Cyclizations of Hydroxy Dithioketals. New Synthetic Technology for the Construction of Oxocenes and Related Medium-Ring Systems

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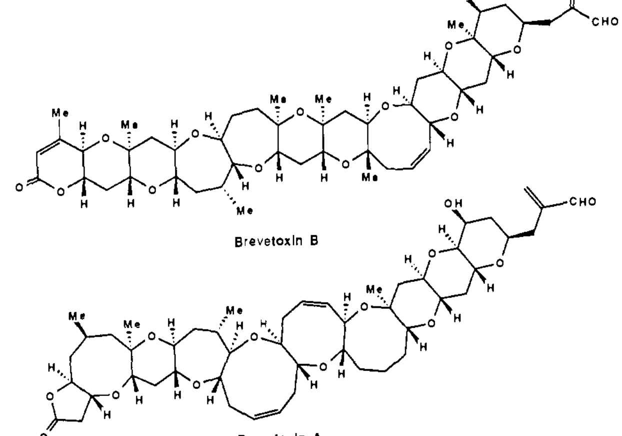
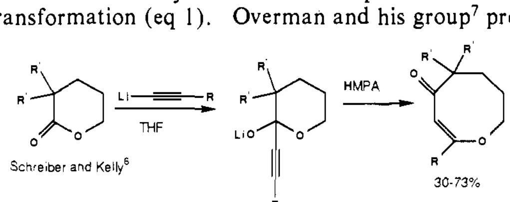
Abstract: A highly efficient cyclization reaction of hydroxy dithioketals leading to oxocene and related systems is described. The Ag^+-induced ring closures occur in high yield under mild conditions and the resulting cyclic systems may be manipulated via homolytic or heterolytic C–S bond cleavage leading to a variety of cyclic systems with defined stereochemistry and flexible substitution. The versatility, scope, limitations, and potential applications of the present technology are discussed.

Oxocene and oxocane ring systems are frequently encountered structural units in naturally occurring substances such as brevetoxins A[1] and B[2] and other marine-derived products.[3,4] Due to


Brevetoxin B
Brevetoxin A

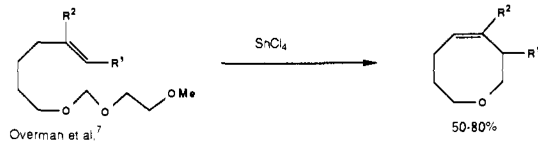
the increasing interest in these bioactive molecules and the well-recognized problems in building medium-sized rings, the synthesis of these structural units became a challenging and attractive synthetic objective.

Until recently, few methods existed for constructing medium-ring cyclic ethers (8–11-membered) due to severe difficulties caused by entropic disfavor, angle deformations, bond opposition forces, and transannular interactions.[5] In 1984, Schreiber and Kelly[6] reported the ring expansion of δ-lactones to oxocenes by insertion of an acetylene unit via the equivalent of a Michael-like transformation (eq 1). Overman and his group[7] prepared me-



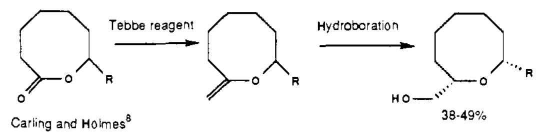
(Eq 1)

dium-ring cyclic ethers by a method involving intramolecular trapping of an oxonium species (generated from the corresponding acetal) by an olefin (eq 2). Carling and Holmes[8] approached



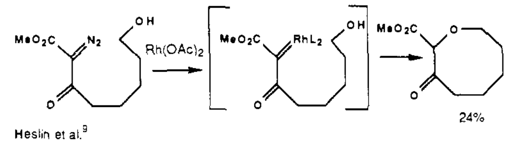
(Eq 2)

the problem from the corresponding lactones which were transformed to cyclic ethers by treatment with Tebbe reagent followed by hydroboration of the resulting enol ether (eq 3). Cyclization



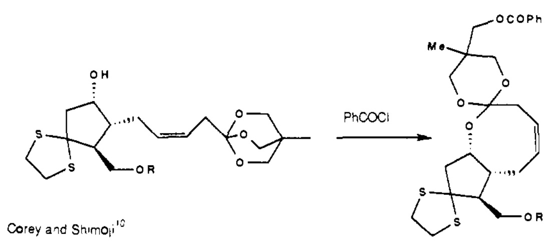
(Eq 3)

involving a rhodium carbenoid leading to an oxocane system, albeit in low yield, was recently reported by Moody and his group[9] (eq 4).



(Eq 4)

In 1983, Corey and Shimoji[10] reported the formation of an oxocene–ortho ester derivative from a hydroxy ortho ester by the action of benzoyl chloride and pyridine (eq 5). Apparently the



(Eq 5)

pyridinium hydrochloride formed in the reaction medium caused transetherification, a process favored no doubt by the conformational effect of the cis double bond in this system. In connection with our program directed toward the total synthesis of brevetoxins A and B, we initiated a search for a practical method for the synthesis of oxocenes and related systems. In this article, we have detailed our own strategy for the construction of these and related systems.[11]

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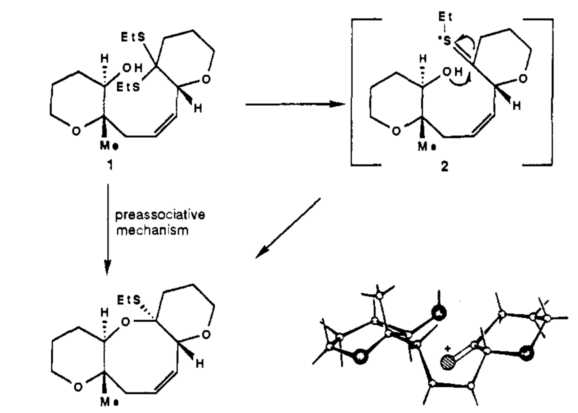
Scheme I. The Hydroxy Dithioketal Strategy for the Construction of Oxocenes



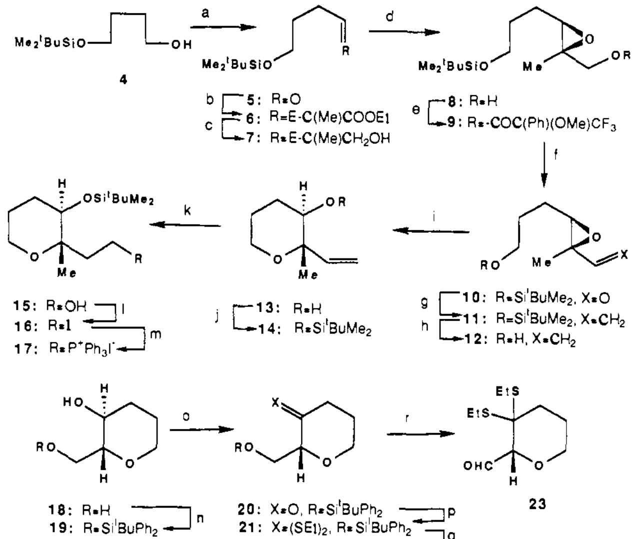
Results and Discussion

The Hydroxy Thioketal Strategy. Of the medium-sized rings, the 8-membered ring appears to be the most strained in the series.[12] This fact was taken into account when designing a synthetic strategy for the oxocene ring system. For example, in a nucleophile/electrophile combination scenario directed toward this system, the looser the transition state (the earlier along the reaction coordinate) the less effect the strain of the product will have on its activation energy.[13] A cationic or a preassociative mechanism[14] would be in line with the postulate that strain in the transition state will be minimized if kinetic assistance of the nucleophile is decreased in comparison to a classical S_N2 reaction. These concepts led to the design of the strategy depicted in Scheme I for the particular case of the brevetoxin B oxocene ring. Activation of the sulfur of the dithioketal **1**, chosen as the precursor, was expected to induce cyclization, either through a polar reactive intermediate (**2**) or directly, via a preassociative mechanism.[14]

Several cyclizations involving C–C bond formation via nucleophilic capture of intermediate thiocarbocations generated from dithioketals have recently been reported.[15] Jencks[14a] has shown that many substitution reactions which occur at a center carrying both a leaving group and an atom able to donate a pair of electrons proceed through a preassociative pathway. This pathway can be described as an unusually loose S_N2 reaction or a mechanism involving a carbocation simultaneously stabilized by the leaving group and the nucleophile. Dreiding and computer-generated models indicated that a relatively strain-free conformation (**2a**, Scheme I) could be realized in which the p orbital of the electrophilic sp^2 carbon of **2** is appropriately oriented for intramolecular capture by the nearby nucleophilic oxygen giving rise to the trans-fused oxocene system **3** (Scheme I).

The attractiveness of this strategy is further amplified if one considers the ease by which sulfonium ions (or their equivalents) can be generated from dithioketals and the synthetically rich chemistry of the residual thio group. Thus, chemoselectivity between oxygen and the sulfur groups should be easily accomplished. After cyclization, the remaining sulfur group could be removed by homolytic or heterolytic[16] C–S bond cleavage leading to the desired functionality. Finally, this method may become practical and suitable for a highly convergent approach to brevetoxins A and B.

Scheme II. Synthesis of Intermediates **17** and **23**[a]



[a] Reagents and conditions: (a) 1.5 equiv of $(COCl)_2$, 2.0 equiv of DMSO, 4.0 equiv of NEt_3, CH_2Cl_2, −78 °C; (b) $Ph_3PC(CH_3)CO_2Et$, C_6H_6, 25 °C, 4 h, 88% from **4**; (c) 2.6 equiv of DIBAL, CH_2Cl_2, −78 °C, 1 h, 100%; (d) 1.0 equiv of (−)-diethyltartrate, 0.75 equiv of Ti(O-^{i}Pr)$_4$, 2.0 equiv of ^{t}BuOOH, CH_2Cl_2, −20 °C, 12 h, 89%, 93% ee; (e) 1.5 equiv of (*S*)-(−)$C_6H_5C(OCH_3)(CF_3)CO_2H$, 1.5 equiv of DCC, 0.45 equiv of DMAP, THF, 25 °C, 16 h, 95%; (f) 4.0 equiv of SO_3·pyr, DMSO–CH_2Cl_2 (1:6), 0 °C, 4 h, 95%; (g) 2.0 equiv of $Ph_3P^+CH_2Br^-$, 2.0 equiv of $NaN(SiMe_3)_2$, THF, 0 °C, 0.5 h, 80%; (h) 1.5 equiv of ^{n}Bu$_4$NF, THF, 25 °C, 1 h, 100%; (i) 0.08 equiv of CSA, CH_2Cl_2, 0 °C, 15 min, 91%; (j) 1.25 equiv of ^{t}BuMe$_2$SiOTf, 2.5 equiv of 2,6-lutidine, 0 °C, 10 min, 91% from **12**; (k) 1.3 equiv of 9-BBN, THF, 0 °C, 1 h, then 4.0 equiv of NaOH, 4.5 equiv of H_2O_2, 0 °C, 1.5 h, 85%, (l) 2.0 equiv of I_2, 3.0 equiv of imidazole, C_6H_6, 25 °C, 20 min, 90%; (m) 8.0 equiv of PPh_3, CH_3CN, 90 °C, 24 h, 94%; (n) 1.28 equiv of ^{t}BuPh$_2$SiCl, 2.8 equiv of imidazole, DMF, 0 °C, 1.5 h, 97%; (o) 1.5 equiv of $(COCl)_2$, 2.0 equiv of DMSO, 4.0 equiv of Et_3N, CH_2Cl_2, −78 °C, 45 min, 92%; (p) 4.5 equiv of EtSH, 0.5 equiv of $TiCl_4$, CH_2Cl_2, −50 to −10 °C, 0.5 h, 88%; (q) 1.5 equiv of ^{n}Bu$_4$NF, THF, 25 °C, 3 h, 96%; (r) 5.0 of equiv SO_3·pyr, 5.0 equiv of NEt_3, DMSO–CH_2Cl_2 (1:1), 0 °C, 1.5 h, 90%.

