H), 2.35 – 2.28 (m, 1H), 2.27 (dd, $J = 19.0$, 7.0 Hz, 1H), 1.91 (s, 3H, CH_3), 1.90 (ddd, $J = 12.0$, 12.0, 12.0 Hz, 1H), 1.58 (ddd, $J = 10.5$, 10.5, 5.5 Hz, 1H), 1.44 – 1.32 (m, 3H), 1.14 (s, 3H, CH_3), 0.87 (dd, $J = 7.0$, 7.0 Hz, 3H, CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 167.3$, 152.0, 117.2, 76.5, 74.8, 70.0, 68.3, 42.0, 41.3, 33.9, 26.8, 15.8, 14.7, 14.6; HRMS calcd for $C_{14}H_{22}O_4$ ($[M + H^+]$) 255.1596, found 255.1602.

Alcohol 56: A solution of olefin **55** (0.246 g, 0.975 mmol) in EtOAc (20 mL) was treated with 10 % Pd/C (0.240 g) under H_2 atmosphere for 12 h. The reaction mixture was filtered through a short pad of silica gel (EtOAc). After concentration, the residue was purified by flash chromatopraphy (silica gel, 1:1, EtOAc:hexanes) to provide pure lactone **56** (0.223 g, 90 %). **56**: $R_f = 0.32$ (silica gel, 1:1, EtOAc:hexanes); $[\alpha]_D^{25} = +33.5$ ($c = 1.0$, CH_2Cl_2); IR (thin film): $\tilde{\nu}_{max} = 3426, 2959, 2875, 1726, 1461, 1358, 1268, 1189, 1079, 1041\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta =$ 4.01 (ddd, $J = 11.0$, 9.5, 6.0 Hz, 1H), 3.57 (ddd, $J = 10.5$, 9.5, 4.0 Hz, 1H), 3.53 (dd, $J = 12.0$, 4.5 Hz, 1H), 2.78 (dd, $J = 14.0$, 2.0 Hz, 1H), 2.58 (ddd, $J = 14.0$, 6.5, 2.0 Hz, 1H), 2.29 – 2.20 (m, 2H), 2.18 (br m, 1H), 1.97 (br d, $J = 13.5$ Hz, 1H), 1.87 (ddd, $J = 12.0$, 12.0, 12.0 Hz, 1H), 1.68 – 1.58 (m, 2H), 1.43 – 1.34 (m, 3H), 1.14 (s, 3H, CH_3), 1.05 (d, $J = 7.5$ Hz, 3H, CH_3), 0.88 (dd, $J = 7.0$, 7.0 Hz, 3H, CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 173.5$, 77.2, 75.9, 70.4, 66.9, 42.1, 41.9, 40.5, 34.2, 25.8, 17.8, 15.8, 14.6, 14.4; HRMS calcd for $C_{14}H_{24}O_4$ ($[M + H^+]$) 257.1753, found 257.1745.

MEM Ether 39: A solution of alcohol **56** (0.223 g, 0.877 mmol) in CH_2Cl_2 (5 mL) was treated with (iPr)$_2$EtN (0.49 mL, 3.51 mmol) and MEMCl (0.6 mL, 5.26 mmol) at room temperature for 24 h. The reaction mixture was diluted with CH_2Cl_2 (15 mL) and extracted with saturated aqueous ammonium chloride solution (10 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash column chromatography (silica gel, 1:5 →1:1, EtOAc:hexanes) to provide pure MEM ether **39** (0.255 g, 85 %). **39:** $R_f = 0.37$ (silica gel, 1:1, EtOAc:hexanes); $[\alpha]_D^{25} = +60.8$ ($c = 1.0$, CH_2Cl_2); IR (thin film): $\tilde{\nu}_{max} =$ 2960, 1742, 1462, 1358, 1262, 1189, 1081, 1038, 596 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 4.76$ (dd, $J = 7.0$, 1.5 Hz, 1H), 4.68 (dd, $J = 7.0$, 1.5 Hz, 1H), 3.97 (ddd, $J = 10.0$, 10.0, 6.0 Hz, 1H), 3.74 – 3.67 (m, 1H), 3.65 – 3.60 (m, 1H), 3.59 (ddd, $J = 10.0$, 10.0, 4.0 Hz, 1H), 3.55 – 3.50 (m, 2H), 3.47 (ddd, $J = 12.0$, 5.0, 1.5 Hz, 1H), 3.34 (s, 3H), 2.78 (d, $J = 14.0$ Hz, 1H), 2.58 (dd, $J = 14.0$, 6.5 Hz, 1H), 2.37 (ddd, $J = 12.0$, 4.5, 4.5 Hz, 1H), 2.24 (br m, 1H), 1.96 (br d, $J = 14.0$ Hz, 1H), 1.83 (ddd, $J = 12.0$, 12.0, 12.0 Hz, 1H), 1.66 – 1.51 (m, 2H), 1.43 – 1.33 (m, 3H), 1.13 (s, 3H, CH_3), 1.06 (d, $J = 6.5$ Hz, 3H, CH_3), 0.87 (ddd, $J = 6.0$, 6.0, 1.5 Hz, 3H, CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 173.2$, 94.8, 77.0, 75.9, 75.2, 71.6, 67.1, 66.9, 59.0, 42.0, 41.9, 40.5, 31.8, 25.8, 17.8, 15.6, 15.4, 14.5; HRMS calcd for $C_{18}H_{32}O_6$ ($[M + Na^+]$) 367.2097, found 367.2089.

Diene 58: A solution of lactone **39** (43 mg, 0.13 mmol) and Tf_2NPh (187 mg, 0.52 mmol) in DME (4 mL) was cooled to −78 °C and treated with NaHMDS (785 μL of 1 M in THF, 0.79 mmol) and stirred for 15 min. The reaction mixture was diluted with ether (25 mL) containing Et_3N (0.5 mL) and poured into a saturated aqueous sodium bicarbonate solution (25 mL). The aqueous layer was washed with ether (2 × 25 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by flash column chromatography (silica gel, 1:9, ether:hexanes, 2 % Et_3N) to afford the desired enol triflate (**57**). A solution of triflate **57**, flame-dried LiCl (16.6 mg, 0.39 mmol), tri-*n*-butyl(vinyl)tin (230 μL, 0.79 mmol), and $Pd(PPh_3)_4$ (16 mg) in THF (3 mL) was stirred at

85 °C for 2 h. The reaction mixture was cooled, concentrated, and purified by flash column chromatography (silica gel, 1:49, ether:hexanes) to afford diene **58** (36 mg, 82 %). **58**: IR (thin film): $\tilde{\nu}_{max}$ = 2958, 2875, 1599, 1458, 1286, 1075, 1043 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.02 (dd, J = 17.0, 11.0 Hz, 1H, =CH), 5.40 (dd, J = 17.0, 2.0 Hz, 1H, =CH), 4.95 (dd, J = 10.5, 1.5 Hz, 1H, =CH), 4.86 (d, J = 5.5 Hz, 1H, =CH), 4.79 (d, J = 7.0 Hz, 1H), 4.68 (d, J = 7.0 Hz, 1H), 3.76–3.64 (m, 3H), 3.54 (dd, J = 5.0, 5.0 Hz, 2H), 3.52–3.47 (m, 2H), 3.38 (s, 3H), 2.70–2.60 (m, 1H), 2.37 (ddd, J = 12.0, 4.5, 4.5 Hz, 1H), 1.93 (ddd, J = 14.0, 9.0, 5.5 Hz, 1H), 1.79 (ddd, J = 12.0, 12.0, 12.0 Hz, 1H), 1.60–1.50 (m, 2H), 1.44-1.33 (m, 3H), 1.15 (s, 3H), 1.04 (d, J = 7.0 Hz, 3H), 0.87 (dd, J = 7.0, 7.0 Hz, 3H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 154.3, 134.0, 117.8, 112.2, 94.5, 78.4, 76.8, 75.7, 71.6, 70.6, 67.0, 59.0, 42.4, 39.7, 32.8, 27.4, 21.4, 16.2, 15.7, 14.6; HRMS calcd for $C_{20}H_{34}O_5$ ([M + H$^+$]) 355.2485, found 355.2496.

Diol 59: A solution of 2,3-dimethylbutene (2.1 mL of 1.0 M in THF, 2.1 mmol) at −10 °C was added dropwise to a solution of borane · THF (2.0 mL of 1.0 M in THF, 2.0 mmol) over 5 min, and the resulting mixture was stirred at 0 °C for 2 h. A solution of diene **58** (470 mg, 1.33 mmol) in THF (5 mL) was added to the freshly prepared thexylborane solution at 0 °C and stirred at 0 °C for 24 h. The reaction mixture was quenched by slow addition of a saturated aqueous $NaHCO_3$ solution (5.0 mL), followed by 30 % H_2O_2 (1.0 mL), and the mixture was stirred at 25 °C for 2 h. The aqueous phase was separated and washed with EtOAc (4 × 5 mL), and the combined organic extracts were dried (Na_2SO_4), concentrated, and purified by flash column chromatography (silica gel, EtOAc) to afford diol **59** (275 mg, 53 %). **59**: R_f = 0.45 (silica gel, EtOAc); $[\alpha]_D^{25}$ = −20.8 (c = 0.6, CH_3OH); IR (thin film): $\tilde{\nu}_{max}$ = 3403, 2957, 2876, 1459, 1377, 1043 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.74 (d, J = 7.0 Hz, 1H), 4.63 (d, J = 7.0 Hz, 1H), 3.78–3.59 (m, 4H), 3.53–3.46 (m, 3H), 3.45–3.35 (m, 2H), 3.35 (s, 3H), 3.18 (dd, J = 7.0, 7.0 Hz, 1H), 3.12–3.05 (m, 1H), 3.00 (br m, 2H), 2.22 (ddd, J = 12.0, 4.5, 4.5 Hz, 1H), 2.00–1.90 (m, 2H), 1.82–1.65 (m, 3H), 1.58–1.48 (m, 2H), 1.40–1.30 (m, 3H), 1.07 (d, J = 7.0 Hz, 3H, CH_3), 1.07 (s, 3H, CH_3), 0.84 (dd, J = 7.0, 7.0 Hz, 3H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 94.3, 85.0, 80.3, 79.7, 76.9, 75.7, 71.6, 69.9, 67.0, 60.4, 59.0, 42.4, 37.0, 35.9, 35.8, 33.3, 19.4, 16.1, 15.7, 14.6; HRMS calcd for $C_{20}H_{38}O_7$ ([M + Na$^+$]) 413.2515, found 413.2526.

