Reprinted from the Journal of the American Chemical Society, 1990, *112*.

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

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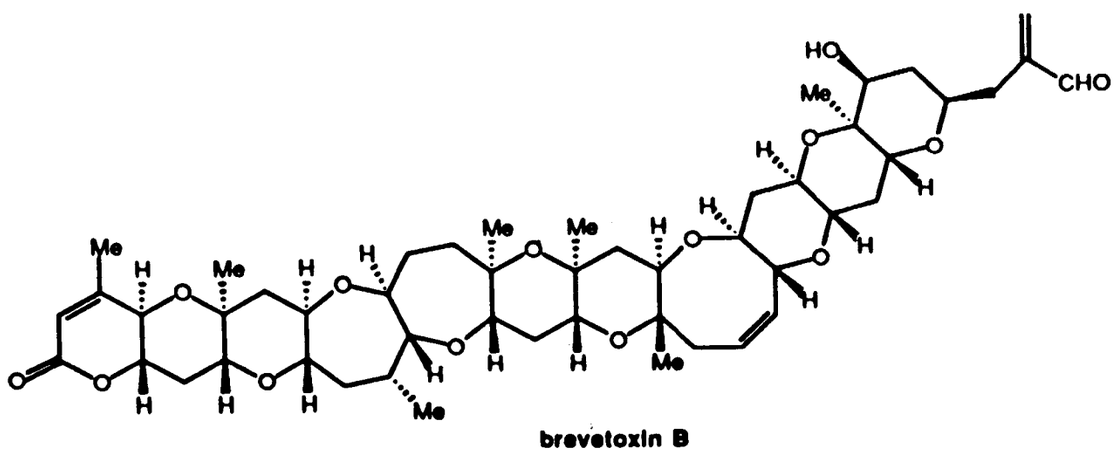
Abstract: A new reaction involving bridging of macrodithionolactones to bicyclic systems is described. A series of macrodiolides was prepared and converted to the requisite macrodithionolactones. The latter substrates were induced to undergo bridging across the macrocyclic ring by exposure to sodium 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.

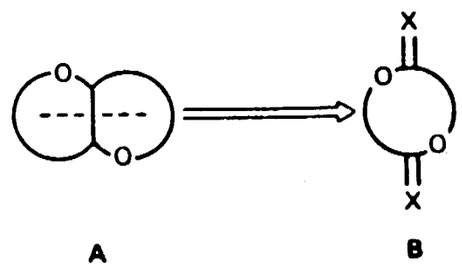
As frequently encountered molecular structures, polycyclic systems are constantly challenging synthetic chemists. Cis- and trans-fused oxabicyclic and oxapolycyclic systems of type A (Scheme I) are becoming increasingly recognized as common structural subunits of marine and other natural products such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



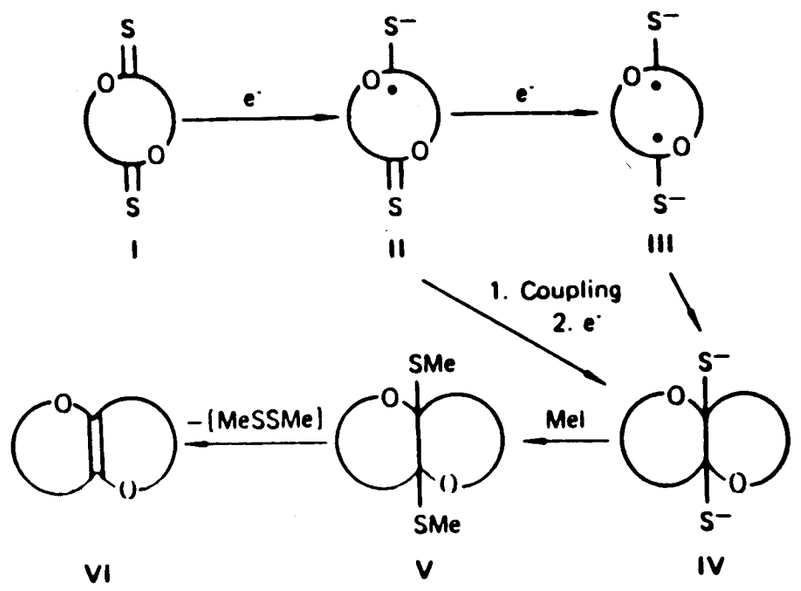
brevetoxin B

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 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.