Model Studies for Brevetoxins A and B. In order to test the feasibility of the above strategy and its potential in the total synthesis of the brevetoxins, the hydroxy dithioketal **1** (Schemes I and III) was synthesized in optically active form as it corresponds to brevetoxin B. The synthesis involved coupling of phosphonium salt **17** and aldehyde **23** (Schemes II and III); two fragments were synthesized as summarized in Scheme II. The synthesis of phosphonium salt **17** started with the monosilyl ether of 1,4-butanediol (**4**) which was oxidized under Swern conditions to afford the aldehyde **5**. In situ reaction of **5** with (carbethoxyethylidene)triphenylphosphorane furnished the *E* olefin **6** as the major product (88% yield, *E*:*Z* ratio ca 8:1, separated by chromatography). Reduction of **6** with DIBAL gave in quantitative yield the alcohol **7**, which was subjected to Sharpless asymmetric epoxidation conditions[17] to afford epoxide **8** in 89% yield (93% ee, determined by ^{1}H NMR analysis of its Mosher[18] ester **9**). The aldehyde **10**, obtained by SO_3·pyr oxidation was reacted immediately with the appropriate phosphorane, to afford olefin **11** in 80% yield. The silyl protecting group was then removed from **10** with fluoride ion leading to hydroxy epoxide **12**, which was cyclized and protected by a one-pot procedure. Thus, **12** was dissolved in CH_2Cl_2 and treated sequentially with CSA, 2,6-lutidine, and Me$_2$^{t}BuSiOTf, to afford the tetrahydropyran derivative **14** via alcohol **13** (91% overall yield). Finally, the olefin **14** was hy-

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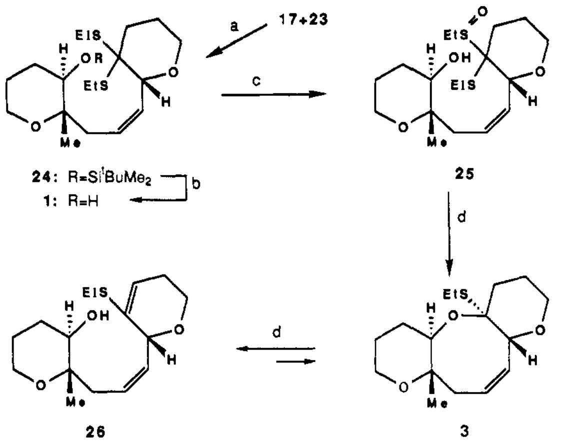
Scheme III. Synthesis of Hydroxy Dithioketal **1** and Its Cyclization via Oxidation–Acid Activation[a]



[a] Reagents and conditions: (a) 1.0 equiv of n-BuLi, 1.0 equiv of **17**, 3.0 equiv of HMPA, 0.86 equiv of **23**, THF, −78 °C, 1 h, 78%; (b) 1.8 equiv of Bu_4NF, THF, 25 °C, 2 h, 100%; (c) 1.0 equiv of mCPBA, CH_2Cl_2, 0 °C; (d) 0.2 equiv of CSA, 45 min, 55% **3** and 29% **26**.

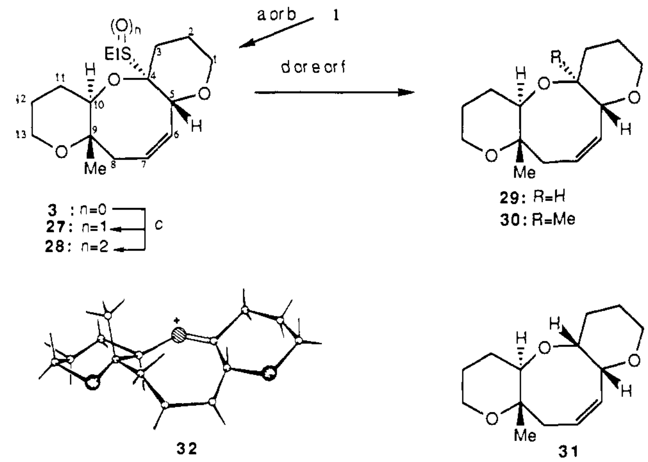
droborated with 9-BBN to give alcohol **15**, which was sequentially transformed[19] to iodide **16** and phosphonium salt **17** in 69% overall yield for the three steps.

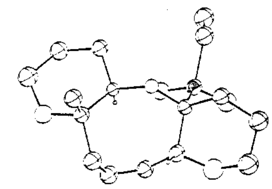
The synthesis of the other requisite segment, dithioketal aldehyde **23** began from the readily available diol **18**[20] and proceeded as also outlined in Scheme II. Thus, selective silylation of **18** was accomplished in high yield (97%) leading to the monosilyl ether **19**. Swern oxidation of alcohol **19** gave the crystalline ketone **20** (92% yield, mp 70–71.5 °C from ether–hexane). Careful thioketalization of **20** was accomplished with EtSH–$TiCl_4$[21] in CH_2Cl_2 at -50 to -10 °C, furnishing dithioketal **21** in 88% yield. Variance from these conditions produced either a substantial amount of unreacted starting material (**20**) or desilylation. Fluoride-induced deprotection of the silyl ether **21** followed by oxidation with SO_3·pyr–Et_3N, 1:1 stoichiometry) furnished the highly labile aldehyde **23** in 90% yield. Elimination of one ethylthio group from **23** occurred quite readily, leading to the corresponding α,β-unsaturated aldehyde, which itself was rather unstable.

The aldehyde **23** was immediately used for the Wittig reaction with the ylide derived from **17** to produce olefin **24** (Scheme III). Thus, phosphonium salt **17** was treated with ^{n}BuLi at -78 °C in THF–HMPA to produce the corresponding ylide to which aldehyde **23** was added (-78 to 0 °C). The cis olefin **24** was isolated in 78% yield and structurally defined by spectroscopic means ($J_{6,7}$ = 11.3 Hz by decoupling experiments). Subsequent desilylation of **24** led, quantitatively, to the requisite hydroxy dithioketal **1**.

Several initial attempts to induce ring closure in **1** using conventional methods for dithioketal hydrolysis such as $CuCl_2$–DMF,[22a] $HgCl_2$–MeCN,[22b] NO_2BF_4,[22c] and MeI–acetone[22d] failed. We then turned our attention to a two-step procedure involving oxidation–acid activation.[23] Thus, exposure of the hydroxy dithioketal **1** to a stoichiometric amount of mCPBA (CH_2Cl_2, 0 °C) gave, after 5 min, the intermediate sulfoxide **25** in high yield which was then treated in situ with CSA catalyst (0 to 25 °C) to furnish the oxocene derivative **3** (55%) and the hydroxy thioenol ether **26** (29% yield). The indicated stereochemistry of the newly generated stereogenic center in **3** was tentatively assigned at this point on the basis of transition-state modeling (Scheme I, **2a**); it was later confirmed by an X-ray crystallographic analysis of a crystalline derivative (vide infra). Treatment of the oxocene **3** or the hydroxy thioenol ether **26** with CSA catalyst in CH_2Cl_2 at 25 °C for 1 h resulted in essentially the same ratio of the two compounds (**3**:**26** ca. 2:1). This observation suggested that the acidic environment of the cyclization was producing a thermodynamic mixture of the two compounds, presumably through the expected thiocarbocation intermediate. This conclusion stirred us toward nonacidic conditions for the efficient generation of oxocene **3**, under which the strained octacycle would not rupture once formed.

Scheme IV[a]





ORTEP Drawing of **28**

[a] Reagents and conditions: (a) 4.0 equiv of $AgClO_4$, 5.0 equiv of $NaHCO_3$, 3A MS, silica gel, CH_3NO_2, 25 °C, 3 h, 93%; (b) 1.1 equiv of NCS, 1.1 equiv of $AgNO_3$, 2.0 equiv of 2,6-lutidine, 3A MS, silica gel, CH_3CN, 25 °C, 5 min, 92%; (c) 1.5 equiv of mCPBA, CH_2Cl_2, 0 °C, 1 h, 86%; (d) 2.5 equiv of Ph_3SnH, 0.2 equiv of AIBN, toluene, 110 °C, 2 h, 95%; (e) 2.0 equiv of mCPBA, CH_2Cl_2, 0 °C, 1 h, then 1.0 equiv of BF_3·Et_2O, 5.0 equiv of Et_3SiH, CH_2Cl_2, 0 °C, 2 h, 91%; (f) 2.0 equiv of mCPBA, CH_2Cl_2, 0 °C, 1 h, then 5.0 equiv of $AlMe_3$, 0 °C, 1 h, 93%.

A highly efficient method for oxocene formation and subsequent manipulation of the mixed thioketal formed are exhibited in Scheme IV. After considerable experimentation, an excellent system for the efficient cyclization of **1** to **3** was found: *N*-chlorosuccinimide (NCS)–silver nitrate ($AgNO_3$)[24] in the presence of 2,6-lutidine, dry silica gel, and 3A molecular sieves (MS) in acetonitrile (MeCN) at 25 °C produced, in 5 min, oxocene **3** in 92% yield. The addition of silica gel led to a ca. 3-fold rate increase of cyclization. Presumably, adsorption onto silica gel induces a conformational change favoring the ring closure. This reaction embodies a number of other interesting features. The $AgNO_3$ must be added before the NCS for favorable results. The 2,6-lutidine is needed to buffer the reaction medium, otherwise thioenol ether **26** (Scheme III) starts to appear. Systematic exploration of reaction conditions (vide infra) led to another excellent combination of reagents, which proved to be even more reliable in highly complex situations: silver perchlorate ($AgClO_4$)–sodium bicarbonate ($NaHCO_3$) or pyridine in nitromethane ($MeNO_2$) converted **1** to **3** in 93% yield. Small amounts (ca. 5%) of the thioenol ether **26** (Scheme III) was also formed in these $AgClO_4$-induced reactions.

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Table I. Conditions for the Cyclization of Hydroxy Dithioketal 1[a]

entry	solvent	Ag salt	base	time, h	cyclized product, % yield	thioenol ether, % yield
1	CH_3CN	$AgNO_3$–NCS	2,6-lutidine	0.35	92	trace
2	THF	$AgNO_3$–NCS	2,6-lutidine	0.5	73	18
3	benzene	$AgNO_3$–NCS	2,6-lutidine	0.5	41	53
4	CH_2Cl_2	$AgNO_3$–NCS	2,6-lutidine	1	18	63
5	CH_3CN	$AgNO_3$–NCS	pyridine	0.25	91	trace
6	CH_3NO_2	$AgNO_3$	$NaHCO_3$	2	89	7
7	CH_3NO_2	$AgClO_4$	$NaHCO_3$	2	92	5
8	CH_3NO_2	$AgPF_6$	$NaHCO_3$	1.5	16	36
9	THF	$AgClO_4$	$NaHCO_3$	4	21	56
10	DMSO	$AgClO_4$	$NaHCO_3$	12	0[b]	0
11	benzene	$AgClO_4$	$NaHCO_3$	6	9	30[c]
12	CH_2Cl_2	$AgClO_4$	$NaHCO_3$	6	trace[d]	0
13	CH_3CN	$AgClO_4$	$NaHCO_3$	4	15	67
14	CH_3NO_2	$AgClO_4$	Na_2CO_3	2	42	33
15	CH_3NO_2	$AgClO_4$	NaOAc	3	50	50
16	CH_3NO_2	$AgClO_4$	pyridine	2	93	5
17	CH_3NO_2	$AgClO_4$	2,6-lutidine	3	45	45
18	CH_3NO_2	$AgClO_4$	$(^iPr)_2NEt$	2	5	80
19	CH_3NO_2	$AgClO_4$	Et_3N	1	9	79
20	CH_3NO_2	$AgOCOCF_3$	$NaHCO_3$	2	50	44
21	CH_3NO_2	$AgBF_4$	$NaHCO_3$	2	24	56
22	CH_3NO_2	$AgOSO_2CF_3$	$NaHCO_3$	1.5	90	8
23	CH_3NO_2	Ag–Ts	$NaHCO_3$	2	14	69

[a] Experiments were performed at 25 °C on 0.05–5.0-mmol scale. Substrate concentration was 0.05 M for entries 1–5 or 0.1 M for entries 6–23. Reagents were used in excess: Ag salt (3.0 equiv), NCS (1.5 equiv), base (2.0 equiv for entries 1–5, 3.0 equiv for entries 6–23). In all experiments flamed-dried 4A molecular sieves and flamed-dried silica gel-60 (E. Merck, 0.040–0.063-mm particle size) were added (2 × substrate weight). [b] Starting material was recovered in 79% yield. [c] Three other, as yet unidentified, products were formed. [d] Decomposition was observed.