Bis-silyl ether 60: A solution of diol **59** (210 mg, 0.54 mmol) in CH_2Cl_2 (5 mL) was treated with 2,6-lutidine (190 mL, 1.6 mmol) and TBSOTf (310 mL, 1.4 mmol) at 0 °C for 30 min. After addition of a saturated aqueous NH_4Cl solution (2 mL), the mixture was extracted with ether (3 × 5 mL), and the combined organic extracts were dried (Na_2SO_4), concentrated, and purified by flash column chromatography (silica gel, 3:7, ether:hexanes) to afford disilyl ether **60** (314 mg, 94 %). **60**: R_f = (0.75, silica gel, 3:7, ether:hexanes); $[\alpha]_D^{25}$ = −30.0 (c = 1.0, CH_3OH); IR (thin film): $\tilde{\nu}_{max}$ = 2930, 2858, 1470, 1254, 1080, 836, 775 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.77 (d, J = 7.0 Hz, 1H), 4.66 (d, J = 7.0 Hz, 1H), 3.70–3.62 (m, 4H), 3.57–3.52 (m, 1H), 3.53 (dd, J = 5.0, 5.0 Hz, 2H), 3.47–3.40 (m, 3H), 3.37 (s, 3H), 3.06–3.00 (m, 1H), 2.19 (ddd, J = 12.0, 4.5, 4.5 Hz, 1H), 2.03–1.95 (m, 2H), 1.79–1.72 (m, 1H), 1.60–1.50 (m, 4H), 1.44–1.35 (m, 3H), 1.11 (s, 3H, CH_3), 1.07 (d, J = 7.0 Hz, 3H, CH_3), 0.89–0.83 (m, 3H), 0.87 (s, 9H, tBuSi), 0.85 (s, 9H, tBuSi), 0.03 (s, 3H, CH_3Si), 0.02 (s, 3H, CH_3Si), 0.01 (s, 3H, CH_3Si), 0.00 (s, 3H, CH_3Si); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 94.4, 84.1, 80.7, 79.9, 77.0, 75.4, 71.6, 69.8, 67.0, 59.8, 59.0, 42.5, 39.3, 36.9, 33.2, 33.1, 25.9, 25.8, 18.0, 17.9, 17.3, 16.1, 15.7, 14.6, −4.5, −4.7, −5.3, −5.4.

Alcohol 61: The bis-silyl ether **60** (310 mg, 0.5 mmoL) was dissolved in a mixture of CH_3OH (3.0 mL) and CH_2Cl_2 (3.0 mL), and treated with CSA (20 mg, 0.08 mmol) at 25 °C for 1.5 h. After addition of Et_3N (50 mL), the solvent was removed and the residue was subjected to flash column chromatography (silica gel, 3:7, ether:hexanes) to afford alcohol **61** (231 mg, 91 %). **61**: R_f = 0.65 (silica gel, 3:7, ether:hexanes); $[\alpha]_D^{25}$ = −19.8 (c = 0.91, CH_3OH); IR (thin film): $\tilde{\nu}_{max}$ = 3478, 2930, 2880, 1469, 1254, 1079, 837, 775 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.75 (d, J = 7.0 Hz, 1H), 4.63 (d, J = 7.0 Hz, 1H), 3.71–3.58 (m, 6H), 3.51 (dd, J = 4.5, 4.5 Hz, 2H), 3.47 (dd, J = 3.5, 3.5 Hz, 1H), 3.41 (ddd, J = 11.0, 11.0, 4.0 Hz, 1H), 3.35 (s, 3H), 3.13–3.08 (m, 1H), 2.69 (br s, 1H, OH), 2.22 (ddd, J = 12.0, 4.5, 4.5 Hz, 1H), 2.03–1.93 (m, 2H), 1.78–1.68 (m, 2H), 1.60–1.47 (m, 3H), 1.40–1.30 (m, 3H), 1.08 (s, 3H, CH_3), 1.07 (d, J = 7.0 Hz, 3H, CH_3), 0.88–0.78 (m, 3H), 0.83 (s, 9H, tBuSi), −0.02 (s, 3H, CH_3Si), −0.02 (s, 3H, CH_3Si); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 94.3, 88.5, 80.9, 79.6, 76.7, 75.4, 71.6, 69.5, 67.0, 61.8, 59.0, 42.4, 38.0, 36.6, 33.3, 33.1, 25.7, 17.9, 17.1, 16.0, 15.6, 14.6, −4.6, −4.7; HRMS calcd for $C_{26}H_{52}O_7Si$ ([M + Cs$^+$]) 637.2537, found 637.2558.

Iodide 62: A mixture of alcohol **61** (220 mg, 0.44 mmol), imidazole (44 mg, 0.65 mmol), and triphenylphosphane (230 mg, 0.88 mmol) in CH_2Cl_2 (10 mL) was treated with I_2 (121 mg, 0.48 mmol) at 25 °C for 15 min. After removing the solvent, the residue was purified by flash column chromatography (silica gel, 2:8, ether:hexanes) to afford iodide **62** (232 mg, 89 %). **62**: R_f = 0.7 (silica gel, 2:8, ether:hexanes); $[\alpha]_D^{25}$ = −47.2 (c = 0.54, MeOH); IR (film): $\tilde{\nu}_{max}$ = 2930, 1462, 1254, 1076, 838, 775 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.77 (d, J = 7.5 Hz, 1H), 4.66 (d, J = 7.5 Hz, 1H), 3.72–3.63 (m, 2H), 3.54 (dd, J = 4.5, 4.5 Hz, 2H), 3.47–3.39 (m, 4H), 3.37 (s, 3H, CH_3), 3.27 (ddd, J = 11.0, 7.0, 4.0 Hz, 1H), 3.19 (ddd, J = 9.5, 9.5, 6.0 Hz, 1H), 3.09–3.04 (m, 1H), 2.23 (ddd, J = 12.0, 4.5, 4.5 Hz, 1H), 2.03–1.94 (m, 3H), 1.86–1.77 (m, 1H), 1.62–1.48 (m, 3H), 1.44–1.32 (m, 3H), 1.10 (s, 3H, CH_3), 1.05 (d, J = 7.5 Hz, 3H, CH_3), 0.88–0.85 (m, 3H), 0.86 (s, 9H, tBuSi), 0.01 (s, 3H, CH_3Si), 0.00 (s, 3H, CH_3Si); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 94.4, 87.0, 81.4, 79.4, 76.9, 75.5, 71.7, 69.6, 67.0, 59.1, 42.5, 39.4, 37.0, 33.1, 25.7, 17.9, 17.6, 16.1, 15.7, 14.6, 3.8, −4.4, −4.6; HRMS (FAB) calcd for $C_{26}H_{51}O_6ISi$ ([M + Cs$^+$]) 747.1554, found 747.1580.

Phosphonium salt 37: A mixture of the iodide **62** (220 mg, 0.37 mmol) and triphenylphosphane (0.96 g, 3.7 mmol) was fused at 85 °C for 2.5 h. After cooling to room temperature, the solid was purified by flash column chromatography (silica gel, 3:7, acetone:CH_2Cl_2) to afford the phosphonium salt **37** (297 mg, 94 %) as a pale yellow solid. **37**: R_f = 0.40 (silica gel, 3:7, acetone:CH_2Cl_2); $[\alpha]_D^{25}$ = +2.44 (c = 1.19, CH_3OH); IR (thin film): $\tilde{\nu}_{max}$ = 2928, 1437, 1110, 1075, 1040, 839, 690 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.76–7.65 (m, 15H, ArH), 4.76 (d, J = 7.0 Hz, 1H), 4.62 (d, J = 7.0 Hz, 1H), 3.62 (dd, J = 4.5, 4.5 Hz, 2H), 3.58–3.49 (m, 1H), 3.47–3.40 (m, 5H), 3.39–3.30 (m, 2H), 3.23 (s, 3H, CH_3), 3.07–3.00 (m, 1H), 2.25 (ddd, J = 11.5, 4.5, 4.5 Hz, 1H), 1.94–1.82 (m, 3H), 1.57–1.44 (m, 4H), 1.35–1.26 (m, 3H), 1.04 (s, 3H, CH_3), 0.92 (d, J = 7.0 Hz, 3H, CH_3), 0.80–0.75 (m, 3H, CH_3), 0.66 (s, 9H, tBuSi), −0.12 (s, 3H, CH_3Si), −0.29 (s, 3H, CH_3Si); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 135.4, 133.5, 133.4, 130.8, 130.7, 118.1, 117.4, 94.3, 85.4, 85.3, 81.6, 79.5, 76.5, 75.5, 71.6, 69.2, 67.1, 58.9, 42.2, 36.9, 33.5, 33.1, 25.7, 18.3, 17.7, 16.1, 15.6, 14.6, −4.4, −4.5.

Silyl ether 64: A solution of diol **63** (43.7 g, 336 mmol) in DMF (700 mL) was treated with imidazole (46 g, 670 mmol) and TBDPSCl (96 mL, 370 mmol) at 0 °C for 1 h. The reaction mixture was concentrated and the residue was diluted with ether (1 L) and washed with water (3 × 500 mL) and brine (500 mL). The organic layer was dried ($MgSO_4$), concentrated, and purified by flash column chromatography (silica gel, 4:6, ether:-hexanes) to afford silyl ether **64** (116 g, 94 %). **64**: R_f = 0.7 (silica gel, 1:1, ether:hexanes); $[\alpha]_D^{25}$ = −23.6 (c = 2.93, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max}$ = 3450, 3080, 3045, 2940, 2860, 1600, 1460, 1100 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.75–7.65 (m, 4H, ArH), 7.50–7.33 (m, 6H, ArH), 5.81 (s, 2H), 4.29 (ddd, J = 8.0, 3.0, 3.0 Hz, 1H), 4.17–4.06 (m, 2H), 3.94 (dd, J = 10.0, 5.0 Hz, 1H), 3.81 (dd, J = 10.0, 7.0 Hz, 1H), 3.45 (ddd, J = 7.0, 7.0, 5.0 Hz, 1H), 1.09 (s, 9H, tBuSi); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 135.6, 133.2, 129.6, 127.9, 127.7, 127.3, 77.1, 66.7, 66.2, 65.2, 26.8, 19.2; HRMS calcd for $C_{22}H_{28}O_3Si$ ([M + NH_4^+]) 386.2151, found 386.2112.