Scheme I



Scheme II



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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(5) Nicolaou, K. C.; Hwang, C.-K.; Duggan, M. E.; Bal Reddy, K.; Marron, B. E.; McGarry, D. G. *J. Am. Chem. Soc.* **1986**, *108*, 6800.

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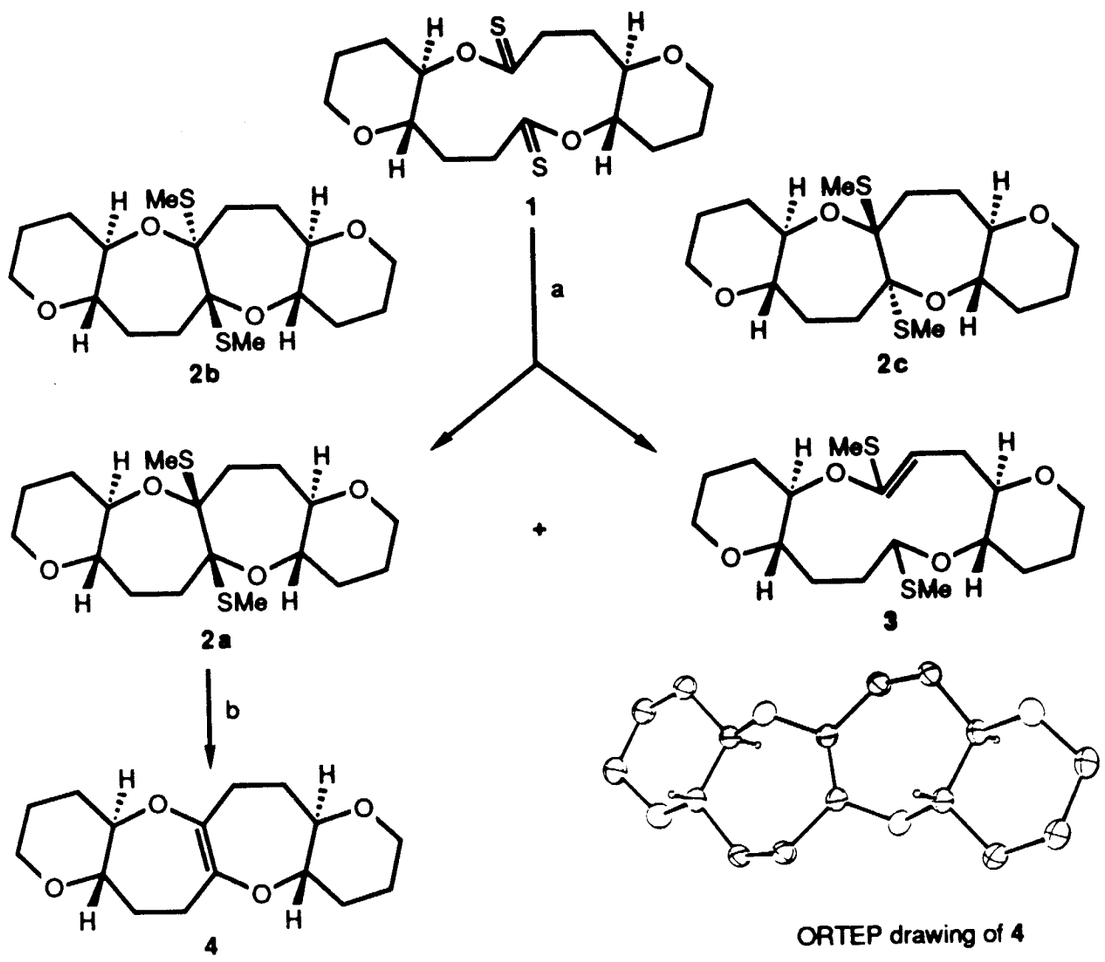
Scheme III[a]



