Total Synthesis of Brevetoxin B. 1. First Generation Strategies and New Approaches to Oxepane Systems

K. C. Nicolaou,* C.-K. Hwang, M. E. Duggan, D. A. Nugiel, Y. Abe, K. Bal Reddy, S. A. DeFrees, D. R. Reddy, R. A. Awartani, S. R. Conley, F. P. J. T. Rutjes, and E. A. Theodorakis

Contribution from the Department of Chemistry, The Scripps Research Institute, 10666 N. Torrey Pines Road, La Jolla, California 92037, and Department of Chemistry and Biochemistry, University of California, San Diego, 9500 Gilman Drive, La Jolla, California 92093

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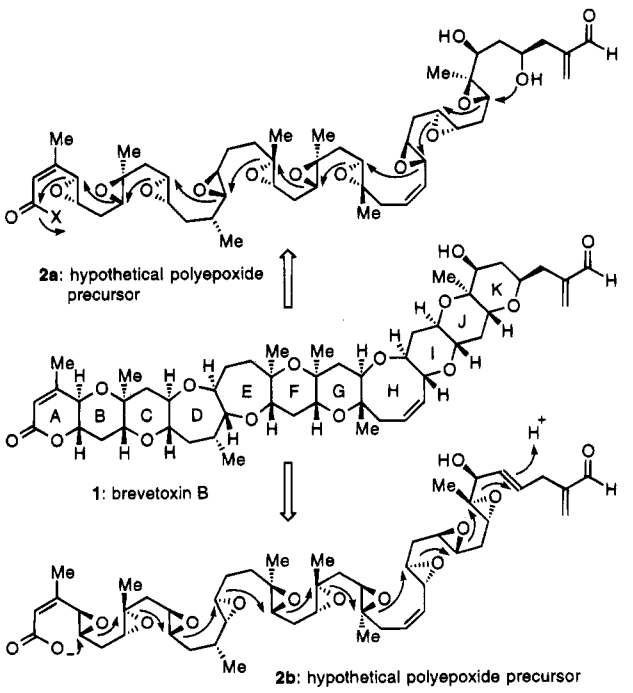
Abstract: The first generation strategies toward the total synthesis of brevetoxin B (**1**) are presented and the syntheses of the key intermediates **3**, **4**, **5**, **67**, **83**, and **94**−**98** required for the projected construction are described. The earliest and most convergent strategy required the application of the hydroxy epoxide cyclization and the intramolecular conjugate addition as key reactions for the construction of the fused tetrahydropyran ring systems (**4**) [ABC], (**7**) [FG], and (**8**) [IJK]. The oxocene ring (H) was formed via a Wittig reaction followed by a hydroxy dithioketal cyclization to produce the hexacyclic fragment [FGHIJK] (**6** → **5**). The 12-membered dithionolactone **18** was envisioned as the precursor of the dioxepane system of the molecule via a projected bridging reaction, to construct simultaneously both oxepane rings. However, the dithionation of dilactone **17** proved unsuccessful. In a subsequently evolved strategy, a new photolytic approach toward the dioxepane region was developed, starting from the acyclic dithiono progenitor **20** (**20** → **23**). Application of this reaction to the brevetoxin B skeleton afforded the desired oxepene (**96** → **97**), which after deprotection produced oxepanone **98**. A specifically designed reductive hydroxy ketone cyclization (**98** → **99**) was then employed in an attempt to close the remaining ring [E], but, again, without success. The novel rearrangement of hydroxy ketone **87** to the pentacyclic system **89** was observed in a less elaborate skeleton. The scope and generality of these silicon-induced reductive cyclizations are also described.

Introduction

"Red tides" is the name used to describe vast blooms of unicellular algae (phytoplankton) which constitute the base of the marine food chain. The name is derived from the color of certain of these blooms even though in the broader sense the term includes other colorations and colorless outbreaks. These phenomena are often associated with catastrophic consequences for marine and land life, including humans.[1] Among the earliest episodes of "red tide" phenomena is a 1793 incident in Canada, involving Captain George Vancouver and his crew who suffered poisoning upon seafood consumption in the coastal area of British Columbia.[2] Next to be recorded were two incidents in 1972, the first along the coast of New England following a severe hurricane originating in the Gulf of Mexico and allegedly carrying the poisonous algae with it, and the second in the Seto Inland Sea, off the coast of Japan, where more than half a billion dollars worth of caged yellow-tail fish perished. In the period 1987−1988, several incidents occurred, in which mussels, fish, dolphins, whales, and humans were fatally affected in the US and Canada.[2] In 1991 a "red tide" occurrence was responsible for hundreds of sick and dying pelicans found on the beaches near Monterey, CA.[2] Responsible for the catastrophic effects of the "red tide" phenomena are a class of biotoxins, among which the brevetoxins constitute a prominent subclass.

Brevetoxin B (**1**, Scheme 1), the first and most prominent member of the brevetoxin family, produced by the dinoflaggelate

Scheme 1. Structure of Brevetoxin B (**1**) and of Hypothetical Polyepoxide Precursors **2a** and **2b**



Ptychodiscus brevis Davis (*Gymnodinium breve* Davis) was isolated and characterized by spectroscopic and X-ray crystallographic means in 1981 by the groups of Lin, Nakanishi, and Clardy.[3] Its highly complex molecular architecture is characterized by a novel array of ether oxygen atoms, regularly placed on a single carbon chain. This remarkable structure includes

* Address correspondence to this author at either The Scripps Research Institute or The University of California, San Diego.

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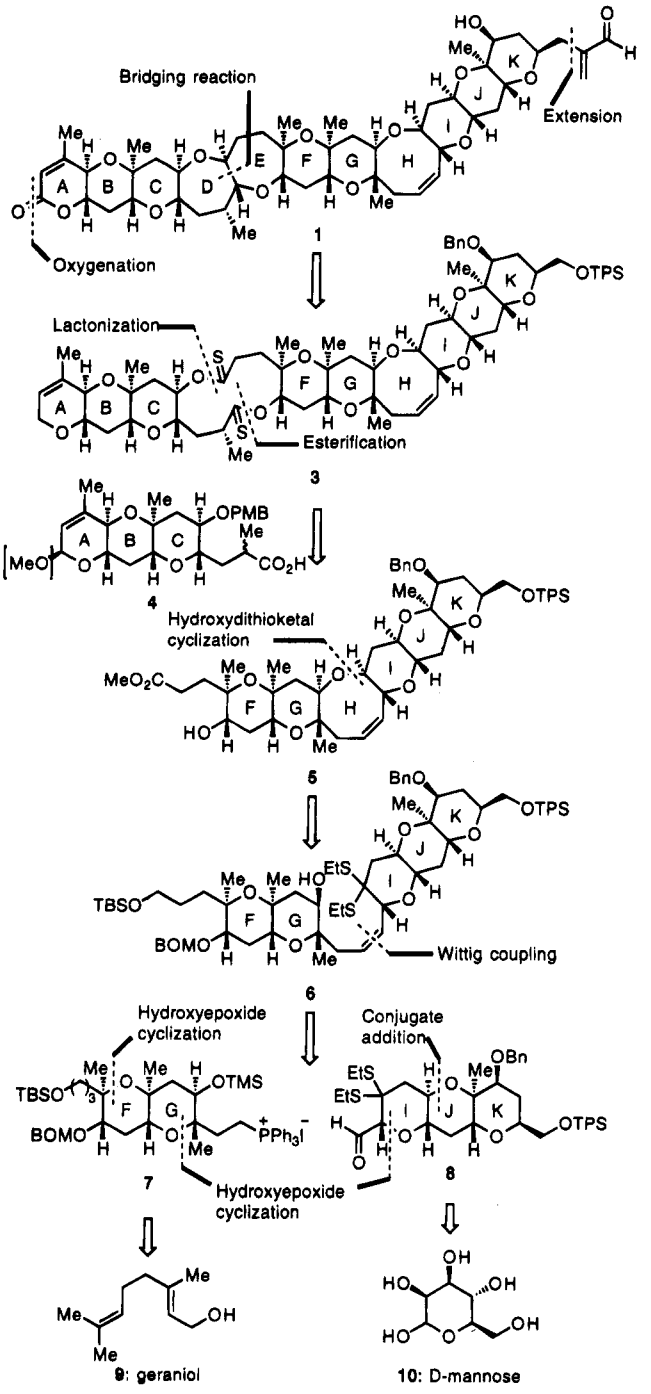
11 rings, 23 stereogenic centers, and 3 carbon–carbon double bonds. Furthermore, brevetoxin B (**1**) exhibits intriguing regularity with regard to its ring fusions which are all *trans*, its rings, each of which contains a single oxygen, and its ring oxygens, all pairs of which are separated by a C–C bond. All substituents flanking the ring oxygens are *syn* to each other except those on ring K which are *anti*. Although the structure of brevetoxin B (**1**) was unprecedented at the time of its discovery, its unique patterns were subsequently found in several marine natural products including brevetoxin A,[4] ciguatoxin,[5] gambieric acids,[6] yessotoxin,[7] and maitotoxin.[8]

Brevetoxin B (**1**) exhibits potent neurotoxicity, exerting its biological action by binding to sodium channels, keeping them open and causing continuous and damaging sodium ion influx.[9] Its unique and fascinating molecular architecture, its association with the "red tide" catastrophes, and its novel mechanism of action as a biotoxin prompted intense investigations in both chemistry[10] and biology.[11] In this series of papers[12,13] we describe the total synthesis of brevetoxin B (**1**), placing special emphasis on the development of new synthetic technologies and the evolution of the strategies that eventually led to success.

Retrosynthetic Analysis and Strategy

A brief inspection of the brevetoxin B (**1**) structure leads to the intriguing and tempting idea of polyepoxides **2a** and **2b** (Scheme 1) serving as potential precursors via "zip" type reactions as indicated.[14] The question of whether Nature uses any of these pathways for the biosynthesis of brevetoxin B (**1**) has not been experimentally proven, as yet.[15] Furthermore, the possibility of such ambitious operations in the laboratory by chemical means, given our present limitations, was quickly discarded as remote at best. A more realistic and highly convergent approach was, therefore, sought. The first retrosynthetic analysis of brevetoxin B (**1**) (Scheme 2) was based on three important reactions, each of which was developed for the

Scheme 2. Retrosynthetic Analysis and Strategic Bond Disconnections of Brevetoxin B (**1**): First Generation Approach



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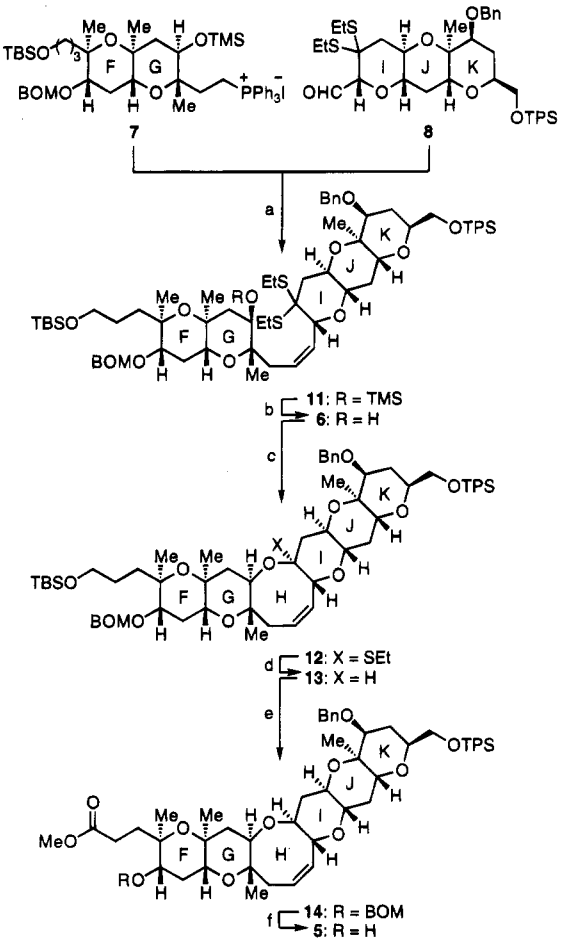
specific purpose of addressing the total synthesis of brevetoxin B (**1**). These new reactions were the following: (a) the regioselective and stereospecific opening of hydroxy epoxides for the construction of tetrahydropyran systems;[16] (b) the facile cyclization of hydroxy dithioketals to form oxocene systems;[17] and (c) the bridging of macrocycles to bicycles.[18] Thus, removing the two ends of the molecule from the polycyclic skeleton and rupturing retrosynthetically the central dioxepane C−C bond leads to the 12-membered ring dithionolactone **3** as a potential progenitor of brevetoxin B (**1**). Disassembly of the latter intermediate (**3**) as indicated in Scheme 2 unravels the ABC ring system **4**, or its demethoxy derivative, and the FGHIJK ring system **5** as precursors, reducing the level of complexity of the target molecule (**1**) considerably. Applying the powerful *retro* hydroxy dithioketal cyclization reaction followed by a *retro* Wittig coupling leads rapidly to key intermediates FG (**7**) and IJK (**8**) via hydroxy dithioketal **6**. Finally, the two tetrahydropyran-containing fragments **7** and **8** can be traced back to the readily available starting materials, geraniol (**9**)[19] and D-mannose (**10**),[20] respectively via hydroxy epoxide cyclizations and hydroxy α,β-unsaturated ester conjugate additions, as indicated (Scheme 2).

