Bridging of Macrodithionolactones to Bicyclic Systems. Synthesis and Modeling of Oxapolycyclic Frameworks

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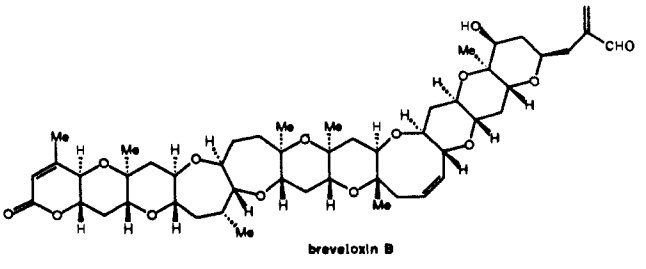
Abstract: A new reaction involving bridging of macrodithionolactones to bicyclic systems is described. A series of macrodiolides was prepared and converted to the requisite macrodithionolactones. The latter substrates were induced to undergo bridging across the macrocyclic ring by exposure to sodium naphthalenide, leading to stable bicyclic systems upon addition of methyl iodide. The mixed thioketals so obtained were converted to a number of saturated or unsaturated bicyclic or polycyclic systems by removal of the sulfurs. The stereochemistry of bridging follows the relative energy of the cis and trans products rather than the conformational preferences of the macrocycles. This is confirmed by MM2 calculations and X-ray crystal structure determinations. The unusual stereochemical course of some of the reported reactions, elucidated by X-ray, has been given a mechanistic basis by conformation searching coupled by energy evaluation by MM2 and PRDDO. Several new sets of MM2 parameters were evolved during this work.

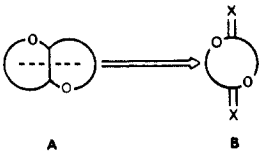
As frequently encountered molecular structures, polycyclic systems are constantly challenging synthetic chemists. Cis- and trans-fused oxabicyclic and oxapolycyclic systems of type A (Scheme I) are becoming increasingly recognized as common structural subunits of marine and other natural products such as the brevetoxins[1] [e.g., brevetoxin B (**1**)] and halichondrins.[2]



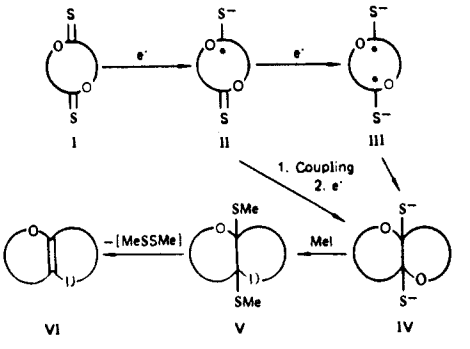
brevetoxin B

Whereas the rings of the bicyclic system A (Scheme I) could be constructed sequentially, a potentially more efficient and economical retrosynthetic disconnection of A would be the indicated rupture of the central C–C bond, suggesting the macrocycle B as a precursor. In the synthetic direction, the construction of one bond would result in the simultaneous generation of two rings.[3] Based on this concept, a method for bridging macrocycles of type B (Scheme I) that would allow stereoselective entry into both the cis- and trans-fused systems A was sought. Due to the relatively low reduction potential of the C=S bond[4] and the synthetic potential of sulfur for further chemical transformations, macrodithionolactones were chosen as starting materials. The general strategy for bridging these macrocycles to bicycles is shown in Scheme II. According to this strategy, it was anticipated that electron transfer from a suitable donor to a thiocarbonyl group of the macrodithionolide system I would generate a radical anion (II), initiating a sequence leading to a bridged product (IV) as outlined in Scheme II. Quenching of the resulting dianion IV with an electrophile, such as MeI, was then expected to lead to a stable bis(methylthio) ether (V), which could be chemically manipulated[3b] to a variety of systems including the olefinic framework VI and the cis- and trans-fused polycycles A (Scheme I). A preliminary communication on this work has appeared.[5] In this article we examine the scope and limitations of this synthetic

Scheme I



Scheme II



strategy and offer mechanistic explanations for the observed results. Conformational analysis using primarily the MM2 force field provides deeper insights into the course of some of the reactions. A series of X-ray crystal structures confirms product assignments and supports the conformational calculations.

Results and Discussion

Bridging of Macrodithionolactones and Chemistry of the Products. As a model for the 7,7 ring system of brevetoxin B (**1**), the frameworks shown in Scheme III were chosen to test the above ideas. When the dithionolide **1** (meso compound, C_i symmetry)

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(3) For our recent stepwise entries into oxo rings via C–O bond forming reactions, see (a) tetrahydropyrans: Nicolaou, K. C.; Duggan, M. E.; Hwang, C.-K.; Somers, P. K. *J. Chem. Soc., Chem. Commun.* **1985**, 1359. And see (b) oxocenes: Nicolaou, K. C.; Duggan, M. E.; Hwang, C.-K. *J. Am. Chem. Soc.* **1986**, *108*, 2468.

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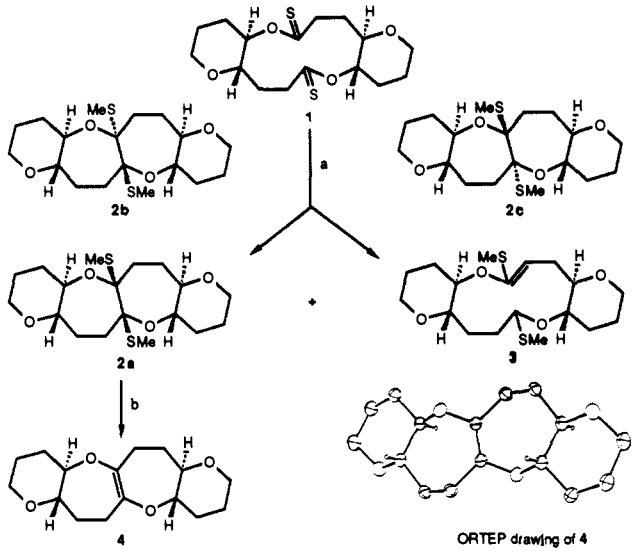
Scheme III[a]



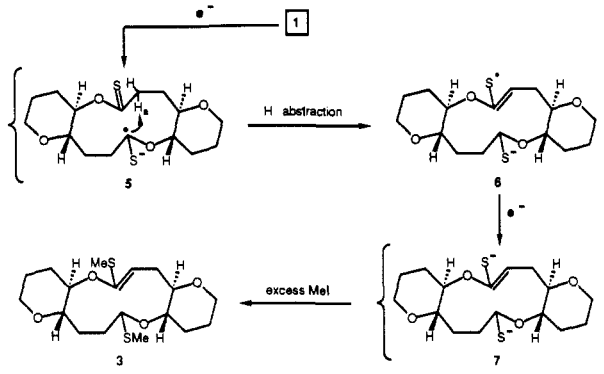
[a] Bridging of dithionolides. Reagents and conditions: (a) 2.2 equiv of sodium naphthalene, THF, −78 °C, 30 s, then 10 equiv of MeI, −78 to +25 °C, 30 min, **2a** (80%), **3** (12%); (b) 1.2 equiv of $^nBu_3SnH$, 0.1 equiv of AIBN, toluene, 120 °C, 15 min, 99%, or 1.2 equiv of $^nBu_3SnH$, *hν*, toluene, 25 °C, 1 h, 99%, or Raney Ni, EtOH, 25 °C, 30 min, 82%.

was exposed to sodium naphthalenide in THF at −78 °C followed by quenching with MeI, the cis tetracycle **2a** (racemic sample) was obtained in 80% yield. The ^1H NMR spectrum of **2a** exhibits 2 methylthio signals [(250 MHz, $CDCl_3$) δ 2.03, 1.89], while the ^{13}C NMR spectrum shows 18 signals. Interpretation of the NMR data rests on knowledge of the conformational profile of the three diastereomers **2a–c** in Scheme III. The two trans isomers **2b** and **2c** in principle can reside in global minimum energy conformations with C_1 symmetry (meso form). As shall be evident below, the stereochemistry of trans **2b** meets this criterion as a single low-energy conformer. Trans diastereomer **2c**, on the other hand, does not. That both stereoisomeric forms are possible in fact is evident from the X-ray structures of the bis(methylthio) ethers **9**, **104**, and **106** on the one hand, and **110** on the other; trans and cis isomers, respectively. A combination of NMR proton shift and force field calculations permit the assignment of cis **2a** to the 6,7,7,6 bis(methylthio) ether. Conformational preferences for both the bis(methylthio) ethers and the thionolactones will be detailed in the computational sections below.

In addition to the bridged product **2a**, the methylthioenol ether **3** was also formed in this reaction in 12% yield. The presence of a thioenol ether grouping in **3** was suggested by signals in the ^1H NMR [(250 MHz, $CDCl_3$) δ 5.30 (d, J = 11.0 Hz, 1 H), 2.21 (s, 3 H)], ^{13}C NMR [(50.3 MHz, benzene-d_6) δ 150.30, 115.63], IR [(neat) ν_{max} 1640 cm^{-1}], and UV [(CH_2Cl_2) λ_{max} 232, 245 nm] spectra, and by its facile conversion to a lactone functionality under mildly acidic (PPTS) conditions. The methylthioacetal group in **3** was evident from ^1H [δ 4.42 (d, J = 12.2 Hz, 1 H), 2.0 (s, 3 H)] and ^{13}C (δ 84.51) NMR signals.

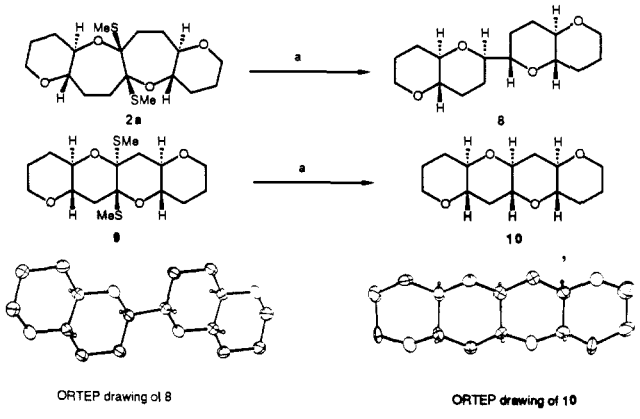
The methylthioenol ether byproduct in this bridging reaction was also formed in the examples of entries 3 (3%), 4 (44%), 5 (10%), 6 (44%, isolated as the corresponding lactone), 7 (22%), 8 (28%), 9 (15%), and 10 (68%, isolated as the corresponding lactone) (Table I). A plausible mechanism for the formation of this byproduct is shown in Scheme IV. According to this intramolecular hydrogen atom abstraction mechanism, the initially formed anion radical **5** abstracts a hydrogen atom (H_a) from the methylene group adjacent to the remaining thionocarbonyl across the ring to give, upon rearrangement, species **6**, which is converted to the dianion **7** by accepting a second electron. Quenching of this dianion **7** with MeI then produces the observed product **3**. It is interesting to note that in the examples of entries 3, 4, and 6 (Table I) in which two rings of different sizes are being formed, the reaction is regioselective with the thioenol ether group gen-

Scheme IV[a]



[a] Plausible mechanism for the formation of macrocycle **3** from **1**.

Scheme V[a]



[a] Reduction of disulfides **2a** and **9**. Reagents and conditions: (a) 10 equiv of Et_3SiH, 2.2 equiv of $AgBF_4$, CH_2Cl_2, 25 °C, 2 h, **8** (92%), **10** (92%).

erated on the shorter chain linking the thionocarbonyl with the pyran rings. Compound **111** (Table I, entry 7) was formed as a mixture of two diastereomers, **111a** (R_f = 0.36, silica, 30% ether in petroleum ether plus 2% Et_3N) and **111b** (R_f = 0.31, same chromatographic conditions). The crystalline, less polar isomer **111a** (mp 165–167 °C dec) was subjected to X-ray crystallographic analysis, which confirmed the structure shown in Figure 1. The remaining byproducts in Table I were isolated as single isomers; the stereochemistry of the methylthio group was not assigned. Further discussion regarding the specificity of this reaction will be found below in the computation section.

Treatment of either the diolide or dithionolide **1** with Na or K,[6] $TiCl_3$–$LiAlH_4$,[7] SmI_2,[8] or SmI_2–$FeCl_3$[9] failed to produce any bridged product. Treatment of the bis(methylthio) ether **2a** with $^nBu_3SnH$ in the presence of AIBN resulted in its high-yield conversion to the olefinic compound **4** (Scheme III) (meso compound, C_1 symmetry), mp 163–165 °C (ether–hexane). The same reaction occurred with $^nBu_3SnH$ under photolytic conditions (Hanovia UV quartz lamp, toluene), $NiCl_2$–$NaBH_4$,[10] or upon treatment with Raney Ni. An X-ray crystallographic analysis of compound **4** (see ORTEP drawing, Scheme III) proved its structure, which was also suggested from its spectroscopic data (vide infra). Table I includes a number of other examples demonstrating the generality and scope of this bridging reaction in constructing oxygenated polycyclic systems. The synthesis of the starting dithionolactones will be dealt with in a section below.

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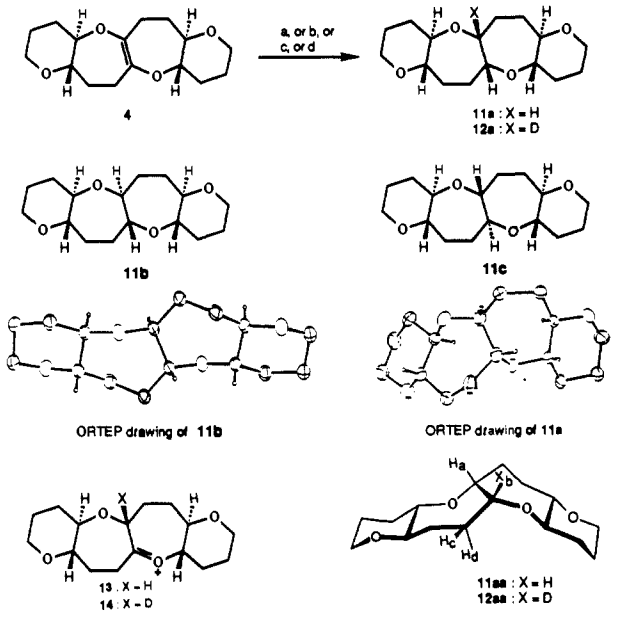
Scheme VI[a]

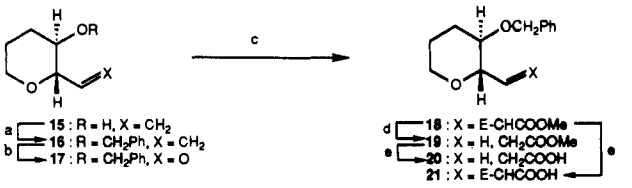


[a] Reduction of olefin **4**. Reagents and conditions: (a) H_2, $Pd(OH)_2$ catalytic, EtOAc, 12 h, **11a** (75%), **11b** (12%); (b) 1.1 equiv of CF_3COOH, 10.0 equiv of Et_3SiH, CH_2Cl_2, 0 °C, 30 min, **11a** (85%); (c) 1.1 equiv of CF_3COOH, 3.0 equiv of $Na(CN)BH_3$, CH_2Cl_2, 0 °C, 30 min, **11a** (90%); (d) 1.1 equiv of CF_3COOD, 10 equiv of Et_3SiH, CH_2Cl_2, 0 °C, 30 min, **12a** (88%).

In order to develop stereoselective routes to cis- and trans-fused ring systems, the reduction studies shown in Scheme V were undertaken. Thus, treatment of bis(methylthio) ether **2a** with $AgBF_4$ in the presence of excess Et_3SiH produced a single product in 92% yield. The spectral data indicated a symmetrical structure (eight ^{13}C NMR signals) but failed to distinguish between the 6,6,6,6 structure **8** and the initially suspected isomeric 6,7,7,6 structure corresponding to the bis(methylthio) ether **2a**. X-ray crystallographic analysis, however, revealed structure **8** as the product (see ORTEP drawing, Scheme V), proving that a skeletal rearrangement had taken place. A speculative mechanism for the rearrangement would be similar to that observed for dithiatopazine under similar conditions.[11] Interestingly, the bis(methylthio) ether **9**, when treated with $AgBF_4$ and Et_3SiH under conditions identical with those used for **2a**, resulted only in the formation of the all-trans 6,6,6,6 ring structure **10** (see ORTEP structure, Scheme V). On the other hand, hydrogenation of the olefin **4** [H_2, 10% $Pd(OH)_2$] resulted in the cis-fused tetracycle **11a** (Scheme VI) in 75% yield together with the trans-fused tetracyclic system **11b** (12% yield) apparently formed by initial isomerization of the double bond into one of the rings, followed by hydrogen addition. Theoretically, the olefin **4** could be converted to a trans-fused product via an oxonium species under protic/hydride conditions. In the event, however, treatment of **4** with trifluoroacetic acid (TFA) in the presence of either Et_3SiH or $NaBH_3CN$ gave, almost exclusively, the cis product **11a** in 85 and 90% yields, respectively. The structures of **11a** and **11b** were proven by spectroscopic and X-ray crystallographic techniques (see ORTEP drawings, Scheme VI). The olefin migration mechanism leading to trans **13a** is treated in detail in a subsequent section.