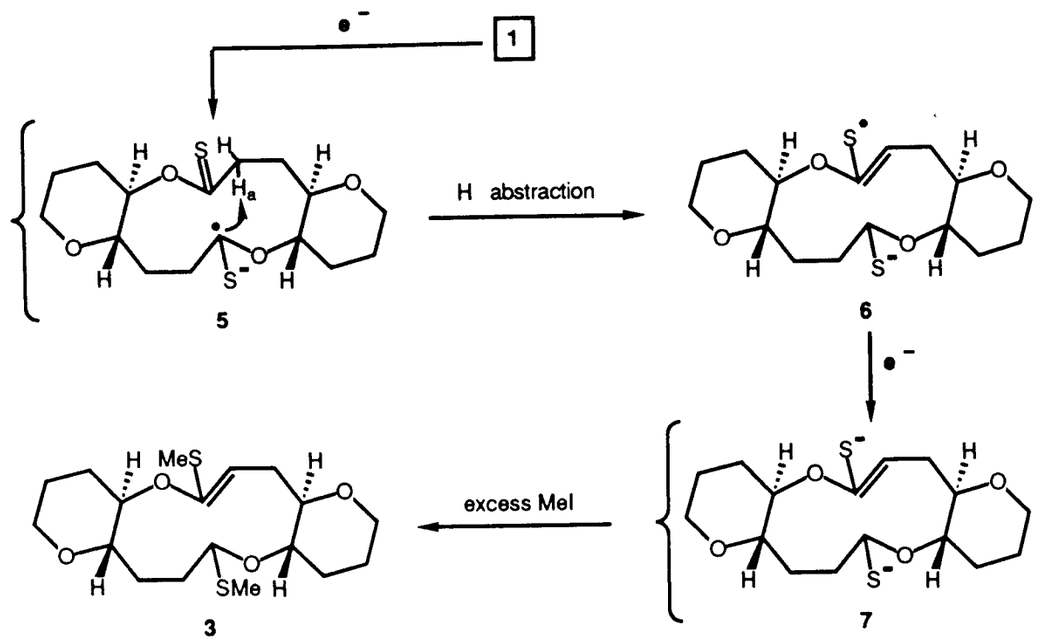
[a] Bridging of dithionolides. Reagents and conditions: (a) 2.2 equiv of sodium naphthalene, THF, −78 °C, 30 s, then 10 equiv of MeI, −78 to +25 °C, 30 min, **2a** (80%), **3** (12%); (b) 1.2 equiv of $^nBu_3SnH$, 0.1 equiv of AIBN, toluene, 120 °C, 15 min, 99%, or 1.2 equiv of $^nBu_3SnH$, *hν*, toluene,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

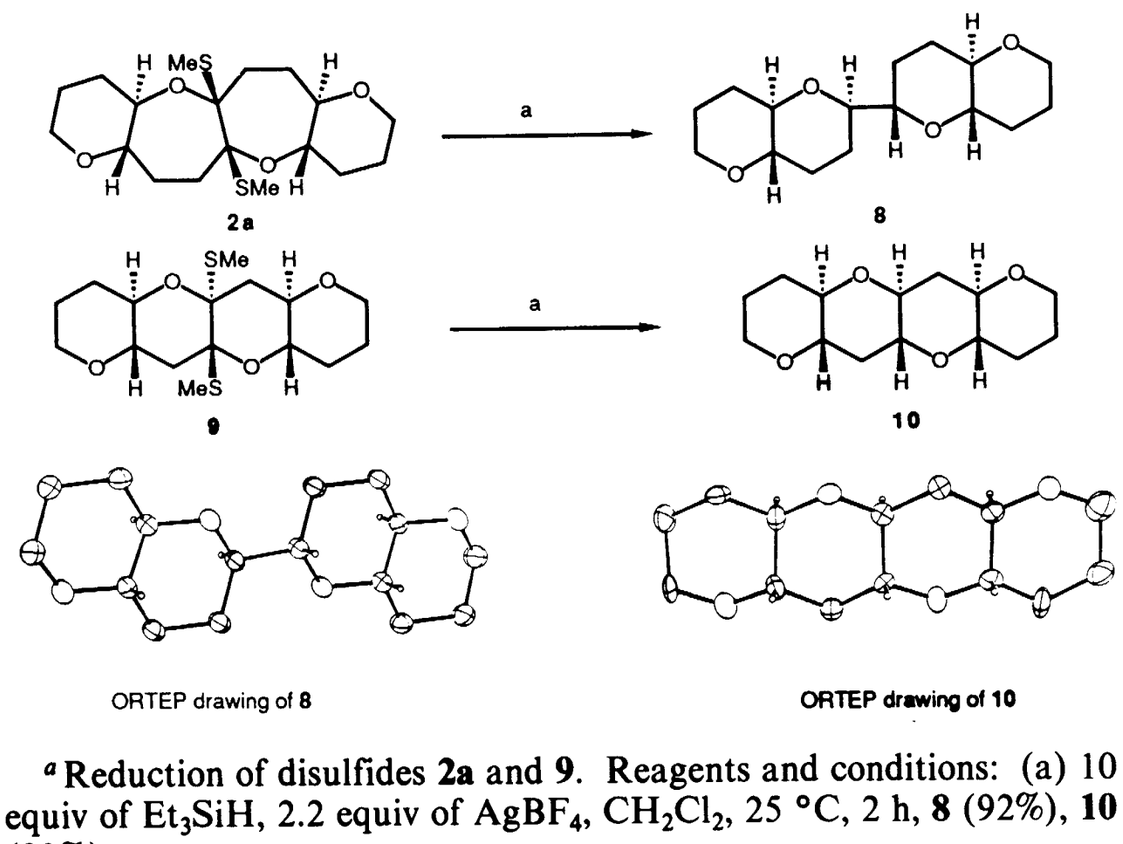
The methylthioenol ether byproduct in this bridging reaction was also formed in the examples of entries 3 (3%), 4 (44%), 5 (10%), 6 (44%, isolated as the corresponding lactone), 7 (22%), 8 (28%), 9 (15%), and 10 (68%, isolated as the corresponding lactone) (Table I). A plausible mechanism for the formation 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 generated 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.