Epoxy alcohol 65: A solution of allylic alcohol **64** (116 g, 316 mmol) in CH_2Cl_2 (1 L) was treated with *m*-chloroperbenzoic acid (65.3 g, 379 mmol) at 0 °C and the resulting solution was stirred at 25 °C for 12 h. The excess *m*-chloroperbenzoic acid was consumed by the addition of dimethyl sulfide (5 mL), and the solvent was removed by evaporation. The resulting oil was diluted with ether (1 L) and washed with a saturated aqueous sodium carbonate solution (3 × 300 mL), water (2 × 100 mL) and brine (100 mL). The organic phase was dried ($MgSO_4$), concentrated, and the residue was purified by flash column chromatography (silica gel, 6:4, ether:hexanes) to afford **65** (90.9 g, 75 %). **65**: R_f = 0.4 (silica gel, 6:4, ether:hexanes); $[\alpha]_D^{25}$ = −1.1 (c = 0.45, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max}$ = 3440, 3080, 3060, 2980, 2860, 1600, 1100 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.75–7.62 (m, 4H, ArH), 7.48–7.35 (m, 6H, ArH), 4.08–4.01 (m, 2H), 3.83 (dd, J = 10.5, 5.0 Hz, 1H), 3.81 (d, J = 13.5 Hz, 1H), 3.78 (dd, J = 10.5, 5.0 Hz, 1H), 3.52–3.48 (m, 2H), 3.33 (dt, J = 8.5, 4.5 Hz, 1H), 2.79 (d, J = 6.0 Hz, 1H, OH), 1.06 (s, 9H, tBuSi); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 135.6, 133.3, 129.9, 127.8, 74.2, 67.7, 65.0, 64.3, 55.5, 53.9, 26.8, 19.2; HRMS calcd for $C_{22}H_{28}O_4Si$ ([M + NH_4^+]) 402.2101, found 402.2093.

Epoxy ketone 66: A mixture of alcohol **65** (59.7 g, 155 mmol) and 3 Å molcular sieves in CH_2Cl_2 (500 mL) was treated with pyridinium dichro-

0947-6539/99/0502-0612 $ 17.50+.50/0 *Chem. Eur. J.* **1999**, *5*, No. 2

mate (116 g, 310 mmol) at 25 °C for 6 h. The reaction mixture was diluted with EtOAc (1 L) and filtered through a pad of celite. The filtrate was washed with water (5 × 300 mL) and brine (300 mL). The organic phase was dried ($MgSO_4$), concentrated, and purified by flash column chromatography (silica gel, 4:6, ether:hexanes) to afford **66** (50.8 g, 86 %). **66**: white solid; mp 145–146 °C; $R_f = 0.50$ (silica gel, 1:1, ether:hexanes); $[\alpha]_D^{25} = +25.4$ ($c = 1.27$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3100$, 3030, 2980, 2960, 2880, 1740, 1600, 1480, 1160, 1140, 1000, 710 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.70–7.58$ (m, 4H, ArH), 7.48–7.33 (m, 6H, ArH), 4.50 (d, $J = 13.0$ Hz, 1H), 4.22–4.18 (m, 2H), 4.04 (dd, $J = 11.5$, 4.5 Hz, 1H), 3.97 (dd, $J = 11.5$, 2.5 Hz, 1H), 3.70 (d, $J = 4.0$ Hz, 1H), 3.49 (d, $J = 4.0$ Hz, 1H), 1.02 (s, 9H, *t*BuSi); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta =$ 202.4, 135.7, 133.3, 129.9, 127.8, 79.1, 66.1, 61.6, 55.5, 53.1, 26.5, 19.1; HRMS calcd for $C_{22}H_{26}O_4Si$ ($[M + H^+]$) 383.1679, found 383.1680.

Hydroxy ketone 67: A solution of ketone **66** (59.7 g, 155 mmol) in acetone (560 mL) was treated with sodium iodide (84 g, 560 mmol), sodium acetate (4.6 g, 56 mmol), and acetic acid (31.9 mL, 560 mmol) at 25 °C for 10 min. The iodine formed from the reaction was reduced by addition of a saturated aqueous sodium thiosulfate solution (500 mL), and the acetone was removed by evaporation. The remaining aqueous mixture was diluted with EtOAc (1 L) and washed with water (2 × 500 mL), saturated aqueous sodium carbonate solution (3 × 500 mL), and brine (500 mL). The organic layer was dried ($MgSO_4$) and concentrated. The residue crystallized upon addition of ether to afford ketone **67** (38.3 g, 80 %). **67**: white solid, mp 134 °C; $R_f = 0.5$ (silica gel, 8:2, ether:hexanes); $[\alpha]_D^{25} = +83.8$ ($c = 0.48$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3620$, 3500, 3080, 3020, 2940, 2880, 1730, 1480, 1475, 1120, 710 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.74–7.60$ (m, 4H, ArH), 7.48–7.32 (m, 6H, ArH), 4.42 (ddd, $J = 10.0$, 5.0, 5.0 Hz, 1H), 4.36 (dd, $J = 11.5$, 4.5 Hz, 1H), 4.03–3.93 (m, 3H), 3.65 (ddd, $J = 11.5$, 5.0, 1.0 Hz, 1H), 2.90 (dd, $J = 16.0$, 4.5 Hz, 1H), 2.60 (dd, $J = 16.0$, 5.0 Hz, 1H), 1.02 (s, 9H, *t*BuSi); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 208.2$, 135.6, 133.0, 132.8, 129.8, 127.7, 82.9, 70.1, 66.5, 64.6, 46.7, 26.7, 14.2; HRMS calcd for $C_{22}H_{28}O_4Si$ ($[M + NH_4^+]$) 402.2101, found 402.2118.

Dithioketal 68: A solution of ketone **67** (39.9 g, 103 mmol) in CH_2Cl_2 (260 mL) was treated with ethanethiol (76 mL, 1.0 mol) and $BF_3 \cdot Et_2O$ (31.6 mL, 257 mmol) at −78 °C for 1 h. The reaction mixture was diluted with ether (1 L) and washed with a saturated aqueous sodium carbonate solution (30 mL), water (2 × 300 mL), and brine (300 mL). The organic layer was dried ($MgSO_4$), concentrated, and purified by flash column chromatography (silica gel, 1:1, ether:hexanes) to afford thioketal **68** (37.2 g, 74 %). **68**: $R_f = 0.4$ (silica gel, 1:1, ether:hexanes); $[\alpha]_D^{25} = +11.2$ ($c = 0.84$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3450$, 3080, 3060, 2980, 2940, 2860, 1600, 1100 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.75–7.64$ (m, 4H, ArH), 7.45–7.32 (m, 6H, ArH), 4.15–4.08 (m, 2H), 4.12 (dd, $J = 11.5$, 2.5 Hz, 1H), 3.84 (dd, $J = 11.5$, 8.0 Hz, 1H), 3.63 (dd, $J = 8.0$, 2.0 Hz, 1H), 3.24 (ddd, $J =$ 11.0, 11.0, 2.5 Hz, 1H), 2.60–2.30 (m, 6H), 1.79 (dd, $J = 13.5$, 8.5 Hz, 1H), 1.12 (t, $J = 7.5$ Hz, 3H), 1.12 (t, $J = 7.5$ Hz, 3H), 1.05 (s, 9H, *t*BuSi); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 135.7$, 133.9, 132.8, 129.6, 127.6, 84.9, 71.5, 64.2, 63.3, 59.5, 42.3, 26.8, 23.3, 22.6, 19.2, 14.0, 13.9; HRMS calcd for $C_{26}H_{38}O_3S_2Si$ ($[M - SEt^-]$) 429.1920, found 429.1924.

Dithioketal 69: A solution of the hydroxy dithiolketal **68** (13.0 g, 27 mmol), Et_3N (7.4 mL, 53 mmol), and DMAP (0.2 g, 1.6 mmol) in CH_2Cl_2 (100 mL) was treated with trimethylacetyl (pivaloyl) chloride (4.9 mL, 40 mmol) at 25 °C for 2 h. The reaction mixture was quenched with a saturated aqueous NH_4Cl solution (20 mL), and the aqueous phase was extracted with ether (2 × 30 mL). The combined organic extracts were dried (Na_2SO_4), concentrated, and purified by flash column chromatography (silica gel, 1:2, ether:hexanes) to afford ester **69** (14.3 g, 94 %). **69**: $R_f = 0.60$ (silica gel, 1:2, ether:hexanes); $[\alpha]_D^{25} = -26.9$ ($c = 0.81$, $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 2990$, 1932, 1456, 1285, 1152, 1112, 708, 506 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.74–7.67$ (m, 4H), 7.43–7.32 (m, 6H, ArH), 5.20 (ddd, $J = 10.5$, 5.0, 5.0 Hz, 1H), 4.20–4.13 (m, 2H), 3.80 (dd, $J = 11.5$, 8.0 Hz, 1H), 3.63 (dd, $J = 8.0$, 1.5 Hz, 1H), 3.27 (dd, $J = 10.5$, 10.5 Hz, 1H), 2.70 (ddd, $J = 15.0$, 11.0, 7.5 Hz, 1H), 2.57–2.51 (m, 2H), 2.44 (ddd, $J = 15.0$, 11.5, 7.5 Hz, 1H), 2.30 (ddd, $J = 15.0$, 11.0, 7.5 Hz, 1H), 1.69 (dd, $J = 13.0$, 10.5 Hz, 1H), 1.19 (t, $J = 7.5$ Hz, 3H, CH_3), 1.17 (s, 9H, *t*Bu), 1.07 (t, $J = 7.5$ Hz, 3H, CH_3), 1.05 (s, 9H, *t*Bu); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 178.4$, 135.6, 133.9, 132.8, 129.5, 127.6, 86.7, 69.4, 65.6, 63.9, 59.4, 40.1, 27.1, 26.8, 26.5, 23.7, 22.7, 19.3, 14.0, 13.7; HRMS (FAB) calcd for $C_{31}H_{46}O_4S_2Si$ ($[M + Na^+]$) 597.2505, found 597.2526.

Hydroxy dithioketal 70: A solution of silyl ether **69** (57.2 g, 100 mmol) in THF (50 mL) was treated with TBAF (150 mL, 150 mmol) at 25 °C for 3 h. The reaction mixture was diluted with ether (500 mL) and washed with water (3 × 200 mL). The organic phase was dried ($MgSO_4$), concentrated, and purified by flash column chromatography (silica gel, 1:1, ether:hexanes) to afford alcohol **70** (31.9 g, 95 %). **70**: $R_f = 0.50$ (silica gel, 1:1, ether:hexanes); $[\alpha]_D^{25} = -20.2$ ($c = 0.4$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3450$, 2980, 2940, 2880, 1740, 1480, 1290, 1160, 880 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 5.25–5.15$ (m, 1H), 4.14 (ddd, $J = 10.5$, 5.5, 1.5 Hz, 1H), 3.98 (dd, $J = 12.0$, 3.0 Hz, 1H), 3.68 (dd, $J = 11.5$, 9.0 Hz, 1H), 3.60 (dd, $J = 9.0$, 3.0 Hz, 1H), 3.27 (dd, $J = 11.0$, 11.0 Hz, 1H), 2.80–2.52 (m, 6H), 1.71 (dd, $J = 13.0$, 11.0 Hz, 1H), 1.24 (t, $J = 7.5$ Hz, 3H), 1.19 (t, $J = 7.5$ Hz, 3H), 1.15 (s, 9H, *t*BuSi); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 177.6$, 110.1, 85.3, 69.5, 65.4, 62.0, 59.0, 39.8, 27.0, 24.0, 22.9, 14.2, 13.7; HRMS calcd for $C_{15}H_{28}O_4S_2$ ($[M^+]$) 336.1431, found 336.1443.