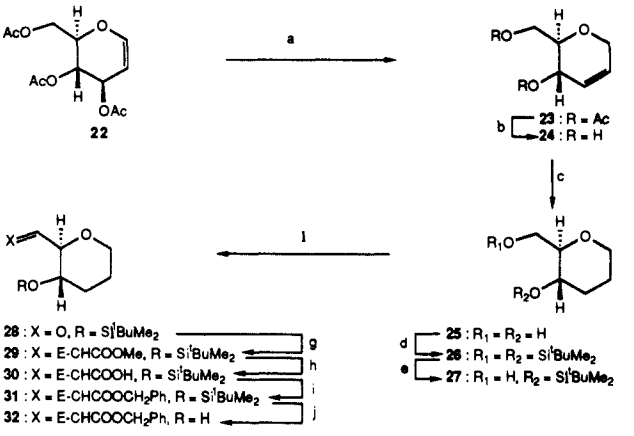
In order to explain the interesting stereochemical outcome for the acid-induced reduction of **4** (Scheme VI), the following mechanism was advanced. Protonation of **4** proceeds stereospecifically to form oxonium species **13** (X = H), which then accepts a hydride from the exo side (same face as the syn hydrogens on the adjacent fusions) to give the cis product **11a**. To test this hypothesis, the olefin **4** was treated with CF_3COOD–Et_3SiH, leading to a single compound **12a** (88% yield). The stereochemistry of **12a** was determined by ^1H NMR spectroscopy and molecular mechanics evaluation. Thus, MM2 calculations reveal that the conformer **12a** (Scheme VI) in which both oxepane rings were in twist–chair conformations, was at least 2.5 kcal/mol lower in energy than other cis conformers (see computations section). The NMR signal of the proton at the central bridge in **12a** [(250 MHz, $CDCl_3$) δ 3.65 (dd, J = 6.6, 6.1 Hz)] was then compared to the proton signals corresponding to the central fusion of **11a** [δ 3.65 (dd, J = 6.6, 6.1 Hz), 3.41 (ddd, J = 10.2, 6.6, 6.1 Hz)], leading to the following chemical shifts and coupling constants. H_a: δ 3.41; H_b: δ 3.65; J_{ab} = 6.1 Hz, J_{bc} = 6.6 Hz, J_{bd} = 10.3 Hz (see **11aa** Scheme VI). The 10.3 Hz coupling constant for H_b requires a ca. 180° relationship to one of its vicinal protons (H_d), which can be seen in conformers **11aa** and **12aa**. The fact that this proton (H_b) resonates further downfield is indicative of its pseudoequatorial relationship to the vicinal oxygen, further substantiating the assignment.

Scheme VII[a]



[a] Synthesis of compound **21**. Reagents and conditions: (a) 1.2 equiv of $PhCH_2Br$, 1.5 equiv of KH, THF, 0 °C, then 25 °C, 3 h, 92%; (b) O_3, CH_2Cl_2, −78 °C, 30 min, then 5.0 equiv of Me_2S, 1 h, 92%; (c) 1.2 equiv of Ph_3P=CHCOOMe, benzene, 25 °C, 3 h, 91%; (d) H_2, Pd–C(5%) catalytic, hexane, 25 °C, 3 h, 100%; (e) 3.0 equiv of LiOH, THF–H_2O (4:1), 50 °C, 5 h, 92%.

Scheme VIII[a]

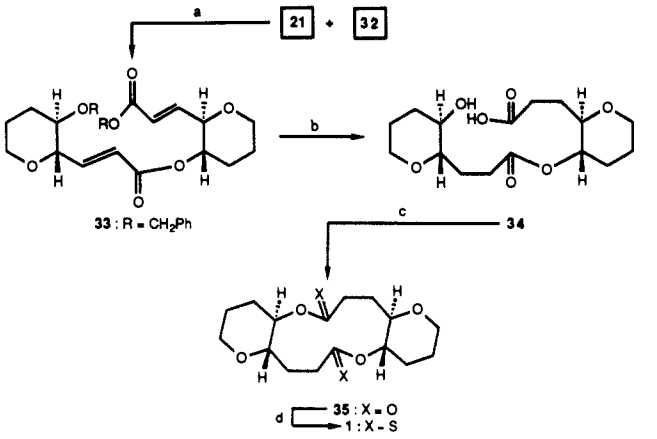


[a] Synthesis of compound **32**. Reagents and conditions: (a) 1.2 equiv of Et_3SiH, 1.0 equiv of BF_3·Et_2O, CH_2Cl_2, 0 °C, 30 min, 94%; (b) 0.5 equiv of NaOMe, MeOH, 25 °C, 2 h, 95%; (c) H_2, Pd–C(5%) catalytic, MeOH, 25 °C, 16 h, 95%; (d) 2.3 equiv of ^{t}BuMe$_2$SiCl, 2.5 equiv of imidazole, DMF, 25 °C, 16 h, 92%; (e) TFA–THF–H_2O (1:1:1), 0 °C, 10 min, 72%; (f) 1.5 equiv of oxalyl chloride, 2.0 equiv of DMSO, CH_2Cl_2, −78 °C, 30 min, then 4.0 equiv of Et_3N, 95%; (g) 1.2 equiv of Ph_3P=CHCOOMe, benzene, 25 °C, 3 h, 89%; (h) 3.0 equiv of LiOH, THF–H_2O (4:1), 50 °C, 5 h, 88%; (i) 1.2 equiv of $PhCH_2OH$, 1.2 equiv of DCC, 0.3 equiv of DMAP, 0.3 equiv of CSA, CH_2Cl_2, 25 °C, 6 h, 82%; (j) 1.2 equiv of ^{n}Bu$_4$NF, THF, 25 °C, 3 h, 88%.

Synthesis of Macrodithionolactones. The dithionolactones utilized in this study are shown in Table I. They were synthesized from the corresponding dilactones, which were, in turn, constructed from the appropriate, optically active hydroxy acids. To exemplify the chemistry involved in these syntheses, we detail here the construction of the dithionolide **1** from its components **21** (Scheme VII) and **32** (Scheme VIII). The synthesis of the first tetrahydropyran ring system was based on our recently developed methodology for constructing such compounds via stereospecific 6-endo cyclizations of hydroxy epoxides.[3a] Thus, the so obtained optically active intermediate **15**[3a] was converted to the requisite

(11) Nicolaou, K. C.; DeFrees, S.; Hwang, C.-K.; Stylianides, M.; Carrol, P. J.; Snyder, J. P. *J. Am. Chem. Soc.*, preceding article in this issue.
(12) Danishefsky, S.; Kerwin, J. F. *J. Org. Chem.* **1982**, *47*, 3803.

Scheme IX[a]



[a] Synthesis of dithionolactone 1. Reagents and conditions: (a) 1.2 equiv of DCC, 0.5 equiv of DMAP, 0.3 equiv of CSA, CH_2Cl_2, 25 °C, 4 h, 72%; (b) H_2, $Pd(OH)_2$ catalytic, EtOAc, 25 °C, 2 h, 99%; (c) 1.5 equiv of pyr–SS–pyr, 1.5 equiv of Ph_3P, toluene, 25 °C, 3 h, then toluene (0.05 M), reflux, 12 h, 75%; (d) 2.0 equiv of Lawesson's reagent, toluene reflux, 16 h, 78%.

component **21** as summarized in Scheme VII. Benzylation of **15**[3a] (92%) followed by ozonolysis of the terminal olefin furnished the aldehyde **17** (92%) via compound **16**. Standard olefination followed by selective hydrogenation converted **17** to **18** and then **19**. Basic hydrolysis of **18** and **19** led to the requisite carboxylic acids **20** and **21**, respectively, in excellent overall yields. To demonstrate the feasibility of another approach to these systems, the enantiomerically related (to **21**) system, compound **32**, was synthesized from tri-*O*-acetyl-D-glucal **22** as detailed in Scheme VIII. Thus, **22** was converted to **24** by sequential exposure to $BF_3{\cdot}Et_2O$–Et_3SiH[12] (affording **23**, 94%) and NaOMe–MeOH (**23** → **24**, 95%) followed by catalytic hydrogenation (H_2, 5% Pd–C, 95%) to afford **25**. Differentiation of the primary and secondary hydroxyls was then achieved by bis(silylation) (92%) to form **26**, followed by selective mono(desilylation) (TFA–THF–H_2O, 0 °C, 72%) of the primary position, leading to compound **27**. Swern oxidation of **27** then gave aldehyde **28** (95%), which was converted to the α,β-unsaturated ester **29** by standard olefination reaction. Exchange of the methyl ester for a benzyl ester proceeded smoothly by (i) alkaline hydrolysis (LiOH–THF–H_2O, leading to **30**, 88%) and (ii) esterification with $PhCH_2OH$ (DCC–DMAP–CSA catalytic, 82%) furnishing **31**, the hydroxy group of which was deprotected (n-Bu_4NF, 88%) to give the desired optically active hydroxybenzyl ester **32**.

Scheme IX summarizes the completion of the synthesis of **1**. Thus, coupling of components **21** and **32** in the presence of DCC–DMAP and CSA (catalytic) led to ester **33** in 72% yield. The saturated hydroxy acid **34** was then generated from **33** in one step (99% yield) by reduction/hydrogenolysis using H_2–$Pd(OH)_2$. Macrolactonization[13] of **34** via its 2-pyridinethiol ester in refluxing toluene gave the diolide **35** (75%) as a colorless crystalline solid, mp 114–115 °C (ether–hexane). Diolide **35** was then reacted with Lawesson's reagent[14] in refluxing xylene, producing the dithionolide **1** (78%) as a light yellow solid, mp 191–192 °C (ether–hexane) along with small amounts of the corresponding monothionolactone (10%, mp 119–120 °C from ether–hexane). By use of similar and/or other standard synthetic methodology, the remaining thionolactones of Table I were synthesized. The hydroxy acid derivatives required for these constructions were synthesized as detailed in Schemes X–XIV. Experimental conditions and data for these compounds are included in the supplementary material. Table II summarizes the esterification, deprotection/reduction, macrolactonization, and thionation re-

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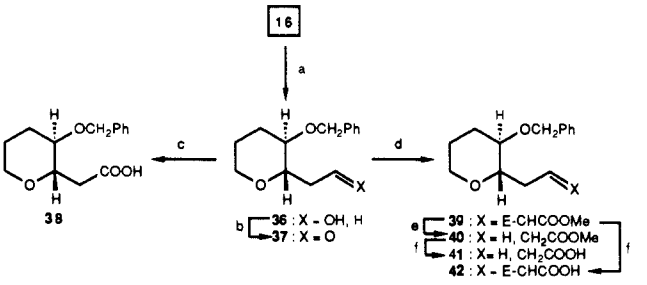
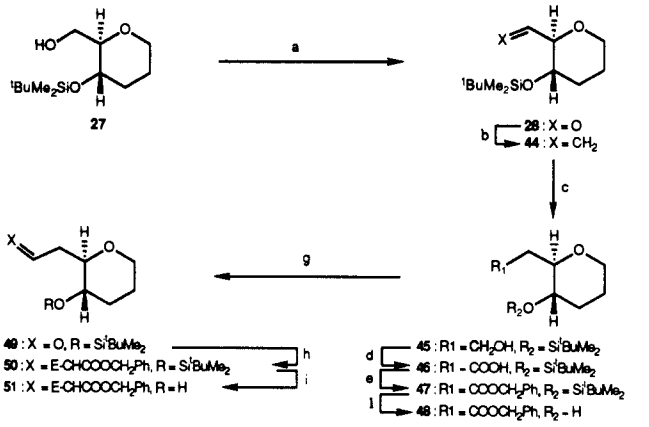
Scheme X[a]



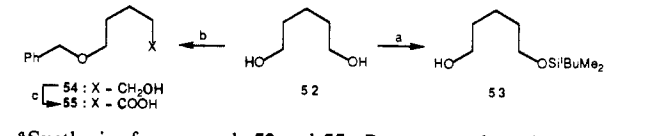
[a] Synthesis of compounds **38**, **41**, and **42**. Reagents and conditions: (a) 1.5 equiv of 9-BBN, THF, 0 °C, 3 h, then excess 3 N NaOH, excess 30% H_2O_2, 92%; (b) 1.5 equiv of $(COCl)_2$, 2.0 equiv of DMSO, CH_2Cl_2, −78 °C, 30 min, then 4.0 equiv of Et_3N, 98%; (c) Jones' reagent, acetone, 0 °C, 1 h, 82%; (d) 1.2 equiv of $Ph_3P{=}CHCOOMe$, benzene, 25 °C, 3 h, 85%; (e) H_2, Pd–C (5%) catalytic, hexane, 25 °C, 30 min, 99%; (f) 3.0 equiv of LiOH, THF–H_2O (4:1), 45 °C, 3 h, 92%.

Scheme XI[a]



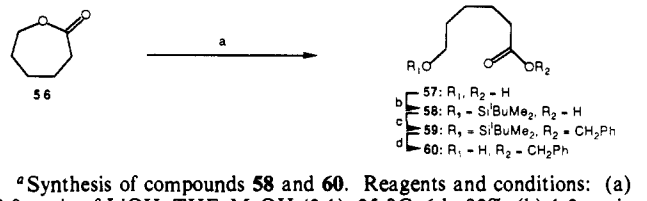
[a] Synthesis of compounds **48** and **51**. Reagents and conditions: (a) 1.5 equiv of $(COCl)_2$, 2.0 equiv of DMSO, CH_2Cl_2, −78 °C, 30 min, then 4.0 equiv of Et_3N, 95%; (b) 1.2 equiv of $Ph_3P{=}CH_2$, THF, 0 °C, 1 h, 82%; (c) 1.5 equiv of 9-BBN, THF, 0 °C, 3 h, then excess 3 N NaOH, excess H_2O_2, 91%; (d) Jones' reagent, acetone, 0 °C, 30 min, 72%; (e) 1.2 equiv of $PhCH_2OH$, 1.2 equiv of DCC, 0.3 equiv of DMAP, 0.3 equiv of CSA, CH_2Cl_2, 25 °C, 1.2 h, 91%; (f) 1.2 equiv of ^{n}Bu_4NF, THF, 25 °C, 3 h, 98%; (g) same as (a), 93%; (h) 2.7 equiv of $Ph_3P{=}CHCOOCH_2Ph$, DMF, 25 °C, 30 min, 98%; (i) same as (f), 93%.

Scheme XII[a]



[a] Synthesis of compounds **53** and **55**. Reagents and conditions: (a) 0.12 equiv of ^{t}$BuMe_2SiCl$, 0.12 equiv of imidazole, DMF, 25 °C, 94%; (b) 0.14 equiv of $PhCH_2Br$, 0.16 equiv of NaH, THF, 0 °C, then 25 °C, 5 h, 70%; (c) Jones' reagent, acetone, 0 °C, 1 h, 93%.

Scheme XIII[a]



[a] Synthesis of compounds **58** and **60**. Reagents and conditions: (a) 3.0 equiv of LiOH, THF–MeOH (3:1), 25 °C, 6 h, 92%; (b) 1.3 equiv of ^{t}$BuMe_2SiCl$, 2.4 equiv of imidazole, DMF, 25 °C, 15 min, 87%; (c) 1.3 equiv of $PhCH_2Br$, 5.0 equiv of K_2CO_3, acetone, reflux, 1 h, 96%; (d) 2.0 equiv of HF–pyridine, THF, 0 °C, 0.5 h, 96%.