Encouraged by the results of relevant model studies and with confidence in the convergent strategy derived from the analysis of Scheme 2, we proceeded to test the designed, first generation route toward brevetoxin B (**1**) as described below.

Synthesis of the FGHIJK Ring System

The convergent synthesis of the FGHIJK ring system **5** is summarized in Scheme 3. The constructions of the requisite FG[19] and IJK[20] frameworks **7** and **8** have been described previously. Wittig coupling of phosphonium salt **7** with aldehyde **8** proceeded smoothly under conditions favoring (*Z*)-double bond formation (*n*-BuLi, HMPA, THF, −78 °C) to afford olefin **11** in 70% yield. The (*Z*)-geometry of the generated double bond was confirmed by ^{1}H NMR decoupling experiments revealing a coupling constant of $J = 11.5$ Hz. Removal of the TMS group from **11** followed by $AgClO_4$/NCS-induced ring closure resulted in the formation of oxocene **12** (78%, yield unoptimized), from which the ethylthio group was reductively removed using Ph_3SnH−AIBN furnishing compound **13** (92%) as a single stereoisomer. The desired *trans* stereochemistry at the newly generated ring junction was proven by ^{1}H NMR decoupling experiments ($J = 8.1$ Hz, compare $J = 7.9$ Hz for brevetoxin B). Jones oxidation of **13** led directly to the corresponding carboxylic acid and then to methyl ester **14** (CH_2N_2, 80% overall yield). Finally, selective removal of the benzyloxymethyl (BOM) group from **14** was achieved by exposure to excess EtSH in the presense of $BF_3{\cdot}Et_2O$ affording the targeted hydroxy methyl ester **5** in 84% yield.

Scheme 3[a] Synthesis of FGHIJK Ring System **5**



[a] Reagents and conditions: (a) 0.9 equiv of *n*-BuLi, 3.0 equiv of HMPA, THF, −78 °C, then add **8**, 30 min, 70%; (b) 0.1 equiv of PPTS, MeOH, 25 °C, 90%; (c) 3.0 equiv of $AgClO_4$, 4.0 equiv of K_2CO_3, 3 Å MS silica, 2.0 equiv of NCS, MeCN, 25 °C, 3 h, 78%; (d) 1.8 equiv of Ph_3SnH, 0.1 equiv of AIBN, toluene, 110 °C, 3 h, 92%; (e) Jones' reagent, then CH_2N_2, Et_2O, 0 °C, 80%; (f) 1.0 equiv of $BF_3{\cdot}Et_2O$, CH_2Cl_2/EtSH (8:1), -40 °C, 30 min, 84%.

Construction of Macrocycles and Attempted Bridging Reactions Toward the Brevetoxin B Skeleton

As planned, attempts were then made to reach the complete skeleton of brevetoxin B (**1**) via a bridging reaction, whereby a 12-membered ring dithionolactone was to serve as a precursor to the dioxepane system of the molecule. To this end, the ABC ring system **4** (Scheme 4)[21] was coupled with the FGHIJK segment **5** under the influence of DCC, CSA, and DMAP in 85% yield. Selective cleavage of the methyl ester from **15** was achieved by reaction with lithium ethylthiolate in HMPA to give the corresponding carboxylic acid. The *p*-methoxybenzyl (PMB) group was then removed from the latter compound by exposure to DDQ leading to hydroxy acid **16** in 78% overall yield. Finally, macrolactonization of **16** using the 2-pyridinethiol ester method[22] furnished dilactone **17** in 70% yield.

Unfortunately, the dithionation of dilactone **17** proved unsuccessful. With a large excess of Lawesson's reagent, and at high temperatures, only a monothionolactone could be obtained (at less sterically demanding position). Our inability to introduce a second sulfur, adjacent to the methyl substituent (C-13), was attributed to steric hindrance provided by the latter group. A

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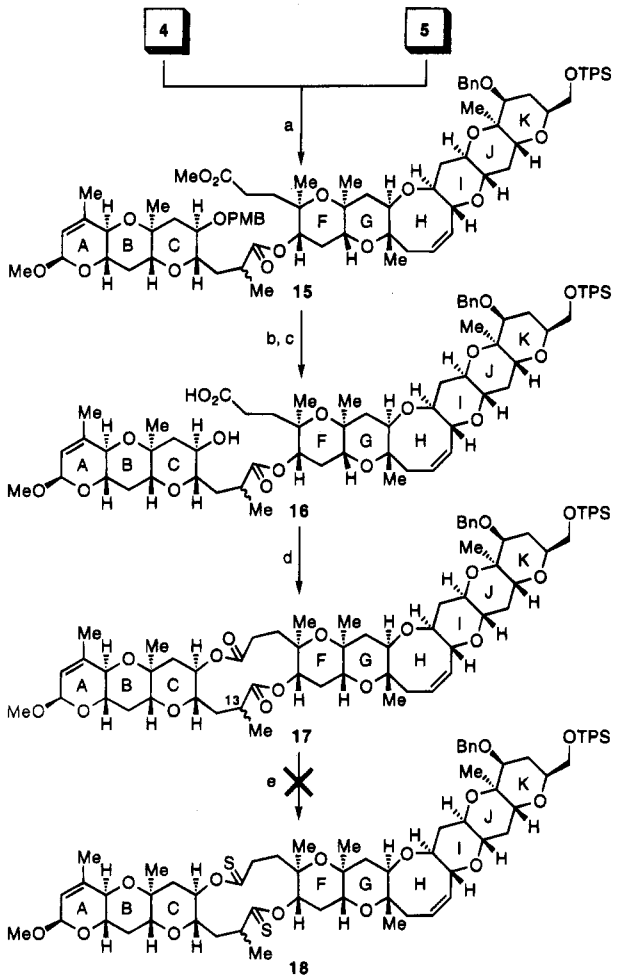
Scheme 4[a] Coupling of ABC and FGHIJK Ring Systems **4** and **5** and Failed Bridging Attempts



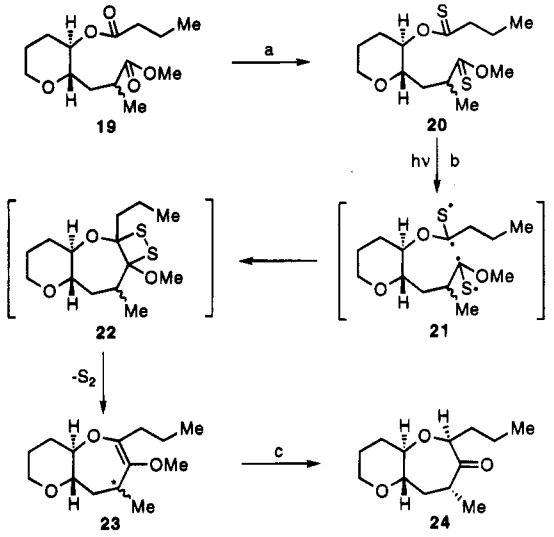
[a] Reagents and conditions: (a) 1.1 equiv of **4**, 1.0 equiv of **5**, 1.2 equiv of DCC, 0.4 equiv of CSA, 0.4 equiv of DMAP, CH_2Cl_2, 10 h, 85%; (b) EtSH, LiH, HMPA, 25 °C, 8 h; (c) 2.0 equiv of DDQ, CH_2Cl_2/H_2O (5:1), 25 °C, 3 h, 78% (2 steps); (d) 1.5 equiv of pyr-SS-pyr, 1.5 equiv of Ph_3P, toluene, 25 °C, then toluene (0.05 M), reflux, 12 h, 70%; (e) 10 equiv of Lawesson's reagent, 6.0 equiv of 1,1,3,3-tetramethylthiourea, xylene, 160 °C, 2 h.

variety of other, new[23] and old,[24] Lawesson type reagents failed to improve the situation, and the thionation of **17** (and a number of related systems) remained an obstacle to further progress along this route. We, therefore, decided to abandon the simultaneous construction of both oxepane rings via macrocycle bridging and to seek a stepwise approach to the dioxepane region of brevetoxin B (**1**).

A Photolytic Approach to Oxepane Systems

Scheme 5 demonstrates, with an example, the adopted concept for a new method of forming oxepane systems from acyclic precursors. According to this plan a diester, such as **19**, is converted to its dithiono counterpart (**20**) under the standard Lawesson conditions,[23,24] and the latter compound is irradiated, presumably generating the radical species **21**, and thence the 1,2-dithietane system **22**.[25] Under the irradiation conditions, the latter compound loses sulfur to afford oxepene **23**, which is

Scheme 5[a] A Photolytic Approach to Oxepane Systems



[a] Reagents and conditions: (a) 3.0 equiv of Lawesson's reagent, 3.0 equiv of 1,1,3,3-tetramethylthiourea, xylene, 160 °C, 2 h, 47%; (b) *hv*, Hanovia 450 W UV lamp, Pyrex filter, toluene, 70 °C, 2 h, 63%; (c) 2.0 M HCl, 25 °C, 2 h, 80%.

then regioselectively hydrolyzed to oxepanone **24**.[26] Despite the mixture of isomers at C* in oxepene **23**, the final product **24** is obtained, via equilibration under the employed conditions, as a single stereoisomer with the two stereocenters flanking the carbonyl group firmly established on *pseudo*-equatorial positions.

The scope and generality of this method is demonstrated in Table 1 which shows several examples of dithionoesters serving as precursors to a series of oxepenes and oxepanones. Thionations were carried out using excess Lawessons's reagent in the presence of 1,1,3,3-tetramethylthiourea at 150–160 °C (50–55% yield). The final hydrolytic step was effected either under acid conditions (HCl–H_2O) or in the presence of fluoride (TBAF–THF) (75–95% yield).

A Reductive Hydroxy Ketone Cyclization Approach to Oxepanes

Based on precedent from Olah's work on the intermolecular construction of C–O bonds using carbonyl and hydroxyl components,[27] we proceeded to design a new method for the synthesis of oxepanes from hydroxy ketones as outlined in Scheme 6.[28] According to this idea, silicon activation of the carbonyl oxygen followed by expulsion of the silicon–oxygen group by intramolecular attack should lead to oxonium species **41** via the silylated lactol **40** (Scheme 6). Subsequent capture of the oxonium species **41** by a hydride ion from a suitable silane donor, was then expected to form the oxepane system **42** with considerable stereocontrol, depending on the precise structure of the substrate.

Exposure of hydroxy ketone **39** to 1.0 equiv of TMSOTf and an excess of Et_3SiH in CH_2Cl_2 at 0 °C furnished oxepane **42** in

(23) For several new thionating agents, see: Nicolaou, K. C.; McGarry, D. G.; Somers, P. K.; Kim, B. H.; Ogilvie, W. W.; Yiannikouros, G.; Prasad, C. V. C.; Veale, C. A.; Hark, R. R. *J. Am. Chem. Soc.* **1990**, *112*, 6263.

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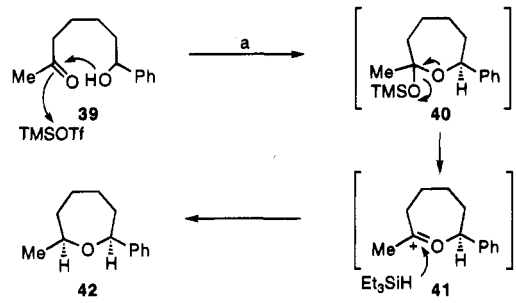
Table 1. Cyclization of Dithionoesters

entry	dithionoester[a]	yield (%)	oxepene[b]	yield (%)	hydroxyketone[c]	yield (%)
1	**25**: R = Me, R_1 = H	50	**26**: R = Me, R_1 = H	63	**27**: R = H (*trans:cis* 1:1)	80
2	**28**: R = CH_2CH_2TMS, R_1 = Me	50	**29**: R = CH_2CH_2TMS, R_1 = Me	66	**24**: R = Me	95
3	**30**	55	**31**	62	**32**	94
4	**33**: R = Me, R_1 = $CH_2CH_2CH_3$, R_2 = Me		**34**: R = Me, R_1 = $CH_2CH_2CH_3$, R_2 = Me	75	**35**: R = $CH_2CH_2CH_3$, R_1 = Me	75
5	**36**: R = CH_2CH_2TMS, R_1 = $(CH_2)_4OBn$, R_2 = H		**37**: R = CH_2CH_2TMS, R_1 = $(CH_2)_4OBn$, R_2 = H	72	**38**: R = $(CH_2)_4OBn$, R_1 = H	95

[a] 3.0 equiv of Lawesson's reagent, 3.0 equiv of 1,1,3,3-tetramethylthiourea, xylene, 160 °C, 2 h. [b] *hν*, Hanovia 450 W UV lamp, Pyrex filter, toluene, 70 °C, 2 h. [c] For methyl enol ethers: 2.0 M HCl, 25 °C, 2 h. For 2-(trimethylsilyl)ethyl enol ethers: 3.0 equiv of TBAF, THF, 45 °C, 8 h.

Scheme 6[a] Mechanistic Rationale for the Silicon-Induced Cyclization of Hydroxy Ketones to Oxepanes



[a] Reagents and conditions: (a) 10 equiv of Et_3SiH, 1.0 equiv of TMSOTf, CH_2Cl_2, 0 °C, 15 min, 85%.