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%).

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_i 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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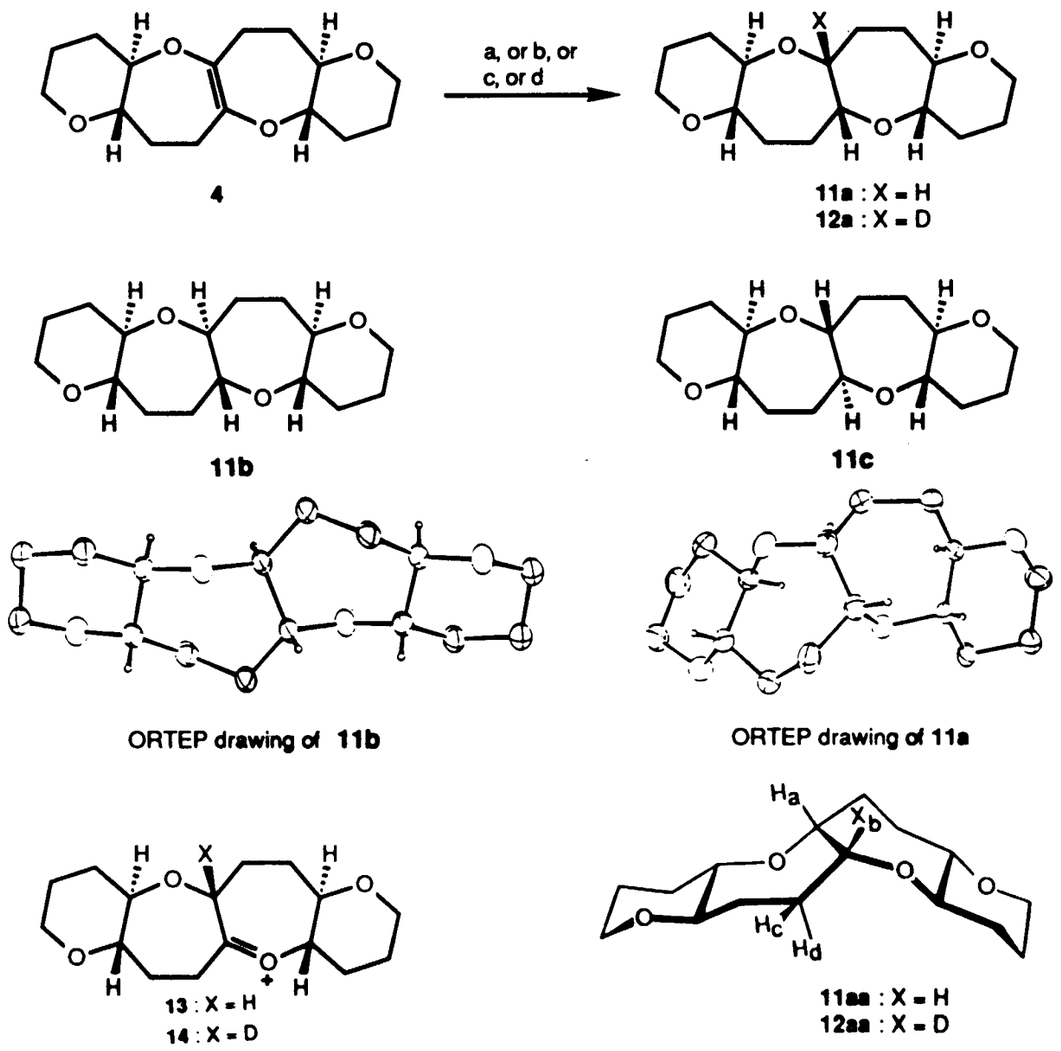
Scheme VI[a]