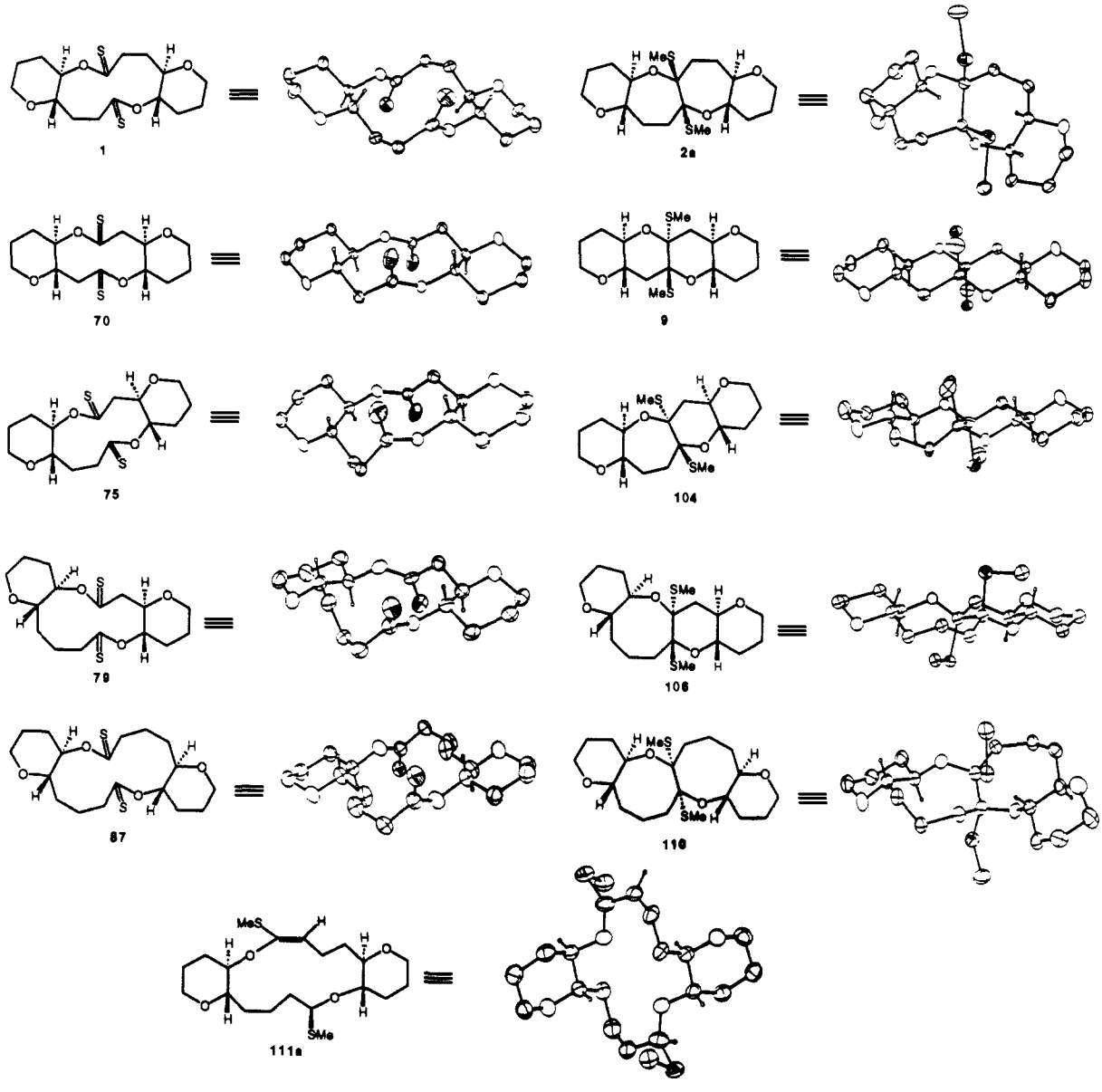
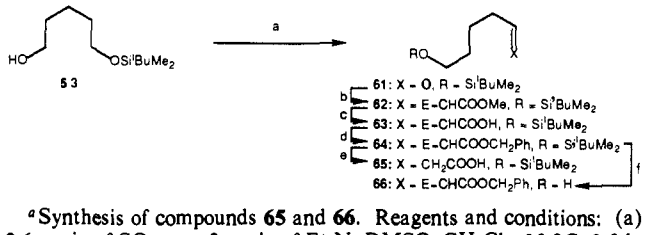


Figure 1. ORTEP drawings of compounds **1**, **2a**, **9**, **70**, **75**, **79**, **87**, **104**, **106**, **110**, and **111a**.

Scheme XIV[a]



[a] Synthesis of compounds **65** and **66**. Reagents and conditions: (a) 2.6 equiv of SO_3-pyr, 3 equiv of Et_3N, DMSO–CH_2Cl_2, 25 °C, 3.5 h; (b) 1.8 equiv of $Ph_3P{=}CHCOOMe$, CH_2Cl_2, 25 °C, 6 h, 94%; (c) 3.0 equiv of LiOH, THF–MeOH (3:1), 25 °C, 4 h, 84%; (d) 1.3 equiv of $PhCH_2Br$, 5.0 equiv of K_2CO_3, acetone, reflux, 2 h, 93%; (e) H_2, 20% wt/wt, $Pd(OH)_2$, THF, 24 h, 99%; (f) 2.0 equiv of HF–pyridine, THF, 0 °C, 30 min, 87%.

actions leading to the requisite dithionolactones from the corresponding hydroxy acid components.

The Conformational Manifold of Dithionolides. Single-crystal X-ray structure determinations were carried out for dithionolides **1**, **70**, **75**, **79**, and **87** (see ORTEP drawings, Figure 1). Each of these medium-size rings (10–14-membered) in the solid state demonstrates an anti relationship between the pair of C=S moieties (Figure 1). Treatment of thionolactones **70**, **75**, and **79** with sodium naphthalenide delivers the trans-fused dithioethers **9**, **104**, and **106**, respectively. By contrast, thionolides **1** and **87** provide the cis-fused dithioethers **2a** and **110**, respectively.

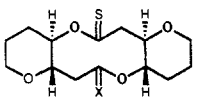
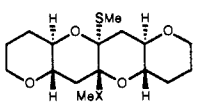
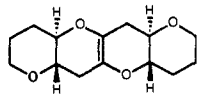
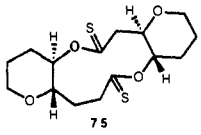
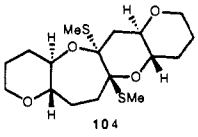
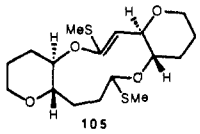
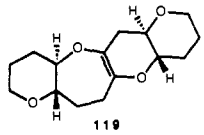
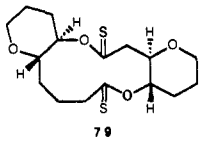
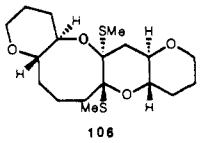
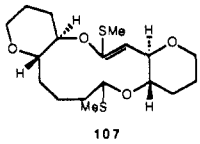
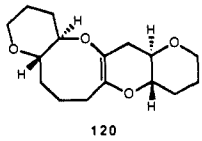
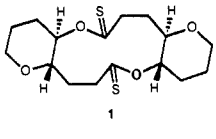
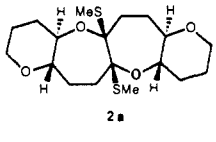
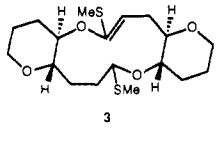
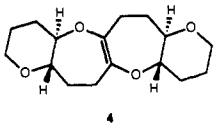
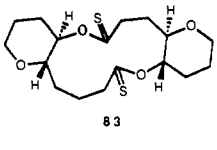
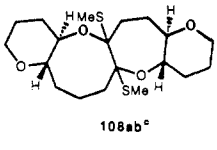
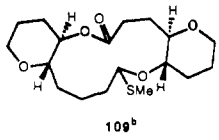
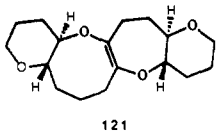
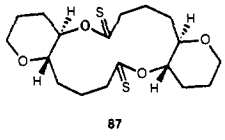
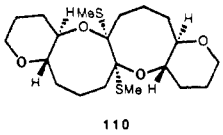
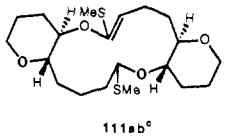
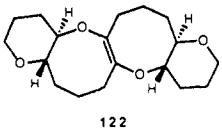
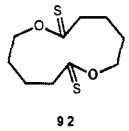
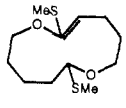
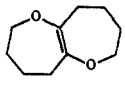
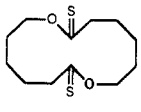
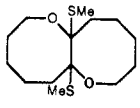
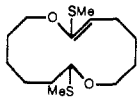
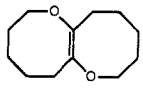
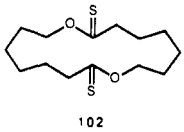
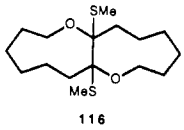
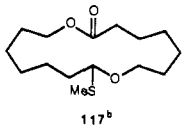
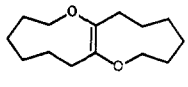
This pattern suggests several explanations for the stereochemical outcome. Two possibilities are the following. Radical-promoted ring closures (Scheme II) through cyclic transition states reflecting product strain energies imply thermodynamic control. Alternatively, the X-ray structures of the anti thionolactones may lie above C=S syn-oriented global minima, the stereochemistry of the latter directing the reaction's course.

To test these proposals conformationally required parameterizing MM2 for the C(=S)O thioester function and the C(OR)S thioketal moiety. A comparison of the crystal structures for **1** and **70** and the corresponding force field energy minima (Figure 2) shows the thionolactones to be well-represented by the current parameters (Table III, supplementary material). Further details are presented in the Experimental Section.

Evaluation of the conformational surface of the 12-membered thionolactone **1** was accomplished by subjecting the X-ray structure to a nine-bond torsional search with an efficient ring-searching program.[15] The CS–O bonds were allowed six values each (−15, 0, +15, +165, +180, +195°) while the remaining nonring bonds were explored in 30° increments. Of the 9 million or so theoretical rotamers, 170 sterically reasonable ring-closed

(15) Smith, G. M. *QCPE* **1986**, *No. 6*, 510.

Table I. Synthesis of Oxapolycyclic Systems by Bridging of Dithionolides[a]

entry	dithionolide	disulfide	yield, %	byproduct	yield, %	olefin	yield, %
1	 70 : X = S	 9 : X = S	82	—		 118	100
2	71 : X = O	103 : X = O	85				
3	 75	 104	84	 105	3	 119	98
4	 79	 106	45	 107	44	 120	99
5	 1	 2a	80	 3	10	 4	99
6	 83	 108ab[c]	53	 109[b]	44	 121	97
7	 87	 110	68	 111ab[c]	22	 122	96
8	 92	 112	53	 113	28	 123	92
9	 97	 114	52	 115	15	 124	96
10	 102	 116	12	 117[b]	68	 125	95

[a] Reaction conditions as in Scheme III. [b] Byproduct isolated as the macrolactone. [c] Mixture of two isomers.

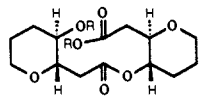
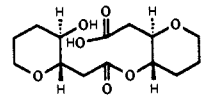
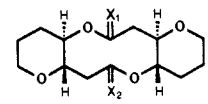
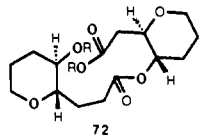
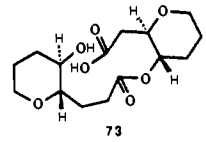
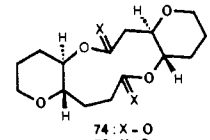
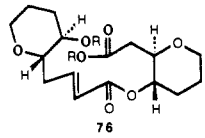
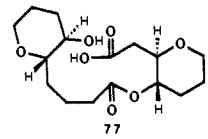
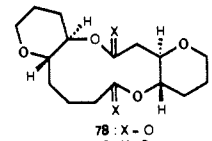
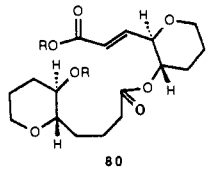
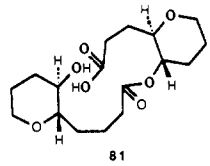
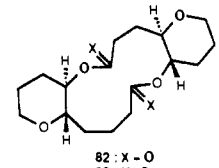
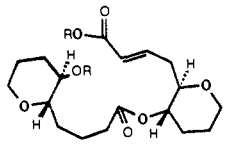
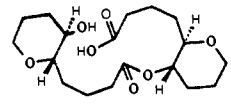
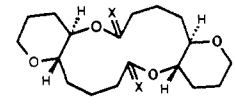
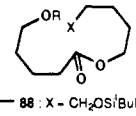
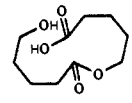
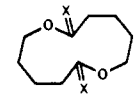
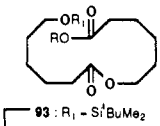
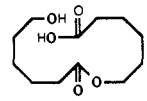
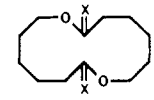
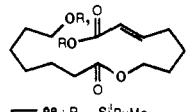
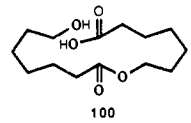
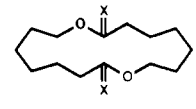
solutions emerged. Each was geometry optimized with MM2 and ranked by energy. Thirty-five conformational minima were found within 10 kcal/mol of the lowest (see Experimental Section for further details).

Eight conformers with Boltzmann populations (298 K) ranging from 0.7 to 55% are found within 3 kcal/mol of the minimum. Evidently thionolide **1** is not only very mobile but also conformationally rich at ambient temperatures. The experimentally determined X-ray structure is predicted to lie 1.5 kcal/mol above the global minimum and to be present to the extent of 5%. The finding is in agreement with the rule of thumb[16] that the X-ray conformation is within at least 1–2 kcal/mol of the lowest in the collection of low-energy conformers. Equally noteworthy, the lowest six calculated conformations display anti C=S groups; the seventh and eighth (4 and 0.7%, respectively) are syn. We conclude that the torsional freedom of a given ground-state thionolactone is retained by the corresponding radical anion (Scheme II), which closes by the energetically most favorable cis or trans pathway. This, in turn, is strongly reflected by the relative energies of potential dithioether products.

Stereochemistry of Bridging Reaction. Cis versus Trans Closure. To explore the basis of the stereochemical outcome for production of central bridgehead diastereomers from thionolactones, conformational searching was performed for isomers of bis(methylthio) ethers **9**, **104**, **106**, and **110**. The **a–c** stereochemical rearrangements referred to below are symbolized in Chart I. Each

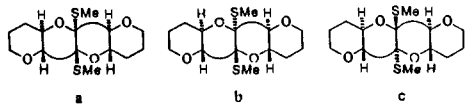
(16) This X-ray crystallographic analysis was carried out after the spectroscopic analysis on a series of related compounds was completed.[17]

Table II. Synthesis of the Macrocyclic Dithionolides[a]

entry	carboxylic acid	hydroxy compd	ester[a]	yield, %	hydroxy acid	yield, %	macrodiolide and macrodithionolide	yield, %
1	38	48	 67	72	 66	95	 69 : X_1 - X_2 - O 70 : X_1 - X_2 - S 71 : X_1 - O, X_2 - S	72 56 20
2	20	48	 72	68	 73	90	 74 : X - O 75 : X - S	78 62
3	42	48	 76	65	 77	98	 78 : X - O 79 : X - S	72 31
4	41	32	 80	86	 81	92	 82 : X - O 83 : X - S	80 70
5	41	51	 84	87	 85	98	 86 : X - O 87 : X - S	80 72
6	55	53	 [c] 88 : X - $CH_2OSi^tBuMe_2$ 89 : X - COOH	70 88	 90	99	 91 : X - O 92 : X - S	48 60
7	58	60	 [d] 93 : R_1 - Si^tBuMe_2 94 : R_1 - H	95 89	 95	93	 96 : X - O 97 : X - S	45 75
8	65	66	 [d] 98 : R_1 - Si^tBuMe_2 99 : R_1 - H	92 86	 100	98	 101 : X - O 102 : X - S	39 41

[a] Reaction conditions similar to Scheme IX. [b] R = CH_2Ph. [c] Jones' oxidation, acetone, 0 °C. [d] HF–pyr., THF, 0 °C.

Chart I



a b c

of the compounds was isolated as a single product from the electron capture and subsequent bridging by precursors. Each in turn was examined by X-ray crystallography (Figure 1). The 6,6,6,6 cyclic thioether product **9** admits only two low-energy forms by force field optimization. The anti global minimum **9b** is an all-chair structure identical with the crystal structure of the isolated product (Figure 1). The syn isomer **9a** is forced to abide three chair and one boat six-membered rings and lies 3.5 kcal/mol higher in energy. The latter is a consequence of the symmetric trans fusion of the oxacyclohexane rings at the periphery of the inner rings of compounds **9** and **70**. By the same token, the alternative anti fusion **9c** is still higher in energy as a result of the necessity to introduce a minimum of two twist–boat rings in its lowest energy conformation.

Thionolactone **75**, an 11-membered ring at its core, proceeds to ring close to give the 6,7,6,6 trans compound **104b**. The X-ray conformation with a central 7,6-membered ring chair/twist–chair orientation lies 0.2 kcal/mol above the MM2 global minimum, a slightly different chair/twist–chair conformer. The latter falls 0.6 and 8.8 kcal/mol below the lowest **104a** and **104c** diastereomers, respectively. Dithioether **104b** is obtained in 85% yield. In agreement with our failure to observe it, isomer **104a** is predicted to appear as a minor product in less than 15% yield (Boltzmann distribution at 195 K).