Aldehyde 71: A solution of the hydroxy dithioketal **70** (7.5 g, 22 mmol), Et_3N (20 mL), and DMSO (20 mL) in CH_2Cl_2 (60 mL) was treated with $SO_3 \cdot pyr$ (10.7 g, 67 mmol) at 0 °C for 1 h. After addition of a saturated aqueous NH_4Cl solution (200 mL), the mixture was extracted with ether (3 × 100 mL), and the combined organic extracts were dried (Na_2SO_4). The solvent was removed and the residue was purified by flash column chromatography to afford aldehyde **71** (6.3 g, 85 %). **71**: $R_f = 0.65$ (silica gel, 3:2, ether:hexanes); $[\alpha]_D^{25} = -4.8$ ($c = 2.04$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} =$ 2970, 2870, 1740, 1456, 1284, 1154 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta =$ 9.69 (s, 1H), 5.19 (ddd, $J = 15.5$, 10.5, 5.0 Hz, 1H), 4.16 (ddd, $J = 10.5$, 5.0, 1.5 Hz, 1H), 3.96 (s, 1H), 3.23 (dd, $J = 10.5$, 10.5 Hz, 1H), 2.75–2.50 (m, 6H), 1.77 (dd, $J = 13.0$, 10.5 Hz, 1H), 1.20 (t, $J = 7.5$ Hz, 3H), 1.18 (t, $J =$ 7.5 Hz, 3H), 1.11 (s, 9H, *t*Bu); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 196.7$, 177.5, 118.0, 86.7, 68.9, 64.7, 58.4, 39.9, 26.9, 23.6, 22.9, 13.9, 13.5.

Olefin 73: The ylide of phosphonium salt **37** was prepared by addition of *n*-butyllithium (34 mL of 1.6 M in hexanes, 55 mmol) to a solution of the phosphonium salt **37** (43 g, 61 mmol) in THF (200 mL) at −78 °C, and the resulting bright orange solution was stirred at −78 °C for 1 h. To the ylide was added HMPA (38 mL, 220 mmol) and a solution of aldehyde **71** (60 mmol) in THF (100 mL), and the resulting reaction mixture was kept at −78 °C for 1 h and then allowed to warm to 25 °C for 12 h. The reaction mixture was diluted with ether (1 L) and quenched by addition of a saturated aqueous ammonium chloride solution (500 mL). The organic phase was washed with water (5 × 500 mL), brine (500 mL), dried ($MgSO_4$), and concentrated. The residue was purified by flash column chromatography (silica gel, 1:9, ether:hexanes) to afford olefin **73** (26.1 g, 74 %). **73**: $R_f = 0.4$ (silica gel, 1:9, ether:hexanes); $[\alpha]_D^{25} = -44.7$ ($c = 0.45$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3040$, 2980, 2940, 2865, 1740, 1480, 1460, 1170, 1120, 780 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.50–7.41$ (m, 2H, ArH), 7.34–7.26 (m, 3H, ArH), 5.96–5.88 (m, 1H, =CH), 5.67 (dd, $J = 10.5$, 9.0 Hz, 1H, =CH), 5.45 (s, 1H), 5.28–5.20 (m, 1H), 4.27 (d, $J = 8.5$ Hz, 1H), 4.15 (d, $J = 7.0$ Hz, 1H), 4.09 (ddd, $J = 10.0$, 5.0, 1.0 Hz, 1H), 3.62–3.52 (m, 3H), 3.24 (t, $J = 10.5$ Hz, 1H), 2.97 (dd, $J = 15.5$, 9.0 Hz, 1H), 2.79–2.69 (m, 1H), 2.68–2.52 (m, 4H), 2.30–2.22 (m, 1H), 1.58 (dd, $J =$ 13.0, 10.5 Hz, 1H), 1.26 (t, $J = 7.5$ Hz, 3H), 1.16 (s, 9H, *t*Bu), 1.04 (t, $J =$ 7.5 Hz, 3H), 0.91 (s, 9H, *t*BuSi), 0.14 (s, 3H, CH_3Si), 0.09 (s, 3H, CH_3Si); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 177.5$, 137.8, 132.0, 128.7, 128.1, 127.0, 126.1, 118.5, 100.8, 82.4, 81.7, 71.6, 69.2, 66.8, 65.3, 62.1, 40.3, 30.6, 27.1, 25.8, 23.7, 22.2, 17.9, 14.0, 13.8, -4.2, -4.7; HRMS calcd for $C_{33}H_{54}O_6S_2Si$ ($[M - Et^-]$) 609.2740, found 609.2702.

Hydroxy dithioketal 74: A solution of olefin **73** (20.7 g, 32 mmol) in THF (20 mL) was treated with TBAF (48 mL, 48 mmol) at 25 °C for 12 h. The reaction mixture was diluted with ether (1 L) and washed with water (3 × 300 mL). The organic phase was dried ($MgSO_4$), concentrated, and purified by flash column chromatography (silica gel, 1:1, ether:hexanes) to afford hydroxy dithioketal **74** (16.5 g, 98 %). **74**: $R_f = 0.40$ (silica gel, 1:1, ether:hexanes); $[\alpha]_D^{25} = +4.0$ ($c = 0.47$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3450$, 3020, 2980, 2910, 2870, 1730, 1480, 1150, 790, 690 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.46–7.40$ (m, 2H, ArH), 7.35–7.25 (m, 3H, ArH), 5.97 (ddd, $J = 11.0$, 8.0, 8.0 Hz, 1H, =CH), 5.77 (dd, $J = 10.5$, 9.0 Hz, 1H, =CH), 5.46 (s, 1H), 5.29–5.22 (m, 1H), 4.34 (d, $J = 8.5$ Hz, 1H), 4.21 (dd, $J = 10.5$, 4.0 Hz, 1H), 4.13 (ddd, $J = 10.5$, 5.0, 1.0 Hz, 1H), 3.69–3.60 (m, 2H), 3.62 (dd, $J = 8.5$, 4.5 Hz, 1H), 3.56 (dd, $J = 10.0$, 10.0 Hz, 1H), 3.36 (dd, $J = 10.5$, 10.5 Hz, 1H), 2.79–2.55 (m, 7H), 1.65 (dd, $J = 13.0$, 10.5 Hz, 1H), 1.28 (t, $J = 7.5$ Hz, 3H), 1.16 (s, 9H, *t*Bu), 1.12 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 177.6$, 137.7, 132.6, 128.9, 128.2, 126.6, 126.1, 107.8,

101.0, 81.3, 80.9, 70.8, 69.2, 66.0, 65.2, 61.4, 40.0, 32.0, 27.0, 25.6, 24.0, 22.2, 13.9, 13.7; HRMS calcd for $C_{27}H_{40}O_6S_2$ ($[M+NH_4^+]$) 542.2610, found 542.2687.

Mixed thioketal 75: A solution of hydroxy dithioketal **74** (877 mg, 1.67 mmol), $NaHCO_3$ (705 mg, 8.4 mmol), 3 Å molcular sieves (175 mg, freshly activated), and silica gel (175 mg, dried under vacuum) in $MeNO_2$ (30 mL) was treated with $AgClO_4$ (1.39 g, 6.7 mmol) at 25 °C for 4 h. The reaction mixture was treated with Et_3N (1 mL), diluted with ether (30 mL), and filtered through a pad of silica gel. The filtrate was concentrated and purified by flash column chromatography (silica gel, 1:49, acetone:benzene) to afford mixed thioketal **75** (570 mg, 74 %). **75**: $R_f = 0.55$ (silica gel, 1:49, acetone:benzene); $[\alpha]_D^{25} = +46.1$ ($c = 0.32$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3090$, 3070, 2990, 2960, 2880, 1740, 1490, 1460, 1160, 1100, 990, 780, 760, 710 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.49-7.42$ (m, 2H, ArH), 7.38–7.28 (m, 3H, ArH), 5.94 (ddd, $J = 9.5$, 9.5, 9.0 Hz, 1H, =CH), 5.70 (dd, $J = 11.0$, 6.5 Hz, 1H, =CH), 5.41 (s, 1H), 5.13 (ddd, $J = 15.5$, 10.5, 5.0 Hz, 1H), 4.62 (ddd, $J = 10.0$, 10.0, 5.0 Hz, 1H), 4.11 (ddd, $J = 10.5$, 5.0, 1.5 Hz, 1H), 4.05 (d, $J = 7.0$ Hz, 1H), 3.98–3.92 (m, 2H), 3.54 (dd, $J = 10.5$, 10.5 Hz, 1H), 3.30 (dd, $J = 10.5$, 10.5 Hz, 1H), 2.80–2.70 (m, 2H), 2.70–2.61 (m, 1H), 2.56–2.38 (m, 2H), 1.62 (dd, $J = 12.0$, 12.0 Hz, 1H), 1.29 (dd, $J = 7.5$, 7.5 Hz, 3H), 1.17 (s, 9H, *t*Bu); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta =$ 177.6, 137.6, 131.5, 129.2, 129.0, 128.2, 126.2, 101.5, 90.2, 83.3, 81.6, 69.8, 69.2, 66.1, 63.9, 40.4, 38.7, 30.8, 27.0, 20.9, 14.1; HRMS calcd for $C_{25}H_{34}O_6S$ ($[M+H^+]$) 463.2154, found 463.2176.