85% yield. The *syn* relationship of the protons flanking the oxepane oxygen was confirmed by NOE ^1H NMR studies. As Table 2 demonstrates, this reaction proved quite general and efficient, accommodating substrates of considerable complexity and resemblance to the brevetoxin B (**1**) dioxepane region. The stereoselectivity of the cyclizations varied from *ca.* 3:1 to *ca.* 4:1 at the newly generated fusion, but was always in favor of the stereoisomer with the *trans* arrangement as indicated in the structures of Table 2. Whereas the stereochemistries of the newly generated ring fusions of compounds **51** and **53** were tentatively assigned by comparing ^1H NMR spectra and R_f values with the two isomers of **47**, the *trans* arrangement of the major isomer of the latter compound was firmly established by an X-ray crystallographic analysis (see ORTEP drawing, Figure 1).

Thus, the second required method for oxepane construction was developed, and the stepwise construction of the dioxepane region of brevetoxin B (**1**) could now be contemplated.

Construction of Precursors and Attempted Hydroxy Ketone Cyclization Toward Brevetoxin B. Encouraged by the performance of the two oxepane-forming reactions described above, we proceeded to apply them to the brevetoxin B (**1**) problem. First, the BC ring system **67** (Scheme 7) was defined as the requisite intermediate onto which the remaining rings were to be built starting from ring B and proceeding to the "right". Scheme 7 summarizes the construction of this intermediate starting with the previously described ring B system **54**.[29] Thus, replacement of the benzylidene group in **54** with benzyl ethers by acid hydrolysis (CSA, MeOH) followed by benzylation under standard KH–BnBr conditions furnished compound **56** via diol **55** (83% overall yield). Hydroboration

Table 2. Reductive Cyclization of Hydroxy Ketones

entry	hydroxyketone	oxepane[a]	yield (%)
1	**43**: X = H, OH; Y = O	**42**	83
2	**44**: X = Y = O		83
3	**45**	**46**	50 (*trans:cis* 1:1)
4	**32**: R = H	**47**: R = H	81 (*trans:cis* 4:1)
5	**48**: R = Me	**49**: R = Me	90 (*trans:cis* 3:1)
6	**50**: R = $(CH_2)_4OH$	**51**	75 (*trans:cis* 3:1)
7	**52**	**53**[b]	55 (*trans:cis* 3:1)

[a] 10 equiv of Et_3SiH, 1.0 equiv of TMSOTf, CH_2Cl_2, 0 °C, 15 min. [b] Ph_2MeSiH was used as the hydride donor.

(29) Nicolaou, K. C.; Nugiel, D. A.; Couladouros, E.; Hwang, C.-K. *Tetrahedron* **1990**, *46*, 4517.

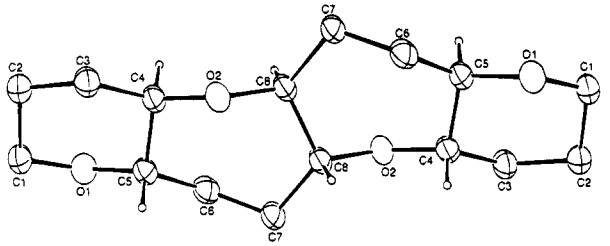
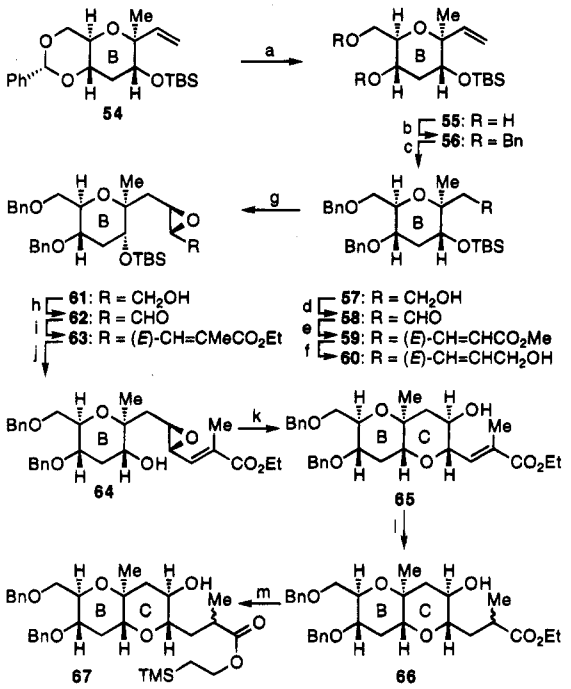


Figure 1. ORTEP drawing of **47**.

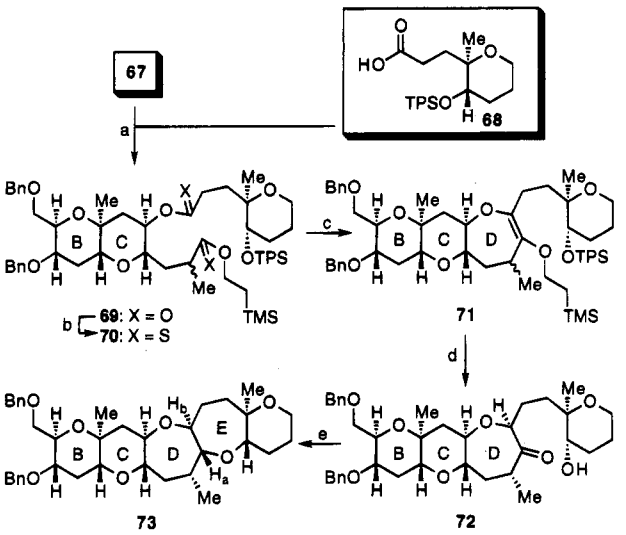
Scheme 7[a] Construction of the BC Ring System **67**



[a] Reagents and conditions: (a) 0.2 equiv of CSA, MeOH, 0 °C, 1 h, 92%; (b) 2.5 equiv of KH, 2.7 equiv of BnBr, 45 °C, THF, 1 h, 90%; (c) 1.5 equiv of 9-BBN, THF, 25 °C, 1.5 h, then 10 equiv of 3 N NaOH, 20 equiv of 30% H_2O_2, 0 °C, 1 h, 94%; (d) 1.5 equiv of $(COCl)_2$, 2.0 equiv of DMSO, 5.0 equiv of Et_3N, CH_2Cl_2, −78 °C, 1 h, 96%; (e) 1.2 equiv of $Ph_3P{=}CHCO_2Me$, benzene, 50 °C, 1 h, 90%; (f) 2.2 equiv of DIBALH, CH_2Cl_2, −78 °C, 30 min, 96%; (g) 0.25 equiv of (−)-diethyl tartrate, 0.2 equiv of Ti(O-*i*-Pr)$_4$, 1.5 equiv of *t*-BuOOH, CH_2Cl_2, −25 °C, 14 h, 92%; (h) 3.0 equiv of SO_3·pyridine, 5.0 equiv of Et_3N, CH_2Cl_2:DMSO (4:1), 0 °C, 4 h, 94%; (i) 1.1 equiv of $Ph_3P{=}CMeCO_2Et$, 0.1 equiv of $PhCO_2H$, benzene, 25 °C, 30 min, 90%; (j) 1.5 equiv of TBAF, THF, 25 °C, 30 min, 96%; (k) 0.8 equiv of PPTS, CH_2Cl_2, 25 °C, 13 h, 97%; (l) H_2, 10% Pd/C, EtOAc, 25 °C, 48 h, 100%; (m) 5.0 equiv of $TMSCH_2CH_2OH$, 0.15 equiv of KH, THF, 25 °C, 15 min, 91%.

of the terminal olefin in **56** with 9-BBN followed by basic hydrogen peroxide workup gave primary alcohol **57** (94% yield) which was then oxidized under Swern conditions to the aldehyde **58** (96%). Condensation of the latter compound with the appropriate phosphorane afforded the α,β-unsaturated ester **59** (90%) whose DIBALH reduction led to allylic alcohol **60** (96% yield). Sharpless AE of **60** using (−)-diethyl tartrate as the chiral auxiliary gave epoxide **61** (92% yield), oxidation of which with SO_3·pyr led to aldehyde **62** in 94% yield. Olefination of **62** with $Ph_3P{=}CMeCO_2Et$ under the influence of $PhCO_2H$ as catalyst gave compound **63**, which upon exposure to fluoride ion suffered desilylation furnishing hydroxy epoxide **64** in 86% overall yield. Exposure of **64** to mild acid conditions (PPTS, CH_2Cl_2) induced regio- and stereospecific ring closure affording bicyclic ether **65** in 97% yield. Hydrogenation of the latter compound followed by *trans*-esterification with $TMSCH_2CH_2$-

Scheme 8[a] Construction of the Advanced Dioxepane Model **73**



[a] Reagents and conditions: (a) 1.5 equiv of DCC, 0.3 equiv of CSA, 0.3 equiv of DMAP, 1.0 equiv of **68**, CH_2Cl_2, 10 h, 85%; (b) 3.0 equiv of Lawesson's reagent, 3.0 equiv of 1,1,3,3-tetramethylthiourea, xylene, 180 °C, 2 h, 58%; (h) hν, Hanovia UV lamp, 450 W, Pyrex filter, toluene, 70 °C, 20 h, 72%; (d) 1.2 equiv of TBAF, THF, 45 °C, 8 h, 88%; (e) 10 equiv of Ph_2MeSiH, 1.0 equiv of TMSOTf, CH_2Cl_2, 0 °C, 20 min, 62% (6:1 mixture of *trans*:*cis* isomers).

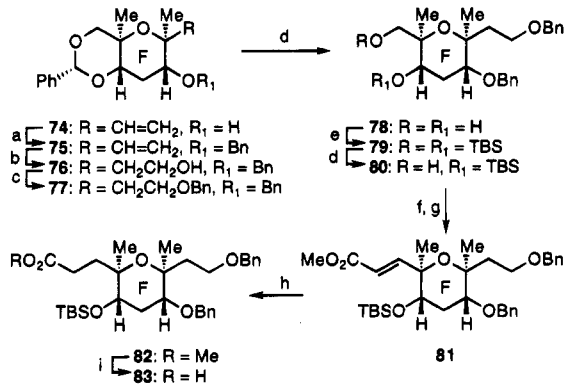
OH and KH gave hydroxy ester **67** in 91% yield as a 1:1 mixture of diastereoisomers.

Coupling of **67** with carboxylic acid **68**[30] (Scheme 8) via esterification (DCC, DMAP, CSA, 85% yield), followed by thionation using Lawesson's reagent as described above for the model diesters, gave rise to dithionoester **70** via **69** (58% yield). Photolysis of **70** in toluene at 70 °C for 20 h led to oxepene system **71** in 72% yield. Exposure of **71** to TBAF at 45 °C in THF furnished oxepanone **72** as a single stereoisomer and in 88% yield. Finally, reductive cyclization of **72** using TMSOTf and Ph_2MeSiH resulted in the desired pentacyclic system **73** containing the BCDE framework of brevetoxin B (**1**) (62% yield, *ca.* 6:1 ratio of *trans*:*cis* isomers). The *trans* stereochemistry of the newly generated DE ring fusion in the major product **73** was assigned on the basis of the coupling constant $J_{a,b} = 7.7$ Hz, which is almost identical to the corresponding value for brevetoxin B (**1**) (7.73 Hz). Encouraged by the success of these advanced model studies, we proceeded to implement the latest strategy with two real systems for brevetoxin B (**1**).

Ring F, as intermediate **83**, was synthesized in a straightforward manner from the previously reported compound **74**[29] as detailed in Scheme 9. Carboxylic acid **83** was then coupled with alcohol **67** via ester bond formation as shown in Scheme 10 to afford diester **84** in 88% yield. The latter compound was elaborated to hydroxy ketone **87** via intermediates **85** and **86** according to the general methods described above [thionation (56%), photolytic ring closure (64%), and hydrolysis (91%)]. Treatment of hydroxy ketone **87** with TMSOTf and excess Ph_2MeSiH under the standard cyclization conditions led to a single compound in 46% yield. The latter compound, originally thought to be the desired product **88**, was taken through a series of reactions toward what was projected to be a more advanced intermediate (**90a**) for brevetoxin B (**1**) as shown in Scheme 11. Finally, however, an X-ray crystallographic analysis of the crystalline *p*-nitrobenzoate derivative **91** (see ORTEP drawing, Figure 2) revealed a rearranged structure which was traced back

(30) Compound **68** was synthesized from 1,4-butanediol in 12 steps, see: Duggan, M. E. Ph.D. Dissertation, University of Pennsylvania, 1987.

Scheme 9[a] Construction of F Ring Intermediate **83**



[a] Reagents and conditions: (a) 1.2 equiv of KH, 1.3 equiv of BnBr, THF, 45 °C, 1 h, 90%; (b) 1.5 equiv of 9-BBN, THF, 25 °C, 1 h, then 7.5 equiv of 3 N NaOH, 10 equiv of 30% H_2O_2, 0 °C, 1 h, 93%; (c) 1.2 equiv of KH, 1.3 equiv of BnBr, THF, 45 °C, 1 h, 88%; (d) 0.2 equiv of CSA, MeOH, 0 °C, 1 h, 89%; (e) 2.5 equiv of TBSCl, 3.0 equiv of imidazole, DMF, 45 °C, 14 h, 95%; (f) 1.5 equiv of $(COCl)_2$, 2.0 equiv of DMSO, 5.0 equiv of Et_3N, CH_2Cl_2, −78 °C, 1 h; (g) 1.1 equiv of $Ph_3P{=}CHCO_2Me$, benzene, 50 °C, 12 h, 81% (2 steps); (h) H_2, 10% Pd/C, EtOAc, 6 h, 25 °C, 100%; (i) 1.6 equiv of LiOH, THF:MeOH:H_2O (1:1:1), 55 °C, 3 h, 94%.