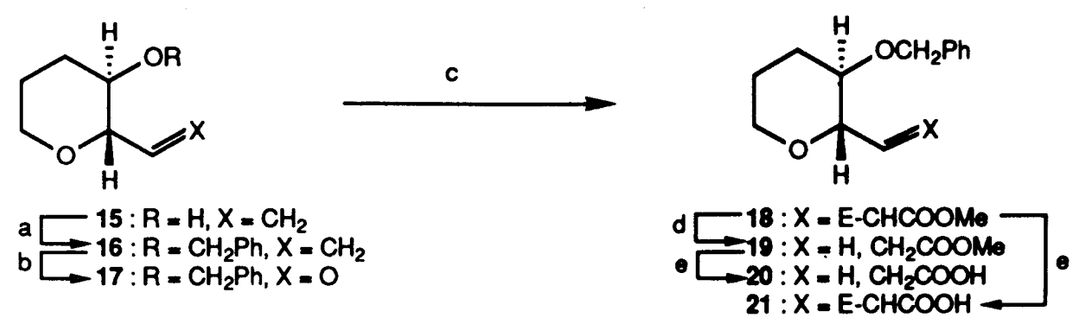
[a] Reduction of olefin **4**. Reagents and conditions: (a) H_2, $Pd(OH)_2$ catalytic, EtOAc, 12 h, **11a** (75%), **11b** (12%); (b) 1.1 equiv of CF_3COOH, 10.0 equiv of Et_3SiH, CH_2Cl_2, 0 °C, 30 min, **11a** (85%); (c) 1.1 equiv of CF_3COOH, 3.0 equiv of $Na(CN)BH_3$, CH_2Cl_2, 0 °C, 30 min, **11a**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

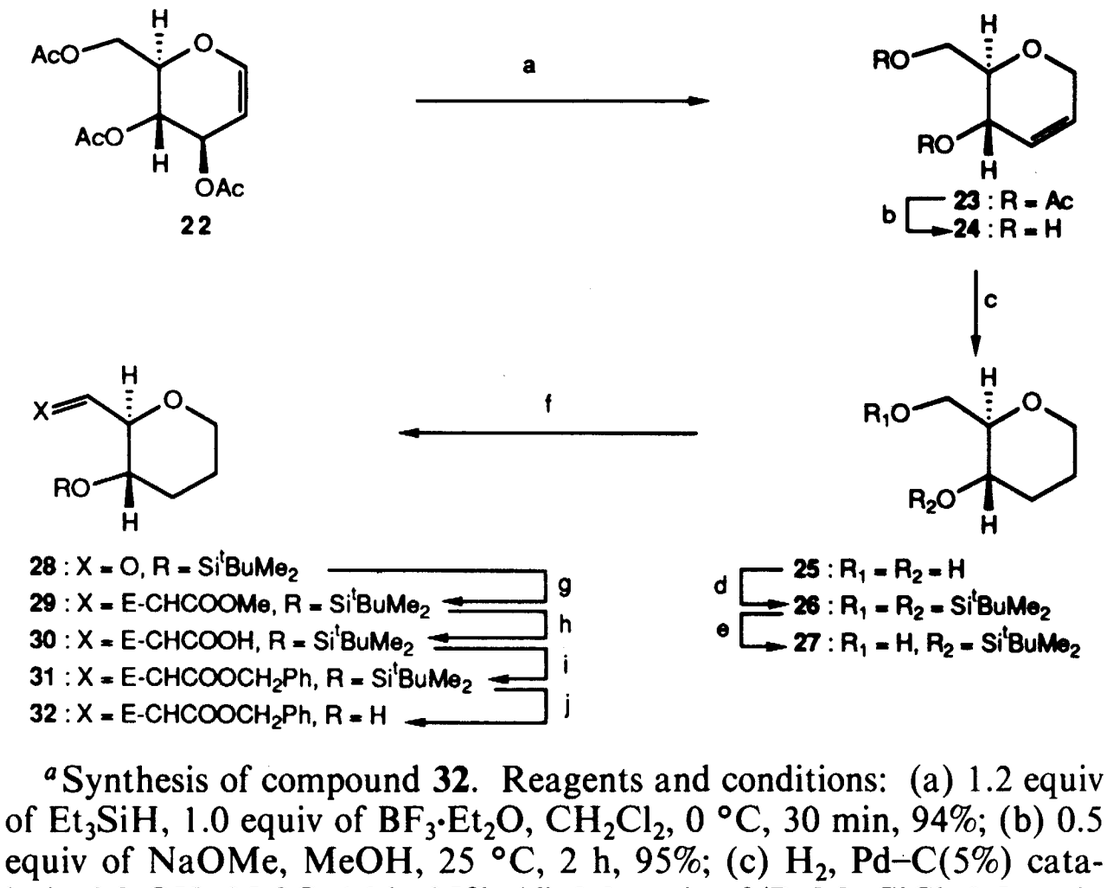
Synthesis of Macrodithionolactones. The dithionolactones utilized in this study are shown in Table I. They were synthesized from the corresponding dilactones, which were, in turn, constructed from the appropriate, optically active hydroxy acids. To exemplify the chemistry involved in these syntheses, 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