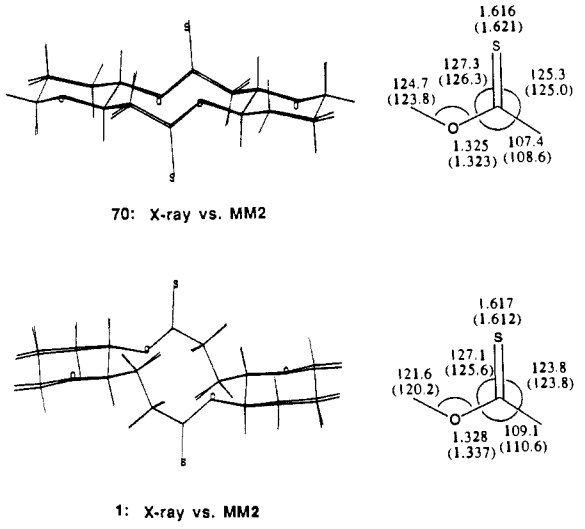


Figure 2. Comparison of the X-ray and MM2-optimized structures of dithionolides **1** and **70**. X-ray values are in parentheses.

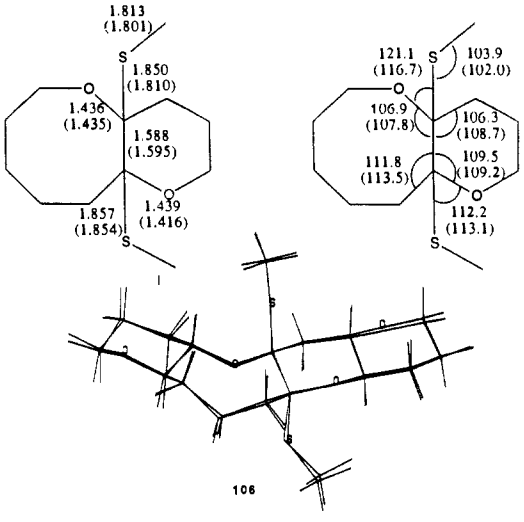


Figure 3. Comparison of the X-ray and MM2-optimized structure of one conformer of the 6,8,6,6 bis(methylthio) ketal **106**. X-ray values are in parentheses.

Similarly, the 12-membered thionolactone **79** yields its 6,8,6,6 bis(methylthio) ketal as trans **106b**. Like the corresponding systems **9** and **104**, the bridgehead atoms along one edge of the structure are all syn to one another. Conformational searching for **106b** results in four structures each with chair six-membered rings and different shapes in the eight-membered ring. The global minimum is identical with the crystal structure and exists with the eight-membered ring in a crown conformation (Figure 3). The next lowest conformational isomer is 3.3 kcal/mol (MM2) higher in energy. The cis diastereomer **106a** likewise delivers four conformers by searching. The two most stable are predicted at 1.5 and 7.5 kcal/mol above the trans **106b** minimum. The more stable of the pair contains a chair–boat conformation in the eight-membered ring. Compound **106b** is obtained as a single isomer in 46% yield. Again in agreement with experiment, **106a** is predicted to appear as a minor product in ~1% yield (Boltzmann distribution at 195 K). Finally, several structures representing the alternative trans **106c** conformational surface were located. Each of these is higher than the trans **106b** global minimum by at least 6.9 kcal/mol.

The three reactions described above, **70** → **9**, **75** → **104**, and **79** → **106**, have resulted in the X-ray-confirmed formation of trans dithioethers. The 6,8,8,6 cis case (**87** → **110**) resulting in cis selection remains to be examined. Cis **110a** delivers three conformations within 10 kcal/mol of the global minimum (0.0, 6.3 and 6.9 kcal/mol). The lowest is the crown/twist–chair conformation found in the X-ray crystal structure (Figure 1). The trans variant **110b** also provides three ring shapes, the lowest of which is a crown–crown conformer, 2.0 kcal/mol above the cis global minimum. Again, conformational ring search coupled to full MM2 optimization provides a correlation with observation. In the present series, analysis of the MM2 energy components suggests that subtle differences in the van der Waals interactions and the dihedral angle terms are responsible for the stability of **110a** over **110b**.

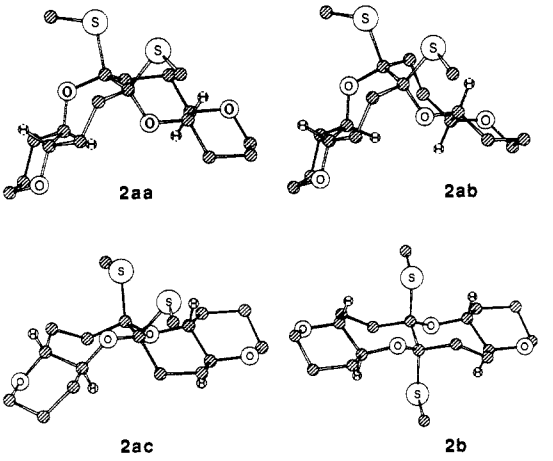


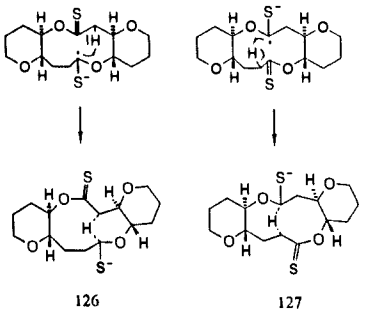
Figure 4. MM2-optimized structures for the three low-energy cis conformations **2a** and the trans isomer **2b** of the 6,7,7,6 bis(methylthio) ether **2**.

In summary, the X-ray-determined conformations for bis(methylthio) ethers **9**, **104**, **106**, and **110**, unlike the thionolactones, are coincident in each case with the MM2 global minima found by exhaustive ring search. This is certainly due to the fact that, with the exception of the nearly degenerate low-energy pair of conformers of **104b**, second conformations in the various ring-shape manifolds are no closer than 1.5 kcal/mol. This energy difference arising as a blend of bending, torsion, and van der Waals strain, is easily discriminated by a reasonably well parametrized force field. Thus, MM2 not only matches the global minima for dithioethers with the crystal structures, but also rationalizes their laboratory isolation by comparison with less stable diastereomers.

For the sodium naphthalenide induced ring closure of dithionolides to polycyclic dithioethers (Table I), a clear trend is evident: a gradual shift from trans to cis dithioether as the ring size increases. The 10-membered thionolactone **70** furnishes a trans product (**9b**) favored over the cis (**9a**) by 3.5 kcal/mol. The energy difference drops to 0.8 and 1.5 kcal/mol for the 6,7,6,6 (**104b** versus **104a**) and the 6,8,6,6 systems (**106b** versus **106a**), respectively, and then reverses itself by 2.0 kcal/mol in the 6,8,8,6 framework (**110a** versus **110b**). The trend can be understood as a combination of conformational ring strain and a preference for a gauche relative to a trans SMe–SMe relationship in the embedded 2,3-dimethoxy-2,3-bis(methylthio)butane moiety. The corresponding MM2 gap for the separate butane conformers themselves is 1.4 kcal/mol. A predictive model of thionolactone cyclization stereochemistry thereby arises from product energy differences, no doubt reflecting the early introduction of the strain factors in the transition state.

Stereochemistry of Ring Bridging to Give 6,7,7,6 Bis(methylthio) Ether 2a. It can be expected that the 6,7,7,6 system should fall near the transition point in the preferential formation of cis and trans diastereomers in the transformation **1** → **2**. The cis tetracycle **2a** when conformationally searched and MM2 optimized yields four conformers within 4 kcal/mol (Chart I, Figure 4). The chair–chair global minimum is followed closely by two other cis conformations at 0.9 and 1.0 kcal/mol. The first trans dithioether **2b**, a C_i symmetric twist–chair form, falls at 1.0 kcal/mol; the second conformation, at 2.8 kcal/mol. The first conformation of the second trans diastereomer **2c** appears at 2.9 kcal/mol. If these numbers are taken as a measure of transition-state closure, the cis isomer is expected to be formed with a 93% preference.

Chart II



126 127

Indeed, the product derived by bridging compound **1** had the cis stereochemistry **2a** as revealed by NMR spectroscopy. The appearance of 2 methylthio signals in the ^1H NMR spectrum and 18 peaks in the ^{13}C NMR trace rules out the low-energy C_i symmetric trans form **2b**. More strained conformers and the second trans species **2c** can be excluded on energy grounds.

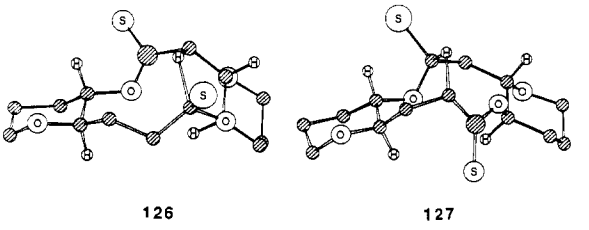
The ^1H NMR spectrum of **2a** also shows the resonance corresponding to the proton γ to sulfur across the oxygen bridge (S–C–O–C–H) at relatively low field [δ 4.21 (ddd, J = 10.0, 10.0, 5.0 Hz)]. The S–C–C–S bridge stereochemistry was assigned by one-dimensional NOE difference techniques. Irradiation of the lowest field proton (δ 4.21) resulted in signal enhancement of both sets of SCH_3 protons. Similar irradiation of the higher field hydrogen (δ 3.62) caused no change. It can be concluded that the bridge sulfurs are cis, and that the low field SCOC*H* proton resides on the syn face of the molecule. The strong deshielding of this hydrogen, presumably by sulfur lone electron pairs, is consistent.

Lowering the temperature of the NMR experiment to −40 °C leads to reversible changes in the proton chemical shifts. In agreement with the force field analysis, the presence of more than one accessible conformation is signified. A more detailed analysis of the NMR spectra of the bridged bis(methylthio) ethers will appear elsewhere.[17] An X-ray crystallographic analysis[16] of **2a** confirms the spectroscopically assigned structure (see ORTEP drawing, Figure 1).

Preference for Short-Bridge Methylthioenol Ethers. As illustrated in Scheme IV and detailed in Table I, thionolactone ring closure delivers an enol byproduct. Analysis of **105**, **107**, and **109** by NMR spectroscopy shows that for these unsymmetrical systems the C=C(SMe)O moiety resides in the shorter link between the terminal THP rings. The implication is that one of two topologically distinct hydrogen-transfer transition states is consistently favored in the series under consideration.

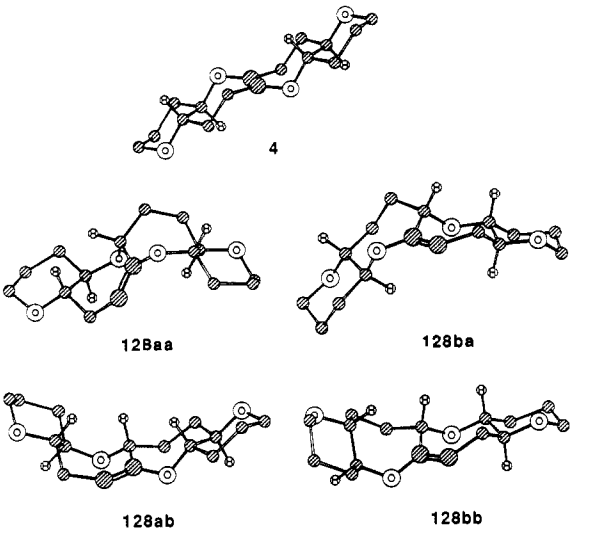
The situation for the 11-membered-ring thionolactone **75** is outlined in Chart II. Hydrogen transfer from the short chain leads to a transition state characterized by a central bicyclo[6,3,1] framework **126**. Long-chain transfer involves a bicyclo[5,4,1] structure **127**. A model for qualitatively assessing the energy differences assumes a transition state with equal C···H bonds at 1.9–1.95 Å and easily deformed bond angles.[18] It is further assumed that the energy differences between the bicyclic structures arise primarily from the overall variation in bicyclic constitution. While the symmetric model of the bond-making and bond-breaking process is surely oversimplified, the relative contributions at the C···H···C centers in the various polycycles are considered. Relative contributions at the C···H···C centers in the various polycycles are considered to approximately cancel. Furthermore, for structures **126** and **127**, two diastereomers were calculated. That is, the hydrogen in transit was located both above and below the average molecular plane. Finally, for each of the four structures a conformational ring search for the virtual 7,8- (**127**) and 6,9-membered (**126**) rings was carried out.

(17) Snyder, J. P.; Bible, R.; Hajdu, E.; Nicolaou, K. C.; Hwang, C.-K.; Marron, B. E.; DeFrees, S. A.; Abe, Y.; Carrol, P. J., unpublished results.
(18) Paddon-Row, M. N.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 7162.



126 127

Figure 5. Transition-state models (MM2 optimized) for hydrogen transfer in the thio enol forming reaction; [6,9]bicycle **126** and [7,8]-bicycle **127**.



4 128aa 128ba 128ab 128bb

Figure 6. The X-ray and PRDDO global minimum conformation for olefin **4**; global minima (**aa**,**ba**), and next lowest conformations (**ab**,**bb**) for **128a** and **128b**.

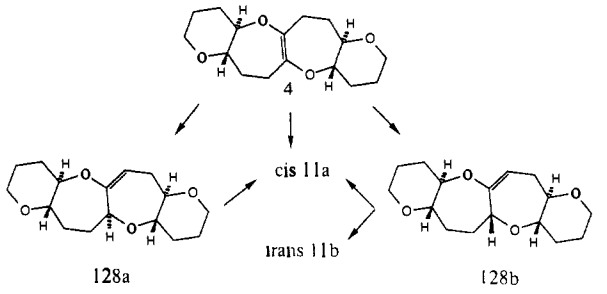
Application of a rough force field (Table IV, supplementary material) led to four global minima: **126** (0.0, 1.3 kcal/mol); **127** (1.8 and 6.9 kcal/mol). Short-chain hydrogen transfer in **126** is preferred by 1.8 kcal/mol (99/1 by Boltzmann, 195 K) relative to **127**. Figure 5 depicts the low-energy transition-state models. Secondly, the two diastereomers of **126** differ by 1.3 kcal/mol (97/3, 195 K), implying enantioselection at the C(–S) terminus of hydrogen migration. This accords well with the experimental results in which all but one case (**111**) yield a single diastereomer.

Based on this model it is reasonable to presume that short-chain thioenol formation occurs as a result of reduced bicyclic ring strain in a transition state containing the largest possible ring. For **126** this is a nine-membered cycle versus seven- and eight-membered in **127**. In the case of 12-membered-ring thionolactone **79**, the short-chain transition state incorporates 6- and 10-membered rings; the long-chain, two 8-membered loops.

The computational strategy employed here places the burden for discriminating atom-transfer transition states on structural features of the system essentially independent of the bonds being made and broken. If this reflects a more general principle, rearrangement regiochemistry in medium-sized rings for a variety of reactions may be predictable on the simple basis of comparative ring size.

Catalytic (H_2) Reduction of 6,7,7,6 Vinyl Ether 4. Structural aspects of the dihydro products from the various regimes for reducing alkene **4** (Scheme VI) are profitably viewed by comparison with the bis(methylthio ether) counterparts **2**. Whereas in the latter, bulkier system, only the cis isomer **2a** was observed, the bridgehead unencumbered oxocycles are isolated as both the cis and trans forms of **11**. The trans species, when it appears, does so in the cis/trans ratio of 6/1. By MM2 the relative energies of global minima for the sulfur-containing systems increases as follows: cis **2a**, 0.0; trans **2b**, 1.0; trans **2c**, 2.9 kcal/mol. Equally satisfying is the result for the reduced species: cis **11a**, 0.0; trans **11b**, 0.4; trans **11c**, 1.7 kcal/mol. By Saunders' MM2 stochastic

Scheme XV



search procedure[19] all three deliver several conformations clustered within 3.0 kcal/mol of the global minima. For cis **11a** and trans **11b**, the global minima are the X-ray crystal conformations (Figure 6).

Catalytic hydrogenation of vinyl ether **4** with H_2–$Pd(OH)_2$ is the experimental recipe from which both cis and trans diastereomers are isolated. As suggested in the opening "bridging" section above, double-bond migration through either of two diastereomeric forms of isomer **128** (Scheme XV) is a plausible route. Accordingly, each of the bridgehead alkenes was subjected to a conformational search followed by MM2 optimization. Since the C=C isomers **4** and **128** are not directly comparable in the force field framework, the lowest lying structures were reevaluated for energy by single-point PRDDO[20] calculations. For compound **4** the global minimum again proves to be the X-ray crystal conformation (Figure 6). Relative energies for the three olefins [**4**, 0.0; **128aa**, 9.4; **128ba**, 5.2 (ΔE_{MM2}(**ba** − **aa**) = −3.9) kcal/mol] rationalize the lack of appearance of C=C isomers of **4**, but also indicate the potential for isomerizing through **128b** on the surface of the catalyst.