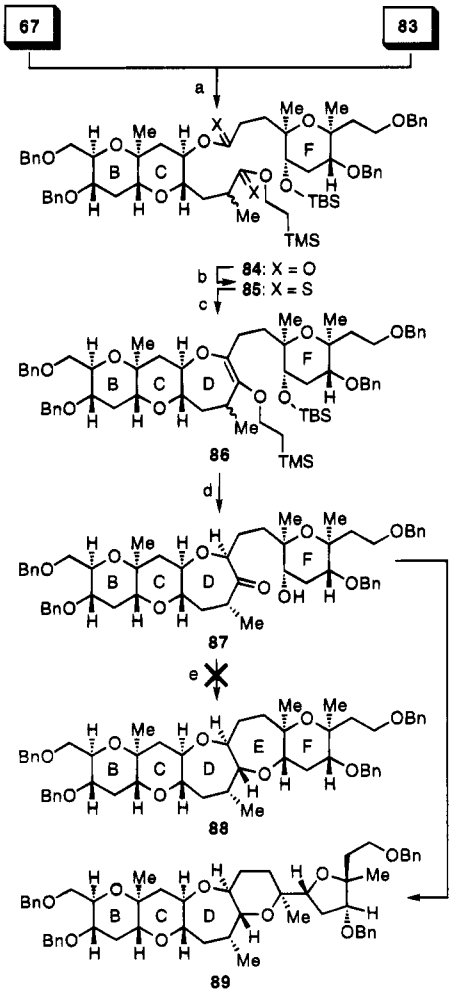
to the cyclization reaction of compound **87** (Scheme 10). Thus, it became clear that the reductive ring closure of the latter compound (**87**) was accompanied by a drastic skeletal rearrangement giving compound **89**, rather than the expected **88** (Scheme 10). Two alternative and speculative mechanisms for this novel skeletal rearrangement are presented in Scheme 12. A common underlying driving force to both mechanisms is the severe 1,3-diaxial interaction of the two methyl groups on ring F, which is thought to be facilitating the rupture of the latter ring. The two pathways differ in which C−O bond breaks, and which methyl group contributes to stabilization of the incipient positive charge on one of the reactive species of each sequence (structures **92** and **92a**, Scheme 12).

Since FGHIJK intermediate **5** (Scheme 4) was available from the previous studies of the bridging approach, a final attempt to secure the BCDEFGHIJK framework of brevetoxin B (**1**) was made according to Scheme 13. Thus, coupling of alcohol **67** with the carboxylic acid **94**, derived from **5** in the presence of DCC, DMAP, and CSA, furnished ester **95** in 85% yield. Thionation of the ester **95** using Lawesson's reagent and 1,1,3,3-tetramethylurea as described above afforded the desired dithionoester **96** (20% yield). Photolytically-induced ring closure of **96** furnished oxepene **97** (63%) which underwent selective hydrolysis to the hydroxy ketone **98**, obtained as a single isomer, upon exposure to TBAF in THF (70%). Attempts to cyclize hydroxy ketone **98**, however, were unsuccessful, and under no circumstances could the expected product **99** be detected. It was of interest to observe that the main product in this, rather sluggish, reaction was the reduced, open-chain diol, corresponding to **98**, and that no rearranged product corresponding to compound **89** (Scheme 10) was detected.

Conclusion

A number of convergent strategies toward brevetoxin B (**1**) were considered and pursued in this initial phase of the brevetoxin B project. The originally favored approach enjoying optimum convergency involved generation, coupling, and elaboration of three key intermediates containing the ABC, FG, and IJK frameworks, respectively (e.g., **4**, **7**, and **8**, Scheme 2). The construction of all three tetrahydropyran-containing key segments proceeded well, and so did the Wittig coupling of the

Scheme 10[a] Coupling of BC and F Ring Systems **67** and **83** and Failed Hydroxy Ketone Cyclization Attempts

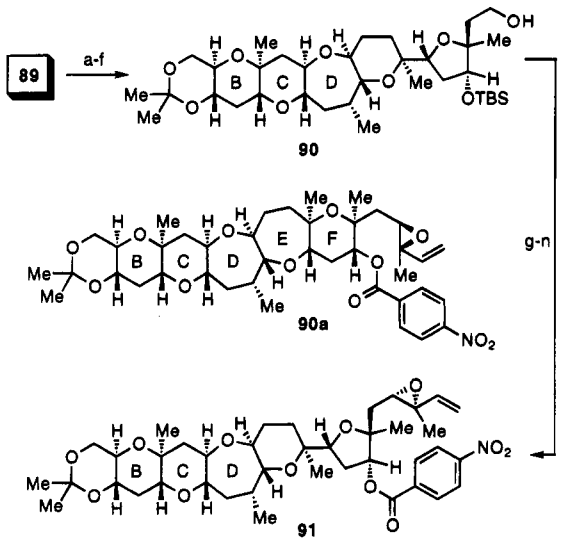


[a] Reagents and Conditions: (a) 1.5 equiv of DCC, 0.3 equiv of CSA, 0.3 equiv of DMAP, CH_2Cl_2, 10 h, 88%; (b) 3.0 equiv of Lawesson's reagent, 3.0 equiv of 1,1,3,3-tetramethylthiourea, xylene, 160 °C, 2 h, 56%; (c) *hν*, 450 W Hanovia lamp, Pyrex filter, benzene 25 °C, 2 h, 64%; (d) 3.0 equiv of TBAF, THF, 50 °C, 10 h, 91%; (e) 3.5 equiv of Ph_2MeSiH, 1.5 equiv of TMSOTf, CH_2Cl_2, 0 °C, 40 min, 46%.

FG and IJK segments (**7** and **8**) and the cyclization to install the oxocene ring system, leading smoothly to the FGHIJK ring framework (**5**, Scheme 3). Coupling of the latter system with the ABC ring framework (**4**) via esterification followed by macrolactonization led to potential precursors to the complete framework of brevetoxin B (**1**). All attempts, however, to thionate and subsequently bridge the 12-membered macrocycle, in order to form the last remaining bond required for completion of the brevetoxin B skeleton, were unsuccessful, forcing consideration of a revised strategy in which a stepwise approach to the dioxepane region of the molecule was adopted. To this end, two new methods for the construction of oxepane ring systems were invented and explored (Schemes 5 and 6). While both methods proved quite general and successful in model systems, only the first one, involving photolytically-induced ring closure of dithionoesters, proved applicable to the brevetoxin B (**1**) problem. The second approach, utilizing reductive cyclization of hydroxy ketones, led to novel skeletal rearrangements or unproductive reduction of the carbonyl function when applied to real systems (Schemes 10 and 13).

Despite the failure of these first generation approaches to brevetoxin B (**1**) a great deal of new chemistry was developed, including new reactions for the construction of cyclic ethers with 6-, 7-, and 8-membered rings. Furthermore, the informa-

Scheme 11[a] Elaboration of Rearrangement Product **89**



[a] Reagents and conditions: (a) H_2, $Pd(OH)_2$, AcOEt:MeOH (2:1), 25 °C, 14 h, 95%; (b) 3.0 equiv of $Me_2C(OMe)_2$, 0.1 equiv of PPTS, acetone, 25 °C, 14 h, 91%; (c) AcOH:H_2O (2:1), 80 °C, 2.5 h, 88%; (d) 1.2 equiv of PivCl, pyridine, 0 °C, 30 min, 96%; (e) 1.3 equiv of TBSCl, 1.5 equiv of imidazole, DMF, 55 °C, 4 h, 94%; (f) 2.2 equiv of DIBALH, −78 °C, 30 min, 97%; (g) 1.5 equiv of $(COCl)_2$, 2.0 equiv of DMSO, 5.0 equiv of Et_3N, CH_2Cl_2, −78 °C, 1 h, 96%; (h) 1.2 equiv of $Ph_3P{=}CMeCO_2Et$, benzene, 50 °C, 1 h, 87%; (i) 2.2 equiv of DIBALH, −78 °C, 30 min, 97%; (j) 1.2 equiv of *m*-CPBA, CH_2Cl_2, 0 °C, 30 min, 94%; (k) 4.0 equiv of SO_3·pyr, 5.0 equiv of Et_3N, CH_2Cl_2: DMSO (4:1), 0 °C, 3.5 h, 92%; (l) 1.5 equiv of $Ph_3P^+MeBr^-$, 1.3 equiv of NaHMDS, THF, 0 °C, 1 h, 89%; (m) 1.5 equiv of TBAF, THF, 25 °C, 30 min, 96%; (n) 1.1 equiv of *p*-nitrobenzoyl chloride, 2.0 equiv of DMAP, 25 °C, 20 min, 86%.

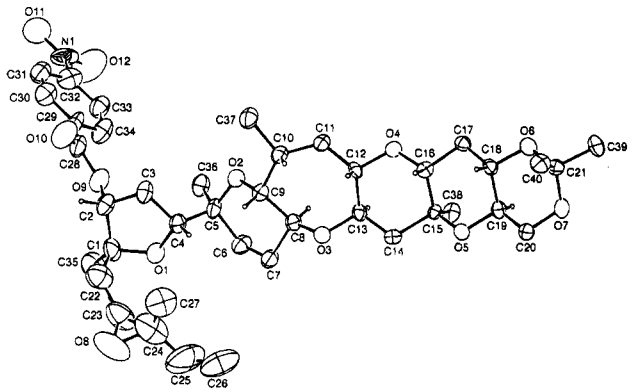


Figure 2. ORTEP drawing of **91**.

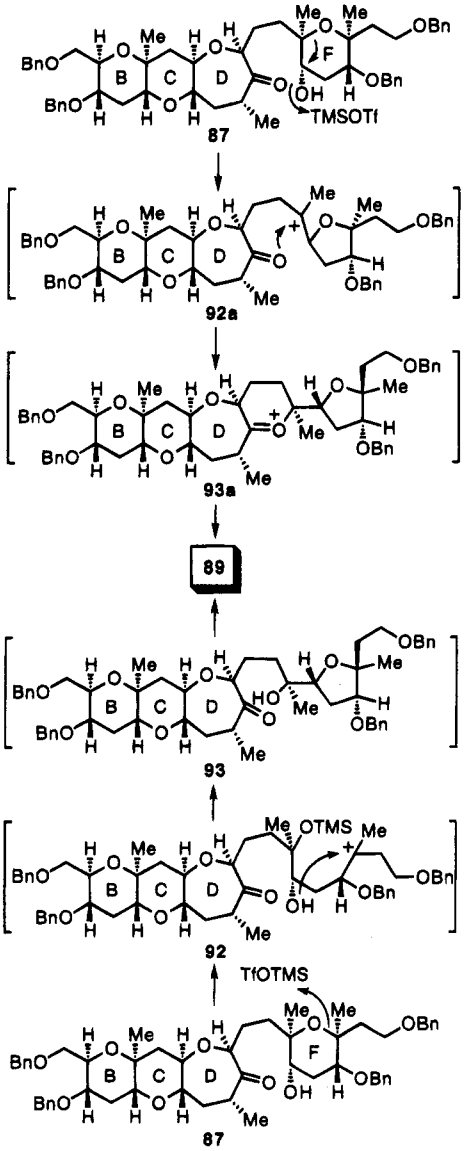
tion gathered was of crucial importance to designing the next generation strategies which are the subject of the following articles.[12,13,31]

Experimental Section

General Techniques. All reactions were carried out under an argon atmosphere in dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium/benzophenone, dichloromethane (CH_2Cl_2) and toluene from calcium hydride, and benzene from potassium. Yields refer to chromatographically and spectroscopically (^1H 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 (60F-254) using UV light as visualizing agent and 7% ethanolic 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 chromatography. Preparative thin-layer chromatography separations were carried out on 0.25 or 0.50 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Brucker AM-500 or WM-250 instruments and calibrated using residual undeuterated solvent as an internal reference. The following abreviations were used to explain the multiplicities: s = singlet; d = doublet, t = triplet, q = quartet, m = multiplet, b = broad. IR spectra were recorded on a Perkin-Elmer Model 781 spectrometer. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter. High resolution mass spectra (HRMS) were recorded on a VG 7070 HS mass spectrometer under chemical ionization (CI) conditions or on a VG ZAB-ZSE mass spectrometer under fast atom bombardment (FAB) conditions. Microanalyses were performed by Robertson Laboratories, Madison, NJ. Melting points (mp) are uncorrected and were recorded on a Thomas Hoover Unimelt capillary melting point apparatus.