Olefin 40: A solution of mixed thioketal **75** (2.1 g, 4.6 mmol) and triphenyltin hydride (4.7 mL, 18.4 mmol) in toluene (9 mL) was treated dropwise with a solution of AIBN (38 mg, 0.23 mmol) in toluene (3 mL) at 110 °C over 2 h. After heating the dark solution for an additional 1 h, the solvent was removed under vacuum, and the residue was purified by flash column chromatography (silica gel, 1:49, acetone:benzene) to afford ether **40** (1.75 g, 95 %). **40**: $R_f = 0.50$ (silica gel, 1:49, acetone:benzene); $[\alpha]_D^{25} = +53.7$ ($c = 0.095$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3450$, 3040, 2980, 2940, 2860, 1740, 1480, 1140, 1100, 780, 710 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.49-7.42$ (m, 2H, ArH), 7.38–7.28 (m, 3H, ArH), 5.86–5.79 (m, 1H, =CH), 5.74 (dd, $J = 11.0$, 5.0 Hz, 1H, =CH), 5.41 (s, 1H), 4.79 (ddd, $J = 15.5$, 10.5, 5.0 Hz, 1H), 4.14 (dd, $J = 10.5$, 3.0 Hz, 1H), 3.99 (dd, $J = 10.5$, 5.0 Hz, 1H), 3.85 (dd, $J = 8.0$, 6.0 Hz, 1H), 3.78 (br s, 2H), 3.63–3.55 (m, 1H), 3.42–3.33 (m, 1H), 3.13 (dd, $J = 10.5$, 10.5 Hz, 1H), 2.77 (dd, $J = 10.0$, 10.0 Hz, 1H), 2.45 (dd, $J = 13.5$, 6.0 Hz, 1H), 1.53–1.46 (m, 1H), 1.17 (s, 9H, *t*Bu); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 177.5$, 137.5, 134.3, 128.9, 128.2, 126.7, 126.1, 101.6, 82.1, 79.5, 76.9, 71.5, 69.5, 68.3, 66.3, 38.7, 36.8, 30.3, 27.0; HRMS calcd for $C_{23}H_{30}O_6$ ($[M+H^+]$) 403.2121, found 403.2091.

Diol 76: A solution of ether **40** (1.15 g, 2.9 mmol) and ethanethiol (3 mL, 40.5 mmol) in CH_2Cl_2 (30 mL) was treated with $Zn(OTf)_2$ (200 mg, 0.6 mmol) at 25 °C for 4 h. After removal of the solvent, the residue was purified by flash column chromatography (silica gel, EtOAc) to afford diol **76** (850 mg, 94 %). **76**: $R_f = 0.45$ (silica gel, EtOAc); $[\alpha]_D^{25} = +97.8$ ($c = 1.01$, CH_3OH); IR (thin film): $\tilde{\nu}_{max} = 3391$, 2961, 2872, 1730, 1283, 1162, 1100 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 5.85-5.78$ (m, 1H, =CH), 5.74 (dd, $J = 11.0$, 5.0 Hz, 1H, =CH), 4.78 (dddd, $J = 11.5$, 10.0, 5.0, 5.0 Hz, 1H), 3.98 (ddd, $J = 10.5$, 5.0, 2.0 Hz, 1H), 3.93 (br d, $J = 8.5$ Hz, 1H), 3.86 (dd, $J = 7.5$, 5.0 Hz, 1H), 3.76 (dd, $J = 11.0$, 5.0 Hz, 1H), 3.67 (dd, $J = 11.0$, 5.0 Hz, 1H), 3.50–3.44 (m, 1H), 3.35 (ddd, $J = 11.5$, 9.5, 5.0 Hz, 1H), 3.14 (dd, $J = 10.5$, 10.5 Hz, 1H), 2.66 (ddd, $J = 13.5$, 10.0, 3.0 Hz, 1H), 2.50–2.44 (m, 1H), 2.35 (br s, 1H, OH), 2.31 (ddd, $J = 13.5$, 6.5, 3.0 Hz, 1H), 2.22 (br s, 1H, OH), 1.53 (ddd, $J = 11.5$, 11.5, 11.5 Hz, 1H), 1.17 (s, 9H, *t*Bu); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 177.7$, 133.5, 126.4, 81.5, 79.4, 78.8, 72.1, 68.1, 66.5, 63.8, 38.6, 37.0, 32.5, 26.9; HRMS calcd for $C_{16}H_{26}O_6$ ($[M+Na^+]$) 337.1627, found 337.1622.

Bis-silyl ether 77: A solution of diol **76** (1.5 g, 4.7 mmol) in CH_2Cl_2 (50 mL) was treated with 2,6-lutidine (1.67 mL, 14.2 mmol) and TBSOTf (2.4 mL, 10.0 mmol) at 0 °C for 30 min. The reaction mixture was then quenched by addition of a saturated aqueous NH_4Cl solution (15 mL) and extracted with ether (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4), concentrated, and purified by flash column chromatography (silica gel, 3:7, ether:hexanes) to afford bis-silyl ether **77** (2.38 g, 92 %). **77**: $R_f = 0.70$ (silica gel, 3:7, ether:hexanes); $[\alpha]_D^{25} = +98.1$ ($c = 1.02$, CH_3OH); IR (thin film): $\tilde{\nu}_{max} = 2930$, 2857, 1736, 1471, 1254, 1155, 1101, 989, 935, 834, 776, 675 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 5.74-5.64$ (m, 2H, =CH), 4.75 (ddd, $J =$ 15.5, 10.0, 5.0 Hz, 1H), 3.96 (ddd, $J = 10.5$, 5.0, 2.0 Hz, 1H), 3.82–3.75 (m, 2H), 3.74 (dd, $J = 10.5$, 1.5 Hz, 1H), 3.48 (dd, $J = 10.5$, 7.0 Hz, 1H), 3.40 (ddd, $J = 9.0$, 9.0, 1.5 Hz, 1H), 3.29 (ddd, $J = 11.5$, 9.5, 4.5 Hz, 1H), 3.07 (dd, $J = 10.0$, 10.0 Hz, 1H), 2.59 (ddd, $J = 13.0$, 10.0, 3.0 Hz, 1H), 2.48–2.42 (m, 1H), 2.14 (ddd, $J = 13.0$, 6.0, 3.0 Hz, 1H), 1.53 (ddd, $J = 11.5$, 11.5, 11.5 Hz, 1H), 1.15 (s, 9H, *t*Bu), 0.87 (s, 9H, *t*Bu), 0.85 (s, 9H, *t*Bu), 0.06 (s, 3H, CH_3), 0.02 (s, 3H, CH_3), 0.02 (s, 3H, CH_3), 0.00 (s, 3H, CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 177.3$, 133.1, 126.8, 83.8, 79.7, 79.1, 72.0, 68.4, 66.6, 64.6, 38.6, 37.0, 32.9, 27.0, 25.8, 25.6, 18.2, 17.8, -4.5, -5.1, -5.4; HRMS (FAB) calcd for $C_{28}H_{54}O_6Si_2$ ($[M+Cs^+]$) 675.2513, found 675.2533.

Silyl ether 78: The bis-silyl ether **77** (2.3 g, 4.3 mmol) was dissolved in a solution of CH_2Cl_2 (10 mL) and MeOH (10 mL) and treated with CSA (150 mg, 0.65 mmol) at 25 °C for 2 h. After addition of Et_3N (200 μL), the mixture was concentrated and the residue was purified by flash column chromatography (silica gel, 3:7, ether:hexanes) to give silyl ether **78** (1.67 g, 92 %). **78**: $R_f = 0.30$ (silica gel, 3:7, ether:hexanes); $[\alpha]_D^{25} = +118.4$ ($c = 1.07$, CH_3OH); IR (thin film): $\tilde{\nu}_{max} = 3509$, 2957, 2931, 2858, 1732, 1464, 1253, 1160, 1095, 833 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 5.77-5.68$ (m, 1H, =CH), 5.65 (dd, $J = 11.5$, 5.0 Hz, 1H, =CH), 4.74 (dddd, $J = 11.0$, 10.5, 5.0, 5.0 Hz, 1H), 3.95 (dd, $J = 10.0$, 5.0 Hz, 1H), 3.87–3.80 (m, 2H), 3.73–3.65 (m, 1H), 3.50–3.41 (m, 2H), 3.34–3.27 (m, 1H), 3.08 (dd, $J = 10.5$, 10.5 Hz, 1H), 2.55 (ddd, $J = 11.5$, 11.5, 3.0 Hz, 1H), 2.48–2.41 (m, 1H), 2.16 (ddd, $J = 13.5$, 6.5, 3.0 Hz, 1H), 2.01 (br s, 1H), 1.50 (ddd, $J = 11.5$, 11.5, 11.5 Hz, 1H), 1.13 (s, 9H, *t*Bu), 0.83 (s, 9H, *t*Bu), 0.06 (s, 3H, CH_3), 0.01 (s, 3H, CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 177.3$, 132.8, 126.8, 82.5, 79.4, 78.7, 71.8, 68.2, 66.4, 63.1, 38.5, 37.1, 32.7, 26.9, 25.5, 17.7, −4.6, −5.2; HRMS (FAB) calcd for $C_{22}H_{40}O_6Si$ ($[M+H^+]$) 429.2672, found 429.2687.

Aldehyde 79: A solution of alcohol **78** (1.6 g, 3.7 mmol) in CH_2Cl_2 (30 mL) was treated with NMO (1.32 g, 11 mmol) and TPAP (50 mg, 0.14 mmol) at 25 °C for 1 h. After filtering the reaction mixture through a pad of silica gel, the filtrate was concentrated, and the residue was purified by flash column chromatography to afford the aldehyde **79** (1.29 g, 82 %). **79**: $R_f = 0.45$ (silica gel, 3:7, ether:hexanes); $[\alpha]_D^{25} = +112.2$ ($c = 1.02$, CH_3OH); IR (thin film): $\tilde{\nu}_{max} = 3480$, 2929, 1732, 1464, 1362, 1262, 832, 740 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 9.73$ (s, 1H), 5.83–5.68 (m, 2H, =CH), 4.78 (dddd, $J = 11.0$, 10.0, 5.5, 5.0 Hz, 1H), 3.11 (ddd, $J = 9.5$, 3.0, 3.0 Hz, 1H), 4.00 (ddd, $J = 10.5$, 5.0, 2.0 Hz, 1H), 3.90–3.84 (m, 2H), 3.28 (ddd, $J = 11.0$, 9.0, 5.0 Hz, 1H), 3.13 (dd, $J = 10.5$, 10.5 Hz, 1H), 2.66–2.52 (m, 2H), 2.34–2.24 (m, 1H), 1.60 (ddd, $J = 11.5$, 11.5, 11.5 Hz, 1H), 1.17 (s, 9H, *t*Bu), 0.88 (s, 9H, *t*Bu), 0.12 (s, 3H, CH_3), 0.04 (s, 3H, CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 200.3$, 177.3, 133.6, 126.2, 85.6, 79.4, 79.1, 71.6, 68.3, 66.2, 38.5, 36.6, 32.8, 27.0, 25.5, 17.7, −4.5, −5.2; HRMS (FAB) calcd for $C_{22}H_{38}O_6Si$ ($[M+H^+]$) 427.2516, found 427.2526.