Classical cis hydrogenation of vinyl ether **4** provides dihydro cis **11a** as the predominant product. Similarly, cis hydrogen delivery to the cup-shaped minimum-energy conformation of **128b** (Scheme XV, Figure 6, **128ba**) is expected to give cis **11a** by reagent attack on the convex face of the molecule. The next conformation **128bb** lies 2.7 kcal/mol (PRDDO) higher. As is evident, **128bb** can serve as a path to trans **11b**. Alternatively, isomer **128aa**, though considerably higher in energy, is also poised to provide cis **11a** by convex H_2 delivery. These high-energy forms presumably reflect the relative energies of product. The observed 6/1 cis/trans ratio corresponds to the Boltzmann ratio of 9/1 (198 K) as derived from PRDDO energies [ΔE(cis **11a** − trans **11b**) = 1.3 kcal/mol]. Trans **11c** is calculated to be 5.6 kcal/mol higher than cis **11a** and therefore not an energetically viable product candidate. The hydrogenation reaction then, similar to the situation for formation of bis(methylthio) ethers, can be interpreted as governed by thermodynamic factors.

Hydride Reduction of Vinyl Ether 4. Stereospecificity of Protonation. Empirical evidence was presented in the opening section that protonation with trifluoroacetic acid (TFA) and subsequent hydride reduction of compound **4** leads to cis **11a**/**12a**. Cationic species **14** (Scheme VI) is the suggested intermediate. The initial proton (or deuteron) ultimately comes to reside at the center of the edge of **12** anti to the other protons on it. In principle the stereochemical outcome can arise by either of two protonation itineraries (Scheme XVI).

Establishment of the regiochemistry follows both from ^1H NMR coupling constants and from a knowledge of the solution conformation of **11a**. As described above, the MM2 global minimum and X-ray conformations coincide (Figure 7). Application of a parameterized Karplus expression[21] to the latter illustrates that H_a, syn to two other protons on the edge of **11a**, couples to three protons with values of 1.0, 3.9, and 6.5 Hz. The experimental

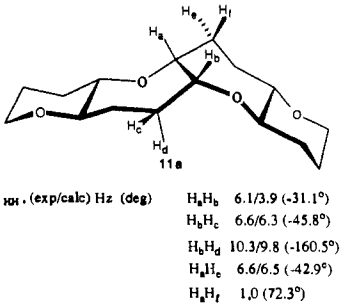
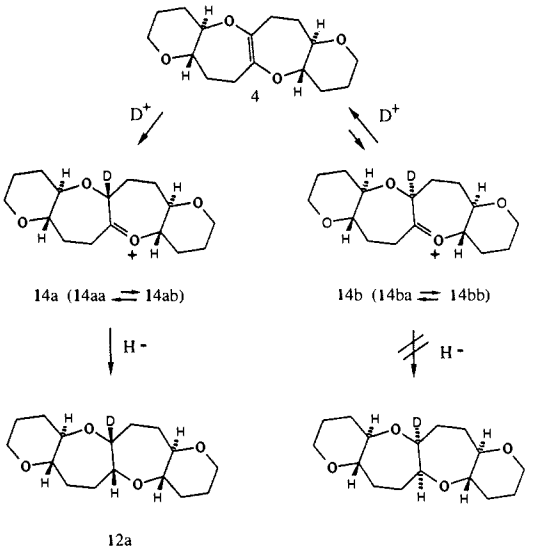


Figure 7. Representation of the X-ray structure and MM2 global minimum for the cis **11a**. Comparison of measured and predicted NMR proton–proton coupling constants. The experimentally unresolved H_aH_f value is predicted to be 1.0 Hz.

Scheme XVI[a]



J's are 6.1 and 6.6 Hz (cf. Figure 7). The smallest coupling is not resolved, while the bridgehead–bridgehead value (J_{ab} = 6.1 vs 3.9 Hz) is somewhat underestimated. Proton H_b, anti to its edge partner bridgehead protons, is predicted to show *J*'s of 3.9, 6.3, and 9.8 Hz. These match the J_{exp} = 6.1, 6.6, and 10.2 Hz. Since the latter signals disappear on deuteration, H_b or D is located as depicted in Schemes VI and XVI.

The result requires two stereospecific events. First, protonation of **4** must occur to give anti **14a** rather than syn **14b**. Second, hydride delivery to **14a** is obligated to proceed cis to the central bridgehead hydrogen (or deuteron) to provide **12a** (Scheme XVI). To evaluate the situation, the syn and anti variants of the intermediate (**14a** and **14b**, respectively) were modeled with MM2 by employing a set of provisional C=O$^+$ parameters (see Experimental Section).

Conformational searching followed by PRDDO evaluation of the MM2-optimized structures indicates that the anti conformer **14aa** (Figure 8) is the lowest minimum, the next conformation **14ab** falling 3.1 kcal/mol higher. Syn **14ba** is calculated to be only 0.4 kcal/mol less stable than anti **14aa** with its closest conformer **14bb** within 0.6 kcal/mol. The complexity of the situation is underscored by noting that hydride attack on the least hindered, convex face of the anti **14aa** cup would yield the high-energy trans **13b** rather than cis **11a**/**12a**. Hydride donation to the least crowded faces of syn isomers **14ba** and **14bb**, on the other hand, would give a regiochemistry for **11a**/**12a** at odds with the deuteration experiment (Scheme XVI). Only the energy-elevated conformation **14ab** permits the original anti proton delivery (through **14aa**) and hydride attack from a relatively unhindered direction.

The steric analysis is derived from the distances given in Figure 8. Paddon-Row and colleagues have shown that the transition state for hydride transfer to C=X is close to tetrahedral.[18] The

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(20) Halgren, T. A. Lipscomb, W. N. *J. Chem. Phys.* **1973**, *58*, 1569. Marynick, D. S.; Lipscomb, W. N. *Proc. Natl. Acad. Sci. U.S.A.* **1982**, *79*, 1341.
(21) Haasnoot, C. A. G.; de Leeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783.

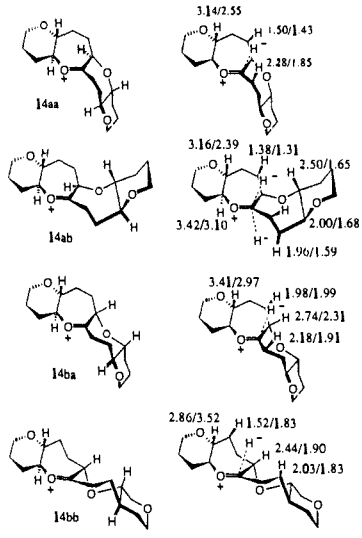

Figure 8. Low-energy conformation of **14a** and **14b** (**14aa**/**14ab** and **14ba**/**14bb**, respectively) at the left. The structures have been supplemented with an H^- 2.0 Å from the carbon of $C{=}O^+$ at two values of the bond angle $H^-{\cdots}C{=}O^+$ (90 and 109°). The numerical values correspond to the distance between the incoming H^- and the specific hydrogens selected. The first value refers to 90° and the second to 109° of the incipient bond angle.

MM2-refined oxycation conformers have been embellished with a dummy atom to represent the incoming H^- placed at 2.0 Å perpendicular to the carbon undergoing attack [$C(=O^+)$]. Distances from H^- and the surrounding H's on the rigid carbon skeletons were measured. The $^+O{=}C{\cdots}H^-$ angle was expanded from 90° to the ideal 109° tetrahedral value, and the distances were remeasured. This provides a range of possible steric contacts for the approach of the hydride reagent from 90 to 109° along the reaction trajectory. For conformation **14aa** only trans delivery of H^- is feasible, but it would involve a less than 2.0-Å contact with two hydrogens flanking the incoming reagent. Similarly, the convex faces of the syn diastereomers **14ba** and **14bb** suffer two and three short contacts, respectively, along the approach channel. In contrast, the anti conformation **14ab** suffers but a single short contact in the model transition state leading to cis **12a**.

The picture that emerges is summarized by Scheme XVI. Protonation of vinyl ether **4** is considered to yield an equilibrium mixture of syn and anti oxycations with a possible preponderance of anti **14ab**. Hydride reduction proceeds through a higher energy conformation of the latter (**14ab**) to give cis **11a**/**12a** on the basis of minimum steric congestion in the transition state for H^- attack.

Conclusion

A new reaction for the bridging of macrocycles to bicyclic systems has been discovered. The details described in this article demonstrate the power of this novel method in the construction of polycyclic systems present in many natural products, including the brevetoxins. X-ray crystallographic and NMR techniques proved the structures of the starting macrodithionolactones and those of the product bis(methylthio) ethers. Calculations corroborated a number of the experimental observations and led to a better understanding of conformational effects in the cyclic systems examined. It is expected that useful applications of the reported reactions will be found in the synthesis of natural and designed molecules. Such applications are currently in progress in these laboratories.

Experimental Section

(±)-(4a*S*,5a*S*,7a*S*,11a*R*,12a*S*,14a*R*)-5a,12a-Bis(methylthio)perhydropyrano[3,2-*b*]pyrano[2′,3′:6,7]oxepano[2,3-*f*]oxepane (2a) and (±)-(4a*R*,8a*R*,12a*S*,16a*S*)(2,3,4,4a,8,8a,10,11,12,12a,14,15,16,16a)-Tetradecahydro-6,14-bis(methylthio)dipyrano[3,2-*b*:3′,2′-*h*][1,7]dioxacyclododec-5-ene (3). A solution of the dithionolide 1 (344 mg, 1.0 mmol) in THF (10 mL) was cooled to −78 °C and magnetically stirred under argon. Sodium naphthalenide solution (3.67 mL, 0.6 M in THF, 2.2 mmol) was added dropwise until a green coloration persisted. Methyl iodide (2.1 g, 15 mmol) was added at −78 °C and the reaction mixture was allowed to warm to 25 °C over 1 h with stirring. The resulting residue was flash chromatographed (silica, 50% ether in petroleum ether) to afford the bis(methylthio) ketal **2a** (296 mg, 80%) and macrocycle **3** (37 mg, 12%). Compound **2a**: colorless solid, mp 128–129 °C (hexane–ether), R_f = 0.30 (silica, 50% ether in petroleum ether); IR (CH_2Cl_2) ν_{max} 2978, 2968, 2929, 1443, 1216, 1101, 1073, 948, 832, 684 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.21 (ddd, J = 10.0, 10.0, 5.0 Hz, 1 H, C*H*OCSMe; H, SMe, syn), 3.90 (br d, J = 12.0 Hz, 2 H, CH_2O), 3.61 (ddd, J = 10.0, 10.0, 5.0 Hz, 1 H, C*H*O), 3.34–3.10 (m, 4 H, C*H*O, CH_2O), 2.28–1.37 (m, 16 H, CH_2), 2.03 (s, 3 H, SCH_3), 1.89 (s, 3 H, SCH_3); ^{13}C NMR (50 MHz, C_6D_6) δ 98.58, 95.98, 81.99, 81.39, 72.82, 71.81, 67.45, 67.33, 33.24, 32.36, 31.89, 31.70, 30.08, 28.78, 26.26, 26.09, 12.55, 11.74; HRMS calcd for $C_{17}H_{27}O_4S$ (M − SMe) 327.1630, found 327.1628. Anal. Calcd for $C_{18}H_{30}O_4S_2$: C, 57.72; H, 8.07. Found: C, 57.70; H, 8.16. Compound **3**: colorless oil; R_f = 0.50 (silica, 50% ether in petroleum ether); IR (neat) ν_{max} 2950, 1882, 1750, 1642, 1443, 1348, 1218, 1117, 1085, 1010, 875, 770, 740, 691 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.18 (dd, J = 8.0, 5.0 Hz, 1 H, C*H*=C(SMe)O), 4.28 (t, J = 5.0 Hz, 1 H, C*H*(SMe)O), 4.15 (ddd, J = 10.0, 10.0, 5.0 Hz, 1 H, C*H*O), 3.85 (br d, J = 10.0 Hz, CH_2O), 3.30 (m, 5 H, C*H*O, CH_2O), 2.68–1.50 (m, 14 H, CH_2), 2.18 (s, 3 H, SCH_3), 2.02 (s, 3 H, SCH_3); ^{13}C NMR (50 MHz, C_6D_6) δ 150.30, 115.63, 84.51, 82.95, 80.79, 79.22, 75.46, 67.89, 67.27, 33.49, 32.87, 32.27, 31.56, 28.63, 25.91, 25.41, 15.97, 8.40; HRMS calcd for $C_{17}H_{27}O_4S$ (M − SMe) 327.1630, found 327.1599.

By use of similar procedures, the following compounds were prepared: **9**, **104–117**; see supplementary material for data.

(±)-(4a*S*,5a*R*,6a*S*,10a*R*,11a*R*,12a*R*)-5a-(Methyloxy)-11a-(methylthio)perhydropyrano[2″,3″:5′,6′]pyrano[2′,3′:5,6]pyrano[3,2-*b*]pyran (103). The monothiono ester **71** (176 mg, 0.533 mmol) was converted to the bis(methylthiono) ketal by the general procedure described above except for continued stirring at 25 °C (3 h) after methyl iodide addition. Flash chromatography (silica, 50% ether in petroleum ether) gave mixed ketal **103** (150 mg, 85%). Compound **103**: colorless solid, mp 205–206 °C (CH_2Cl_2–ether); R_f = 0.55 (silica, 70% ether in petroleum ether); IR (CH_2Cl_2) ν_{max} 2952, 2845, 1473, 1285, 1210, 1120, 1071, 1028, 956 cm^{-1}; ^{1}H NMR (250 MHz, C_6D_6) δ 4.35 (m, 2 H, CH_2O), 3.92 (m, 2 H, C*H*O, CH_2O), 3.80 (m, 1 H, C*H*O), 3.52–3.25 (m, 3 H, C*H*O, CH_2O), 3.18 (s, 3 H, OCH_3), 2.90–1.40 (m, 12 H, CH_2), 1.90 (s, 3 H, SCH_3); ^{13}C NMR (125 MHz, C_6D_6) δ 99.42, 92.21, 78.24, 77.24, 71.90, 71.55, 68.31, 68.24, 46.84, 33.30, 31.38, 29.72, 29.66, 26.62, 26.37, 9.02; HRMS calcd for $C_{15}H_{23}O_4S$ (M − OMe) 299.1327, found 299.1293.

(4a*S*,7a*S*,11a*R*,14a*R*)-(2,3,4,4a,6,7,7a,9,10,11,11a,13,14,14a)-Tetradecahydropyrano[3,2-*b*]pyrano[2′,3′:6,7]oxepino[2,3-*f*]oxepin (4). A solution of the bis(methylthio) ketal **2a** (50 mg, 0.13 mmol), AIBN (catalytic), and nBu$_3$SnH (38.7 mg, 0.16 mmol) in toluene (5 mL) was heated to 110 °C for 30 min. Concentration and flash chromatography (silica, 40% ether in petroleum ether) gave enol ether **4** (36 mg, 99%). Compound **4**: colorless crystals, mp 163–165 °C (ether–hexane); R_f = 0.33 (silica, 50% ether in petroleum ether); IR (CH_2Cl_2) ν_{max} 2950, 2858, 1468, 1459, 1435, 1345, 1226, 1175, 1092, 1021, 958 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.90–3.75 (br d, J = 12.0 Hz, 2 H, CH_2O), 3.38–3.05 (m, 6 H, CH_2O, C*H*O), 2.61–2.45 (br dd, J = 12.0, 12.0 Hz, 2 H, CH_2C(O)=C), 2.24–1.41 (m, 14 H, CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) δ 148.28 (2 C), 82.54 (2 C), 80.48 (2 C), 67.55 (2 C), 31.26 (2 C), 31.26 (2 C), 28.09 (2 C), 26.01 (2 C), HRMS calcd for $C_{16}H_{24}O_4$ (M) 280.1675, found 280.1661.

By use of similar procedures, the following compounds were prepared: **118–125**; see supplementary material for data.

(4a*S*,6*S*,8a*R*,4′a*R*,6′*R*,8′a*S*)-2,2′-Diperhydropyrano[3,2-*b*]pyran (8). Silver tetrafluoroborate (58 mg, 0.3 mmol) was added to a solution of disulfide **2a** (50 mg, 0.13 mmol) and triethylsilane (45 mg, 0.39 mmol) in CH_2Cl_2 at 25 °C. After 2 h, the reaction mixture was concentrated and the residue was flash chromatographed (silica, 30% ether in petroleum ether) to afford **8** (34 mg, 92%). Compound **8**: colorless solid, mp 155–156 °C (hexane); R_f = 0.35 (silica, 50% ether in petroleum ether); IR (CH_2Cl_2) ν_{max} 2950, 2938, 2860, 1457, 1442, 1218, 1095, 1028, 978, 875 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.84 (br d, J = 11.5 Hz, 2 H, CH_2O), 3.45–2.88 (m, 8 H, C*H*O, CH_2O), 2.03–1.36 (m, 16 H, CH_2); ^{13}C NMR (50 MHz, C_6D_6) δ 80.23, 79.10, 78.75, 65.80, 30.26, 29.94, 28.31, 26.21; HRMS calcd for $C_{16}H_{27}O_4$ (M + H) 283.1909, found 283.1897.