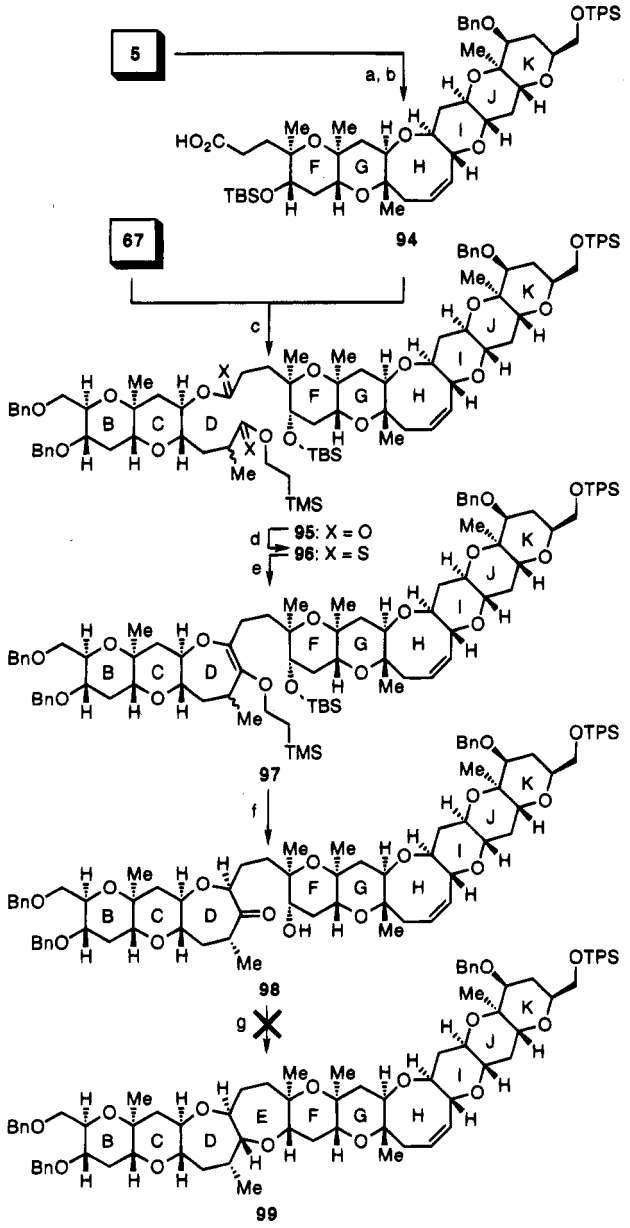
Dithioketal 11. *n*-Butyllithium (0.60 mL, 1.5 M solution in hexane, 0.9 mmol) was added dropwise to a stirred mixture of phosphonium salt **7** (960 mg, 1.0 mmol) and HMPA (0.52 mL, 3.0 mmol) in THF (5 mL) at −78 °C. The mixture was stirred for 10 min at −78 °C and for 10 min at 0 °C before the aldehyde **8** (587 mg, 0.80 mmol) in THF (3 mL) was added dropwise at −78 °C. The mixture was allowed to warm to 25 °C, quenched with aqueous saturated ammonium chloride

Scheme 12. Plausible Mechanisms for the TMSOTf/Ph_2MeSiH-induced Conversion of **87** to **89**



(31) For preliminary communications on the total synthesis of brevetoxin B, see: Nicolaou, K. C.; Theodorakis, E. A.; Rutjes, F. P. J. T.; Tiebes, J.; Sato, M.; Untersteller, E.; Xiao, X.-Y. *J. Am. Chem. Soc.* **1995**, *117*, 1171. Nicolaou, K. C.; Rutjes, F. P. J. T.; Theodorakis, E. A.; Tiebes, J.; Sato, M.; Untersteller, E. *J. Am. Chem. Soc.* **1995**, *117*, 1173.

Scheme 13[a] Coupling of BC and FGHIJK Ring Systems **67** and **94** and Failed Hydroxy Ketone Cyclization Attempts



[a] Reagents and conditions: (a) 1.5 equiv of TBSCl, 2.0 equiv of imidazole, DMF, 50 °C, 5 h; (b) 2.0 equiv of LiOH, DME/H_2O 4:1, 25 °C, 1 h, 81% (2 steps); (c) 2.0 equiv of **67**, 1.0 equiv of **94**, 2.5 equiv of DCC, 2.0 equiv of DMAP, 1.0 equiv of CSA, THF, 10 h, 85%; (d) 3.0 equiv of Lawesson's reagent, 3.0 equiv of 1,1,3,3-tetramethylthiourea, xylene, 185 °C, 2 h, 20%; (e) *hν*, Hanovia 450 W lamp, Pyrex filter, benzene, 70 °C, 2 h, 63%; (f) 3.5 equiv of TBAF, THF, 45 °C, 10 h; then 1.1 equiv of TPSCl, 1.5 equiv of imidazole, DMF, 2 h, 25 °C, 70%; (g) 10 equiv of Ph_2MeSiH, 1.5 equiv of TMSOTf, CH_2Cl_2, 0 °C, 1 h.

(5 mL) and diluted with ether (50 mL). The organic phase was separated, washed with aqueous saturated ammonium chloride (2 × 5 mL), and brine (5 mL), dried ($MgSO_4$), concentrated, and chromatographed (silica, 20% ether in petroleum ether) to give the coupling product **11** (926 mg, 0.70 mmol, 70%). **11**: colorless oil; $R_f = 0.33$ (silica, 20% ether in petroleum ether); $[\alpha]^{22}_D$ +16.6 (*c* 2.8, CH_2Cl_2); IR (film) ν_{max} 3100, 3080, 3041, 2971, 2935, 2900, 2862, 1460, 1385, 1262, 1123, 1050, 892, 845, 746, 708, 688, 621 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.69−7.25 (m, 20 H, ArH), 5.90 (m, 1 H, =CH), 5.69 (t, J = 11.5 Hz, 1 H, =CH), 4.88 (d, J = 8.5 Hz, 1 H, C*H*HPh), 4.77 (d, J = 11.5 Hz, 1 H, C*H*HPh), 4.73 (d, J = 8.5 Hz, 1 H, C*H*HPh), 4.62 (s, 2 H, OCH_2O), 4.57 (d, J = 11.5 Hz, 1 H, C*H*HPh), 4.31 (d, J = 8.0 Hz, 1 H, OC*H*CH=), 4.15−3.54 (m, 11 H, OCH), 3.23 (bd, J = 12.0 Hz, 1 H, OCH), 3.02−2.98 (m, 1 H, OCH), 2.79−1.50 (m, 20 H, SCH_2, CH), 1.33−1.29 (4 × s, 4 × 3 H, CH_3), 1.19 (m, 6 H, 2 × CH_2CH_3), 1.08 (s, 9 H, *t*-Bu), 0.92 (s, 9 H, *t*-Bu), 0.18 (s, 9 H, $Si(CH_3)_3$), 0.06 (s, 6 H, $Si(CH_3)_2$); HRMS (FAB), calcd for $C_{74}H_{113}O_{11}Si_3O_2$ (M + H^+) 1325.7032, found 1325.6946.

Alcohol 6. Pyridinium *p*-toluenesulfonate (7.5 mg, 0.03 mmol) was added to a solution of dithioketal **11** (396 mg, 0.30 mmol) in MeOH (5 mL). The reaction mixture was stirred at 25 °C for 30 min, diluted with ether (50 mL), washed with H_2O (2 × 10 mL) and brine (5 mL), dried ($MgSO_4$), concentrated, and chromatographed (silica, 40→80% ether in petroleum ether) to give the alcohol **6** (270 mg, 72%) and dihydroxy compound (56 mg, 18%). Selective monosilylation (1.1 equiv of *tert*-butyldimethylsilyl chloride, 1.2 equiv of imidazole, DMF, 25 °C) of this diol afforded hydroxy dithioketal **6** quantitatively, raising the total yield of this product to 338 mg (0.27 mmol, 90%). **6**: colorless oil; $R_f = 0.40$ (silica, 40% ether in petroleum ether); $[\alpha]^{22}_D$ +44.2 (*c* 2.2, CH_2Cl_2); IR (film) ν_{max} 3500, 3080, 3038, 2960, 2935, 2900, 2858, 1465, 1382, 1260, 1110, 1050, 842, 781, 741, 702, 681 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.68−7.20 (m, 20 H, ArH), 5.95 (m, 1 H, =CH), 5.80 (t, J = 11.5 Hz, 1 H, =CH), 4.86 (d, J = 8.0 Hz, 1 H, C*H*HPh), 4.73 (d, J = 8.5 Hz, 1 H, C*H*HPh), 4.71 (d, J = 12.0 Hz, 1 H, C*H*HPh), 4.62 (s, 2 H, OCH_2O), 4.54 (d, J = 12.0 Hz, 1 H, C*H*HPh), 4.34 (d, J = 8.5 Hz, 1 H, OC*H*CH=), 4.18−3.52 (m, 11 H, OCH), 4.03−3.97 (m, 1 H, OCH), 3.26 (bd, J = 12.0 Hz, 1 H, OCH), 2.66−1.50 (m, 24 H, SCH_2, CH), 1.31−1.17 (m, 18 H, 4 × CH_3, 2 × SCH_2CH_3), 1.08 (s, 9 H, *t*-Bu), 0.91 (s, 9 H, *t*-Bu), 0.05 (s, 6 H, $Si(CH_3)_2$); HRMS (FAB), calcd for $C_{71}H_{105}O_{11}S_2Si_2$ (M + H^+) 1253.6637, found 1253.6709.

Oxocene 12. A heterogeneous mixture of the hydroxy dithioketal **6** (200 mg, 0.16 mmol), potassium carbonate (88 mg, 0.64 mmol), silica (500 mg), and powdered 3 Å molecular sieves (500 mg) in CH_3CN (10 mL) at 25 °C was treated with anhydrous silver perchlorate (99.0 mg, 0.48 mmol). After stirring for 30 min, *N*-chlorosuccinimide (43 mg, 0.32 mmol) was added followed by vigorous stirring for 4 h. The reaction was quenched with triethylamine (0.5 mL), diluted with ether, and filtered through Celite. The mixture was concentrated and chromatographed (silica, 20% ether in petroleum ether) to give the oxocene **12** (149 mg, 0.13 mmol, 78%). **12**: colorless oil; $R_f = 0.48$ (silica, 30% ether in petroleum ether); $[\alpha]^{22}_D$ +69.0 (*c* 1.0, CH_2Cl_2); IR (film) ν_{max} 3084, 3049, 2987, 2945, 2898, 2878, 1472, 1389, 1276, 1123, 1050, 975, 845, 785, 749, 711, 624 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.68−7.24 (m, 20 H, ArH), 5.97−5.84 (m, 2 H, CH=CH), 4.86 (d, J = 7.0 Hz, 1 H, C*H*HPh), 4.78 (d, J = 12.5 Hz, 1 H, C*H*HPh), 4.73 (d, J = 7.0 Hz, 1 H, C*H*HPh), 4.72 (dd, J = 12.0 Hz, 4.5 Hz, 1 H, C*H*OCSEt), 4.62 (s, 2 H, OCH_2O), 4.54 (d, J = 12.5 Hz, 1 H, C*H*HPh), 4.18−3.53 (m, 10 H, OCH), 3.25 (bd, J = 12.5 Hz, 1 H, OCH), 3.00−2.95 (m, 1 H, OCH), 2.60−1.47 (m, 18 H, SCH_2, CH), 1.31−1.17 (m, 15 H, 4 × CH_3, SCH_2CH_3), 1.07 (s, 9 H, *t*-Bu), 0.92 (s, 9 H, *t*-Bu), 0.04 (s, 3 H, $SiCH_3$), 0.02 (s, 3 H, $SiCH_3$).

Oxocene 13. A mixture of oxocene **12** (130 mg, 0.11 mmol), triphenyltin hydride (70 mg, 0.2 mmol) and 2,2′-azobis(isobutyronitrile) (8 mg) in toluene (2 mL) was heated at 110 °C for 3 h. Concentration and flash chromatography (silica, 20% ether in petroleum ether) afforded oxocene **13** (114 mg, 0.10 mmol, 92%). **13**: colorless oil; $R_f = 0.45$ (30% ether in petroleum ether); $[\alpha]^{22}_D$ +55.0 (*c* 1.5, CH_2Cl_2); IR (film) ν_{max} 3080, 3041, 2996, 2940, 2895, 2861, 1471, 1390, 1271, 1110, 1050, 841, 781, 642, 610 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.70−7.22 (m, 20 H, ArH), 5.80 (m, 2 H, CH=CH), 4.84 (d, J = 7.0 Hz, 1 H, C*H*HPh), 4.78 (d, J = 12.5 Hz, 1 H, C*H*HPh), 4.72 (d, J = 7.0 Hz, 1 H, C*H*HPh), 4.62 (s, 2 H, OCH_2O), 4.52 (d, J = 12.5 Hz, 1 H, C*H*HPh), 4.20−3.22 (m, 13 H, OCH), 2.89−2.85 (m, 1 H, OCH), 2.52−1.35 (m, 16 H, CH), 1.29 (s, 3 H, CH_3), 1.28 (s, 3 H, CH_3), 1.25 (s, 3 H, CH_3), 1.20 (s, 3 H, CH_3), 1.09 (s, 9 H, *t*-Bu), 0.94 (s, 9 H, *t*-Bu), 0.06 (s, 6 H, $Si(CH_3)_2$); HRMS (FAB), calcd for $C_{67}H_{95}O_{11}Si_2$ (M + H^+) 1131.6413, found 1131.6599.