With the oxocene derivative **3** secured, attention was then focused on replacement of the remaining sulfur group with appropriate substituents (Scheme IV). Homolytic cleavage of the C–S bond in **3** occurred cleanly upon exposure to $^nBu_3SnH$–AIBN system in toluene at reflux, furnishing exclusively the desired 4,5-*trans*-oxocene **29**, but the reaction was sluggish and incomplete. The more reactive Ph_3SnH, however, converted, under the same conditions (AIBN catalyst, toluene, reflux) **3** to **29** in 95% yield. The trans stereochemistry of the 4,5 junction in **29** was based on the coupling constant $J_{4,5}$ = 9.2 Hz determined by ^1H NMR decoupling experiments. Heterolytic C–S bond cleavage provided a more versatile route to oxocenes (Scheme IV). Sulfones and sulfoxides have been reported to behave as good leaving groups in the presence of Lewis acids.[16] Thus, it was expected that oxidation of sulfur to the sulfoxide and/or sulfone (to enhance leaving and complexing ability of the group) would facilitate its departure, particularly in the presence of the neighboring ring oxygen lone pair of electrons. These expectations were fully realized and led to a number of new and highly effective transformations. Thus, oxidation of **3** with mCPBA (1.5 equiv) led to sulfoxide **27** (44%) and the highly crystalline sulfone **28** (42%, mp 97–98.5 °C, from ether–hexane). Less (1.1 equiv) or more (2.2 equiv) mCPBA, produced selectively, either sulfoxide **27** (95% yield, single stereoisomer) or sulfone **28** (92% yield). An X-ray crystallographic analysis of sulfone **28** confirmed the expected stereochemistry for this compound and its pregenitors **27** and **3** (see ORTEP drawing, Scheme IV). Treatment of either the sulfoxide **27** or sulfone **28** with $BF_3 \cdot Et_2O$ in the presence of excess Et_3SiH furnished, exclusively and in excellent yield, the 4,5-*trans*-oxocene **29** (≥90% yield). This transformation could be carried out more conveniently from the sulfide **3**, without isolation of the intermediates **27** and/or **28**, in one pot (96% overall yield). Trimethylaluminum ($AlMe_3$) also reacted with intermediates **27** and **28**, to afford the methylated compound **30** in 93% yield via the one-pot procedure. The syn relationship of the newly implanted methyl group at C-4, with the C-10 proton, was assigned on the basis of NOE studies. Thus, irradiation of the C-4 methyl signal (200 MHz, C_6D_6, δ 1.22) resulted in a 30% enhancement of the C-10 proton signal (δ 3.91). The observed retention of stereochemistry in these reactions implicates oxonium species **32** (Scheme IV) as an intermediate. Molecular models demonstrate severe nonbonding interactions between the incoming nucleophile, the 8β-H and the 9-Me, as well as torsional strain[26] with the 3β-H and 5-H in the transition state leading to the 4,5-*cis*-oxocene by β-attack on **32**. In contrast, α-attack may proceed via a significantly less congested transition state leading to the observed 4,5-trans product. Attack of tin hydride reagents on the intermediate radical should encounter similar interactions. This outcome is also in accord with the recent proposal of Cieplak[27] favoring axial (α) attack of the "cyclohexane-like" region of oxonium system **32** by two-electron stabilization of the developing antibonding orbital (σ^*) with the occupied orbitals of the C-3β–H and C-5–H bonds. Interestingly, DIBAL reacted rapidly (-78 °C, 15 min) with the sulfone **28** to afford a mixture of **29** and its cis isomer **31** in ca. 1:1 ratio (94% combined yield, Scheme IV).[28] The cis isomer **31** exhibited a J value for $H_{4,5}$ of 3.7 Hz as determined from decoupling studies. Since DIBAL is a stronger hydride donor than Et_3SiH, this cis isomer (**31**) can arise from β-attack on oxonium species **32** before the leaving group has fully diffused from the solvent cage. This result is also in line with the notion that, since reaction with DIBAL occurs earlier on the reaction coordinate, the more highly strained cis product has less influence on the activation energy of the reaction.

Cyclization Conditions. Our experiences with the cyclization of various hydroxy dithioketals made it clear that the reaction was very sensitive to experimental conditions. This observation led us to investigate the effect of various silver salts, bases, and solvents. Table I summarizes the findings of these studies. The results showed that the best solvents for this reaction were acetonitrile and nitromethane (entries 1, 6, 7, 16, 22). Changing to a solvent of lower dielectric constant such as tetrahydrofuran, methylenechloride, or benzene, led to deleterious results (entries 2–4, 9–12). Most importantly, it was demonstrated that the use of nitromethane, a solvent of high dielectric constant, allowed the reaction to proceed without the requirement of NCS (entries 6, 7, 16, 22). From the various thiophilic reagents studied, silver salts were found to be the most effective. From those investigated, $AgClO_4$, $AgNO_3$, and $AgOSO_2CF_3$ gave consistently higher yields of cyclic products (e.g. entries 1, 6, 7, 16, 22). However, when $AgCOOCF_3$, $AgBF_4$, silver tosylate, and $AgPF_6$ were used considerably higher amounts of the undesired thioenol ether were

(26) Cherest, M.; Felkin, H. *Tetrahedron Lett.* **1968**, 2205.
(27) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540.
(28) Janseen, C. G. M.; Lier, P. M. V.; Schipper, P.; Simons, L. G. J. G.; Godefroi, E. F. *J. Org. Chem.* **1980**, *45*, 3159.

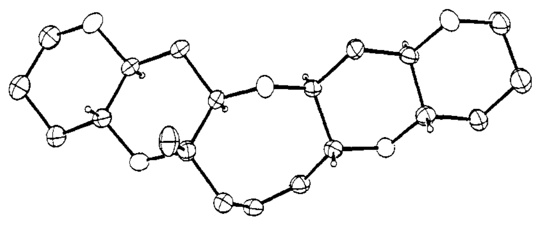


Figure 1. ORTEP drawing of **51**.

formed. It appears that hard counterions favor formation of thioenol ether, whereas the silver salts to the "super" acids are the reagents of choice for ring formation. The effect of the base on the reaction was also investigated. As seen from the results of Table I, the preferred bases are $NaHCO_3$ from the inorganic bases and pyridine from the organic bases in the case of $AgClO_4$–nitromethane. In the case of $AgNO_3$–NCS, 2,6-lutidine proved to be an excellent base.

Versatility and Scope. The versatility and scope of these reactions were tested in a number of other situations. Tables II and III summarize our findings. Thus, a series of hydroxy dithioketals were synthesized,[29] by methods similar to those described in Scheme II for the synthesis of **1**, and subjected to cyclization. Table II includes the conditions, products, and yields for these experiments. As one can infer from these data, substrates with a cis double bond led efficiently to oxocene systems (entries 1–6). Systems of higher rigidity and steric demand due to the presence of additional rings, cyclized at lower rates, but also in excellent yields (entries 2–4). However, removal of the cis double bond in the substrate, as in entry 8 (compound **39** obtained by diimide reduction of **24** and desilylation) resulted in failure to cyclize. Instead, ketone **47** was formed under various conditions, presumably by trapping of the intermediate sulfonium species by traces of water. It thus appears that a cis double bond is essential for the success of this process. Another limitation of the cyclization reaction was detected when substrate **38** (entry 7) failed to produce any cyclic product, leading, instead, to the ketone **46**, again showing that a reduction in the number of rotational degrees of freedom is necessary for cyclization to occur. A rather interesting cyclization is presented in entry 9 in which substrate **40** reacted with $AgClO_4$–$NaHCO_3$ in CH_3NO_2 to afford the highly strained and sterically congested 9-membered oxocycle **48**, albeit in low yield (30%). This last reaction may prove useful in constructing the 9-membered ring system of brevetoxin A. Further work to refine it and apply it to the aforementioned problem is in progress.

Table III summarizes some chemistry of the cyclized products leading to a number of interesting polycyclic heterocycles. Thus, in entries 1, 3, 4, and 5, the sulfur group was replaced with a hydrogen (H) with retention of stereochemistry, whereas in entries 2, 6, and 7 a methyl group (Me) was implanted, also with retention of stereochemistry, by using the methods described above. An X-ray crystallographic analysis (see ORTEP drawing, Figure 1) of the crystalline pentacyclic compound **51** (mp 209–210 °C ether–CH_2Cl_2) confirmed the assignment of stereochemistry for this compound (and the other compounds of Table III by analogy and NMR comparison). Also, note the twisting of the 8-membered ring in this system, relieving the 1,3 diaxial interaction between the hydrogens across the oxygen bridge. These results demonstrate the potential of this technology to the construction of novel polycyclic systems and the total synthesis of the brevetoxins A and B in which these functionalities are present.

Conclusion

A highly efficient cyclization reaction of hydroxy dithioketals leading to oxocene systems is described. The versatility, scope, and limitations of this process have been investigated. The applicability of this method to the formation of other medium oxorings has also been demonstrated. The synthetic strategy outlined should be applicable to the total synthesis of brevetoxins A and B. Furthermore, the concepts and guidelines utilized in this strategy toward oxocenes should be helpful in designing further technology for building other medium-sized rings. The described hydroxy dithioketal cyclization has two advantages for oxocycle formation. Firstly, ring closures occur in high yields under mild conditions and secondly, the ring juncture may easily be manipulated via either homolytic or heterolytic C–S bond cleavage, leading to specific stereochemistry and flexible substitution. In summary, a highly flexible and versatile method for the construction of oxocenes and related systems is presented. This method is currently being applied in the total synthesis of brevetoxins A and B.

Experimental Section

General Procedures. NMR spectra were recorded on one of the following instruments: IBM WP-200, Bruker WM-250, IBM AF-250, or Bruker AM-500. IR spectra were recorded on a Perkin-Elmer Model 781 infrared spectrophotometer. UV and visible spectra were recorded on a Perkin-Elmer Model 553 ultraviolet–visible spectrophotometer.

High-resolution mass spectra (HRMS) were recorded on a VG 7070 HS mass spectrometer under chemical ionization (CI) conditions or on a VC ZAB E instrument under FAB conditions. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN, or Robertson Laboratories, Inc., Madison, NJ.

All reactions were monitored by thin-layer chromatography carried out on 0.25-mm E. Merck silica gel plates (60F-254) with UV light and 7% ethanolic phosphomolybdic acid–heat as developing agent. Preparative layer chromatography was performed on 0.5 or 0.25 mm × 20 cm × 20 cm E. Merck silica gel plates (60F-254). E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography.

All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise noted. Yields refer to chromatographically and spectroscopically (^1H NMR) homogeneous materials, unless otherwise stated.