Olefin 80: Methyltriphenylphosphonium bromide (1.2 g, 3.3 mmol) was suspended in THF (70 mL) and treated with NaHMDS (3.2 mL of 1 M in THF, 3.2 mmol) at 0 °C for 20 min. To this solution was added aldehyde **79** (1.17 g, 2.74 mmol) in THF (20 mL) at 0 °C and the resulting reaction mixture was stirred at 0 °C for 1 h. After addition of acetone (2 mL), the reaction mixture was concentrated, and the residue was purified by flash column chromatography (silica gel, 3:7, ether:hexanes) to afford the olefin **80** (0.92 g, 79 %). **80**: $R_f = 0.80$ (silica gel, 3:7, ether:hexanes); $[\alpha]_D^{25} = +126.6$ ($c = 1.13$, CH_3OH); IR (thin film): $\tilde{\nu}_{max} = 2929$, 2857, 1732, 1472, 1362, 1282, 1256, 1158, 1097, 833, 776 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 5.88$ (ddd, $J = 17.0$, 10.5, 4.5 Hz, 1H, =CH), 5.77–5.70 (m, 1H), 5.69 (dd, $J = 11.0$, 4.5 Hz, 1H, =CH), 5.24 (d, $J = 17.0$ Hz, 1H, =CH), 5.08 (d, $J = 10.5$ Hz, 1H, =CH), 4.77 (dddd, $J = 11.0$, 10.5, 5.5, 5.0 Hz, 1H), 3.97 (ddd, $J = 10.5$, 5.0, 2.0 Hz, 1H), 3.85 (dd, $J = 8.5$, 4.0 Hz, 1H), 3.80 (dd, $J = 9.0$, 4.5 Hz, 1H), 3.66 (ddd, $J = 9.0$, 3.0, 3.0 Hz, 1H), 3.22 (ddd, $J = 11.5$, 9.0, 4.5 Hz, 1H), 3.12 (dd, $J = 10.5$, 10.5 Hz, 1H), 2.66 (ddd, $J = 13.0$, 9.5, 3.0 Hz, 1H), 2.51–2.45 (m, 1H), 2.19 (ddd, $J = 13.0$, 6.5, 3.0 Hz, 1H), 1.54 (ddd, $J = 11.5$, 11.5, 11.5 Hz, 1H), 1.16 (s, 9H, *t*Bu), 0.86 (s, 9H, *t*Bu), 0.06 (s, 3H, CH_3), -0.01 (s, 3H, CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 177.3$, 137.2, 133.0, 126.6, 114.4, 82.4, 79.7, 78.0, 75.5, 68.3, 66.4, 38.5, 36.9, 33.2, 27.0, 25.7, 17.8, −4.6, −4.9; HRMS (FAB) calcd for $C_{23}H_{40}O_5Si$ ($[M+Cs^+]$) 557.1699, found 557.1684.

Alcohol 81: To a solution of olefin **80** (0.91 g, 2.2 mmol) in THF (20 mL) was added 9-BBN (4.94 mL of 0.5 M in hexanes, 2.47 mmol) during 20 min at 0 °C. The mixture was stirred at 0 °C for an additional 5 h before the addition of a saturated aqueous $NaHCO_3$ solution (15 mL) and 30 % H_2O_2 (2.5 mL) at 0 °C. After stirring at 25 °C for 1.5 h, a saturated aqueous Na_2SO_3 solution (5 mL) was slowly added and the mixture was extracted with EtOAc (3 × 15 mL). The combined organic extracts were dried (Na_2SO_4), concentrated, and the residue was purified by flash column

0947-6539/99/0502-0614 $ 17.50+.50/0 *Chem. Eur. J.* **1999**, *5*, No. 2

chromatography (silica gel, 3:7, EtOAc:hexanes) to afford alcohol **81** (0.83 g, 88%). **81**: R_f = 0.60 (silica gel, 3:7, EtOAc:hexanes); $[\alpha]_D^{25}$ = +130.6 (c = 1.01, CH_3OH); ^1H NMR (400 MHz, $CDCl_3$): δ = 5.73–5.64 (m, 1H, =CH), 5.61 (dd, J = 11.0, 4.5 Hz, 1H), 4.73 (dddd, J = 11.0, 10.5, 5.5, 5.0 Hz, 1H), 3.92 (ddd, J = 10.5, 5.5, 1.5 Hz, 1H), 3.79 (dd, J = 8.5, 4.5 Hz, 1H), 3.73–3.64 (m, 3H), 3.54 (ddd, J = 9.0, 9.0, 2.5 Hz, 1H), 3.26 (ddd, J = 11.5, 9.5, 4.5 Hz, 1H), 3.05 (dd, J = 10.5, 10.5 Hz, 1H), 2.60 (ddd, J = 13.0, 10.0, 3.0 Hz, 1H), 2.45–2.33 (m, 2H), 2.20–2.10 (m, 2H), 1.73–1.38 (m, 2H), 1.12 (s, 9H, *t*Bu), 0.82 (s, 9H, *t*BuSi), 0.04 (s, 3H, CH_3Si), −0.01 (s, 3H, CH_3Si); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 177.5, 132.8, 126.8, 79.8, 79.5, 78.6, 75.7, 68.3, 66.5, 59.6, 38.6, 36.9, 35.5, 33.1, 27.0, 25.6, 17.8, −4.4, −4.9; HRMS (FAB) calcd for $C_{23}H_{42}O_6Si$ ($[M+H^+]$) 443.2829, found 443.2814.

Acetate 82: A solution of alcohol **81** (0.82 g, 1.9 mmol) in CH_2Cl_2 (10 mL) was treated with Et_3N (0.39 mL, 2.8 mmol) and acetic anhydride (0.19 mL, 2.1 mmol) at 25 °C for 40 min. After addition of a saturated aqueous NH_4Cl solution (4 mL), the mixture was extracted with EtOAc (2 × 5 mL), and the combined organic extracts were dried (Na_2SO_4), concentrated, and purified by flash column chromatography (silica gel, 3:7, EtOAc:hexanes) to afford acetate **82** (0.84 g, 94%). **82**: R_f = 0.75 (silica gel, 3:7, EtOAc:hexanes); $[\alpha]_D^{25}$ = +164.0 (c = 0.86, CH_3OH); IR (thin film): $\tilde{\nu}_{max}$ = 2957, 2858, 1733, 1464, 1364, 1250, 1095, 832 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 5.76–5.68 (m, 1H, =CH), 5.65 (dd, J = 11.0, 4.5 Hz, 1H, =CH), 4.76 (dddd, J = 11.0, 10.5, 5.5, 5.5 Hz, 1H), 4.25–4.18 (m, 1H), 4.04 (ddd, J = 10.0, 10.0, 5.5 Hz, 1H), 3.97 (ddd, J = 10.5, 5.5, 1.5 Hz, 1H), 3.81 (dd, J = 8.5, 5.0 Hz, 1H), 3.64 (ddd, J = 8.5, 3.0, 3.0 Hz, 1H), 3.42 (ddd, J = 8.5, 8.5, 1.5 Hz, 1H), 3.18 (ddd, J = 11.5, 9.0, 4.5 Hz, 1H), 3.06 (dd, J = 10.5, 10.5 Hz, 1H), 2.62 (ddd, J = 13.0, 9.5, 3.0 Hz, 1H), 2.45–2.37 (m, 1H), 2.20–2.14 (m, 1H), 2.05–1.97 (m, 1H), 2.03 (s, 3H, CH_3), 1.54–1.42 (m, 2H), 1.15 (s, 9H, *t*Bu), 0.85 (s, 9H, *t*Bu), 0.08 (s, 3H, CH_3), 0.02 (s, 3H, CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 177.5, 171.0, 132.9, 126.8, 79.6, 79.1, 78.9, 76.1, 68.3, 66.5, 61.4, 38.6, 36.8, 33.0, 32.6, 27.0, 25.7, 21.0, 17.9, −4.3, −4.9; HRMS (FAB) calcd for $C_{25}H_{44}O_7Si$ ($[M+Cs^+]$) 617.1911, found 617.1927.

Alcohol 83: A solution of silyl ether **82** (0.81 g, 1.7 mmol) in THF (15 mL) was treated with TBAF (2.7 mL of 1M in THF, 2.7 mmol) at 25 °C for 3 h. After addition of a saturated aqueous NH_4Cl solution (5 mL), the mixture was extracted with EtOAc (3 × 15 mL), and the combined organic extracts were dried (Na_2SO_4). The solvent was removed, and the residue was purified by flash column chromatography (silica gel, 4:6, EtOAc:hexanes) to afford the alcohol **83** (0.58 g, 94%). **83**: R_f = 0.40 (silica gel, 4:6, EtOAc:hexanes); $[\alpha]_D^{25}$ = +109.7 (c = 0.94, CH_3OH); IR (thin film): $\tilde{\nu}_{max}$ = 3482, 2960, 2871, 1734, 1367, 1248, 1159, 1094, 1036 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 5.80–5.75 (m, 1H, =CH), 5.70 (dd, J = 11.0, 4.5 Hz, 1H, =CH), 4.75 (dddd, J = 11.0, 10.5, 5.5, 5.0 Hz, 1H), 4.23 (ddd, J = 11.0, 6.5, 4.5 Hz, 1H), 4.08 (ddd, J = 9.5, 9.5, 5.5 Hz, 1H), 3.97 (ddd, J = 10.5, 5.0, 1.5 Hz, 1H), 3.81 (dd, J = 8.5, 4.5 Hz, 1H), 3.69 (ddd, J = 9.0, 3.0, 3.0 Hz, 1H), 3.44 (ddd, J = 9.5, 9.5, 1.5 Hz, 1H), 3.21 (ddd, J = 11.5, 9.0, 4.5 Hz, 1H), 3.07 (dd, J = 10.5, 10.5 Hz, 1H), 2.69 (ddd, J = 13.0, 10.0, 3.0 Hz, 1H), 2.45–2.39 (m, 1H), 2.27 (ddd, J = 13.5, 6.5, 3.0 Hz, 1H), 2.14–2.07 (m, 1H), 2.04 (s, 3H, CH_3), 1.61–1.54 (m, 1H), 1.51 (ddd, J = 11.5, 11.5, 11.5 Hz, 1H), 1.15 (s, 9H, *t*Bu); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 177.5, 171.0, 133.8, 125.8, 79.4, 78.9, 78.8, 75.4, 68.2, 66.3, 61.2, 38.6, 36.7, 32.9, 32.6, 26.9, 20.9; HRMS (FAB) calcd for $C_{19}H_{30}O_7$ ($[M+H^+]$) 371.2070, found 371.2083.