Methyl Ester 14. Jones' reagent (ca. 20 drops, prepared from chromium trioxide (11.1 g), sulfuric acid (9.7 mL), and H_2O (25 mL)) was added dropwise to a stirred solution of oxocene **13** (114 mg, 0.10 mmol) in acetone (1 mL) at 0 °C. After completion of the reaction, isopropyl alcohol (0.5 mL) was added at 0 °C, followed by ether (100 mL). The solution was washed with H_2O (2 × 10 mL) and brine (2 × 10 mL), dried ($MgSO_4$), and concentrated. The resulting crude carboxylic acid was dissolved in ether (2 mL) and treated with excess

diazomethane (ether solution) at 0 °C to afford, after flash chromatography (silica, 40% ether in petroleum ether), methyl ester **14** (85 mg, 0.080 mmol, 80%). **14**: colorless oil; $R_f = 0.50$ (silica, 40% ether in petroleum ether); $[\alpha]^{22}_D$ +55.7 (*c* 2.3, CH_2Cl_2); IR (film) ν_{max} 3095, 3078, 3017, 2980, 2880, 2858, 1733, 1413, 1382, 1268, 1112, 1051, 825, 740, 705, 682, 613 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.70–7.22 (m, 20 H, ArH), 5.80 (m, 2 H, CH=CH), 4.86 (d, $J = 7.5$ Hz, 1 H, C*H*HPh), 4.78 (d, $J = 12.0$ Hz, 1 H, C*H*HPh), 4.72 (d, $J = 7.5$ Hz, 1 H, C*H*HPh), 4.62 (s, 2 H, OCH_2O), 4.52 (d, $J = 12.0$ Hz, 1 H, C*H*HPh), 4.20–3.20 (m, 11 H, OCH), 3.66 (s, 3 H, CO_2CH_3), 2.90–2.85 (m, 1 H, OCH), 2.56–1.40 (m, 14 H, CH), 1.30 (s, 6 H, 2 × CH_3), 1.28 (s, 3 H, CH_3), 1.16 (s, 3 H, CH_3), 1.08 (s, 9 H, *t*-Bu); HRMS (FAB), calcd for $C_{62}H_{80}O_{12}SiNa$ (M + Na^+) 1067.5317, found 1067.5339. Anal. Calcd for $C_{62}H_{80}O_{12}Si$: C, 71.23; H, 7.71. Found: C, 71.13; H, 8.10.

Alcohol 5. Methyl ester **14** (104 mg, 0.10 mmol) was dissolved in CH_2Cl_2 (2 mL) and ethanethiol (0.25 mL) and cooled to −40 °C. Boron trifluoride etherate (0.10 mL of a 1.0 M solution in CH_2Cl_2, 0.10 mmol) was added and stirring was continued for 30 min at −40 °C before quenching with triethylamine (0.2 mL). The reaction mixture was poured into aqueous saturated sodium bicarbonate (5 mL) and ether (10 mL). The organic layer was washed with H_2O (5 mL), brine (5 mL), dried ($MgSO_4$), concentrated and chromatographed (silica, 50% ether in petroleum ether) to afford alcohol **5** (78 mg, 0.084 mmol, 84%). **5**: colorless oil; $R_f = 0.33$ (silica, 80% ether in petroleum ether); $[\alpha]^{22}_D$ +52.4 (*c* 1.6, CH_2Cl_2); IR (film) ν_{max} 3430, 3080, 3061, 3041, 2960, 2939, 2896, 2882, 1735, 1442, 1382, 1221, 1110, 1062, 831, 745, 707, 618 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.68–7.24 (m, 20 H, ArH), 5.79 (m, 2 H, CH=CH), 4.78 (d, $J = 12.5$ Hz, 1 H, C*H*HPh), 4.51 (d, $J = 12.5$ Hz, 1 H, C*H*HPh), 4.18–3.22 (m, 11 H, OCH), 3.70 (s, 3 H, CO_2CH_3), 2.87 (m, 1 H, OCH), 2.50–1.40 (m, 14 H, CH), 1.30 (s, 3 H, CH_3), 1.27 (s, 3 H, CH_3), 1.25 (s, 3 H, CH_3), 1.17 (s, 3 H, CH_3), 1.08 (s, 9 H, *t*-Bu); HRMS (FAB), calcd for $C_{52}H_{73}O_{11}Si$ (M + H^+) 925.4922, found 925.4850.

Dithionoester 20. A stirred solution of diester **19**[26] (186 mg, 0.68 mmol), Lawesson's reagent (0.72 g, 2.1 mmol), and 1,1,3,3-tetramethylthiourea (310 mg, 2.1 mmol) in xylene (2.5 mL) was heated at 160 °C in a sealed tube. After 2 h, the reaction mixture was concentrated and subjected to flash chromatography (silica, 10→30% ether in petroleum ether) to give the dithionoester **20** (52 mg) and a mixture of monothionated product and unreacted starting material. This mixture was recycled twice to give additional product (total 97 mg, 0.32 mmol, 47%) as a mixture of diastereoisomers. **20**: colorless oil; $R_f = 0.68$ (silica, 20% ether in petroleum ether); IR (film) ν_{max} 2960, 2870, 1460, 1440, 1190, 1100, 1030, 760 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.17 (m, 1 H, C(S)OCH), 4.07, 4.04 (s, 3 H, OCH_3), 3.88 (m, 1 H, OCH), 3.48–3.02 (m, 3 H, OCH), 2.68 (m, 2 H, OCH), 2.32–1.34 (m, 8 H, CH), 1.19 (m, 3 H, CH_3), 0.93 (m, 3 H, CH_3); HRMS (FAB), calcd for $C_{14}H_{25}O_3S_2$ (M + H^+) 305.1245, found 305.1281.

Oxepene 23. A solution of dithionoester **20** (86 mg, 0.28 mmol) in benzene (23 mL) was deoxygenated with argon for 30 min and then irradiated with a Hanovia lamp (450 W) using a Pyrex filter (λ_{max} > 285 nm). After 2 h, the reaction mixture was concentrated and subjected to flash chromatography (silica, 10→30% ether in petroleum ether) to give the oxepene **23** (42 mg, 0.175 mmol, 63%) as a mixture of diastereoisomers. **23**: colorless oil; $R_f = 0.48$ (silica, 30% ether in petroleum ether); IR (film) ν_{max} 2940, 1200, 1110 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.83 (m, 1 H, OCH), 3.47, 3.40 (s, 3 H, OCH_3), 3.39–2.91 (m, 3 H, OCH), 2.53 (m, 1 H, CH), 2.21–1.37 (m, 10 H, CH), 1.22, 1.13 (d, $J = 7.4$ Hz, 3 H, CH_3), 0.88 (m, 3 H, CH_3); HRMS (CI), calcd for $C_{14}H_{24}O_3$ (M^+) 240.1725, found 240.1718.

Oxepanone 24. A solution of oxepene **23** (107 mg, 0.33 mmol) in THF (1.5 mL) was treated with aqueous hydrochloric acid (0.2 mL, 2.0 M in H_2O) at 25 °C. After 2.5 h, the reaction mixture was diluted with ether (5 mL), washed with saturated aqueous sodium bicarbonate (4 mL), dried ($MgSO_4$), and concentrated. The solvent was evaporated and the residue subjected to flash chromatography (silica, 30→50% ether in petroleum ether) to give oxepanone **24** (60 mg, 0.26 mmol, 80%) as a single diastereoisomer. **24**: colorless oil; $R_f = 0.17$ (silica, 30% ether in petroleum ether); $[\alpha]^{22}_D$ −153.6 (*c* 0.25, CH_2Cl_2); IR (film) ν_{max} 2940, 2880, 1720, 1465, 1385, 1130, 1100, 960 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.88 (dd, $J = 9.4$, 3.6 Hz, 1 H, C(O)-CHO), 3.82 (dd, $J = 9.4$, 3.6 Hz, 1 H, OCH), 3.59 (m, 1 H, OCH), 3.34 (m, 1 H, OCH), 2.92 (m, 1 H, OCH), 2.69 (m, 1 H, C*H*(CH_3)C-(O)), 2.04 (m, 1 H, CH), 1.94 (m, 1 H, CH), 1.73–1.42 (m, 8 H, CH), 1.35 (d, $J = 7.4$ Hz, 3 H, CH_3), 0.90 (t, $J = 7.3$ Hz, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 217.60, 86.95, 80.20, 80.47, 67.52, 38.79, 37.72, 35.18, 30.92, 25.67, 18.65, 16.33, 13.70; HRMS (CI), calcd for $C_{13}H_{22}O_3$ (M^+) 226.1569, found 226.1567.

Dithionoester 30. Dithionoester **30** was prepared following the same procedure as for **20** from the corresponding diester[26] (265 mg, 0.38 mmol). Flash chromatography (silica, 10→30% ether in petroleum ether) gave dithionoester **30** (153 mg, 0.22 mmol, 55%). **30**: colorless oil; $R_f = 0.71$ (silica, 20% ether in petroleum ether); IR (film) ν_{max} 2970, 2860, 1470, 1430, 1250, 1170, 1100, 845, 740, 705, 615 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.65–7.35 (m, 10 H, ArH), 5.24 (m, 1 H, CHO(S)C), 4.52 (m, 2 H, CH_2O(S)C), 3.91 (m, 1 H, OCH), 3.72 (m, 1 H, OCH), 3.47–3.10 (m, 5 H, OCH), 2.75 (m, 3 H, CH_2C(S)), 2.33 (m, 1 H, CH_2C(S)), 2.08–1.22 (m, 12 H, CH), 1.07 (m, 2 H, CH_2Si), 1.01 (s, 9 H, *t*-Bu), 0.02 (s, 9 H, $Si(CH_3)_3$); HRMS (FAB), calcd for $C_{37}H_{56}O_5S_2Si_2Na$ (M + Na^+) 723.3005, found 723.3110.

Oxepene 31. Oxepene **31** was prepared following the same procedure as for **23** above from dithionoester **30** (87 mg, 0.12 mmol). Flash chromatography (silica, 10→30% ether in petroleum ether) gave oxepene **31** (49 mg, 0.077 mmol, 62%). **31**: colorless oil; $R_f = 0.34$ (silica, 30% ether in petroleum ether); IR (film) ν_{max} 2940, 2850, 1420, 1100, 860, 840, 740, 705, 610 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.65–7.35 (m, 10 H, ArH), 3.76 (m, 1 H, OCH), 3.59 (m, 1 H, OCH), 3.40–2.94 (m, 8 H, OCH), 2.50 (m, 2 H, CH_2C=C), 2.23–1.20 (m, 16 H, CH), 1.01 (s, 9 H, *t*-Bu), 0.02 (s, 9 H, $Si(CH_3)_3$); HRMS (FAB), calcd for $C_{37}H_{57}O_5Si_2$ (M + H^+) 637.3744, found 637.3661.

Oxepanone 32. A stirred solution of oxepene **31** (41 mg, 0.060 mmol) in THF (1.5 mL) was treated with tetra-*n*-butylammonium fluoride (0.2 mL of a 1.0 M in THF, 0.20 mmol) at 50 °C for 10 h. The solvent was evaporated and the residue subjected to flash chromatography (silica, 50→80% ether in petroleum ether) to give oxepanone **32** (19 mg, 0.064 mmol, 94%). **32**: colorless oil; $R_f = 0.51$ (silica, 100% ether); $[\alpha]^{22}_D$ −22.8 (*c* 0.05, CH_2Cl_2); IR (film) ν_{max} 3460, 2940, 2870, 1715, 1440, 1380, 1100, 985, 960, 735, 705 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.82 (m, 3 H, OCH), 3.24 (m, 4 H, OCH), 2.92 (m, 2 H, OCH), 2.82 (m, 1 H, CH_2C(O)), 2.31 (m, 1 H, CH_2C(O)), 2.12–1.82 (m, 6 H, CH, OH), 1.71–1.20 (m, 9 H, CH); HRMS (FAB), calcd for $C_{16}H_{27}O_5$ (M + H^+) 299.1858, found 299.1844.

Oxepane 42. A solution of hydroxy ketone **39** (81 mg, 0.39 mmol) and triethylsilane (0.60 mL, 3.90 mmol) in CH_2Cl_2 (2 mL) was treated at 0 °C with trimethylsilyl trifluoromethanesulfonate (70 μL, 0.39 mmol). After 15 min, aqueous saturated sodium bicarbonate (2 mL) was added and the mixture was diluted with ether (10 mL), washed with H_2O (2 mL), dried ($MgSO_4$), concentrated, and chromatographed (silica, 5% ether in petroleum ether) to give oxepane **42** (63 mg, 0.033 mmol, 85%). **42**: colorless oil; $R_f = 0.55$ (silica, 5% ether in petroleum ether); IR (film) ν_{max} 2913, 2843, 1452, 1103, 700 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.37–7.16 (m, 5 H, ArH), 4.55 (dd, $J = 8.8$, 3.9 Hz, 1 H, OCH), 3.83 (m, 1 H, OCH), 2.05–1.99 (m, 2 H, CH), 1.87–1.58 (m, 6 H, CH), 1.21 (d, $J = 6.2$ Hz, 3 H, CH_3); HRMS (FAB), calcd for $C_{13}H_{19}O$ (M + H^+) 191.1436, found 191.1422.