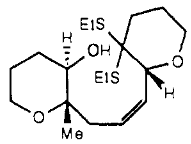
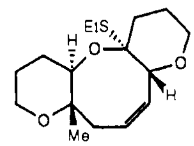
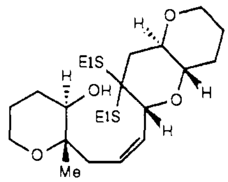
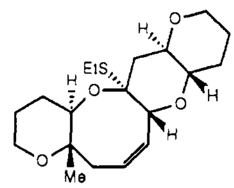
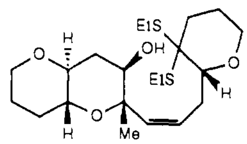
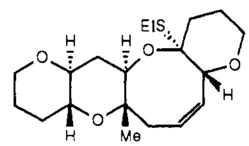
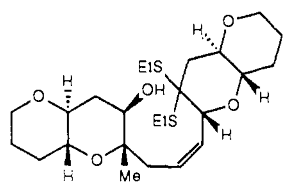
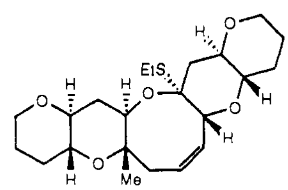
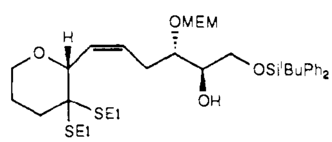
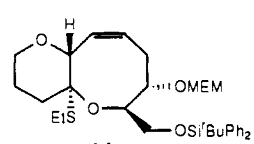
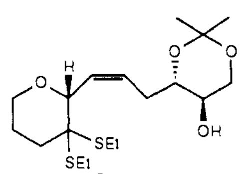
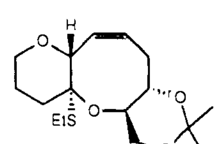
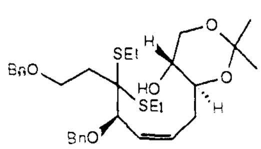
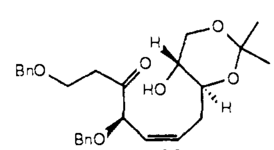
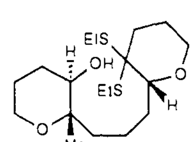
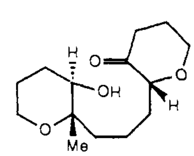
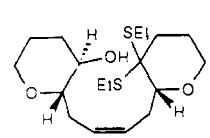
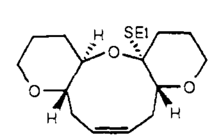
4-(*tert*-Butyldimethylsiloxy)-1-butanol (4). *tert*-Butyldimethylsilyl chloride (30.14 g, 0.20 mol) was added in one portion to a cooled (0 °C) and stirred solution of 1,4-butanediol (100 g, 1.11 mol) and imidazole (17 g, 0.25 mol) in dry DMF (400 mL) under an argon atmosphere. The reaction mixture was stirred for 30 min before dilution with ether (2.0 L) and washing with aqueous saturated NH_4Cl solution (2 × 300 mL) and brine (200 mL) and then dried ($MgSO_4$). Concentration followed by flash column chromatography (silica, 30% ether in petroleum ether) gave compound 4 (33.05 g, 81%). **4**: oil; R_f = 0.28 (silica, 30% ether in petroleum ether); IR (neat) ν_{max} 3360 (s, OH), 2955, 2862, 1475, 1468, 1392, 1258, 1100, 842, 780, 715, 622 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.64 (m, 4 H, CH_2O), 2.60 (s, 1 H, O*H*), 1.64 (m, 4 H, CH_2), 0.88 (s, 9 H, ^tBu), 0.04 (s, 6 H, Si*Me*$_2$); HRMS calcd for $C_{10}H_{25}O_2Si$ $(M + H)^+$ 205.1624, found 205.1657.

Ethyl (*E*)-6-(*tert*-Butyldimethylsiloxy)-2-methyl-2-hexenoate (6). To a stirred mixture of oxalyl chloride (6.6 mL, 100 mmol) and dichloromethane (400 mL) at -78 °C was added dry DMSO (7.1 mL, 75 mmol) dropwise, followed by addition of alcohol 4 (10.3 g, 50 mmol) in dichloromethane (50 mL). After 1 h the reaction mixture was treated dropwise with triethylamine (28.0 mL, 200 mmol) and allowed to warm to room temperature (ca. 20 min), and then the resulting aldehyde (**5**) was reacted with (carbethoxyethylidene)triphenylphosphorane (21.7 g, 60 mmol), for 4 h. The reaction mixture was diluted with ether (1.5 L), washed with H_2O (2 × 100 mL) and brine (50 mL) and dried ($MgSO_4$). Concentration followed by flash chromatography (silica, 5% ether in petroleum ether) afforded the olefin **6** (12.6 g, 88%). **6**: oil; R_f = 0.48 (silica, 10% ether in petroleum ether); IR (neat) ν_{max} 2960, 2935, 2900, 2865, 1720 (s, COOEt), 1655 (m, C=C(CH_3)COOEt), 1475, 1465, 1395, 1370, 1265, 1200, 1135, 1105, 840, 760 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.77 (t, *J* = 6.2 Hz, 1 H, *H*C=C), 4.17 (q, *J* = 7.0 Hz, 2 H, OCH_2CH_3), 3.62 (t, *J* = 6.2 Hz, 2 H, OCH_2), 2.25 (dt, *J* = 7.4, 7.4 Hz, 2 H, CH_2C=C), 1.83 (s, 3 H, CH_3C=C), 1.65 (dq, *J* = 6.3, 6.3 Hz, 2 H, CH_2), 1.29 (t, *J* = 7.0 Hz, 3 H, CH_2CH_3), 0.89 (s, 9 H, ^tBu), 0.05 (s, 6 H, Si*Me*$_2$); HRMS calcd for $C_{15}H_{31}O_3Si$ $(M + H)^+$ 287.2034, found 287.2023.

(*E*)-6-(*tert*-Butyldimethoxylsiloxy)-2-methyl-2-hexen-1-ol (7). DIBAL (50 mL, 125 mmol, 1 M in hexanes) was added dropwise to a stirred solution of ester **6** (5.5 g, 19 mmol) in dry dichloromethane (100 mL) at −78 °C. After stirring of the solution for an additional 45 min at −78 °C, the excess DIBAL was quenched with methanol (5 mL) and the reaction mixture was poured directly into EtOAc (300 mL) and a saturated aqueous solution of sodium potassium tartrate (50 mL). After

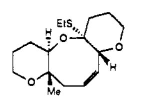
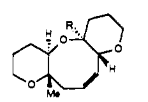
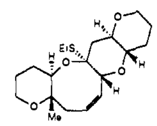
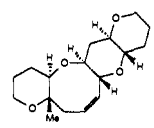
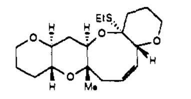
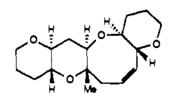
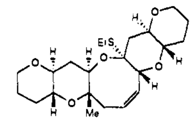
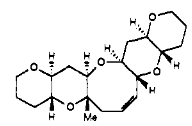
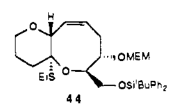
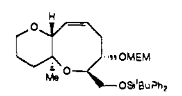
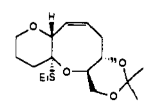
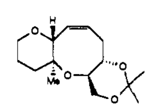
(29) Compound **39** (Table II) was prepared by diimide reduction of **24**, followed by desilylation, whereas the rest of the hydroxy dithioketals shown in Table II were synthesized by similar chemistry described for **1** with the Wittig reaction as the key coupling process to join the appropriate fragments.

Table II. Cyclization of Hydroxy Thioketals

Entry	Hydroxythioketal	Conditions[a]	Time(h)	Cyclized Product	Yield(%)
1	 1	Method B	0.5	 3	92
2	 33	Method B	0.5	 41	82
3	 34	Method A	0.5	 42	85
4	 35	Method A	0.5	 43	91
5	 36	Method B	1.0	 44	70
6	 37	Method A	4.0	 45	79
7	 38	Method A	4.0	 46	75
8	 39	Method B	0.5	 47	74
9	 40	Method A	1.0	 48	30

[a] Method A: 4.0 equiv of $AgClO_4$, 5.0 equiv of $NaHCO_3$, 3A MS, silica gel, CH_3NO_2, 25 °C; method B: 1.1 equiv of NCS, 1.1 of equiv $AgNO_3$, 2.0 equiv of 2,6-lutidine, 3A MS, silica gel, CH_3CN, 25 °C.

Table III. Reactions of Oxocene and Oxecane Mixed Thioketals with Hydride and Methyl Donors

Entry	Compounds	Conditions[a]	Product	Yield(%)
1	 3			
		Method A	29: R=H	96
		Method B	29: R=H	95
2		Method C	30: R=Me	93
3	 41	Method B	 49	92
4	 42	Method B	 50	89
5	 43	Method B	 51	91
6	 44	Method C	 52	76
7	 45	Method C	 53	67

[a] Method A: 2.0 equiv of mCPBA, CH_2Cl_2, 0 °C, 1 h, then 1.0 of equiv $BF_3 \cdot Et_2O$, 5.0 equiv of Et_3SiH, CH_2Cl_2, 0 °C, 2 h; method B: 2.5 equiv of Ph_3SnH, AIBN catalyst toluene, 110 °C, 2 h; method C: 2.0 equiv of mCPBA, CH_2Cl_2, 0 °C, 1 h, then 5.0 equiv of $AlMe_3$, 0 °C, 1 h.

shaking and separation, the organic portion was dried ($MgSO_4$) and concentrated and the allylic alcohol **7** (4.7 g, 100%) was carried on directly to the next step. **7**: oil; R_f = 0.34 (silica, 30% ether in petroleum ether); IR (neat) ν_{max} 3360 (s, OH), 2960, 2935, 2900, 2865, 1475, 1464, 1395, 1260, 1100, 1010, 840, 760 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.41 (br t, J = 7.3 Hz, 1 H, HC=C), 4.00 (br s, 2 H, CH_2OH), 3.61 (t, J = 6.4 Hz, 2 H, OCH_2), 2.09 (dt, J = 7.5, 7.3 Hz, 2 H, CH_2C=C), 1.67 (s, 3 H, CH_3C=C), 1.60 (dq, J = 6.5, 6.4 Hz, CH_2), 1.42 (br s, 1 H, OH), 0.90 (s, 9 H, ^{t}Bu), 0.05 (s, 6 H, SiMe_2); HRMS calcd for $C_{13}H_{29}O_2Si$ (M + H)$^+$ 245.1929, found 245.1906.

4,5-Anhydro-1-*O*-(*tert*-butyldimethylsilyl)-5-methyl-2,3-dideoxy-D-*threo*-hexitol (8). To a stirred solution of the allylic alcohol **7** (4.6 g, 19.0 mmol), (−)-diethyltartrate (3.3 mL, 19.0 mmol), and dry dichloromethane (100 mL) at −20 °C was added titanium(IV) isopropoxide (4.2 mL, 14.2 mmol). After 15 min *tert*-butyl hydroperoxide (8.8 mL, 38 mmol, 4.3 M in 1,2-dichloromethane) was added and the resulting solution was kept at −20 °C overnight (16 h). The reaction mixture was diluted with ether (100 mL) and saturated aqueous Na_2SO_4 (4.2 mL), stirred vigorously for 1 h, and filtered through a pad of Celite. Concentration of the filtrate, followed by flash chromatography (silica, 40% ether in petroleum ether) gave the epoxide **8** (4.4 g, 89%, 93% ee). **8**: oil; R_f = 0.11 (silica, 30% ether in petroleum ether); $[\alpha]^{21}{}_D$ +10.7° (*c* 2.21, $CHCl_3$); IR (neat) ν_{max} 3440 (s, OH), 2960, 2935, 2900, 2865, 1475, 1465, 1395, 1370, 1260, 1100, 1045, 840, 760 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.76–3.63 (m, 3 H, CH_2O), 3.58 (dd, J = 12.2, 8.4 Hz, 1 H, CH_2OH), 3.07 (m, 1 H, H-epox), 1.82 (dd, J = 8.4, 4.6 Hz, 1 H, OH), 1.67 (m, 4 H, CH_2), 1.29 (s, 3 H, CH_3), 0.89 (s, 9 H, ^{t}Bu), 0.05 (s, 6 H, SiMe_2); HRMS calcd for $C_{13}H_{29}O_3Si$ (M + H)$^+$ 261.1888, found 261.1920.

4,5-Anhydro-1-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-5-*C*-methyl-L-*threo*-hexitol β,β,β-Trifluoro-α-methoxyhydratropate (9). A stirred heterogeneous mixture of the epoxy alcohol **8** (30 mg, 0.11 mmol), (s)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (40 mg, 0.17 mmol), DCC (35 mg, 0.17 mmol), and dry THF (1.0 mL) at 25 °C was treated with DMAP (6 mg, 0.05 mmol). After 16 h the solvent was removed and the residue was subjected to flash chromatography (silica, 15% ether in petroleum ether) to afford the ester **9** (49 mg, 95%). **9**: oil; R_f = 0.37 (silica, 15% ether in petroleum ether); IR (neat) ν_{max} 2960, 2935, 2865, 1760 (s, COOR), 1475, 1455, 1260, 1180, 1100, 840, 760 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) major diastereomer, 7.60–7.39 (m, 5 H, aromatic), 4.41–4.15 (2 × d, J = 11.5 Hz, 2 × 1 H, CH_2O_2C), 3.56 (s, 3 H, CH_3O), 2.88 (m, 1 H, H-epox), 2.75–2.50 (m, 4 H, CH_2), 1.27 (s, 3 H, CH_3), 0.89 (s, 9 H, ^{t}Bu), 0.05 (s, 6 H, SiMe_2).