Ketone 84: A solution of alcohol **83** (0.55 g, 1.5 mmol) in CH_2Cl_2 (20 mL) was treated with NMO (0.52 g, 4.5 mmol) and TPAP (50 mg, 0.14 mmol) at 25 °C for 30 min. After filtering the mixture through a pad of silica gel, the filtrate was concentrated and purified by flash column chromatography to afford ketone **84** (506 mg, 93%). **84**: R_f = 0.60 (silica gel, 3:7, EtOAc:hexanes); $[\alpha]_D^{25}$ = +283.3 (c = 1.14, CH_3OH); IR (thin film): $\tilde{\nu}_{max}$ = 2968, 1724, 1241, 1154, 1100, 1038, 751 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 5.73 (dd, J = 11.0, 4.5 Hz, 1H), 5.63–5.54 (m, 1H), 4.78 (dddd, J = 11.0, 10.0, 6.0, 5.0 Hz, 1H), 4.19–4.07 (m, 3H), 4.02–3.96 (m, 2H), 3.94 (dd, J = 10.0, 10.0 Hz, 1H), 3.30 (ddd, J = 11.5, 9.0, 5.0 Hz, 1H), 3.12 (dd, J = 10.5, 10.5 Hz, 1H), 2.81 (dd, J = 11.0, 7.5 Hz, 1H), 2.55–2.47 (m, 1H), 2.15–2.05 (m, 1H), 2.01 (s, 3H, CH_3), 1.76–1.68 (m, 1H), 1.63 (ddd, J = 11.5, 11.5, 11.5 Hz, 1H), 1.15 (s, 9H, *t*Bu); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 210.1, 177.5, 170.8, 135.1, 122.3, 81.4, 81.3, 79.3, 68.2, 66.2, 60.3, 41.4, 38.7, 37.0, 31.0, 27.1, 20.9; HRMS (FAB) calcd for $C_{19}H_{28}O_7$ ($[M+H^+]$) 369.1913, found 369.1924.

Dithioketal 85: A solution of ketone **84** (0.49 g, 1.3 mmol) and ethanethiol (1.5 mL, 20 mmol) in CH_2Cl_2 (5.0 mL) was treated with $Zn(OTf)_2$ (50 mg, 0.14 mmol) at 25 °C for 16 h. After addition of Et_3N (200 mL), the solvent was removed and the residue was subjected to flash column chromatography (silica gel, 2:8, EtOAc:hexanes) to afford the dithioketal **85** (0.56 g, 89%). **85**: R_f = 0.80 (silica gel, 2:8, EtOAc:hexanes); $[\alpha]_D^{25}$ = +99.6 (c = 0.98, CH_3OH); IR (thin film): $\tilde{\nu}_{max}$ = 2967, 2930, 2870, 1732, 1456, 1365, 1237, 1158, 1101, 1037, 987 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 5.81–5.74 (m, 1H, =CH), 5.70 (dd, J = 11.0, 4.5 Hz, 1H, =CH), 4.76 (dddd, J = 11.0, 10.5, 5.5, 5.0 Hz, 1H), 4.27 (ddd, J = 12.0, 5.0, 5.0 Hz, 1H), 4.04 (ddd, J = 10.5, 7.5, 7.5 Hz, 1H), 4.02–3.96 (m, 1H), 3.89 (dd, J = 9.0, 4.0 Hz, 1H), 3.81 (dd, J = 7.0, 5.5 Hz, 1H), 3.17–3.10 (m, 1H), 3.08 (dd, J = 10.5, 10.5 Hz, 1H), 3.02 (dd, J = 13.0, 10.0 Hz, 1H), 2.82–2.64 (m, 4H), 2.50 (dd, J = 13.0, 6.0 Hz, 1H), 2.47–2.43 (m, 1H), 2.06 (s, 3H, CH_3), 2.05–1.98 (m, 2H), 1.58 (ddd, J = 11.5, 11.5, 11.5 Hz, 1H), 1.25 (dd, J = 7.5, 7.5 Hz, 3H, CH_3), 1.19 (dd, J = 7.5, 7.5 Hz, 3H, CH_3), 1.16 (s, 9H, *t*Bu); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 177.5, 171.0, 133.8, 125.8, 82.7, 79.3, 78.7, 68.3, 66.7, 66.4, 61.4, 38.6, 36.7, 36.0, 32.5, 27.1, 24.7, 23.7, 21.0, 14.2, 14.0; HRMS (FAB) calcd for $C_{23}H_{38}O_6S_2$ ($[M+Cs^+]$) 607.1164, found 607.1180.

Alcohol 86: A solution of dithioketal **85** (0.45 g, 0.95 mmol) in CH_3OH (2 mL) was treated with K_2CO_3 (20 mg, 0.15 mmol) at 25 °C for 2 h. After evaporation of the methanol, the resulting residue was purified by flash column chromatography (silica gel, 1:1, EtOAc:hexanes) to afford alcohol **86** (381 mg, 93%). **86**; R_f = 0.20 (silica gel, 3:7, EtOAc:hexanes); $[\alpha]_D^{25}$ = +34.2 (c = 0.84, CH_3OH); IR (thin film): $\tilde{\nu}_{max}$ = 3501, 2930, 1732, 1456, 1283, 1161, 1101, 979, 733 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 5.78–5.70 (m, 1H), 5.67 (dd, J = 11.0, 5.0 Hz, 1H), 4.74 (dddd, J = 11.5, 10.0, 5.0, 5.0 Hz, 1H), 3.96–3.92 (m, 2H), 3.86 (dd, J = 8.5, 4.5 Hz, 1H), 3.76 (br m, 1H), 3.68–3.61 (m, 1H), 3.25 (ddd, J = 11.5, 9.5, 5.0 Hz, 1H), 3.08 (dd, J = 10.5, 10.5 Hz, 1H), 2.99 (dd, J = 13.0, 10.0 Hz, 1H), 2.79–2.61 (m, 4H), 2.50–2.42 (m, 2H), 1.91–1.85 (m, 2H), 1.78 (br m, 1H), 1.52 (ddd, J = 11.5, 11.5, 11.5 Hz, 1H), 1.21 (dd, J = 7.5, 7.5 Hz, 3H, CH_3), 1.16 (dd, J = 7.5, 7.5 Hz, 3H, CH_3), 1.13 (s, 9H, *t*Bu); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 177.6, 133.8, 125.7, 82.3, 79.4, 78.3, 68.3, 66.9, 66.5, 59.4, 38.7, 36.8, 36.3, 35.8, 27.0, 24.7, 23.7, 14.2, 14.0; HRMS (FAB) calcd for $C_{21}H_{36}O_5S_2$ ($[M+Na^+]$) 455.1902, found 455.1914.

Aldehyde 38: A mixture of alcohol **86** (95 mg, 0.22 mmol), Et_3N (250 μL), and DMSO (250 μL) in CH_2Cl_2 (0.5 mL) was treated with SO_3·pyridine (105 mg, 0.66 mmol) at 0 °C for 1 h. After addition of a saturated aqueous NH_4Cl solution (2.0 mL), the mixture was extracted with CH_2Cl_2 (3 × 5 mL), and the organic extracts were washed with brine (2 × 2 mL) and dried (Na_2SO_4). The solvent was removed, and the residue was purified by flash column chromatography (silica gel, 3:7, EtOAc:hexanes) to afford aldehyde **38** (79 mg, 83%). **38**: R_f = 0.75 (silica gel, 3:7, EtOAc:hexanes); $[\alpha]_D^{25}$ = +29.1 (c = 0.61, CH_3OH); IR (thin film): $\tilde{\nu}_{max}$ = 2966, 2991, 2870, 1732, 1458, 1282, 1159, 1101, 1082, 989 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 9.82 (s, 1H), 5.82–5.72 (m, 2H, =CH), 4.78 (dddd, J = 10.5, 10.5, 5.0, 4.5 Hz, 1H), 4.30 (d, J = 9.5 Hz, 1H), 4.00 (dd, J = 10.5, 5.0 Hz, 1H), 3.88 (dd, J = 9.5, 3.5 Hz, 1H), 3.51 (ddd, J = 11.0, 11.0, 4.5 Hz, 1H), 3.11–3.00 (m, 3H), 2.90–2.66 (m, 5H), 2.50 (dd, J = 12.5, 6.0 Hz, 1H), 2.31–2.23 (m, 1H), 1.47 (ddd, J = 11.5, 11.5, 11.5 Hz, 1H), 1.24 (dd, J = 7.5, 7.5 Hz, 3H, CH_3), 1.21 (dd, J = 7.5, 7.5 Hz, 3H, CH_3), 1.15 (s, 9H, *t*Bu); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 200.1, 177.3, 134.2, 125.2, 80.0, 79.0, 78.3, 68.2, 66.3, 65.8, 48.3, 38.5, 36.6, 35.5, 26.9, 24.6, 23.6, 14.1, 13.9; HRMS (FAB) calcd for $C_{21}H_{34}O_5S_2$ ($[M+H^+]$) 431.1926, found 431.1942.

Olefin 87: To a solution of the phosphonium salt **37** (95 mg, 0.11 mmol) in THF (5.0 mL) was added *n*BuLi (88 mL of 1.5M in hexanes, 0.13 mmol) at −78 °C, and the resulting mixture was stirred at −78 °C for 20 min. After addition of HMPA (0.2 mL, 1.1 mmol) to the reaction mixture, a solution of aldehyde **38** (57 mg, 0.13 mmol) in THF (4 mL) was added, and the mixture was stirred at −78 °C for 20 min and at 25 °C for 1.5 h. The reaction mixture was quenched by addition of a saturated aqueous NH_4Cl solution (1 mL) and extracted with EtOAc (3 × 3 mL). The combined organic extracts were dried (Na_2SO_4), concentrated, and purified by flash column chromatography (silica gel, 3:7, ether:hexanes) to afford olefin **87** (81 mg, 82%). **87**: R_f = 0.45 (silica gel, 3:7, ether:hexanes); $[\alpha]_D^{25}$ = +4.42 (c = 1.04, CH_3OH); IR (thin film): $\tilde{\nu}_{max}$ = 2956, 1734, 1459, 1157, 1079, 1041, 837 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 5.77–5.68 (m, 1H, =CH), 5.65 (dd, J = 11.0, 5.0 Hz, 1H, =CH), 5.58–5.45 (m, 2H, =CH), 4.77 (d, J = 7.5 Hz, 1H), 4.76–4.68 (m, 1H), 4.64 (d, J = 7.0 Hz, 1H), 3.96–3.91 (m, 1H), 3.85–3.80 (m, 1H), 3.69–3.62 (m, 3H), 3.53–3.49 (m, 3H), 3.45–3.40 (m, 3H), 3.36 (s, 3H, CH_3), 3.12–2.96 (m, 4H), 2.82–2.60 (m, 6H), 2.49–2.31 (m, 6H), 2.21 (ddd, J = 12.0, 5.0, 5.0 Hz, 1H), 2.12–2.04 (m, 1H), 2.00–1.93 (m, 2H), 1.58–1.48 (m, 4H), 1.40–1.36 (m, 3H), 1.22 (dd, J = 7.5, 7.5 Hz, 3H, CH_3),

1.16 (dd, J = 7.5, 7.5 Hz, 3H, CH_3), 1.13 (s, 9H, *t*Bu) 1.09 (m, 6H, CH_3), 0.84 (s, 9H, *t*BuSi), 0.01 (s, 3H, CH_3Si), −0.02 (s, 3H, CH_3Si); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 177.4, 133.8, 128.9, 127.4, 125.7, 94.2, 87.5, 86.4, 80.4, 79.3, 78.7, 78.5, 76.6, 75.3, 71.6, 69.7, 68.3, 67.0, 66.8, 66.4, 59.0, 42.5, 38.6, 36.8, 36.5, 36.0, 34.0, 33.2, 33.1, 31.5, 27.1, 25.8, 24.7, 23.7, 17.9, 17.1, 16.2, 15.6, 14.6, 14.2, 13.9, −4.4, −4.5; HRMS (FAB) calcd for $C_{47}H_{84}O_{10}SiS_2$ ([M + Cs^+]) 1033.4330, found 1033.4368.