Dioxepane 47. Dioxepane **47** was prepared following the same procedure as for **42** from hydroxy ketone **32** (42 mg, 0.15 mmol). Flash chromatography (silica, 40% ether in petroleum ether) gave oxepane **47** (34 mg, 0.12 mmol, 88%) as a 4:1 mixture of *trans/cis* isomers. ***trans*-47**: colorless needles; mp 90–91 °C (ether/hexanes); $R_f = 0.38$ (silica, 50% ether in petroleum ether); IR (film) ν_{max} 2955, 2860, 1470, 1325, 1280, 1080, 1022, 965, 745 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 3.85 (m, 2 H, OCH), 3.52 (m, 2 H, OCH), 3.24 (m, 2 H, OCH), 3.08 (m, 2 H, OCH), 2.95 (m, 2 H, OCH), 2.00 (m, 4 H, CH), 1.72 (m, 6 H, CH), 1.65 (m, 6 H, CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 82.8, 82.6, 82.4, 67.7, 31.3, 30.0, 28.8, 25.9; HRMS (CI), calcd for $C_{16}H_{26}O_4$ (M^+) 282.1831, found 282.1854. ***cis*-47**: white solid; mp 95–96 °C (ether/hexanes); $R_f = 0.35$ (silica, 50% ether in petroleum ether) IR (film) ν_{max} 2948, 2860, 1448, 1345, 1219, 1140, 1110, 1086, 1062, 968, 736 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.90–3.78 (m, 4 H, OCH), 3.39–2.76 (m, 6 H, OCH), 2.06–1.22 (m, 16 H, CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 85.3, 84.8, 82.7, 82.6, 82.0, 79.9, 71.6, 67.7, 67.0, 32.1, 31.8,

29.3, 27.9, 26.9, 26.8, 26.3, 25.9; HRMS (FAB), calcd for $C_{16}H_{27}O_4$ (M + H$^+$) 283.1909, found 283.1901.

Alcohol 64. To a stirred solution of ester **63** (11.5 g, 18.4 mmol) in THF (40 mL) at 25 °C was added dropwise tetra-*n*-butylammonium fluoride (27.6 mL of a 1.0 M solution, 27.6 mmol). After 30 min, the reaction mixture was diluted with ether (200 mL), washed with brine (140 mL), and dried ($MgSO_4$) and the solvent was evaporated. Flash chromatography (silica, 30→70% ether in petroleum ether) gave the epoxy alcohol **64** (9.0 g, 17.6 mmol, 96%). **64**: colorless oil; R_f = 0.38 (silica, 70% ether in petroleum ether); $[\alpha]^{22}_D$ +49.8 (*c* 4.2, CH_2Cl_2); IR (film) ν_{max} 3490, 2960, 1715, 1660, 1460, 1370, 920, 730, 700 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.33 (m, 10 H, ArH), 6.29 (d, J = 8.8 Hz, 1 H, =CH), 4.63 (d, J = 11.7 Hz, 1 H, C*H*HPh), 4.57 (d, J = 12.4 Hz, 2 H, CH_2Ph), 4.40 (d, J = 11.7 Hz, 1 H, C*H*HPh), 4.18 (q, J = 7.3 Hz, 2 H, $CO_2CH_2CH_3$), 3.83−3.52 (m, 3 H, OCH), 3.49−3.25 (m, 4 H, OCH), 2.45 (d, J = 5.4 Hz, 1 H, OH), 2.36 (m, 1 H, CH), 2.14−2.00 (m, 1 H, CH), 1.98 (d, J = 1.3 Hz, 3 H,CH_3C=C), 1.75−1.60 (m, 1 H, CH), 1.28 (t, J = 7.3 Hz, 3 H, $CO_2CH_2CH_3$), 1.22 (s, 3 H, CH_3); HRMS (CI), calcd for $C_{30}H_{38}O_7$ (M$^+$) 510.2779, found 510.2617.

Bicycle 65. A solution of epoxy alcohol **64** (8.9 g, 17.5 mmol) in CH_2Cl_2 (200 mL) at 0 °C was treated with pyridinium *p*-toluenesulfonate (3.7 g, 14.8 mmol). After 13 h, triethylamine (2.5 mL) was added and the solvent was evaporated. Flash chromatography (silica, 70% ether in petroleum ether) gave the cyclized product **65** (8.7 g, 17.1 mmol, 97%). **65**: colorless oil; R_f = 0.32 (silica, 70% ether in petroleum ether); $[\alpha]^{22}_D$ +42.6 (*c* 1.9, CH_2Cl_2); IR (film) ν_{max} 3480, 2960, 2880, 1715, 1665, 1500, 1460, 1375, 1270, 1070, 915, 750, 700 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.33 (m, 10 H, ArH), 6.67 (d, J = 8.8 Hz, 1 H, =CH), 4.68 (d, J = 11.7 Hz, 1 H, C*H*HPh), 4.60 (d, J = 4.5 Hz, 1 H, C*H*HPh), 4.55 (d, J = 4.5 Hz, 1 H, C*H*HPh), 4.39 (d, J = 11.7 Hz, 1 H, C*H*HPh), 4.20 (q, J = 7.3 Hz, 2 H, $CO_2CH_2CH_3$), 4.03 (t, J = 9.0 Hz, 1 H, OCH), 3.80−3.45 (m, 5 H, OCH), 3.20 (dd, J = 12.6, 3.9 Hz, 1 H, OCH), 2.36−2.28 (m, 2 H, CH), 2.12 (m, 1 H, OH), 1.98 (d, J = 1.3 Hz, 3 H, CH_3C=C), 1.70−1.50 (m, 2 H, CH), 1.32 (t, J = 7.3 Hz, 3 H, $CO_2CH_2CH_3$), 1.30 (s, 3 H, CH_3); HRMS (CI), calcd for $C_{30}H_{42}O_7N$ (M + NH_4^+) 528.2961, found 528.2921.

Saturated Ester 66. A mixture of ester **65** (8.6 g, 16.9 mmol) and 10% Pd/C (1.7 g, 20% by weight) in EtOAc (45 mL) was stirred under a H_2 atmosphere for 48 h at 25 °C. The mixture was filtered through Celite and the filtrate was concentrated to give a diastereomeric mixture of esters **66** (8.6 g, 16.8 mmol, 100%). **66**: colorless oil; R_f = 0.28 (silica, 70% ether in petroleum ether); IR (film) ν_{max} 3470, 2960, 2880, 1730, 1460, 750, 700 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.33 (m, 10 H, ArH), 4.56 (m, 3 H, CH_2Ph), 4.35 (d, J = 12.4 Hz, 1 H, C*H*HPh), 4.09 (q, J = 7.3 Hz, 2 H, $CO_2CH_2CH_3$), 3.63 (m, 2 H, OCH), 3.45 (m, 3 H, OCH), 3.04 (m, 2 H, OCH), 2.71 (m, 1 H, CH), 2.52 (m, 1 H, OH), 2.21 (m, 3 H, CH), 1.51 (m, 3 H, CH), 1.25−1.15 (m, 9 H, 2 × CH_3, $CO_2CH_2CH_3$); HRMS (CI), calcd for $C_{30}H_{44}O_7N$ (M + NH_4^+) 530.3118, found 530.3163.

2-(Trimethylsilyl)ethyl Ester 67. A solution of ester **66** (8.5 g, 16.6 mmol) in THF (45 mL) was added to a stirred solution of 2-(trimethylsilyl)ethanol (11.9 mL, 83 mmol) and potassium hydride (0.1 g, 2.5 mmol) in THF (50 mL) at 25 °C. After 15 min, MeOH (1 mL) was added and the reaction mixture was diluted with ether (200 mL), washed with water (100 mL), dried ($MgSO_4$) and concentrated. Excess 2-(trimethylsilyl)ethanol was removed by azeotroping with toluene. Flash chromatography (silica, 50% ether in petroleum ether) gave the silyl ester **67** (8.8 g, 15.1 mmol, 91%) as a 1:1 mixture of diastereoisomers. **67**: colorless oil; R_f = 0.15 (silica, 50% ether in petroleum ether); IR (film) ν_{max} 3460, 2960, 2880, 1725, 1500, 1465, 845, 740, 700 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.33 (m, 10 H, ArH), 4.56 (m, 3 H, CH_2Ph), 4.32 (d, J = 12.4 Hz, 1 H, C*H*HPh), 4.13 (m, 2 H, OCH), 3.63 (m, 2 H, OCH), 3.44 (m, 3 H, OCH), 3.05 (m, 2 H, OCH), 2.73 (m, 1 H, CH), 2.25 (m, 4 H, CH, OH), 1.51 (m, 3 H, CH), 1.18 (m, 6 H, 2 × CH_3), 0.90 (t, J = 8.1 Hz, 2 H, CH_2Si), 0.05 (s, 9 H, $Si(CH_3)_3$); HRMS (CI), calcd for $C_{33}H_{52}O_7SiN$ (M + NH_4^+) 602.3513, found 602.3471. Anal. Calcd for $C_{33}H_{48}O_7Si$: C, 65.74; H, 7.97. Found: C, 66.07; H, 8.11.

Dithionoester 70. Dithionoester **70** was prepared following the same procedure as for **20** from the corresponding diester **69**[26] (347 mg, 0.35 mmol). Flash chromatography (silica, 10→30% ether in petroleum ether) gave dithionoester **70** (208 mg, 0.20 mmol, 58%) as a 1:1 mixture of diastereoisomers. **70**: colorless oil; R_f = 0.68 (silica, 20% ether in petroleum ether); IR (film) ν_{max} 2960, 2860, 1595, 1455, 1430, 860, 840, 740, 700, 610 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.80−7.25 (m, 20 H, ArH), 5.38 (m, 1 H, CHO(S)C), 4.68−4.30 (m, 6 H, CH_2Ph, CH_2O(S)C), 3.74−3.00 (m, 9 H, OCH), 2.70−1.14 (m, 20 H, CH_2C(S), CH), 1.30 (2 × s, 6 H, 2 × CH_3), 1.00 (s, 9 H, *t*-Bu), 0.04 (s, 9 H, $Si(CH_3)_3$); HRMS (CI), calcd for $C_{58}H_{80}O_8S_2Si_2$ (M$^+$) 1024.4833, found 1024.4824.

Oxepene 71. Oxepene **71** was prepared following the same procedure as for **23** from dithionoester **70** (167 mg, 0.16 mmol). Flash chromatography (silica, 10→30% ether in petroleum ether) gave oxepene **71** (110 mg, 0.12 mmol, 72%) as a 1:1 mixture of diastereoisomers. **71**: colorless oil; R_f = 0.42 (silica, 30% ether in petroleum ether); IR (film) ν_{max} 2960, 2860, 1460, 1380, 1245, 1100, 865, 840, 740, 705, 615 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.80−7.25 (m, 20 H, ArH), 5.38 (m, 1 H, CHO(S)C), 4.63 (d, J = 11.5 Hz, 1 H, C*H*HPh), 4.58 (d, J = 11.4 Hz, 2 H, C*H*HPh), 4.39 (d, J = 11.5 Hz, 1 H, C*H*HPh), 3.74−3.05 (m, 12 H, OCH), 2.70−2.50 (m, 2 H, CH), 2.32 (m, 4 H, CH), 1.93-1.46 (m, 12 H, CH), 1.24, 1.11 (s, 3 H, CH_3), 1.07 (d, J = 6.3 Hz, 3 H, CH_3), 1.00 (s, 9 H, *t*-Bu), 0.01 (s, 9 H, $Si(CH_3)_3$); HRMS (FAB), calcd for $C_{58}H_{81}O_8Si_2$ (M + H$^+$) 961.5470, found 961.5466.

Oxepanone 72. Oxepane **72** was prepared following the same procedure as for **32** from oxepene **71** (96 mg, 0.10 mmol). Flash chromatography (silica, 40→80% ether in petroleum ether) gave oxepanone **72** (55 mg, 0.088 mmol, 88%) as a single isomer. **72**: colorless oil; R_f = 0.60 (silica, 100% ether); $[\alpha]^{22}_D$ −18.2 (*c* 0.95, CH_2Cl_2); IR (film) ν_{max} 3450, 1715 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54−7.24 (m, 10 H, ArH), 4.62 (d, J = 11.5 Hz, 1 H, C*H*HPh), 4.54 (d, J = 12.0 Hz, 1 H, C*H*HPh), 4.52 (d, J = 11.5 Hz, 1 H, C*H*HPh), 4.38 (d, J = 12.0 Hz, 1 H, C*H*HPh), 3.80 (m, 1 H, OCH), 3.70−3.00 (m, 11 H, OCH), 2.30−1.50 (m, 14 H, CH), 1.15 (s, 3 H, CH_3), 1.09 (s, 3 H, CH_3), 1.05 (d, J = 7.3 Hz, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 216.9, 138.0, 137,9, 128.3, 128.3, 128.3, 128.3, 128.2, 127.7, 127.7, 127.7, 127.7, 127.4, 87.7, 81.4, 77.9, 77.7, 75.9, 73.3, 73.1, 72.5, 72.3, 71.6, 71.0, 69.6, 60.5, 44.6, 38.5, 37.9, 34.0, 30.2, 29.6, 27.6, 26.5, 24.0, 16.3, 15.2; HRMS (CI), calcd for $C_{37}H_{50}O_8$ (M$^+$) 622.3505, found 622.3540.