***tert*-Butyl[[(4*R*,5*R*)-4,5-epoxy-5-methyl-6-heptenyl]oxy]dimethylsilane (11).** To a stirring mixture of the epoxy alcohol **8** (4.0 g, 15 mmol), dry DMSO (10 mL), triethylamine (14.0 mL, 105 mmol), and dichloromethane (60 mL) at 0 °C was added pyridine–sulfur trioxide complex (10.0 g, 60 mmol). After 4 h at 0 °C the reaction mixture was diluted with ether (200 mL) and washed with H_2O (2 × 50 mL) and brine (50 mL). Drying ($MgSO_4$) and concentration afforded the crude aldehyde **10** (ca. 95% pure) which was used immediately.

To a stirred suspension of methyltriphenylphosphonium bromide (10.7 g, 30 mmol) in dry THF (70 mL) at 0 °C was added sodium bis(trimethylsilyl)amide (30 mL, 30 mmol, 1 M in THF). After 30 min the yellow ylide was treated with the crude aldehyde **10** in dry THF (30 mL) and the reaction was stirred for 30 min at 0 °C. Dilution with ether (200 mL) followed by washing with H_2O (2 × 50 mL) and brine (50 mL), drying ($MgSO_4$), and concentration gave an orange oil. Flash chromatography (silica, 5% ether in petroleum ether) afforded the pure olefin **11** (6.2 g, 80%). **11**: oil; R_f = 0.58 (silica, 10% ether in petroleum ether); $[\alpha]^{21}{}_D$ −2.1° (*c* 1.13, $CHCl_3$); IR (neat) ν_{max} 2960, 2935, 2900, 2865, 1390, 1260, 1100, 840, 760 cm^{-1}: ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.65 (dd, J = 17.4, 10.7 Hz, 1 H, HC=CH_2), 5.31 (dd, J = 17.4, 1.2 Hz, 1 H, HC=CH_2), 5.18 (dd, J = 10.7, 1.2 Hz, 1 H, HC=CH_2), 3.67 (m, 2 H, CH_2O), 2.83 (m, 1 H, H-epox), 1.69 (m, 4 H, CH_2), 1.39 (s, 3 H, CH_3), 0.89 (s, 9 H, ^{t}Bu), 0.05 (s, 6 H, SiMe_2); HRMS calcd for $C_{14}H_{29}O_2Si$ (M + H)$^+$ 257.1937, found 257.1975.

(4*R*,5*R*)-4,5-Epoxy-5-methyl-6-hepten-1-ol (12). To the silyl ether **11** (3.1 g, 12 mmol) in dry THF (20 mL) at 25 °C was added tetrabutylammonium fluoride (18.0 mL, 18 mmol, 1 M in THF). After 1 h the solvents were removed, and the residue was subjected to flash chromatography (silica, 20% → 70% ether in petroleum ether) to afford the alcohol **12** (1.7 g, 100%). **12**: oil; R_f = 0.30 (silica, 70% ether in petroleum ether); $[\alpha]^{21}{}_D$ −4.8° (*c* 0.29, $CHCl_3$); IR (neat) ν_{max} 3420 (s, OH), 2960, 2940, 2875, 1645, 1420, 1390, 1070, 995, 925, 885 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$), δ 5.67 (dd, J = 17.3, 10.6 Hz, 1 H, HC=CH_2), 5.32 (dd, J = 17.3, 1.0 Hz, 1 H, HC=CH_2), 5.19 (dd, J = 10.6, 1.0 Hz, 1 H, HC=CH_2), 3.71 (t, J = 6.0 Hz, 1 H, CH_2O), 2.84 (dd, J = 7.0, 4.0 Hz, 1 H, H-epox), 1.84-1.60 (m, 4 H, CH_2), 1.41 (s, 3 H, CH_3); HRMS calcd for $C_8H_{15}O_2$ (M + H)$^+$ 143.1072, found 143.1077.

(2*S*,3*R*)-3-(*tert*-Butyldimethylsiloxy)tetrahydro-2-methyl-2-vinyl-2*H*-pyran (14). To the epoxy alcohol **12** (1.7 g, 12 mmol) in dry dichloromethane (100 mL) at 0 °C was added camphorsulfonic acid (250 mg, 1.0 mmol). TLC indicated the reaction was complete in 15 min. The reaction mixture was then treated sequentially with 2,6-lutidine (3.5 mL, 30 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (3.5 mL, 15 mmol) at 0 °C. After 10 min the reaction mixture was diluted with ether (300 mL) and washed with H_2O (50 mL) and brine (50 mL). Drying ($MgSO_4$) and concentration followed by flash chromatography (silica, 5% ether in petroleum ether) afforded the tetrahydropyran **14** (2.8 g, 91%). **14**: oil; R_f = 0.50 (silica, 5% ether in petroleum ether); $[\alpha]^{21}{}_D$ −17.1° (*c* 0.80, $CHCl_3$); IR (neat) ν_{max} 2960, 2935, 2890, 2865, 1475, 1365, 1260, 1110, 1075, 1010, 875, 840, 760, 675 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.95 (dd, J = 17.6, 10.9 Hz, 1 H, HC=CH_2), 5.42 (dd, J = 17.6, 1.4 Hz, 1 H, C=CH_2), 5.11 (dd, J = 10.9, 1.4 Hz 1 H, C=CH_2), 3.68 (m, 2 H, H-13), 3.49 (dd, J = 8.3, 3.8 Hz, 1 H, H-10), 1.80–1.50 (m, 4 H, CH_2), 1.21 (s, 3 H, CH_3C), 0.88 (s, 9 H, ^{t}Bu), 0.04, 0.03 (2 × s, 2 × 3 H, SiMe_2); HRMS calcd for $C_{14}H_{29}O_2Si$ (M + H)$^+$ 257.1937, found 257.1962; Anal. Calcd for $C_{14}H_{28}O_2Si$: C, 65.56, H, 11.00. Found: C, 65.16; H, 11.14.

2-[(2*S*,3*R*)-3-(*tert*-Butyldimethylsiloxy)tetrahydro-2-methyl-2*H*-pyran-2-yl]ethan-1-ol (15). To a stirred solution of olefin **14** (1.5 g, 5.8 mmol) in dry THF (15 mL) at 0 °C was added 9-BBN (15.0 mL, 7.5 mmol, 0.5 M in THF). After 15 min the cooling bath was removed and stirring was continued for 1 h. The homogeneous solution was recooled to 0 °C and treated dropwise with a solution of 3 N NaOH (7.7 mL, 23 mmol) and 30% hydrogen peroxide (3.1 mL, 26 mmol), and the resulting mixture was stirred vigorously for 15 min. Dilution with ether (50 mL), washing with H_2O (50 mL) and brine (50 mL), drying ($MgSO_4$), and concentration followed by flash chromatography (silica, 50% ether in petroleum ether) furnished the alcohol **15** (1.3 g, 85%). **15**: oil; R_f = 0.53 (silica, 70% ether in petroleum ether); $[\alpha]^{21}{}_D$ −7.1° (*c* 0.86, $CHCl_3$);

IR (neat) ν_{max} 3420 (s, OH), 2960, 2935, 2865, 1475, 1465, 1380, 1365, 1260, 1115, 1095, 1010, 1000, 990, 980, 875, 860, 840, 760, 680 cm^{-1}; ^{1}H NMR (250 MHz, CDCl$_3$) δ 3.82 (dt, *J* = 6.0, 5.0 Hz, 2 H, H-7), 3.58 (m, 3 H, H-10 and H-13), 3.43 (br t, *J* = 5.0 Hz, 1 H, O*H*), 1.86–1.40 (m, 6 H, C*H*$_2$), 1.21 (s, 3 H, C*H*$_3$C), 0.85 (s, 9 H, ^{t}*Bu*), 0.05, 0.04 (2 × s, 2 × 3 H, Si*Me*$_2$); HRMS calcd for $C_{14}H_{31}O_3Si$ (M + H)$^+$ 275.2034, found 275.2034.

2-[(2*S*,3*R*)-3-(*tert*-Butyldimethylsiloxy)tetrahydro-2-methyl-2*H*-pyran-2-yl]ethyl Iodide (16). To a stirred heterogeneous mixture of the alcohol **15** (1.1 g, 3.9 mmol), triphenylphosphine (3.0 g, 11.7 mmol), imidazole (0.8 g, 11.7 mmol), and dry benzene (40 mL) at 25 °C was added iodine (2.0 g, 7.8 mmol). After 20 min, the iodine color dissipated and the clear benzene solution was decanted away from the orange residue. The residue was washed with benzene (2 × 20 mL), and the benzene portions were combined, followed by concentration and flash chromatography (silica, 3% ether in petroleum ether) to give the pure iodide **16** (1.3 g, 90%). **16**: oil; R_f = 0.72 (silica, 5% ether in petroleum ether); $[\alpha]^{21}{}_D$ −41.7° (*c* 0.68, CHCl$_3$); IR (neat) ν_{max} 2960, 2935, 2865, 1475, 1465, 1445, 1380, 1360, 1260, 1255, 1215, 1175, 1100, 1075, 990, 870, 840, 780, 670 cm^{-1}; ^{1}H NMR (250 MHz, CDCl$_3$) δ 3.61–3.39 (m, 3 H, H-10 and H-13), 3.23 (*t*, *J* = 8.8 Hz, 2 H, H-7), 2.20 (m, 2 H, H-8), 1.78–1.50 (m, 4 H, C*H*$_2$), 1.11 (s, 3 H, C*H*$_3$), 0.88 (s, 9 H, ^{t}*Bu*), 0.07, 0.05 (2 × s, 2 × 3 H, Si*Me*$_2$); HRMS calcd for $C_{14}H_{30}O_2ISi$ (M + H)$^+$ 385.1060, found 385.1097.

[2-[(2*S*,3*R*)-3-(*tert*-Butyldimethylsiloxy)tetrahydro-2-methyl-2*H*-pyran-2-yl]ethyl]triphenylphosphonium Iodide (17). A mixture of the iodide **16** (1.3 g, 3.5 mmol), triphenylphosphine (7.3 g, 28 mmol), and dry acetonitrile (2.0 mL) was heated at 90 °C for 24 h. After cooling, the excess triphenylphosphine was removed by washing with hexanes (10 × 20 mL). The remaining acetonitrile was removed in vacuo to afford the phosphonium salt **17** (2.1 g, 94%). **17**: foam; R_f = 0.31 (silica, 10% methanol in EtOAc); $[\alpha]^{21}{}_D$ −0.6° (*c* 2.23, CHCl$_3$); IR (near) ν_{max} 3100, 3080, 3060, 3040, 2995, 2960, 2935, 2865, 1595, 1485, 1465, 1435, 1385, 1255, 1120, 1095, 1000, 995, 870, 840, 780, 735, 680 cm^{-1}; ^{1}H NMR (250 MHz, CDCl$_3$) δ 7.95–7.70 (m, 15 H, aromatic), 3.70–3.26 (m, 5 H, H-7, H-10, and H-13), 2.00–1.50 (m, 6 H, C*H*$_2$), 1.25 (s, 3 H, C*H*$_3$), 0.72 (s, 9 H, ^{t}*Bu*), 0.00, −0.19 (2 × s, 2 × 3 H, Si*Me*$_2$); HRMS calcd for $C_{32}H_{44}O_2PSi$ (M − H)$^+$ 519.2848, found 519.2847. Anal. Calcd for $C_{32}H_{44}IO_2PSi$ (0.5 H_2O): C, 58.62; H, 6.92; I, 19.36; P, 4.72. Found: C, 58.56; H, 6.73; I, 19.65; P, 4.89.