(±)-(4a*S*,5a*R*,6a*S*,10a*R*,11a*S*,12a*R*)-Perhydropyrano[2″,3″:5′,6′]-pyrano[2′,3′:5,6]pyrano[2,3-*b*]pyran (10). Compound **10** was prepared from **9** (51 mg, 0.147 mmol) by the procedure used to convert **2a** to **8** described above. After the reaction was complete, the reaction mixture was concentrated and the residue flash chromatographed (silica, 40% ether in petroleum ether) to afford **10** (35 mg, 92%). Compound **10**:

colorless crystals, mp 245–247 °C (sublime) (hexane); R_f = 0.32 (50% ether in petroleum ether); IR ($CHCl_3$) ν_{max} 2940, 2845, 1085, 1072, 1030, 1020 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.96–3.83 (m, 2 H, CH_2O), 3.46–3.25 (m, 2 H, CH_2O, CHO), 3.08–2.95 (m, 6 H, CH_2O, CHO), 2.38–2.23 (m, 2 H, CH_2), 2.15–2.0 (m, 2 H, CH_2), 1.85–1.2 (m, 8 H, CH_2); ^{13}C NMR (125 MHz, C_6D_6) δ 78.67 (2 C), 77.85 (2 C), 77.67 (2 C), 67.75 (2 C), 26.43 (2 C), 29.74 (2 C), 25.88 (2 C); HRMS calcd for $C_{14}H_{23}O_4$ (M + H) 255.1596, found 255.1590.

Reduction of Enol Ether 4. Method A. (±)-(4a*S*,5a*R*,7a*S*,11a*R*,12a*R*,14a*R*)-Perhydropyrano[3,2-*b*]pyrano-[2′,3′:6,7]oxepano[2,3-*f*]oxepane (11a) and (4a*S*,5a*R*,7a*S*,11a*R*,12-a*S*,14a*R*)-Perhydropyrano[3,2-*b*]pyrano[2′,3′:6,7]oxepano[2,3-*f*]oxepane (11b). Pd catalyst (5% Pd–C, 10 mg) was added in one portion to a solution of compound **4** (50 mg, 0.18 mmol) in ethyl acetate (2 mL) under a hydrogen atmosphere at 25 °C. The reaction mixture was stirred for 12 h at room temperature before the catalyst was removed by filtration. Concentration followed by flash chromatography (silica, 30% ether in petroleum ether) gave the reduced products **11a** (37 mg, 75%) and **11b** (6 mg, 12%). Compound **11a**: colorless crystals, mp 95–96 °C (ether–hexane); R_f = 0.35 (silica, 50% ether in petroleum ether); IR (CH_2Cl_2) ν_{max} 2948, 2860, 1448, 1345, 1219, 1140, 1110, 1086, 1062, 1030, 968, 936, 885 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.90–3.78 (m, 4 H, CHO), 3.39–2.76 (m, 6 H, CHO, CH_2O), 2.06–1.22 (m, 16 H, CH_2); ^{13}C NMR (500 MHz, C_6D_6) δ 85.28, 84.78, 82.74, 82.00, 79.90, 71.62, 67.72, 67.03, 32.80, 31.83, 29.26, 27.87, 26.86, 26.80, 26.29, 25.94; HRMS calcd for $C_{16}H_{27}O_4$ (M + H) 283.1909, found 283.1902. Compound **11b**: colorless crystals, mp 90–91 °C (hexane), R_f = 0.38 (silica, 50% ether in petroleum ether); IR (CH_2Cl_2) ν_{max} 2955, 2860, 1470, 1325, 1280, 1078, 1022, 965, 745 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.85 (m, 2 H, CH_2O), 2.52 (m, 2 H, CHO), 3.24 (m, 2 H, CHO, CH_2O), 3.08 (m,2 H, CHO), 2.95 (m, 2 H, CHO), 2.00 (m, 4 H, CH_2), 1.72 (m, 6 H, CH_2), 1.65 (m, 6 H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 82.78, 82.64, 82.37, 67.74, 31.35, 30.05, 28.87, 25.93; HRMS calcd for $C_{16}H_{26}O_4$ (M) 282.1831, found 282.1833.

Method B. Triethylsilane (45 mg, 0.39 mmol) was added to a solution of enol ether **4** (28 mg, 0.1 mmol) and trifluoroacetic acid (13 mg, 0.11 mmol) in CH_2Cl_2 (2 mL) at 0 °C. The mixture was allowed to react for 5 min and then concentrated and flash chromatographed to afford **11a** (23 mg, 85%).

Method C. Sodium cyanoborohydride (19 mg, 0.3 mmol) was added to a solution of enol ether **4** (28 mg, 0.1 mmol) and trifluoroacetic acid (13 mg, 0.11 mmol) in CH_2Cl_2 (2 mL) at 0 °C. The mixture was stirred at that temperature for 30 min before quenching with MeOH (1 mL). The resulting mixture was diluted with ether (20 mL), washed with H_2O (2 × 3 mL), and dried ($MgSO_4$). Concentration and flash chromatography afforded **11a** (25.4 mg, 90%).

(±)-(4a*S*,5a*R*,7a*S*,11a*R*,12a*R*,14a*R*)-12a-Deuterioperhydropyrano-[3,2-*b*]pyrano[2′,3′:6,7]oxepano[2,3-*f*]oxepane (12a). Reduction method B above was used except that trifluoroacetic acid-*d* (CF_3COOD) was used. Concentration of the reaction mixture and chromatography (silica, 40% ether in petroleum ether) afforded pure **12a** (25 mg, 88%). Compound **12a**: colorless oil, R_f = 0.35 (silica, 50% ether in petroleum ether); IR (neat) ν_{max} 2950, 2860, 1450, 1340, 1220, 1140, 1110, 1086, 1060, 1030, 960, 885, 620 cm^{-1}; ^1H NMR (250 MHz, C_6D_6) δ 3.72 (m, 2 H, CH_2O), 3.48 (m, 1 H, CHO), 3.41 (d, J = 6.6 Hz, 1 H, CHO, oxepane–oxepane juncture), 3.15 (m, 1 H, CHO), 3.08 (ddd, J = 11.4, 11.4, 2.3 Hz, 1 H, CH_2O), 2.60 (ddd, J = 9.8, 9.7, 3.7 Hz, 1 H, CHO), 2.29 (m, 1 H, CH_2), 2.06–1.13 (m, 15 H, CH_2); MS m/e (relative intensity) 284 (M + 1, 95), 265 (23), 243 (12), 184 (26), 157 (43), 110 (100); HRMS calcd for $C_{16}H_{26}DO_4$ (M + H) 284.197, found 284.202.

(2*S*,3*R*)-3-(Benzyloxy)-2-vinyl-3,4,5,6-tetrahydro-2*H*-pyran (16). To a stirred suspension of potassium hydride (10.78 g, 35% oil dispersion, 94.3 mmol) in dry THF at 0 °C was added alcohol **15**[3a] (9.29 g, 72.5 mmol) in dry THF (50 mL). After stirring for 10 min, benzyl bromide (10.35 mL, 87 mmol) was added dropwise and the reaction mixture was warmed to 25 °C over 3 h. The reaction was quenched with methanol (5 mL) and ether (800 mL), and the ether layer was washed with H_2O (2 × 200 mL) and brine (200 mL) and dried ($MgSO_4$). Concentration and flash chromatography (silica, 5% ether in petroleum ether) afforded the benzyl ether **16** (14.56 g, 92%). Compound **16**: colorless oil; R_f = 0.6 (silica, 10% ether in petroleum ether); $[\alpha]^{20}_D$ −52.19° (*c* 3.6, CH_2Cl_2); IR (neat) ν_{max} 3095, 3075, 3038, 2945, 2860, 1460, 1141, 1094, 1031, 992, 928, 740, 700, 661 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.32 (m, 5 H, aromatic), 6.03 (ddd, J = 16.5, 11.5, 5.5 Hz, 1 H, CH_2=C*H*), 5.37 (d, J = 16.5 Hz, 1 H, CH_2), 5.23 (d, J = 11.5 Hz, 1 H, CH_2), 4.59 (d, J = 12.0 Hz, 1 H, benzylic), 4.50 (d, J = 12 Hz, 1 H, benzylic), 3.94 (br d, J = 10.5 Hz, 1 H, CH_2), 3.66 (dd, J = 5.5, 5.5 Hz, 1 H, CHO), 3.46–3.10 (m, 2 H, CH_2O, CHO), 2.30–1.37 (m, 4 H, CH_2); MS m/e (relative intensity) 236 (M + NH_4, 10), 219 (M + 1, 15), 201 (19), 162 (11), 131 (93), 112 (17), 100 (23), 91 (100), 87 (100); HRMS calcd for $C_{14}H_{22}O_2N$ (M + NH_4) 236.1651, found 236.1650.

Methyl (*E*)-3-[(2*S*,3*R*)-3-(Benzyloxy)-3,4,5,6-tetrahydro-2*H*-pyran-2-yl]propenoate (18). Ozone was passed through a solution of compound **16** (14.56 g, 66.8 mmol) in methylene chloride (300 mL) at −78 °C until a blue coloration persisted (0.5 h). The excess ozone was removed by a stream of oxygen before dimethyl sulfide (10 mL) was added slowly, followed by triphenylphosphine (14.49 g, 66.8 mmol) at −78 °C. The reaction mixture was stirred at ambient temperature for 1 h and then concentrated to afford aldehyde **17**. To a solution of crude **17** in benzene was added methyl (triphenylphosphoranylidene)acetate (22.32 g, 66.8 mmol) and this solution was stirred at room temperature for 3 h. Concentration and flash chromatography (silica, 20% ether in petroleum ether) furnished compound **18** (15.12 g, 82% from **16**). Compound **18**: colorless oil; R_f = 0.45 (silica, 20% ether in petroleum ether); $[\alpha]^{20}_D$ −63.58° (*c* 6.5, CH_2Cl_2); IR (neat) ν_{max} 3092, 3070, 3038, 2950, 2860, 1728 (s, COOMe), 1668 (s, CH=CH—COOMe), 1460, 1440, 1312, 1272, 1165, 1102, 1048, 990, 743, 700, 685 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.32 (m, 5 H, aromatic), 7.18 (dd, J = 16.0, 4.0 Hz, 1 H, olefinic), 6.10 (dd, J = 16.0, 2.0 Hz, 1 H, olefinic), 4.59 (d, J = 12.0 Hz, 1 H, benzylic), 4.47 (d, J = 12.0 Hz, 1 H, benzylic), 3.95 (br d, J = 10.5 Hz, 1 H, CH_2O), 3.82 (m, 1 H, CHO), 3.75 (s, 3 H, $COOCH_3$), 3.47–3.08 (m, 2 H, CH_2O, CHO), 2.14–1.38 (m, 4 H, CH_2); MS m/e (relative intensity) 294 (M + NH_4, 21), 277 (60), 245 (23), 227 (9), 185 (45), 168 (28), 108 (9), 91 (100), 85 (100); HRMS calcd for $C_{16}H_{24}O_4N$ (M + NH_4) 294.1705, found 294.1727.

Methyl 3-[(2*S*,3*R*)-3-(Benzyloxy)-3,4,5,6-tetrahydro-2*H*-pyran-2-yl]propanoate (19). A solution of the α,β-unsaturated ester **18** (2.52 g, 9.13 mmol) in hexanes (37 mL) and 5% palladium on carbon (0.252 g, 10% wt/wt), was stirred at room temperature for 3 h under a hydrogen atmosphere. The catalyst was removed by filtration through Celite and the product was obtained after evaporation of the solvent (2.52 g, 100%). **19**: colorless oil; R_f = 0.15 (silica, 20% ether in petroleum ether); $[\alpha]^{22}_D$ −81.49° (*c* 4.84, CH_2Cl_2); IR (neat) ν_{max} 3040 (w), 2950 (s), 2860 (s), 1740 (s), 1458 (m), 1440 (m), 1270 (m), 1000 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.33 (m, 5 H, aromatic), 4.63 (d, J = 11.5 Hz, 1 H, OCH_2Ph), 4.45 (d, J = 11.5 Hz, 1 H, OCH_2Ph), 3.86 (m, 1 H, CHO), 3.66 (s, 3 H, OCH_3), 3.30 (m, 1 H, CHO), 3.11 (m, 2 H, CH_2O), 2.51–2.20 (m, 4 H, CH_2), 1.79–1.57 (m, 3 H, CH_2), 1.41 (m, 1 H, CH_2); MS m/e (relative intensity) 279 (M^+ + H, 69), 170 (100), 142 (64); HRMS calcd for $C_{16}H_{23}O_4$ (M^+ + H) 279.1596, found 279.1585.

3-[(2*S*,3*R*)-3-(Benzyloxy)-3,4,5,6-tetrahydro-2*H*-pyran-2-yl]-propanoic Acid (20). Ester **19** (2.54 g, 9.13 mmol) in THF (30 mL) and MeOH (30 mL), was stirred at 50 °C and treated with aqueous LiOH solution (1 N, 30 mL, 30 mmol). Stirring was continued at ambient temperature until completion of the reaction (5 h) and then the reaction mixture was diluted with ether (30 mL) and acidified to pH 4.5 with 1 N aqueous HCl. The organic layer was separated, the aqueous phase was extracted with ether (5 × 20 mL), and the extracts were combined and washed with brine (30 mL). Drying ($MgSO_4$) followed by evaporation and flash chromatography gave product **20** (2.22 g, 92%). Compound **20**: colorless oil; R_f = 0.23 (silica, 50% ether in petroleum ether); $[\alpha]^{23}_D$ −76.01° (*c* 2.78, CH_2Cl_2); IR (neat) ν_{max} 3135 (br s), 3016 (m), 2944 (s), 2833 (s), 1714 (s), 1457 (m), 1285 (m), 1213 (m), 1102 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.33 (m, 5 H, aromatic), 4.63 (d, J = 11.6 Hz, 1 H, OCH_2Ph), 4.46 (d, J = 11.5 Hz, 1 H, OCH_2Ph), 3.80 (m, 1 H, CH_2O), 3.31 (m, 1 H, CHO), 3.22–3.09 (m, 2 H, CHO, CH_2O), 2.48 (m, 2 H, CH_2COOH), 2.39–2.21 (m, 2 H, CH_2), 1.67 (m, 3 H, CH_2), 1.42 (m, 1 H, CH_2); MS m/e (relative intensity) 265 (M^+ + H, 100), 247 (26), 158 (100), 140 (100); HRMS calcd for $C_{15}H_{21}O_4$ (M^+ + H) 265.1440, found 265.1631.

(*E*)-3-[(2*S*,3*R*)-3(Benzyloxy)-3,4,5,6-tetrahydro-2*H*-pyran-2-yl]-propenoic Acid (21). Ester **18** (15.12 g, 54.8 mmol) was saponified as described above for **19** → **20**, yielding, after flash chromatography (silica, 50% ether in petroleum ether) pure carboxylic acid **21** (13.20 g, 92%). Compound **21**: colorless oil; R_f = 0.2 (silica, 50% ether in petroleum ether); $[\alpha]^{20}_D$ −71.63° (*c* 1.9, CH_2Cl_2); IR (neat) ν_{max} 3500–2500 (br, COOH), 1700 (s, COOH), 1651 (m, CH=CHCOOH), 1420, 1310, 1270, 1110, 1069, 975, 744, 695 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.35 (m, 5 H, aromatic), 7.28 (dd, J = 15.0, 5.0 Hz, 1 H, olefinic), 6.14 (dd, J = 15.0, 2.0 Hz, 1 H, olefinic), 4.63 (d, J = 11.5 Hz, 1 H, benzylic), 4.50 (d, J = 11.5 Hz, 1 H, benzylic), 3.99 (br d, J = 10.0 Hz, 1 H, CH_2O), 3.87 (m, 1 H, CHO), 3.50–3.10 (m, 2 H, CH_2O, CHO), 2.37–1.42 (m, 4 H, CH_2O); MS m/e (relative intensity) 280 (M + NH_4, 100), 253 (M + 1, 29), 245 (37), 227 (11), 212 (4), 188 (34), 171 (37), 155 (29), 108 (30), 91 (100); HRMS calcd for $C_{15}H_{22}O_4N$ (M + NH_4) 280.1549, found 280.1520. Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.69; H, 6.92. Found: C, 68.72; H, 6.82.