Hydroxy dithioketal 88: A solution of silyl ether **87** (77 mg, 0.085 mmol) in THF (1.5 mL) was treated with TBAF (170 μL of 1M in THF, 0.17 mmol) at 25 °C for 36 h. After addition of a saturated aqueous NH_4Cl solution (2 mL), the mixture was extracted with EtOAc (5 × 5 mL). The combined organic extracts were dried (Na_2SO_4), concentrated, and purified by flash column chramotography (silica gel, 3:7, EtOAc:hexanes) to afford hydroxy dithioketal **88** (58.5 mg, 89%). **88**: R_f = 0.60 (silica gel, 3:7, EtOAc:hexanes); $[\alpha]_D^{25}$ = −5.72 (c = 1.52, CH_3OH); IR (thin film): $\tilde{\nu}_{max}$ = 3504, 2958, 1734, 1458, 1157, 1100, 1043, 735 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.76–5.71 (m, 1H, =CH), 5.69–5.63 (m, 2H, =CH), 5.54–5.47 (m, 1H, =CH), 4.77 (d, J = 7.5 Hz, 1H), 4.73 (dddd, J = 11.0, 10.5, 5.5, 5.0 Hz, 1H), 4.64 (d, J = 7.5 Hz, 1H), 3.95 (dd, J = 10.5, 4.0 Hz, 1H), 3.84 (dd, J = 9.0, 4.0 Hz, 1H), 3.71–3.64 (m, 3H), 3.53 (dd, J = 4.5, 4.5 Hz, 2H), 3.44 (dd, J = 11.5, 4.5 Hz, 1H), 3.42–3.33 (m, 2H), 3.37 (s, 3H, CH_3), 3.23 (dd, J = 7.0, 7.0 Hz, 1H), 3.15–3.00 (m, 3H), 2.99 (dd, J = 13.5, 10.0 Hz, 1H), 2.84–2.63 (m, 4H), 2.58–2.22 (m, 8H), 2.00–1.90 (m, 1H), 1.81 (ddd, J = 14.5, 8.0, 3.5 Hz, 1H), 1.71–1.64 (m, 1H), 1.59–1.46 (m, 2H), 1.42–1.32 (m, 4H), 1.24 (dd, J = 7.5, 7.5 Hz, 3H, CH_3), 1.19 (dd, J = 7.5, 7.5 Hz, 3H, CH_3), 1.14 (s, 9H, *t*Bu), 1.09 (d, J = 6.0 Hz, 3H, CH_3), 1.08 (s, 3H, CH_3), 0.89–0.84 (m, 3H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 177.6, 133.8, 128.4, 127.7, 125.7, 94.3, 86.3, 85.3, 80.3, 79.3, 79.1, 78.7, 76.9, 75.7, 71.6, 70.0, 68.2, 67.1, 66.5, 59.0, 53.8, 42.5, 37.5, 36.5, 36.1, 36.0, 33.2, 32.6, 31.3, 27.1, 24.7, 23.8, 20.8, 19.4, 16.2, 15.7, 14.6, 14.3, 14.0; HRMS (FAB) calcd for $C_{41}H_{70}O_{10}S_2$ ([M + Cs^+]) 919.3465, found 919.3430.

Attempted cylization of hydroxydithioketal 88: A heterogeneous mixture of hydroxy dithioketal **88** (52 mg, 0.066 mmol), powdered 4 Å molcular sieves (freshly activated, 200 mg), silica gel (dried under vacuum, 200 mg), sodium bicarbonate (55 mg, 0.65 mmol), silver perchlorate (41 mg, 0.2 mmol), and dry nitromethane (distilled from CaH_2) was stirred vigorously at 25 °C for 3 h. The reaction mixture was treated with Et_3N (1.0 mL), diluted with ether (30 mL), and filtered through a pad of celite. The filtrate was concentrated, and the residue was purified by flash column chromatography (silica gel, 3:7, EtOAc:hexanes) to afford diene **90** (27 mg, 56%) and ketone **91** (14 mg, 31%). Diene **90**: R_f = 0.40 (silica gel, 3:7, EtOAc:hexanes); $[\alpha]_D^{25}$ = −140.5 (c = 1.52, CH_3OH); IR (thin film): $\tilde{\nu}_{max}$ = 3509, 2957, 1732, 1157, 1097, 1039 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.07 (ddd, J = 11.0, 3.5, 1.5 Hz, 1H, =CH), 5.87 (d, J = 4.0 Hz, 1H, =CH), 5.67–5.60 (m, 1H, =CH), 5.52 (dd, J = 11.0, 5.5 Hz, 1H, =CH), 5.39–5.33 (m, 1H, =CH), 4.85–4.77 (m, 1H), 4.79 (d, J = 7.5 Hz, 1H), 4.66 (d, J = 7.5 Hz, 1H), 4.01 (dd, J = 10.0, 4.5 Hz, 1H), 3.97 (ddd, J = 10.5, 5.0, 2.0 Hz, 1H), 3.72–3.64 (m, 2H), 3.55 (dd, J = 5.0, 5.0 Hz, 2H), 3.47–3.34 (m, 4H), 3.38 (s, 3H, CH_3), 3.18 (br m, 1H), 3.08–3.00 (m, 2H), 2.80–2.66 (m, 3H), 2.62–2.55 (m, 1H), 2.52–2.44 (m, 1H), 2.40–2.30 (m, 1H), 2.24 (ddd, J = 12.0, 4.5, 4.5 Hz, 1H), 2.22–2.15 (m, 1H), 2.00–1.92 (m, 1H), 1.83 (ddd, J = 14.5, 8.0, 4.0 Hz, 1H), 1.68–1.61 (m, 3H), 1.60–1.32 (m, 6H), 1.30 (dd, J = 7.0, 7.0 Hz, 3H, CH_3), 1.14 (s, 9H, *t*Bu), 1.10 (s, 3H, CH_3), 1.08 (d, J = 7.0 Hz, 3H, CH_3), 0.87 (dd, J = 7.0, 7.0 Hz, 3H, CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 177.6, 142.3, 132.8, 128.1, 127.1, 126.1, 121.7, 94.3, 84.1, 81.1, 80.3, 78.8, 76.8, 75.7, 71.7, 70.3, 69.9, 68.0, 67.0, 66.8, 59.0, 42.5, 38.8, 36.6, 36.0, 35.6, 33.2, 32.3, 31.9, 29.5, 27.1, 26.1, 20.0, 16.1, 15.7, 14.6, 13.0; HRMS (FAB) calcd for $C_{39}H_{64}O_{10}S$ ([M + Cs^+]) 857.3275, found 857.3299. Ketone **91**: R_f = 0.30 (silica gel, 3:7, EtOAc:hexanes); $[\alpha]_D^{25}$ = +194.2 (c = 0.82, CH_3OH); IR (thin film): $\tilde{\nu}_{max}$ = 3493, 2958, 1727, 1157, 1102, 1041 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.78–5.66 (m, 2H, =CH), 5.64–5.56 (m, 1H, =CH), 5.48–5.42 (m, 1H, =CH), 4.83–4.75 (m, 1H), 4.78 (d, J = 7.0 Hz, 1H), 4.66 (d, J = 7.0 Hz, 1H), 4.11 (dd, J = 9.5, 3.5 Hz, 1H), 4.05–3.97 (m, 2H), 3.95 (dd, J = 10.0, 10.0 Hz, 1H), 3.73–3.63 (m, 2H), 3.55 (dd, J = 4.5, 4.5 Hz, 2H), 3.45 (dd, J = 11.5, 4.5 Hz, 1H), 3.42–3.30 (m, 3H), 3.38 (s, 3H, CH_3), 3.19–3.14 (m, 1H), 3.14 (dd, J = 10.5, 10.5 Hz, 1H), 3.08–3.00 (m, 1H), 2.82 (dd, J = 11.5, 7.0 Hz, 1H), 2.57–2.45 (m, 2H), 2.44–2.28 (m, 3H), 2.27–2.21 (m, 1H), 2.17–2.11 (m, 1H), 2.00–1.93 (m, 1H), 1.87–1.78 (m, 1H), 1.72–1.63 (m, 2H), 1.59–1.49 (m, 2H), 1.43–1.34 (m, 3H), 1.18 (s, 9H, *t*Bu), 1.10 (d, J = 7.5 Hz, 3H, CH_3), 1.09 (s, 3H, CH_3), 0.87 (dd, J = 7.0, 7.0 Hz, 3H, CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 210.1, 177.6, 135.1, 128.9, 126.3, 122.4, 94.3, 84.7, 84.6, 81.4, 80.3, 79.2, 79.1, 76.9, 75.7, 71.7, 70.0, 68.2, 67.0, 66.4, 59.0, 42.5, 41.6, 38.6, 37.1, 36.4, 35.9, 33.2, 32.3, 30.2, 27.1, 19.8, 16.1, 15.7, 14.6; HRMS (FAB) calcd for $C_{37}H_{60}O_{11}$ ([M + Cs^+]) 813.3190, found 813.3169.

Molcular dynamics and minimization calculations (CV Force Field) were performed on a SGI Indigo-2 workstation using Insight II (Biosym Technologies, Inc., San Diego, CA). Pictures were created using AVS (AVS Inc., Waltham, MA) and locally developed modules running on a DEC Alpha 3000/500 with a Kubota Pacific Denali graphics card (we thank John Trujillo for his assistance in these modeling studies).

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