1,5-Anhydro-6-*O*-(*tert*-butyldiphenylsiloxy)-4-hydroxy-2,3-dideoxy-D-*erythro*-hexitol (19). To a stirred solution of the diol **18** (3.0 g, 22.0 mmol), imidazole (4.2 g, 62.0 mmol), and dry DMF (40 mL) at 0 °C was added *tert*-butylchlorodiphenylsilane (7.4 mL, 28.1 mmol). After stirring for 1.5 h, the reaction mixture was diluted with ether (150 mL), washed with H_2O (2 × 50 mL) and brine (25 mL), and dried (MgSO$_4$). Concentration and flash chromatography (silica, 30% ether in petroleum ether) furnished the silyl ether **19** (7.9 g, 97%). **19**: oil; R_f = 0.60 (silica, 50% ether in petroleum ether); $[\alpha]^{21}{}_D$ −13.4° (*c* 1.95, CHCl$_3$); IR (neat) ν_{max} 3460 (s, OH), 3170, 3150, 2930, 2860, 1595, 1475, 1465, 1430, 1395, 1270, 1150, 1115, 1105, 1030, 1010, 995, 835, 780, 740, 705, 610 cm^{-1}; ^{1}H NMR (250 MHz, CDCl$_3$) δ 7.69–7.41 (m, 10 H, aromatic), 3.90 (dd, *J* = 10.0, 5.0 Hz, 1 H, H-6), 3.85–3.61 (m, 3 H, H-6, H-4, and H-1α) 3.57 (br s, 1 H, O*H*) 3.29 (m, 2 H, H-5 and H-1β), 2.15 (br d, *J* = 10.0 Hz, 1 H, C*H*$_2$), 1.73–1.40 (m, 3 H, C*H*$_2$), 1.12 (s, 9 H, ^{t}*Bu*); HRMS calcd for $C_{18}H_{21}O_3Si$ (M − ^{t}Bu)$^+$ 313.1260, found 313.1276.

(*R*)-2-[(*tert*-Butyldiphenylsiloxy)methyl]dihydro-2*H*-pyran-3(4*H*)-one (20). Dry DMSO (2.9 mL, 40.0 mmol) was added dropwise to a stirred solution of oxalyl chloride (2.6 mL, 30.0 mmol) and dichloromethane (120 mL) at -78 °C followed by addition of the alcohol **19** (7.4 g, 20.0 mmol) in dichloromethane (40 mL) once gas evolution subsided (15 min). After stirring for 45 min, the heterogeneous mixture was treated dropwise with triethylamine (11.1 mL, 80.0 mmol) followed by removal of the cooling bath. After 15 min the reaction was diluted with ether (500 mL), washed with H_2O (2 × 50 mL) and brine (50 mL), and dried (MgSO$_4$). Concentration and flash chromatography (silica, 20% ether in petroleum ether) afforded the crystalline ketone **20** (6.7 g, 92%). **20**: colorless needles (ether–hexane) mp = 70–71.5 °C; R_f = 0.46 (silica, 30% ether in petroleum ether); $[\alpha]^{21}{}_D$ +58.9° (*c* 1.44, CHCl$_3$); IR (neat) ν_{max} 3170, 3150, 2960, 2935, 2890, 2860, 1725 (s, C=O), 1595, 1475, 1465, 1430, 1395, 1365, 1270, 1195, 1135, 1115, 1010, 1000, 825, 740, 705, 690, 610 cm^{-1}; ^{1}H NMR (250 MHz, CDCl$_3$) δ 7.69–7.40 (m, 10 H, aromatic), 4.19 (dt, *J* = 11.6, 5.0 Hz, 1 H, H-1α), 3.97 (br s, 3 H, H-5, H-6), 3.75 (ddd, *J* = 11.6, 4.6, 4.2 Hz, 1 H, H-1β), 2.60 (dt, *J* = 16.0, 7.0 Hz, 1 H, H-3), 2.48 (dt, *J* = 16.0, 8.0 Hz, H-3), 2.21–2.05 (m, 2 H, C*H*$_2$), 1.05 (s, ^{t}*Bu*); HRMS calcd for $C_{18}H_{19}O_3Si$ (M − ^{t}*Bu*)$^+$ 311.1103, found 311.1134.

(*R*)-2-[(*tert*-Butyldiphenylsiloxy)methyl]-3,3-bis(ethylthio)tetrahydro-2*H*-pyran (21). To a stirred mixture of the ketone **20** (6.6 g, 17.9 mmol), ethanethiol (5.9 mL, 80.0 mmol), and dry dichloromethane (40 mL) at −50 °C was added titanium(IV) chloride (0.9 mL, 8.9 mmol) dropwise. After stirring for 30 min, the reaction mixture was slowly warmed to −10 °C over a 30-min period and then poured onto a stirring mixture of ether (200 mL) and saturated aqueous NaHCO$_3$ (50 mL). After separation, the organic portion was washed with brine (50 mL) and dried (MgSO$_4$), and the solvent and ethanethiol were evaporated in vacuo utilizing a dry ice trap. Flash chromatography (silica, 7% ether in petroleum ether) afforded the dithioketal **21** (7.4 g, 88%). **21**: oil; R_f = 0.73 (silica, 30% ether in petroleum ether); $[\alpha]^{21}{}_D$ +23.8° (*c* 1.62, CHCl$_3$); IR (neat) ν_{max} 3170, 3150, 2960, 2935, 2890, 2860, 1595, 1475, 1460, 1430, 1395, 1375, 1265, 1230, 1115, 1000, 885, 825, 790, 740, 705 cm^{-1}; ^{1}H NMR (250 MHz, CDCl$_3$) δ 7.75–7.40 (m, 10 H, aromatic), 4.13 (dd, *J* = 11.1, 1.9 Hz, 1 H, H-5), 4.11 (m, 1 H, H-1α), 3.78 (dd, *J* = 8.1 Hz 1 H, H-6), 3.69 (dd, *J* = 8.1, 1.9 Hz, 1 H, H-6), 3.44 (ddd, *J* = 11.6, 11.6, 2.6 Hz, 1 H, H-1β), 2.50 (m, 4 H, SC*H*$_2$), 2.15 (m, 2 H, C*H*$_2$), 1.89, 1.54 (2 m, 2 H, C*H*$_2$), 1.15 (t, *J* = 7.6 Hz, 3 H, C*H*$_3$CH$_2$), 1.09 (t, *J* = 7.7 Hz, 3 H, C*H*$_3$CH$_2$), 1.05 (s, 9 H, ^{t}*Bu*); HRMS calcd for $C_{22}H_{29}O_2S_2Si$ (M − ^{t}*Bu*)$^+$ 417.1378, found 417.1385.

(*R*)-2-(Hydroxymethyl)-3,3-bis(ethylthio)tetrahydro-2*H*-pyran (22). A mixture of silyl ether **21** (7.1 g, 15.0 mmol), tetrabutylammonium fluoride (20.0 mL, 20.0 mmol, 1 M in THF), and THF (15.0 mL) was stirred at 25 °C for 3 h. Concentration and flash chromatography (silica, 40% → 70% ether in petroleum ether) gave alcohol **22** (3.1 g, 96%). **22**: oil; R_f = 0.14 (silica, 40% ether in petroleum ether); $[\alpha]^{21}{}_D$ +24.1° (*c* 2.12, CHCl$_3$); IR (neat) ν_{max} 3450 (s, OH), 2960, 2930, 2865, 1450, 1430, 1375, 1215, 1195, 1120, 1105, 1095, 1080, 1040, 940, 875, 820, 705, 680 cm^{-1}; ^{1}H NMR (250 MHz, CDCl$_3$) δ 4.10 (dd, *J* = 11.3, 5.5 Hz, 1 H, H-1α), 3.96 (ddd, *J* = 8.4, 8.4, 1.5 Hz, 1 H, H-6), 3.68 (m, 1 H, H-5), 3.65 (m, 1 H, H-6), 3.48 (ddd, *J* = 11.6, 11.3, 2.6 Hz, 1 H, H-1β), 2.65 (m, 4 H, SC*H*$_2$), 2.22 (m, 2 H, C*H*$_2$), 1.90, 1.55 (2 × m, 2 × 1 H, C*H*$_2$), 1.25 (t, *J* = 7.6 Hz, 3 H, SCH$_2$C*H*$_3$), 1.23 (t, *J* = 7.7 Hz, 3 H, SCH$_2$C*H*$_3$); HRMS calcd for $C_{10}H_{20}O_2S_2$ (M)$^+$ 236.0905, found 236.0924.

(*R*)-3,3-Bis(ethylthio)tetrahydro-2*H*-pyran-2-carboxaldehyde (23). To a stirred mixture of the alcohol **22** (100 mg, 0.42 mmol), dry DMSO (1.0 mL), dichloromethane (1.0 mL), and triethylamine (290 μL, 2.1 mmol) at 0 °C was added sulfur trioxide–pyridine complex (335 mg, 2.1 mmol). After 1.5 h at 0 °C the reaction mixture was diluted with ether (10 mL), washed with H_2O (2 × 2 mL) and brine (2 mL), and dried (MgSO$_4$). Concentration and flash chromatography (silica, 50% ether in petroleum ether) afforded the aldehyde **23** (91 mg, 90%, ca. 90% pure). **23**: oil; R_f = 0.52 (silica, 50% ether in petroleum ether); IR (neat) ν_{max} 2965, 2930, 2875, 2865, 2730 (w, HC=O), 1745 (s, HC=O), 1450, 1380, 1260, 1230, 1205, 1120, 1095, 1070, 1055, 815, 685 cm^{-1}; ^{1}H NMR (250 MHz, CDCl$_3$) δ 9.82 (s, 1 H, C*H*O), 4.26 (m, 1 H, 1H-α), 4.06 (s, 1 H, H-5), 3.50 (ddd, *J* = 11.3, 11.2, 1.5 Hz, 1 H, H-1β), 2.70 (m, 4 H, SC*H*$_2$), 2.32–1.50 (m, 4 H, C*H*$_2$), 1.27 (t, *J* = 7.6 Hz, 3 H, SCH$_2$C*H*$_3$), 1.24 (t, *J* = 7.6 Hz, 3 H, SCH$_2$C*H*$_3$); HRMS calcd for $C_{10}H_{19}O_2S_2$ (M + H)$^+$ 235.0826, found 235.0784.

[2α[*Z*(*S)],3β]-2-[3-[3,3-Bis(ethylthio)tetrahydro-2*H*-pyran-2-yl]-2-propenyl]tetrahydro-2-methyl-3-(*tert*-butyldimethylsiloxy)-2*H*-pyran (24).** To a stirred solution of the phosphonium salt **17** (1.9 g, 2.9 mmol) in dry THF (20.0 mL) at −78 °C was added *n*-butyllithium (1.9 mL, 2.9 mmol, 1.55 M in hexanes) dropwise. After 15 min, HMPA (1.6 mL, 8.7 mmol) was added, the cooling bath was removed, and the stirring was continued until the HMPA dissolved (ca. 10 min). The bright red ylide was recooled to −78 °C followed by addition of the aldehyde **23** (0.59 g, 2.5 mmol) in dry THF (10.0 mL). After 10 min, the cooling bath was removed and the reaction mixture was stirred for an additional 1 h. Dilution with ether (100 mL) followed by washing with H_2O (2 × 20 mL) and brine (20 mL), drying (MgSO$_4$), and solvent removal gave an orange residue that was purified by flash chromatography (silica, 10% ether in petroleum ether) to give the cis olefin **24** (0.92 g, 78%). **24**: oil; R_f = 0.26 (silica, 10% ether in petroleum ether); $[\alpha]^{21}{}_D$ −42.0° (*c* 0.54, CHCl$_3$); IR (neat) ν_{max} 3040, 2960, 2940, 2860, 1475, 1460, 1450, 1380, 1365, 1265, 1255, 1230, 1210, 1100, 1050, 1020, 995, 935, 875, 840, 780, 740, 710, 675, 610 cm^{-1}; ^{1}H NMR (250 MHz, CDCl$_3$) δ 5.82 (ddd, *J* = 18.3, 3.9, 3.8 Hz, 1 H, H-7), 5.67 (dd, *J* = 11.3, 8.7 Hz, 1 H, H-6), 4.24 (d, *J* = 8.7 Hz, 1 H, H-5), 4.04 (br d, *J* = 10.0 Hz, 1 H, H-1α), 3.65–3.37 (m, 4 H, H-1β, H-10, and H-13), 2.88 (dd, *J* = 14.8, 9.8 Hz, 1 H, H-8), 2.66 (dq, *J* = 7.6, 1.3 Hz, 2 H, SC*H*$_2$), 2.59 (q, *J* = 7.5 Hz, 2 H, SC*H*$_2$), 2.15 (m, 3 H, C*H*$_2$, H-8), 1.62 (m, 6 H, C*H*$_2$), 1.25 (t, *J* = 7. 5 Hz, 3 H, SC*H*$_2$), 1.14 (t, *J* = 7.6 Hz, 3 H, SC*H*$_2$), 0.91 (s, 9 H, ^{t}*Bu*), 0.11, 0.06 (2 × s, 2 × 3 , Si*Me*$_2$); HRMS calcd for $C_{24}H_{46}O_3S_2Si$ (M)$^+$ 474.2657, found 474.2674.