(2*R*,3*S*)-5-(Acetyloxy)-6-[(acetyloxy)methyl]-5,6-dihydro-2*H*-pyran (23). To a solution of tri-*O*-acetyl-D-glucal (**22**; 54.5 g, 20 mmol) and triethylsilane (3.84 mL, 24 mmol) in CH_2Cl_2 (70 mL) was added drop-

wise $BF_3 \cdot Et_2O$ (1.7 mL, 20 mmol) at 0 °C. After 30 min, the reaction was quenched with 10% aqueous $NaHCO_3$ (10 mL), diluted with ether (300 mL), washed with H_2O (2 × 60 mL) and brine (60 mL), and then dried ($MgSO_4$). Concentration afforded the diacetate **23** (4.04 g, 94%). Compound **23**: colorless oil; R_f = 0.48 (silica, 50% ether in petroleum ether); IR (CH_2Cl_2) ν_{max} 3058, 2942, 2881, 2835, 1752, 1445, 1371, 1221, 1132, 1050, 968, 902, 817, 652, 605 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.95 (dd, J = 10.5, 1.5 Hz, 1 H, olefinic), 5.75 (dd, J = 10.5, 1.5 Hz, 1 H, olefinic), 5.24 (br d, J = 8.5 Hz, 1 H, C*H*O), 4.20 (m, 4 H, C*H*O, CH_2O), 3.70 (m, 1 H, C*H*O), 2.09 (s, 3 H, $CH_3C(O)O$), 2.06 (s, 3 H, $CH_3C(O)O$); MS *m/e* (relative intensity) 232 (M + NH_4, 11), 214 (M + 1, 12), 155 (100), 145 (13), 112 (56), 95 (92); HRMS calcd for $C_{10}H_{18}O_5N$ (M + NH_4) 232.1185, found 232.1186.

(2*R*,3*S*)-5-Hydroxy-6-(hydroxymethyl)-5,6-dihydro-2*H*-pyran (24). A solution containing sodium methoxide (0.54 g, 10 mmol) and compound **23** (4.64 g, 20 mmol) in MeOH (20 mL) was stirred for 2 h at 25 °C. Concentration and flash chromatography (silica, ethyl acetate) gave pure diol **24** (2.55 g, 95%). Compound **24**: colorless oil; R_f = 0.35 (silica, ethyl acetate); $[\alpha]^{20}_D$ +30.15° (*c* 9.6, CH_2Cl_2); IR (neat) ν_{max} 3350 (s, OH), 3050, 2942, 2884, 2841, 1452, 1265, 1182, 1127, 1070, 1012, 968, 815, 688 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.82 (m, 2 H, olefinic), 4.18 (m, 3 H, C*H*O, CH_2O), 3.82 (m, 2 H, C*H*O, CH_2O), 2.34 (br s, 3 H, 2 O*H*); MS *m/e* (relative intensity) 148 (M + NH_4, 68), 129 (8), 113 (100), 99 (22), 95 (63); HRMS calcd for $C_6H_{14}O_3N$ (M + NH_4) 148.0974, found 148.0991.

(2*R*,3*S*)-3-Hydroxy-2-(hydroxymethyl)-3,4,5,6-tetrahydro-2*H*-pyran (25). A suspension containing 5% Pd–C catalyst (300 mg) and compound **24** (2.60 g, 20 mmol) in MeOH (100 mL) at 25 °C was placed under a H_2 atmosphere. After being stirred for 16 h, the reaction mixture was filtered through Celite and the filtrate was concentrated to give diol **25** (2.47 g, 95%). Compound **25**: colorless oil; R_f = 0.32 (silica, ethyl acetate); $[\alpha]^{20}_D$ +33.33° (*c* 5.2, CH_2Cl_2); IR (neat) ν_{max} 3350 (s, OH), 2937, 2850, 1451, 1342, 1271, 1210, 1092, 1071, 982, 943, 860, 681 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.92 (br d, J = 12.5 Hz, 1 H, CH_2O), 3.80 (m, 2 H, C*H*O, CH_2O), 3.56 (m, 1 H, CH_2O), 3.38 (m, 1 H, CH_2O), 3.15 (m, 1 H, C*H*O), 2.25–2.05 (m, 3 H, CH_2, O*H*), 3.15 (m, 1 H, C*H*O), 2.25–2.06 (m, 3 H, CH_2, O*H*), 1.73–1.38 (m, 3 H, CH_2, O*H*), MS *m/e* (relative intensity), 150 (M + NH_4, 92), 132 (m, 44), 115 (100), 101 (75), 97 (33); HRMS calcd for $C_5H_{15}O_3N$ (M + NH_4) 150.1130, found 150.1146.

(2*R*,3*S*)-3-(*tert*-Butyldimethylsiloxy)-2-[(*tert*-butyldimethylsiloxy)-methyl]-3,4,5,6-tetrahydro-2*H*-pyran (26). A solution containing diol **25** (15 g, 114 mmol) and imidazole (19.3 g, 284 mmol) in DMF (120 mL) was cooled to 0 °C and *tert*-butyldimethylsilyl chloride (37.65 g, 250 mmol) was added. The reaction mixture was stirred at 25 °C for 16 h before methanol (20 mL) and ether (600 mL) were added. The ether layer was washed with aqueous saturated NH_4Cl (2 × 100 mL), H_2O (2 × 100 mL), and brine (100 mL) and then dried ($MgSO_4$). Concentration and flash chromatography (silica, 3% ether in petroleum ether) gave compound **26** (37.58 g, 92%). Compound **26**: colorless oil; R_f = 0.52 (silica, 5% ether in petroleum ether); $[\alpha]^{20}_D$ +36.37° (*c* 6.7, CH_2Cl_2); IR (CH_2Cl_2) ν_{max} 2955, 2930, 2885, 2860, 2472, 2465, 1365, 1250, 1129, 1100, 1082, 885, 840, 780, 670 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.8 (m, 2 H, CH_2O), 3.70–3.04 (m, 4 H, CH_2O, C*H*O), 2.06–1.32 (m, 4 H, CH_2), 0.90 (s, 9 H, Si*t*-*Bu*), 0.87 (s, 9 H, Si*t*-*Bu*), 0.07 (s, 3 H, Si*Me*), 0.06 (s, 3 H, Si*Me*), 0.04 (s, 6 H, $SiMe_2$); MS *m/e* (relative intensity) 361 (M + 1, 45), 345 (14), 303 (100), 229 (15), 185 (14), 171 (35), 147 (38), 132 (24); HRMS calcd for $C_{18}H_{41}O_3Si_2$ (M + H) 361.2594, found 361.2584.

(2*R*,3*S*)-3-(*tert*-Butyldimethylsiloxy)-2-(hydroxymethyl)-3,4,5,6-tetrahydro-2*H*-pyran (27). Trifluoroacetic acid (115 mL) was added dropwise to a solution of compound **26** (37.60 g, 104 mmol) in THF (115 mL) and H_2O (115 mL) at 0 °C. After 10 min, $NaHCO_3$ (80 g) was carefully added followed by addition of ether (800 mL). The ether layer was separated and washed with H_2O (2 × 300 mL) and brine (200 mL) and then dried ($MgSO_4$). Concentration and flash chromatography (silica, 50% ether in petroleum ether) gave alcohol **27** (18.50 g, 72%). Compound **27**: colorless oil; R_f = 0.42 (silica, 50% ether in petroleum ether); $[\alpha]^{20}_D$ +46.70° (*c* 2.0, CH_2Cl_2); IR (neat) ν_{max} 3480 (s, OH), 2960, 2935, 3887, 2761, 1468, 1365, 1258, 1132, 1105, 881, 842, 780, 671 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.95–3.08 (m, 6 H, CH_2O, C*H*O), 2.06–1.35 (m, 5 H, CH_2, O*H*), 0.87 (s, 9 H, Si*t*-*Bu*), 0.05 (s, 6 H, $SiMe_2$); MS *m/e* (relative intensity) 247 (M + 1, 100), 229 (17), 189 (72), 171 (89), 145 (77), 131 (14), 115 (96), 97 (98); HRMS calcd for $C_{12}H_{27}O_3Si$ (M + H) 247.1729, found 247.1737.

Methyl (*E*)-3-[(2*R*,3*S*)-3-(*tert*-Butyldimethylsiloxy)-3,4,5,6-tetrahydro-2*H*-pyran-2-yl]propenoate (29). Dimethyl sulfoxide (10.6 mL) was added dropwise to a stirred solution of oxalyl chloride (9.8 mL) in CH_2Cl_2 (50 mL) at −78 °C. After 10 min, alcohol **27** (18.50 g, 75.2 mmol) in CH_2Cl_2 (400 mL) was added dropwise and the solution was stirred for 0.5 h at −78 °C. Triethylamine (40 mL) was then added and the reaction mixture was allowed to warm to 0 °C. After 10 min, the reaction mixture was poured into a mixture of saturated aqueous NH_4Cl solution (300 mL) and ether (1 L). The ether layer was washed with H_2O (2 × 300 mL) and brine (300 mL) and then dried ($MgSO_4$). Concentration afforded the crude aldehyde **28**, which was used in the next step without further purification. Aldehyde **28** was dissolved in benzene (200 mL) and methyl (triphenylphosporanylidene)acetate (30 g) was added at ambient temperature. After stirring at that temperature for 3 h, concentration and flash chromatography (silica, 10% ether in petroleum ether) gave the ester **29** (18.90 g, 84% overall from **27**) as a colorless oil: R_f = 0.50 (silica, 20% ether in petroleum ether); $[\alpha]^{20}_D$ +51.10° (*c* 5.0, CH_2Cl_2); IR (neat) ν_{max} 2958, 2930, 2892, 2863, 1730 (s, COOMe), 1671 (s, CH=CHCOOMe), 1468, 1440, 1312, 1268, 1100, 992, 845, 780, 672 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.10 (dd, J = 15.5, 5.0 Hz, 1 H, olefinic), 6.03 (dd, J = 15.5, 2.0 Hz, 1 H, olefinic), 3.95 (br d, J = 12.5 Hz, 1 H, CH_2O), 3.73 (s, 3 H, $COOCH_3$), 3.70–3.24 (m, 3 H, CH_2O, C*H*O), 2.09–1.40 (m, 4 H, CH_2), 0.87 (s, 9 H, Si*t*-*Bu*), 0.01 (s, 6 H, $SiMe_2$); MS *m/e* (relative intensity) 318 (M + NH_4, 10), 301 (M + 1, 25), 243 (100), 211 (32), 185 (48), 169 (83), 101 (14), 89 (27); HRMS calcd for $C_{15}H_{32}O_4SiN$ (M + NH_4) 318.2101, found 318.2113.

(*E*)-3-[(2*R*,3*S*)-3-(*tert*-Butyldimethylsiloxy)-3,4,5,6-tetrahydro-2*H*-pyran-2-yl]propenoic Acid (30). Ester **29** (18.90 g, 63 mmol) was saponified as described above for **19** → **20**, yielding, after flash chromatography (silica, 50% ether in petroleum ether), carboxylic acid **30** (15.14 g, 88%) as an oil: R_f = 0.20 (silica, 50% ether in petroleum ether); $[\alpha]^{20}_D$ +48.90° (*c* 7.3, CH_2Cl_2); IR (neat) ν_{max} 3300–2500 (br, COOH), 1710 (s, COOH), 1550 (m, CH=CHCOOH), 1454, 1418, 1306, 1270, 1100, 991, 842, 778, 679 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.12 (dd, J = 16.0, 6.0 Hz, 1 H, olefinic), 5.93 (d, J = 16.0 Hz, 1 H, olefinic), 3.86 (br d, J = 12 Hz, 1 H, CH_2O), 3.60 (m, 1 H, C*H*O), 3.24 (m, 2 H, CH_2O, C*H*O), 1.99–1.30 (m, 4 H, CH_2), 0.78 (s, 9 H, Si*t*-*Bu*), 0.08 (s, 6 H, $SiMe_2$); MS *m/e* (relative intensity) 304 (M + NH_4, 18), 287 (M + 1, 16), 269 (12), 229 (100), 211 (21), 185 (39), 144 (82), 137 (51), 109 (19); HRMS calcd for $C_{14}H_{30}O_4SiN$ (M + NH_4) 304.1944, found 304.1975.

Benzyl (*E*)-3-[(2*R*,3*S*)-3-(*tert*-Butyldimethylsiloxy)-3,4,5,6-tetrahydro-2*H*-pyran-2-yl]propenoate (31). 1,3-Dicyclohexylcarbodiimide (11.9 g, 57.7 mmol) was added to a mixture of carboxylic acid **30** (13.76 g, 48.1 mmol), benzyl alcohol (6 mL, 57.7 mmol), 4-(dimethylamino)-pyridine (1.76 g, 14.43 mmol), and camphorsulfonic acid (3.35 g, 14.4 mmol) in CH_2Cl_2 (160 mL) at ambient temperature. After stirring for 6 h at that temperature, ether (500 mL) was added and the resulting mixture was washed with H_2O (2 × 100 mL) and brine (100 mL) and then dried ($MgSO_4$). Concentration and flash chromatography (silica, 10% ether in petroleum ether) gave compound **31** (14.83 g, 82%). **31**: colorless oil; R_f = 0.651 silica, 20% ether in petroleum ether); $[\alpha]^{20}_D$ +42.08° (*c* 7.8, CH_2Cl_2); IR (neat) ν_{max} 3092, 3068, 3038, 2955, 2932, 2855, 1725 (s, $COOCH_2Ph$), 1662 (s, CH=CHCOOCH_2Ph), 1465, 1375, 1302, 1265, 1162, 1100, 985, 845, 778, 698, 672 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.35 (m, 5 H, aromatic), 7.13 (dd, J = 16.0, 4.5 Hz, 1 H, olefinic), 6.08 (dd, J = 16.0, 2.0 Hz, 1 H, olefinic), 4.18 (m, 2 H, benzylic), 3.84 (br d, J = 12.5 Hz, 1 H, CH_2O), 3.68 (m, 1 H, C*H*O), 3.34 (m, 2 H, CH_2O, C*H*O), 2.08–1.44 (m, 4 H, CH_2), 0.85 (s, 9 H, Si*t*Bu), 0.03 (s, 3 H, Si*Me*), 0.00 (s, 3 H, Si*Me*); MS *m/e* (relative intensity 377 (M + 1, 40), 359 (27), 335 (59), 319 (100), 285 (13), 269 (62), 245 (50), 227 (32), 199 (53), 185 (100), 155 (23), 137 (26); HRMS calcd for $C_{21}H_{33}O_4Si$ (M + 1) 377.2148, found 377.2150.

Benzyl (*E*)-3-[(2*R*,3*S*)-3-Hydroxy-3,4,5,6-tetrahydro-2*H*-pyran-2-yl]propenoate (32). Tetra-*n*-butylammonium fluoride (45 mL, 1 M in THF, 45 mmol) was added to a solution of silyl ether **31** (14.83 g, 39.4 mmol) in THF (100 mL) at ambient temperature. After being stirred at that temperature for 3 h, the reaction mixture was concentrated and flash chromatographed (silica, 50% ether in petroleum ether) to afford alcohol **32** (9.10 g, 88%) as a colorless oil. **32**: R_f = 0.20 (silica, 50% ether in petroleum ether); $[\alpha]^{20}_D$ +27.75° (*c* 17.2, CH_2Cl_2); IR (neat) ν_{max} 3450 (s, OH), 3096, 3072, 3039, 2947, 2862, 1726, 1662, 1458, 1382, 1305, 1268, 1170, 1100, 1045, 989, 750, 700, 683 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.38 (m, 5 H, aromatic), 7.14 (dd, J = 16.0, 5.0 Hz, 1 H, olefinic), 6.17 (dd, J = 16.0, 1.5 Hz, 1 H, olefinic), 5.19 (s, 2 H, benzylic), 3.96 (br d, J = 11.5 Hz, 1 H, CH_2O), 3.72–3.30 (m, 3 H, CH_2O, C*H*O), 2.20–1.40 (m, 5 H, CH_2, O*H*); MS *m/e* (relative intensity) 263 (M + 1, 83), 245 (54), 227 (17), 188 (26), 171 (57), 154 (100), 108 (33), 91 (100), 84 (52); HRMS calcd for $C_{15}H_{19}O_4$ (M + 1) 263.1283, found 263.1259. Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.69; H, 6.92. Found: C, 68.44; H, 6.75.

By use of similar and/or standard procedures, the following intermediates were also prepared: **36–51**, **53–55**, **57–66**; see supplementary material for data.

Benzyl (*E*)-3-[(2*R*,3*S*)-3-[(*E*)-3-[(2*S*,3*R*)-3-(Benzyloxy)-3,4,5,6-tetrahydro-2*H*-pyran-2-yl]propenyloxy]-3,4,5,6-tetrahydro-2*H*-pyran-2-yl]propenoate (33). 1,3-Dicyclohexylcarbodiimide (9.3 g, 45 mmol) was added to a mixture of acid **21** (9.8 g, 37.5 mmol), alcohol **32** (9.82 g, 37.5 mmol), 4-(dimethylamino)pyridine (2.39 g, 19 mmol), and camphorsulfonic acid (2.8 g, 12 mmol) in CH_2Cl_2 (50 mL). After stirring for 4 h, ether (100 mL) was added and the solution was washed with H_2O (2 × 50 mL) and brine (50 mL) and then dried ($MgSO_4$). Concentration and flash chromatography (silica, 20% ether in petroleum ether) afforded ester **33** (13.60 g, 72%) as a colorless oil. **33**: R_f = 0.52 (silica, 40% ether in petroleum ether); $[\alpha]^{20}_D$ +10.40° (*c* 0.5, CH_2Cl_2); IR (neat) ν_{max} 3095, 3072, 3038, 2950, 2860, 1730, 1725, 1664, 1458, 1302, 1269, 1154, 1070, 985, 740, 700, 682 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.23 (m, 10 H, aromatic), 7.22 (dd, *J* = 16.0, 5.0 Hz, 1 H, olefinic), 6.97 (dd, *J* = 16.0, 5.0 Hz, 1 H, olefinic), 6.10 (m, 2 H, olefinic), 5.15 (s, 2 H, benzylic), 4.59 (m, 1 H, C(O)OC*H*), 4.59 (d, *J* = 12 Hz, 1 H, benzylic), 4.47 (d, *J* = 12 Hz, 1 H, benzylic), 4.40–3.08 (m, 7 H, C*H*$_2$O, C*H*O), 2.34–1.40 (m, 8 H, C*H*$_2$); MS *m/e* (relative intensity) 524 (M + NH_4, 7), 245 (48), 199 (25), 155 (47), 91 (100); HRMS calcd for $C_{30}H_{38}O_7N$ (M + NH_4) 524.2648, found 524.2592.