Dioxepane 73. Compound **73** was prepared following the same procedure as for **42** from hydroxy ketone **72** (50 mg, 0.08 mmol) and diphenylmethylsilane (0.80 mmol). Flash chromatography (silica, 30% ether in petroleum ether) gave dioxepane **73** (30 mg, 0.050 mmol, 62%) as a 6:1 mixture of *trans/cis* isomers. ***trans*-73**: colorless oil; R_f = 0.77 (silica, 80% ether in petroleum ether); IR (film) ν_{max} 2950, 2830, 1470, 1110, 750 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 7.54−7.24 (m, 10 H, ArH), 4.54 (d, J = 12.3 Hz, 1 H, C*H*HPh), 4.45 (d, J = 12.3 Hz, 1 H, C*H*HPh), 4.45 (d, J = 11.8 Hz, 1 H, C*H*HPh), 4.29 (d, J = 11.8 Hz, 1 H, C*H*HPh), 3.80−3.39 (m, 6 H, OCH), 3.32 (dd, J = 7.7, 4.5 Hz, 1 H, OCH), 3.74 (m, 2 H, OCH), 3.54 (m, 1 H, OCH), 3.46 (m, 1 H, OCH), 3.21−2.92 (m, 4 H, OCH), 2.36−1.21 (m, 12 H, CH), 1.15 (s, 3 H, CH_3), 1.09 (s, 3 H, CH_3), 1.00 (d, J = 6.3 Hz, 3 H, CH_3); HRMS (CI), calcd for $C_{37}H_{50}O_7$ (M$^+$) 606.3556, found 606.3525.

Carboxylic Acid 83. A stirred solution of ester **82** (16.2 g, 28.4 mmol) in THF:MeOH:H_2O (1:1:1, 60 mL) was treated with lithium hydroxide (1.4 g, 46.8 mmol) and heated at 55 °C for 2.5 h. The reaction mixture was cooled, diluted with EtOAc (200 mL), and carefully acidified with 2 N aqueous hydrochloric acid to pH 5. The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 50 mL). The extracts were combined, dried ($MgSO_4$), and concentrated to give the carboxylic acid **83** (14.8 g, 26.6 mmol, 94%). **83**: colorless oil; R_f = 0.44 (silica, 50% ether in petroleum ether); $[\alpha]^{22}_D$ +1.1 (*c* 0.6, CH_2Cl_2); IR (film) ν_{max} 3400, 2970, 2860, 1710, 1620, 1580, 1460, 1370, 1260, 1100, 870, 840, 780, 740, 700 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.54−7.24 (m, 10 H, ArH), 4.53 (d, J = 11.8 Hz, 1 H, C*H*HPh), 4.44 (m, 3 H, CH_2Ph), 3.53 (m, 2 H, OCH), 3.30 (m, 2 H, OCH), 2.29 (t, J = 8.0 Hz, 2 H, CH_2C(O)), 1.91−1.59 (m, 6 H, CH), 1.16 (s, 3 H, $SiCH_3$), 1.10 (s, 3 H, $SiCH_3$), 0.82 (s, 9 H, *t*-Bu), −0.01 (s, 6 H, 2 × CH_3); HRMS (FAB), calcd for $C_{32}H_{49}O_6Si$ (M + H$^+$) 557.3298, found 557.3271. Anal. Calcd for $C_{32}H_{48}O_6Si$: C, 69.06; H, 8.63. Found: C, 69.00 H, 8.57.

Diester 84. A stirred solution of alcohol **67** (2.4 g, 4.1 mmol), acid **83** (2.3 g, 4.1 mmol), *N,N*-dimethyl-4-aminopyridine (150 mg, 1.23 mmol) and camphorsulfonic acid (404 mg, 1.23 mmol) in CH_2Cl_2 (15 mL) at 25 °C was treated with 1,3-dicyclohexylcarbodiimide (1.3 g, 6.2 mmol). After stirring for 10 h at 25 °C, ether (30 mL) was added and the mixture was filtered through Celite. Concentration and flash chromatography (silica, 20% ether in petroleum ether) gave diester **84** (4.1 g, 3.7 mmol, 88%) as a 1:1 mixture of diastereoisomers. **84**: colorless oil; $R_f = 0.44$ (silica, 30% ether in petroleum ether); IR (film) ν_{max} 2940, 2840, 1730, 1490, 1445, 1365, 1245, 855, 830, 770, 730, 690 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.54−7.24 (m, 20 H, ArH), 4.69 (m, 1 H, OCH), 4.62−4.30 (m, 8 H, CH_2Ph), 4.14 (m, 2 H, OCH), 3.68−3.21 (m, 8 H, OCH), 3.04 (m, 2 H, OCH), 2.65 (m, 1 H, C*H*HC(O)), 2.30−1.46 (m, 14 H, CH), 1.28 (s, 3 H, CH_3), 1.20 (s, 3 H, CH_3), 1.09 (s, 3 H, CH_3), 1.05 (d, $J = 6.3$ Hz, 3 H, CH_3), 0.95 (m, 2 H, CH_2Si), 0.86 (s, 9 H, *t*-Bu), 0.03 (s, 3 H, $SiCH_3$), 0.02 (s, 3 H, $SiCH_3$), 0.01 (s, 9 H, $Si(CH_3)_3$); HRMS (FAB), calcd for $C_{65}H_{95}O_{12}Si_2$ (M + H^+) 1123.6361, found 1123.6245.

Dithionoester 85. Dithionoester **85** was prepared following the same procedure as for **69** from diester **84** (3.5 g, 3.1 mmol). Flash chromatography (silica, 10→30% ether in petroleum ether) gave dithionoester **85** (2.0 g, 1.73 mmol, 56%) as a 1:1 mixture of diastereoisomers. **85**: colorless oil; $R_f = 0.76$ (silica, 20% ether in petroleum ether); IR (film) ν_{max} 2950, 2850, 1495, 1455, 1375, 1240, 1085, 860, 835, 775, 730, 700 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.54−7.24 (m, 20 H, ArH), 5.40 (m, 1 H, C(S)OCH), 4.63−4.30 (m, 10 H, CH_2Ph, $C(S)OCH_2$), 3.69−3.00 (m, 10 H, OCH), 2.72−1.41 (m, 15 H, CH), 1.29 (s, 3 H, CH_3), 1.21 (s, 3 H, CH_3), 1.14 (d, $J = 6.3$ Hz, 3 H, CH_3), 1.13 (s, 3 H, CH_3), 1.07 (m, 2 H, CH_2Si), 0.88 (s, 9 H, *t*-Bu), 0.04 (s, 3 H, $SiCH_3$), 0.01 (s, 3 H, $SiCH_3$), 0.00 (s, 9 H, $Si(CH_3)_3$); HRMS (FAB), calcd for $C_{65}H_{95}O_{10}S_2Si_2$ (M + H^+) 1155.5905, found 1155.5772.

Oxepene 86. Oxepene **86** was prepared following the same procedure as for **86** from dithionoester **85** (1.5 g, 1.3 mmol). Flash chromatography (silica, 10→30% ether in petroleum ether) gave oxepene **86** (0.91 g, 0.83 mmol, 64%) as a 1:1 mixture of diastereoisomers. **86**: colorless oil; $R_f = 0.33$ (silica, 30% ether in petroleum ether); IR (film) ν_{max} 2950, 2920, 2860, 1500, 1455, 1380, 1365, 1250, 1075, 860, 835, 775, 730, 700 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.54−7.24 (m, 20 H, ArH), 4.63−4.37 (m, 8 H, CH_2Ph), 3.71−3.01 (m, 13 H, OCH), 2.29 (m, 1 H, CH), 1.90−1.54 (m, 14 H, CH), 1.29 (s, 3 H, CH_3), 1.22 (s, 3 H, CH_3), 1.14 (s, 3 H, CH_3), 1.09 (d, $J = 6.3$ Hz, 3 H, CH_3), 1.01 (m, 2 H, CH_2Si), 0.82 (s, 9 H, *t*-Bu), 0.04 (s, 3 H, $SiCH_3$), 0.01 (s, 3 H, $SiCH_3$), 0.00 (s, 9 H, $Si(CH_3)_3$); HRMS (FAB), calcd for $C_{65}H_{94}O_{10}Si_2Na$ (M + Na^+) 1113.6283, found 1163.6162.

Hydroxy Ketone 87. A stirred solution of oxepene **86** (870 mg, 0.80 mmol) in THF (1.5 mL) was treated with tetra-*n*-butylammonium fluoride (2.4 mL of a 1.0 M solution in THF, 2.4 mmol). The reaction mixture was heated at 50 °C for 10 h and evaporated and the residue was subjected to flash chromatography (silica, 30 → 50% ether in petroleum ether) to give hydroxy ketone **87** (640 mg, 0.73 mmol, 91%) as a single diastereoisomer. **87**: colorless oil; $R_f = 0.21$ (silica, 70% ether in petroleum ether); $[\alpha]^{22}_D$ −21.4 (*c* 0.7, CH_2Cl_2); IR (film) ν_{max} 3460, 2960, 2880, 1715, 1500, 1460, 1370, 915, 735, 700 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.54−7.24 (m, 20 H, ArH), 4.61−4.33 (m, 8 H, CH_2Ph), 3.72 (m, 1 H, OCH), 3.63 (bs, 3 H, OCH), 3.55−3.42 (m, 5 H, OCH), 3.14−2.90 (m, 3 H, OCH), 2.37−1.51 (m, 16 H, CH, OH), 1.18 (s, 3 H, CH_3), 1.15 (s, 3 H, CH_3), 1.12 (s, 3 H, CH_3), 1.05 (d, $J = 6.3$ Hz, 3 H, CH_3); HRMS (FAB), calcd for $C_{54}H_{69}O_{10}$ (M + H^+) 877.4888, found 877.4957. Anal. Calcd for $C_{54}H_{68}O_{10}$: C, 73.97; H, 7.76. Found: C, 73.69; H, 7.94.

Compound 89. To a stirred solution of hydroxy ketone **87** (560 mg, 0.69 mmol) and diphenylmethylsilane (0.5 mL, 2.4 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added trimethylsilyl trifluoromethanesulfonate (125 μL, 1.04 mmol). After 40 min, saturated aqueous sodium bicarbonate (1 mL) was added and the mixture was diluted with ether (30 mL), washed with water (5 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (silica, 30% ether in petroleum ether) gave compound **89** (275 mg, 0.32 mmol, 46%). **89**: colorless oil; $R_f = 0.62$ (silica, 50% ether in petroleum ether); $[\alpha]^{22}_D$ +17.7 (*c* 0.2, CH_2Cl_2); IR (film) ν_{max} 2920, 2850, 1490, 1450, 1370, 1070, 730, 690 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.54−7.24 (m, 20 H, ArH), 4.62−4.34 (m, 8 H, CH_2Ph), 4.18 (dd, $J = 8.6$, 2.1 Hz, 1 H, OCH), 3.88 (t, $J = 8.8$ Hz, 1 H, OCH), 3.69−3.41 (m, 5 H, OCH), 3.31 (m, 2 H, OCH), 3.20−3.10 (m, 1 H, OCH), 3.00 (dd, $J = 10.4$, 3.2 Hz, 1 H, OCH), 2.29−1.52 (m, 15 H, CH), 1.22 (s, 3 H, CH_3), 1.18 (s, 3 H, CH_3), 1.07 (s, 3 H, CH_3), 1.04 (d, $J = 6.3$ Hz, 3 H, CH_3); HRMS (FAB), calcd for $C_{54}H_{69}O_9$ (M + H^+) 861.4941, found 861.4943.

Benzoate 91. To a solution of the appropriate alcohol precursor of **91** (25 mg, 0.05 mmol) and *N,N*-dimethyl-4-aminopyridine (12 mg, 0.1 mmol) in CH_2Cl_2 (1 mL) was added *p*-nitrobenzoyl chloride (11 mg, 0.06 mmol). After 20 min, MeOH (0.1 mL) was added and the reaction mixture was concentrated. Flash chromatography (silica, 30% ether in petroleum ether) gave the benzoate ester **91** (32 mg, 43 μmol, 86%). **91**: white solid, mp 168−170 °C (pentane/CH_2Cl_2); $R_f = 0.22$ (silica, 70% ether in petroleum ether); $[\alpha]^{22}_D$ −18.0 (*c* 0.06, CH_2Cl_2); IR (CH_2Cl_2) ν_{max} 2935, 1725, 1530, 1385, 1350, 1270, 1090, 910, 860 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.28 (d, $J = 8.9$ Hz, 2 H, ArH), 8.12 (d, $J = 8.9$ Hz, 2 H, ArH), 5.62 (dd, $J = 17.4$, 10.6 Hz, 1 H, CH=), 5.35 (m, 1 H, CHO_2C), 5.31 (d, $J = 17.4$ Hz, 1 H, C*H*H=), 5.17 (d, $J = 10.6$ Hz, 1 H, C*H*H=), 4.38 (t, $J =$ Hz, 1 H, OCH), 3.82 (dd, $J = 10.2$, 4.1 Hz, 1 H, OCH), 3.64 (t, $J =$ Hz, 1 H, OCH), 3.54 (m, 3 H, OCH), 3.36 (m, 2 H, OCH), 3.10 (m, 1 H, OCH), 2.94 (dd, $J = 7.2$, 3.2 Hz, 1 H, OCH), 2.11−1.57 (m, 15 H, CH), 1.47 (s, 3 H, CH_3), 1.38 (s, 3 H, CH_3), 1.25 (s, 3 H, CH_3), 1.19 (s, 3 H, CH_3), 1.08 (s, 3 H, CH_3), 0.94 (d, $J = 6.3$ Hz, 3 H, CH_3); HRMS (CI), calcd for $C_{40}H_{55}O_{12}N$ (M + NH_4^+) 741.3724, found 741.3741.

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Supporting Information Available: Procedures for the preparation of and selected physical data for compounds **15−17**, **25−29**, **34**, **35**, **37−39**, **43**, **45**, **46**, **48−53**, **55−63**, **75−82**, and **94−98** and tables of X-ray crystallographic data for compounds **47** and **91** (42 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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