[2α[*Z*(*S)],3β]-2-[3-[3,3-Bis(ethylthio)tetrahydro-2*H*-pyran-2-yl]-2-propenyl]tetrahydro-2-methyl-2*H*-pyran-3-ol (1).** A stirring mixture of the silyl ether **24** (0.90 g, 1.9 mmol), THF (2.0 mL), and tetrabutylamonium fluoride (2.7 mL, 2.7 mmol, 1 M in THF) at 25 °C was allowed to react for 2 h. Concentration and flash chromatography (silica, 40% → 80% ether in petroleum ether) afforded alcohol **1** (0.68 g, 100%). **1**: oil; R_f = 0.32 (silica, 70% ether in petroleum ether); $[\alpha]^{21}{}_D$ +17.8° (*c* 1.10, $CHCl_3$); IR (neat) ν_{max} 3450 (s, OH), 3040, 2960, 2880, 1450, 1380, 1270, 1220, 1210, 1090, 1060, 990, 945, 935, 870, 815, 740, 710 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.85 (m, 1 H, H-7), 5.68 (dd, *J* = 11.4, 11.3 Hz, 1 H, H-6), 4.29 (d, *J* = 11.3 Hz, 1 H, H-5), 4.03 (m, 1 H, H-1α), 3.60–3.36 (m, 4 H, OC*H*), 2.90 (br s, 1 H, O*H*), 2.71–2.42 (m, 5 H, SCH_2 and H-8), 2.29 (dd, *J* = 14.1, 6.9 Hz, 1 H, H-8), 2.18 (m, 2 H, CH_2), 1.81–1.47 (m, 6 H, CH_2), 1.28 (t, *J* = 7.5 Hz, 3 H, SCH_2CH_3), 1.21 (s, 3 H, CH_3-C), 1.16 (t, *J* = 7.5 Hz, 3 H, SCH_2CH_3); HRMS calcd for $C_{18}H_{32}O_3S_2$ $(M)^+$ 360.1793, found 360.1771. Anal. Calcd for $C_{16}H_{26}O_3S_2$: C, 59.96; H, 8.95; S, 17.78. Found: C, 60.12; H, 9.09.; S, 17.49.

(4a*S*,7a*R*,11a*R*,12a*R*)-11a-(Ethylthio)-2,3,4a,5,7a,9,10,11,11a,12a-decahydro-4a-methyl-1*H*-dipyrano[3,2-*b*:2′,3′-*g*]oxocin (3) and (2*S*,3*R*)-2-[(*Z*)-3-[(2*R*)-3-(Ethylthio)-5,6-dihydro-2*H*-pyran-2-yl]allyl]tetrahydro-2-methyl-2*H*-pyran-3-ol (26). Oxidation–Acid Catalysis Method. To a stirring solution of the hydroxy thioketal **1** (50.0 mg, 0.14 mmol) in dry dichloromethane (1.0 mL) at 0 °C was added *m*-chloroperbenzoic acid (28.0 mg, 0.14 mmol). After 5 min, camphorsulfonic acid (7.0 mg, 0.03 mmol) was added, the cooling bath was removed, and stirring was continued for 45 min (until the intermediate sulfoxide disappeared by TLC). The reaction was quenched with triethylamine (70 μL, 0.5 mmol), and the solvents were evaporated. Flash chromatography (silica, 20% → 70% ether in petroleum ether) afforded the oxocene derivative **3** (23.0 mg, 55%) and the hydroxy thioenol ether **26** (12.1 mg, 29%). **3**: oil; R_f = 0.76 (silica, 70% ether in petroleum ether); $[\alpha]^{21}{}_D$ +160.0° (*c* 1.25, $CHCl_3$); IR (neat) ν_{max} 3040, 2970, 2960, 2940, 2870, 1450, 1380, 1300, 1260, 1210, 1160, 1110, 1090, 1070, 1060, 1005, 990, 975, 960, 950, 895, 870, 835, 775, 740, 725, 685 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.81 (m, 1 H, H-7), 5.68 (dd, *J* = 10.9, 7.4 Hz, 1 H, H-6), 4.31 (m, 1 H, H-10), 4.06 (dd, *J* = 11.3, 4.8 Hz, 1 H, H-13), 3.96 (d, *J* = 6.5 Hz, 1 H, H-5), 3.53 (dd, *J* = 8.5, 2.3 Hz, 2 H, H-1), 3.87 (dd, *J* = 11.7, 11.5 Hz, 1 H, H-13), 2.56–2.10 (m, 6 H, SCH_2 and H-8, CH_2), 1.70–1.45 (m, 5 H, CH_2), 1.28 (s, 3 H, CH_3), 1.25 (t, *J* = 7.5 Hz, 3 H, CH_3); ^{13}C NMR (50.3 MHz, C_6D_6) δ 133.7 and 128.7 (C-6 and C-7), 90.9 (C-4), 82.8 (C-5), 80.1 (C-9), 71.4 (C-10), 67.9 and 60.7 (C-1 and C-13), 40.6 and 35.8 (C-8 and S*C*), 27.5, 26.6, 24.4 and 20.9 (C-2, C-3, C-11, and C-12), 17.5 and 14.4 (SC*C*H$_3$ and C-9-*C*H$_3$); HRMS calcd for $C_{16}H_{27}O_3S$ $(M + H)^+$ 299.1673, found 299.1708. *Anal.* Calcd for $C_{16}H_{26}O_3S$: C, 64.39, H, 8.78; S, 10.74. Found C, 64.18; H, 8.78; S, 10.44. **26**: oil; R_f = 0.36 (silica, 70% ether in petroleum ether); $[\alpha]^{21}{}_D$ -2.8° (*c*, 0.35, $CHCl_3$); IR (neat) ν_{max} 3450 (s, OH), 3040, 2960, 2870, 1465, 1460, 1380, 1270, 1215, 1095, 1060, 990, 950, 930, 895, 880, 850, 720 cm^{-1}; ^1H NMR (250 MHz, C_6D_6) δ 6.18 (m, 1 H, H-7), 5.83 (ddd, *J* = 10.0, 10.0, 1.3 Hz, 1 H, H-6), 5.47 (m, 1 H, H-3), 5.00 (br d, *J* = 10.0 Hz, 1 H, H-5), 3.80–3.25 (m, 5 H, H-1, H-10, and H-13), 2.81 (dd, *J* = 14.0, 8.8 Hz, 1 H, H-8), 2.75 (br d, *J* = 6.9 Hz, 1 H, O*H*), 2.57 (ddd, *J* = 14.0, 6.9, 1.8 Hz, 1 H, H-8) 2.33 (q, *J* = 7.5 Hz, 2 H, SCH_2CH$_3$), 2.03 (m, 1 H, H-2), 1.78–1.30 (m, 5 H, CH_2), 1.30 (s, 3 H, CH$_3$-9), 1.03 (t, *J* = 7.5 Hz, 3 H, SCH_2CH_3); ^{13}C NMR (50.3 MHz, C_6D_6) δ 135.7 (C-4), 132.3 and 129.6 (C-6 and C-7), 121.7 (C-3), 77.3 (C-9), 73.0 and 71.2 (C-5 and C-10), 62.5 and 60.5 (C-1 and C-13), 39.2 (S*C*H$_2$), 28.1, 26.8, 26.4, and 26.0 (C-2, C-8, C-11, and C-12), 15.8 and 13.9 (2 *C*H$_3$); HRMS calcd for $C_{16}H_{26}O_3S$ $(M)^+$ 298.1603, found 298.1583.

Method B. To a vigorously stirred mixture of the alcohol **1** (270 mg, 0.76 mmol), 2,6-lutidine (177 μL, 1.52 mmol), dry acetonitrile (15.0 mL), powdered, activated 4A molecular sieves (540 mg, 2 × wt), and Kiesel gel 60 silica gel (230–400 mesh) (540 mg, 2 × wt) at 25 °C was added silver nitrate (230 mg, 1.38 mmol). After 10 min, NCS (135 mg, 1.05 mmol) was added and the reaction mixture was stirred for 15 min. Upon completion (TLC, 15 min) the reaction mixture was quenched with triethylamine (400 μL, 3.0 mmol), diluted with ether (30 mL), and filtered through a pad of Celite. The filtrate was concentrated and the residue was flash-chromatographed (silica, 20% ether in petroleum ether) to yield the oxocene derivative **3** (210 mg, 92%).

Method C. To a vigorously stirred mixture of the alcohol **1** (50 mg, 0.14 mmol), powdered activated 3A molecular sieves (100 mg, 2 × wt), sodium bicarbonate (35 mg, 0.42 mmol), and dry nitromethane (1.4 mL) at 25 °C was added anhydrous silver perchlorate (87 mg, 0.42 mmol). After 3 h the reaction mixture was diluted with ether (15 mL) and filtered through a pad of Celite. The filtrate was washed with saturated aqueous sodium bicarbonate solution (2 × 5 mL) and brine (5 mL) and dried ($MgSO_4$). Concentration and flash chromatography (silica, 20% ether in petroleum ether) furnished the oxocene derivative **3** (37 mg, 90% yield).

(4a*S*,7a*R*,11a*S*,12a*R*)-2,3,4a,5,7a,9,10,11,11a,12a-Decahydro-4a-methyl-1*H*-dipyrano[3,2-*b*:2′,3′-*g*]oxocin (29). Method A. A stirred mixture of the mixed ketal **3** (80.0 mg, 0.26 mmol) in dry toluene was heated at reflux in the presence of triphenyltin hydride (350 mg, 1.0 mmol) and AIBN (7.5 mg, 0.05 mmol) for 4 h. After cooling, the solvent was evaporated and the crude oil obtained was chromatographed (silica, 2% → 5% ether in petroleum ether) to furnish the trans-fused oxocene **29** (57.0 mg, 95%) identical in all respects with that obtained in method B.

Method B. To a stirred solution of the mixed ketal **3** (40.0 mg, 0.13 mmol) in dry dichloromethane (1.0 mL) at 0 °C was added *m*-chloroperbenzoic acid (41.0 mg, 0.20 mmol). After 30 min, triethylsilane (111 μL, 0.65 mmol) and then $BF_3\cdot Et_2O$ (18.0 μL, 0.13 mmol) were added followed by continued stirring for 2 h. Dilution with ether (15 mL), followed by sequential washing with saturated aqueous $NaHCO_3$ (2 × 2 mL) and brine (2 mL), drying ($MgSO_4$), solvent removal, and flash chromatography (silica, 5% ether in petroleum ether) gave the trans-fused oxocene **29** (30.0 mg, 96%). **29**: oil; R_f = 0.41 (silica, 10% ether in petroleum ether); $[\alpha]^{21}{}_D$ +86.4° (*c* 0.74, $CHCl_3$); IR (neat) ν_{max} 3040, 2950, 2870, 1465, 1445, 1365, 1280, 1265, 1225, 1215, 1200, 1150, 1130, 1115, 1090, 990, 975, 895, 855, 770, 715 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.71 (m, 2 H, C*H*=C*H*), 3.87 (m, 1 H, H-12), 3.78 (dd, *J* = 8.9, 3.0 Hz, 1 H, H-5), 3.66 (m, 1 H, H-13α), 3.53 (m, 2 H, H-10 and H-13β), 3.25 (m, 1 H, H-1β), 3.18 (m, 1 H, H-4), 2.47 (m, 1 H, H-8β), 2.15 (m, 1 H, H-8β), 2.07 (m, 1 H, CH_2), 1.75–1.30 (m, 7 H, CH_2), 1.19 (s, 3 H, CH_3); ^{13}C NMR (50.3 MHz, C_6D_6) δ 136.5 and 126.8 (C-6 and C-7), 80.9 (C-5), 78.7 (C-9), 77.9 and 77.7 (C-4 and C-10), 67.1 and 60.6 (C-1 and C-13), 40.3 (C-8), 32.1, 26.9, 26.3, and 26.0 (C-2, C-3, C-11, and C-12), 16.9 (*C*H$_3$); HRMS calcd for $C_{14}H_{22}O_3$ $(M)^+$ 238.1563, Found 238.1542.