By use of similar procedures, the following compounds were also prepared: **67**, **72**, **76**, **80**, **84**, **88**, **93**, **98**; see supplementary material for data.

(2*R*,3*S*)-Tetrahydro-3-hydroxy-2*H*-pyran-2-propionic Acid, Ester with (2*S*,3*R*)-Tetrahydro-3-hydroxy-2*H*-pyran-2-propionic Acid (34). Pearlman's catalyst [$Pd(OH)_2$–C, 1.2 g] was added in one portion to a solution of ester **33** (12.31 g, 24.3 mmol) in ethyl acetate (100 mL) under a hydrogen atmosphere at room temperature. After stirring for 2 h, the catalyst was removed by filtration and the solution was concentrated, yielding compound **34** (8.02 g, 99%) as an oil: R_f = 0.15 (silica, ethyl acetate); $[\alpha]^{20}_D$ +10.50° (*c* 0.2, CH_2Cl_2); IR (neat) ν_{max} 3500–2500 (s, COOH, OH), 2945, 2860, 1742, 1718, 1448, 1376, 1248, 1100, 1048, 960, 923, 875 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz), δ 4.50 (ddd, *J* = 10.0, 10.0, 5.0 Hz, 1 H, C(O)OC*H*), 3.85 (br t, *J* = 10.5 Hz, 2 H, C*H*$_2$O), 3.39–2.93 (m, 6 H, C*H*$_2$O, C*H*O), 2.60–1.29 (m, 16 H, C*H*$_2$); MS *m/e* (relative intensity) 331 (M + 1, 91), 312 (12), 199 (26), 175 (100), 147 (100), 139 (100), 111 (100), 97 (100), 85 (100); HRMS calcd for $C_{16}H_{27}O_7$ (M + H) 331.1757, found 331.1748.

By use of similar procedures, the following compounds were also prepared: **68**, **73**, **77**, **81**, **85**, **90**, **95**, **100**; see supplementary material for data.

(4a*S*,8a*S*,12a*R*,16a*R*)-Perhydrodipyrano[3,2-*b*:3′,2′-*h*][1,7]dioxacyclododecane-6,14-dione (35). Triphenylphosphine (9.6 g, 36.5 mmol) was added to a solution of **34** (8.02 g, 24.3 mmol) and 2,2′-dipyridyl disulfide (6.2 g, 28.1 mmol) in toluene (25 mL) and the mixture was stirred at room temperature until the reaction was completed (TLC). Dilution with toluene (0.05 M) was followed by refluxing for 12 h. Concentration and flash chromatography (silica, 40% ether in petroleum ether) gave macrodiolide **35** (5.86 g, 75%) as colorless crystals: mp 114–115 °C (ether–hexane); R_f = 0.33 (silica, 50% ether in petroleum ether); IR (CH_2Cl_2) ν_{max} 2968, 2860, 1735, 1445, 1325, 1250, 1168, 1092, 1051, 1030, 868 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.46 (ddd, *J* = 10.0, 10.0, 5.0 Hz, 2 H, C*H*O), 3.87 (m, 2 H, C*H*$_2$O), 3.34 (m, 4 H, C*H*$_2$O, C*H*O), 2.50–1.36 (m, 16 H, C*H*$_2$); MS *m/e* (relative intensity) 313 (M + 1, 31), 197 (37), 157 (100), 139 (42), 111 (26), 97 (55), 71 (100); HRMS calcd for $C_{16}H_{25}O_6$ (M^+ + H) 313.1651, found 313.1666. Anal. Calcd for $C_{16}H_{24}O_6$: C, 61.52; H, 7.74. Found: C, 61.45; H, 8.06.

By use of similar procedures, the following compounds were also prepared: **69**, **74**, **78**, **82**, **86**, **91**, **96**, **101**; see supplementary material for data.

(4a*S*,8a*S*,12a*R*,16a*R*)-Perhydrodipyrano[3,2-*b*:3′,2′-*h*][1,7]dioxacyclododecane-6,14-dithione (1). Method A. A mixture of the macrodiolide **35** (4.92 g, 15.8 mmol) and Lawesson's reagent (12.95 g, 32 mmol) in toluene (70 mL) was refluxed for 16 h. The reaction mixture was concentrated and flash chromatographed (silica, 20% ether in petroleum ether) yielding the dithionolide **1** (3.87 g, 78%) as a light yellow solid: mp 191–192 °C (ether–hexane); R_f = 0.55 (silica, 30% ether in petroleum ether); IR (CH_2Cl_2) ν_{max} 2950, 2859, 1478, 1364, 1310, 1285, 1195, 1165, 1094, 1005, 854 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 5.23 (ddd, *J* = 10.0, 5.0 Hz, 2 H, C*H*O), 3.90 (m, 2 H, C*H*$_2$O), 3.44 (m, 4 H, C*H*$_2$O, C*H*O), 3.09 (m, 2 H, C*H*$_2$C(S)OCH), 2.70 (m, 2 H, C*H*$_2$C(S)OCH), 2.34–1.36 (m, 12 H, C*H*$_2$); MS *m/e* (relative intensity) 344 (M, 28), 280 (24), 251 (73), 213 (41), 174 (100), 157 (72), 139 (100), 112 (100), 97 (100), 84 (100); HRMS calcd for $C_{16}H_{24}O_4S_2$ (M) 344.116, found 344.1123. Anal. Calcd for $C_{16}H_{24}O_4S_2$: C, 55.79; H, 7.02. Found: C, 55.98; H, 7.33.

By use of similar procedures, the following compounds were also prepared: **75**, **79**, **83**, **87**, **92**, **97**, **102**; see supplementary material for data.

(4a*S*,7a*S*,11a*R*,14a*R*)-Perhydrodipyrano[3,2-*b*:3′,2′-*g*][1,6]dioxacyclodecane-6,13-dithione (70) and (±)-(4a*S*,7a*S*,11a*R*,14a*R*)-13-Ketoperhydrodipyrano[3,2-*b*:3′,2′-*h*][1,7]dioxacyclododecane-6-dithione (71). Method B. The macrodiolide **69** (20 mg, 0.07 mmol), Lawesson's reagent (60 mg, 0.15 mmol), and 1,1,3,3-tetramethylthiourea (18 mg, 0.14 mmol) were heated in xylene (1.5 mL) in a sealed tube at 140 °C for 12 h. The mixture was concentrated and the residue was flash chromatographed (silica, 0.5 × 20 × 20 mm, 2 × 2% ethyl acetate in benzene) to give the dithionolide **70** (12.6 mg, 56%) and monothionolide **71** (4.3 mg, 20%). Compound **70**: colorless prisms, mp 247–248 °C (ether); R_f = 0.51 (silica, 2% ethyl acetate in benzene); ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.40 (ddd, *J* = 11.0, 9.4, 4.7 Hz, 2 H, C(S)OC*H*), 4.0–3.8 (m, 4 H, C*H*O), 3.46 (ddd, *J* = 11.5, 11.5, 3.3 Hz, 2 H, C*H*$_2$O), 3.15 (dd, *J* = 11.3, 2.5 Hz, 2 H, C*H*$_2$C(S)O), 2.79 (dd, *J* = 11.3, 10.8 Hz, 2 H, C*H*$_2$C(S)O), 2.28–2.14 (m, 2 H, C*H*$_2$), 1.93–1.64 (m, 4 H, C*H*$_2$), 1.64–1.45 (m, 2 H, C*H*$_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 218.93 (2 C, *C*=S), 82.00 (2 C, *C*O), 79.99 (2 C, *C*O), 68.38 (2 C, *C*O), 53.33 (2 C), 28.45 (2 C), 25.01 (2 C); IR ($CHCl_3$) ν_{max} 2950, 2860, 1345, 1315, 1295, 1260, 1196, 1160, 1105, 1082, 1072, 946 cm^{-1}; MS *m/e* (relative intensity) 317 (M + 1, 61), 283 (22), 252 (30), 231 (12), 201 (16), 181 (22), 159 (100), 125 (48); HRMS calcd for $C_{14}H_{20}O_4S_2$ (M + H) 317.0881, found 317.0900. Compound **71**: colorless prisms, mp 221–222 °C (ether–hexane); R_f = 0.63 (15% ethyl acetate in benzene); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 5.32 (ddd, *J* = 11.0, 9.4, 4.7 Hz, 1 H, C(S)OC*H*), 4.83 (ddd, *J* = 11.0, 9.4, 4.7 Hz, 1 H, C(O)OC*H*), 4.00–3.85 (m, 2 H, C*H*O), 3.85–3.73 (m, 1 H, C*H*O), 3.73–3.60 (m, 1 H, C*H*O), 3.52–3.34 (m, 2 H, C*H*O), 3.13 (dd, *J* = 11.4, 2.6 Hz, 1 H, C*H*C(S)O), 2.80 (dd, *J* = 11.4, 11.0 Hz, 1 H, C*H*C(S)O), 2.62 (dd, *J* = 11.7, 2.9 Hz, 1 H, C*H*$_2$), 2.33 (dd, *J* = 11.7, 11.5 Hz, 1 H, C*H*$_2$), 2.30–2.12 (m, 1 H, C*H*$_2$), 2.07–1.93 (m, 1 H, C*H*$_2$), 1.93–1.64 (m, 4 H, C*H*$_2$), 1.64–1.4 (m, 2 H, C*H*$_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 218.90 (*C*=S), 170.09 (*C*=O), 81.50, 80.07, 77.16, 73.71, 68.81, 68.15, 53.25, 40.73, 29.79, 28.15, 25.25, 24.88; IR ($CHCl_3$) ν_{max} 2950, 2860, 1735, 1442, 1380, 1350, 1320, 1290, 1280, 1200, 1165, 1105, 1090, 1080, 1075, 1045, 1005, 950 cm^{-1}; MS *m/e* (relative intensity) 301 (M + 1, 99), 201 (41), 159 (100), 125 (75); HRMS calcd for $C_{14}H_{21}O_5S$ (M + H) 301.1110, found 301.1102.

Calculations on Conformational and Molecular Structure. 1. MM2 Parameterization. All force constants and bond moments were taken by analogy from previous parameters.[21] Length and angle parameters for thionolactones and thioketals (Table III, supplementary material) were derived by matching the X-ray structures of **1**, **70**, and **9**, respectively, by use of an iterative simplex procedure coupled to the MM2 force field.[22] Comparisons are given in Figures 2 and 3.

Equal C···H bond distances of 1.95 Å were adopted for the hydrogen migration thio enol transition states (Figure 5). The distance selection was made with a view to the hydrogen radical work of Paddon-Row and co-workers.[17] Bond angle parameters were chosen by comparison with normally bonded hydrogen, but force constants were reduced to about one-fourth the usual values.[17] Furthermore the C–S anionic centers of **127** and **128** were mimicked in the force fields with C–SH. Figure 5 depicts the low-energy conformations.

The oxygen cation parameterization was preceded by an MNDO[23] optimization of the O^+ methyl derivative of acetone. Both MNDO and PRDDO predict the system to be planar. MNDO bond lengths and mean angles were introduced to the force field (Table IV, supplementary material). For all parameter sets the new torsional parameters were chosen by analogy with previous MM2 values.[21]

2. Conformation Searching. Two procedures were utilized. Where the same system was subjected to both search methods, identical results were obtained for the low-energy, chemically relevant conformations. Smith's program[15] was modified for convenient, interactive use and linked to the Searle modeling system.[24] Applied to the X-ray structures of **1** and **70**, a collection of conformations was optimized with the MM2 parameters to give the thionolactone structures depicted in Figure 2. The dithioketals and thioenol transition states were treated similarly.

In the case of structures **4**, **11**, **13**, **14**, and **128**, Saunder's stochastic search method[18] was applied with the new MM2 parameters. Figures 6–8 display some of the results. The current version of the program permits freezing of user-defined chiral centers, making it convenient to treat polycyclic systems such as **11** and **13** with several asymmetric carbons.

3. Quantum Mechanical Calculations. With the exception of O-alkylated acetone, all quantum mechanical computations were carried out with PRDDO[19] using MM2-optimized structures as input. The acetone derivative [$(CH_3)_2C{=}O^+$] was completely MNDO[23] optimized. To

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check the planarity and C=O⁺—C nonlinearity, several angle and torsional isomers were reevaluated by PRDDO.

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Supplementary Material Available: Preparation procedures and data for compounds **9**, **36–51**, **53**, **55**, **57–69**, **72–102**, and **104–125**, X-ray crystallographic data and ORTEP structures for compounds **1**, **2a**, **4**, **8–10**, **11a**, **11b**, **70**, **75**, **79**, **87**, **104**, **106**, **110**, and **111a**, and MM2 calculation parameters (Tables III and IV) for **1**, **9**, and **70** (149 pages). Ordering information is given on any current masthead page.

Synthesis and Optical Properties of Conformationally Constrained Trimeric and Pentameric Porphyrin Arrays

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Abstract: Synthesis, UV–visible absorption, and fluorescence emission properties are presented for the trimeric and pentameric porphyrins bridged by rigid aromatic spacers (*m*- or *p*-phenylene, anthracene-1,8-diyl, etc.). The synthetic method utilized here is based on the previously reported synthesis of 5,15-diaryloctaalkylporphyrins, with several important improvements. The new method can be generally utilized for preparation of conformationally constrained oligomeric porphyrins sequentially linked with aromatic spacers. The Soret absorption bands of anthracene-linked series were blue shifted, while those of *p*-phenylene series were split, which can be explained in terms of the exciton coupling theory. The relative fluorescence intensity was observed to decrease for higher oligomers. These porphyrin oligomers will be useful for synthetic model studies on photosynthetic charge separation.

Inspired by the determination of the three-dimensional architecture of bacterial photosynthetic reaction centers,[1] many porphyrin-based synthetic models have been prepared to develop an efficient synthetic catalyst for photosynthetic charge separation. Crucial to this end is an understanding of the importance of distance, orientation, and *number of pigments* in the model aggregates. In recent years, synthetic diporphyrins bridged by rigid aromatic spacers, in which the geometry of the two porphyrin rings is rather restricted, have been shown to be useful and promising for studies on intramolecular energy and/or electron-transfer reactions,[2-6] since these porphyrin models allow examination of the dynamics of energy (electron) transfers without concern for the conformational motions that may complicate analyses of flexible systems. As to higher oligomers, however, there has been reported only one example to date of this type, which is the anthracene-pillared trimeric porphyrin synthesized by Chang in 1985.[2d] Here we report the synthesis and optical properties of conformationally restricted trimeric and pentameric porphyrins.

Table I. Fluorescence Data of Di-, Tri-, and Pentameric Zinc Porphyrins[a,b]

compd	λ_{max}/nm (rel intens[c])	compd	λ_{max}/nm (rel intens[c])
2b	583 (49), 639 (40)	**3e**	578 (61), 633 (33)
3b	584 (23), 638 (26)	**5e**	580 (33), 634 (23)
5b	590 (10), 640 (17)	**1e**	576 (100), 628 (34)
2e	578 (58), 632 (33)		

[a] In 1,2-dichlorobenzene. [b] Excitation at Soret maximum. [c] Normalized for constant optical density at the excitation wavelength.

Results

Synthesis of Trimeric and Pentameric Porphyrins. The synthesis of trimeric porphyrins is shown in Scheme I. Condensation of 5-(3-formyl)dihexylhexamethylporphine[7] (**1a**) and bis(3-ethyl-4-methyl-2-pyrrolyl)methane[8] (**4**) in the presence of 4 equiv of trichloroacetic acid in acetonitrile followed by oxidation with *p*-chloranil gave trimeric porphyrin **3a** in 56% isolated yield. Trimeric porphyrins **3b–e** were prepared in a similar manner. This is a modified procedure of the synthetic method originally reported by Abdalmuhdi and Chang in their synthesis of anthracene-pillared triporphyrin.[2d] However, acid-catalyzed condensation of **1a** with **4** under their conditions (0.25 equiv of *p*-toluenesulfonic acid in methanol) afforded only trace amounts of trimer **3a** with most

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