(4a*S*,7a*R*,11*R*,12a*R*)-11a-(Ethylsulfinyl)-2,3,4a,5,7a,9,10,11,11a,12a-decahydro-4a-methyl-1*H*-dipyrano[3,2-*b*:2′,3′-*g*]oxocin (27) and (4a*S*,7a*R*,11*R*,12a*R*)-11a-(Ethylsulfonyl)-2,3,4a,5,7a,9,10,11,11a,12a-decahydro-4a-methyl-1*H*-dipyrano[3,2-*b*:2′,3′-*g*]oxocin (28). A stirred solution of the mixed ketal **3** (60 mg, 0.20 mmol) in dry dichloromethane (2.0 mL) at 0 °C was treated with *m*-chloroperbenzoic acid (60 mg, 0.30 mmol). After 30 min, triethylamine (70 μL, 0.50 mmol) was added followed by solvent removal and flash chromatography (silica, ether then EtOAc) to furnish, in order of elution, sulfone **28** (28 mg, 42%) and sulfoxide **27** (27 mg, 44%). **27**: oil; R_f = 0.15 (silica, EtOAc); $[\alpha]^{21}{}_D$ +121.5° (*c* 1.29, $CHCl_3$); IR (neat) ν_{max} 3560, 3510, 3040, 2960, 2950, 2940, 2880, 2860, 1660, 1460, 1380, 1285, 1105, 1085, 1045, 1035, 1015, 1010, 990, 980, 950, 895, 880, 865, 825, 775, 725 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.25 (ddd, *J* = 10.5, 7.0, 1.2 Hz, 1 H, H-6), 5.00 (dt, *J* = 10.6, 6.9 Hz, 1 H, H-7), 4.45 (m, 1 H, H-10), 4.37 (dd, *J* = 6.9, 1.3 Hz, 1 H, H-5), 4.12 (dd, *J* = 11.1, 4.0 Hz, 1 H, H-1α), 3.50 (m, 3 H, H-1β and H-13), 2.85 (m, 2 H, CH_2CH$_3$), 2.51 (m, 3 H, CH_2 and H-8), 2.32 (dd, *J* = 15.0, 6.9 Hz, 1 H, H-8), 1.91–1.50 (m, 6 H, CH_2), 1.51 (t, *J* = 7.5 Hz, 3 H, CH_2CH_3), 1.21 (s, 3 H, CH_3-C); HRMS calcd for $C_{16}H_{26}O_4S$ $(M)^+$ 314.1545, found 314.1544. **28**: colorless needles (ether–hexanes) mp = 97–98.5 °C; R_f = 0.50 (silica, ether); $[\alpha]^{21}{}_D$ +89.8° (*c* 0.85, $CHCl_3$); IR (neat) ν_{max} 3050, 2990, 2950, 2870, 1460, 1450, 1380, 1350, 1310, 1240, 1205, 1200, 1150, 1135, 1125, 1110, 1080, 1050, 1040, 990, 975, 950, 870, 820, 740, 700, 640 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.12 (ddd, *J* = 10.5, 7.2, 1.0 Hz, 1 H, H-6), 5.96 (m, 1 H, H-7), 5.10 (m, 1 H, H-10), 4.23 (dd, *J* = 7.2, 1.4 Hz, 1 H, H-5), 4.15 (dd, *J* = 11.5, 4.9 Hz, 1 H, H-1α), 3.52 (m, 3 H, H-1β and H-13), 3.20 (dt, *J* = 7.6, 5.0 Hz, 1 H, SCH_2CH$_3$), 3.15 (dt, *J* = 7.6, 5.0 Hz, 1 H, SCH_2CH$_3$), 2.50–2.20 (m, 4 H, H-8 and H-3), 1.95–1.53 (m, 6 H, CH_2), 1.43 (t, *J* = 7.6 Hz, 3 H, SCH_2CH_3), 1.23 (s, 3 H, CH_3C); HRMS calcd for $C_{16}H_{26}O_5S$ $(M)^+$ 330.1494, found 330.1491; Anal. Calcd for $C_{16}H_{26}O_5S$: C, 58.15; H, 7.93. Found: C, 57.88; H, 7.82.

(4s*R*,7a*R*,11a*S*,12a*R*)-2,3,4a,5,7a,9,10,11,11a,12a-Decahydro-4a,11a-dimethyl-1*H*-dipyrano[3,2-*b*:2′,3′-*g*]oxocin (30). To a stirred solution of the mixed ketal **3** (40.0 mg, 0.13 mmol) in dry dichloromethane (1.0 mL) at 0 °C was added *m*-chloroperbenzoic acid (41.0 mg, 0.20 mmol). After 30 min trimethylaluminum (195 μL, 0.39 mmol, 2 M in toluene) was added, the cooling bath removed, and the stirring was continued for 2 h. The excess trimethylaluminum was carefully quenched at 0 °C with methanol (100 μL). Dilution with EtOAc (15 mL), followed by washing with saturated aqueous sodium potassium tartrate (5 mL), drying ($MgSO_4$), concentration, and flash chromatography (silica, 10% ether in petroleum ether) furnished the *trans*-methyloxocene **30** (30.5 mg, 93%). **30**: oil; R_f = 0.42 (silica, 10% ether in petroleum ether); $[\alpha]^{21}{}_D$ +113.8° (*c* 0.90, $CHCl_3$); IR (neat) ν_{max} 3040, 2950, 2870, 1450, 1390, 1260, 1210, 1140, 1110, 1090, 1070, 1020, 995, 970, 945, 895, 870, 825, 800, 710 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.97–5.92 (m, 2 H, H-6 and H-7), 3.91 (dd, *J* = 10.3, 4.5 Hz, 1 H, H-10), 3.83 (d, *J* = 4.0 Hz, 1 H, H-5), 3.74 (m, 1 H, H-1α), 3.46–3.31 (m, 2 H, H-13), 3.04 (ddd, *J* = 9.3, 9.3, 0.6 Hz, 1 H, H-1β), 2.60–2.33 (m, 2 H, H-8), 1.70–1.07 (m, 8 H, CH_2), 1.24 (s, 3 H, CH_3-9), 1.22 (s, 3 H, CH_3-4); HRMS calcd for $C_{15}H_{23}O_3$ $(M)^+$ 252.1725, found 252.1726. Anal. Calcd for $C_{15}H_{23}O_3$: C, 71.39; H, 9.59. Found: C, 71.18; H, 9.27.

Reaction of 3 with DIBAL. (4a*S*,7a*R*,11a*R*,12a*R*)-2,3,4a,5,7a,9,10,11,11a,12a-Decahydro-4a-methyl-1*H*-dipyrano[3,2-*b*:2',3'-*g*]oxocin (31). To a stirred solution of the sulfone **28** (20.0 mg, 0.09 mmol) in dry dichloromethane (1.0 mL) at −78 °C was added DIBAL (0.40 mL, 0.40 mmol, 1 M in hexanes) dropwise. After 15 min, the excess DIBAL was quenched carefully with methanol (1.0 mL), followed by dilution with ether (1.5 mL) and subsequent washing with 1 N HCl (2 × 5 mL) and brine (5 mL). Sequential drying ($MgSO_4$), concentration, and flash chromatography (silica, 5% → 10% ether in petroleum ether) afforded the *cis*-oxocene **31** (10.2 mg, 48%) and its trans isomer **29** (9.8 mg, 46%). **31**: oil; R_f = 0.26 (silica, 10% ether in petroleum ether); $[\alpha]^{21}_D$ +118.2° (*c* 0.28, $CHCl_3$); IR (neat) ν_{max} 3040, 2950, 2870, 1450, 1390, 1260, 1210, 1140, 1110, 1090, 1070, 1020, 995, 970, 945, 895, 870, 825, 800, 710 cm^{-1}; ^1H NMR (250 MHz, C_6D_6) δ 6.50 (dd, *J* = 11.4, 5.0 Hz, H-6), 5.88 (m, 1 H, H-7), 4.46 (m, 1 H, H-5), 4.03 (m, 1 H, H-10), 3.92 (ddd, *J* = 10.0, 3.7, 3.4 Hz, 1 H, H-4), 3.52–3.30 (m, 4 H, H-1 and H-13), 2.44 (dd, *J* = 13.6, 8.6 Hz, 1 H, H-8), 2.30 (dd, *J* = 13.6 and 7.6 Hz, 1 H, H-8), 1.63–1.14 (m, 8 H, CH_2), 1.20 (s, 3 H, CH_3); ^{13}C NMR (50.3 MHz, C_6D_6) δ 132.4 and 128.4 (C-7 and C-8), 76.2, 74.8, 70.2, 63.1, and 60.5 (C-1, C-4, C-5, C-10, and C-13), 40.2 (C-8), 27.6, 27.1, 26.7, and 25.3 (C-2, C-3, C-11, and C-12), 16.7 (CH_3); HRMS calcd for $C_{14}H_{22}O_3$ $(M)^+$ 238.1569, found 238.1554.

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Supplementary Material Available: Data for compounds **33–51** (R_f values, $[\alpha]_D$, IR, ^1H NMR, and MS data) and X-ray crystallographic data for compounds **28** and **51** (11 pages). Ordering information is given on any current masthead page.

Activation of 6-Endo over 5-Exo Hydroxy Epoxide Openings. Stereoselective and Ring Selective Synthesis of Tetrahydrofuran and Tetrahydropyran Systems

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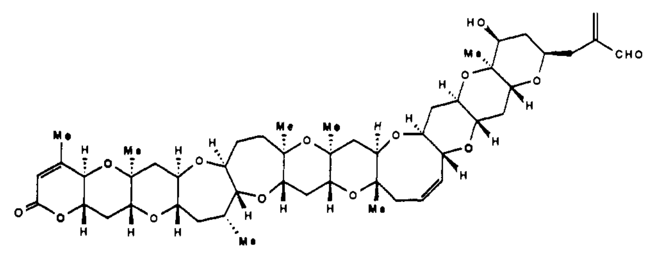
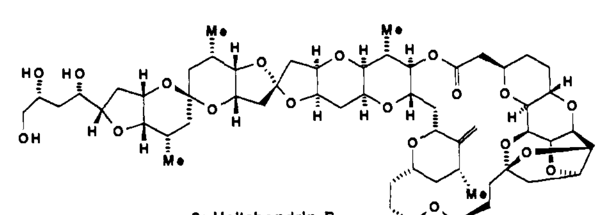
Abstract: A well-defined and predictable route to tetrahydrofurans and tetrahydropyrans is described. The method relies on stereo- and regioselective opening of hydroxy epoxides by acid catalysis. The presence of a saturated chain at the remote (from the hydroxy group) secondary epoxide position leads, as expected, to tetrahydrofuran systems, whereas the placement of an electron-rich double bond at that position leads to the formation of the tetrahydropyran systems. The resulting racemic or optically active systems contain useful functional groups for further elaboration. Reiteration of the sequence provides access to bi- and polycyclic oxaring systems in a predictable way.

Due to their common occurence in nature,[1] O-heterocycles are frequent and important targets for synthesis either as final products or as useful synthetic intermediates. Of particular importance are the ubiquitous tetrahydrofurans and tetrahydropyrans, toward the synthesis of which much work has been done.[2,3] Among recent examples in this field are the elegant contributions of Danishefsky,[4] Still,[5] Schreiber,[6] Hoye,[7] Bartlett,[8] Kozikowski,[9] Simmons,[10] Paquette,[11] Overman,[12] Robinson,[13] Paterson,[14] and Kishi.[15,16] In connection with a program directed toward the total synthesis of marine natural products such as brevetoxins B (**1**)[17] and halichondrin (**2**),[18] we were in need of stereospecific methods for the



1: Brevetoxin B



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