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 $BF_3{\cdot}Et_2O$, 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 $^tBuMe_2SiCl$, 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 $^nBu_4NF$, THF, 25 °C, 3 h, 88%.

(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.
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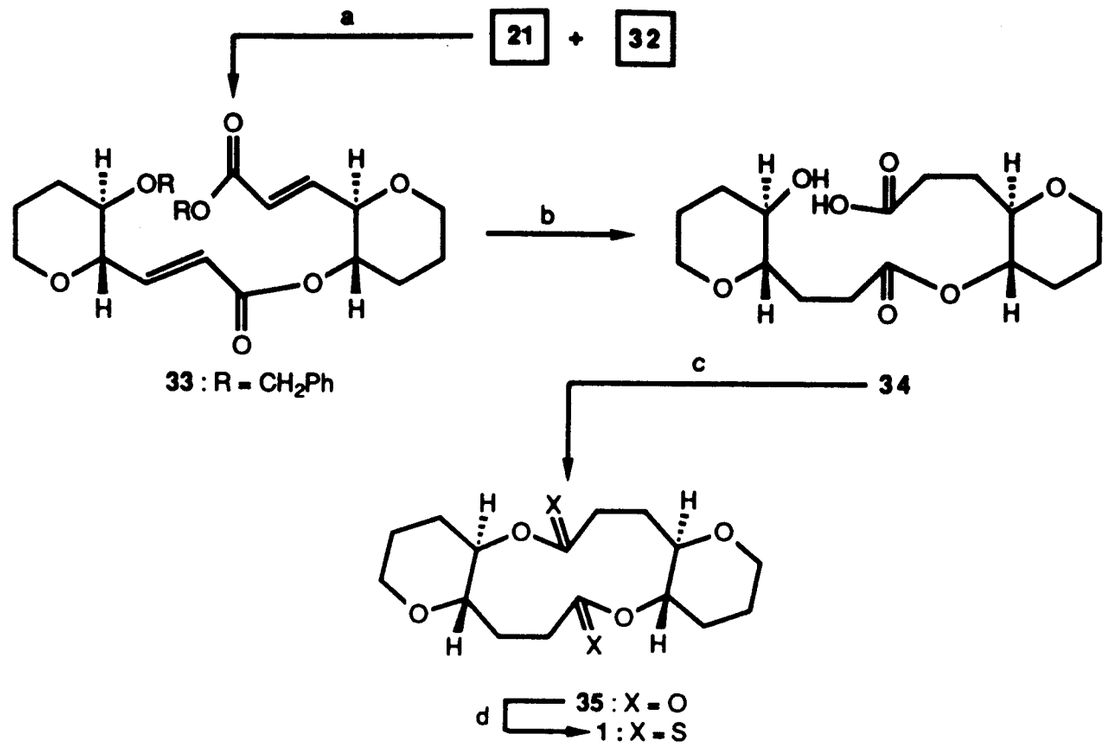
Scheme IX[a]



[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 (nBu_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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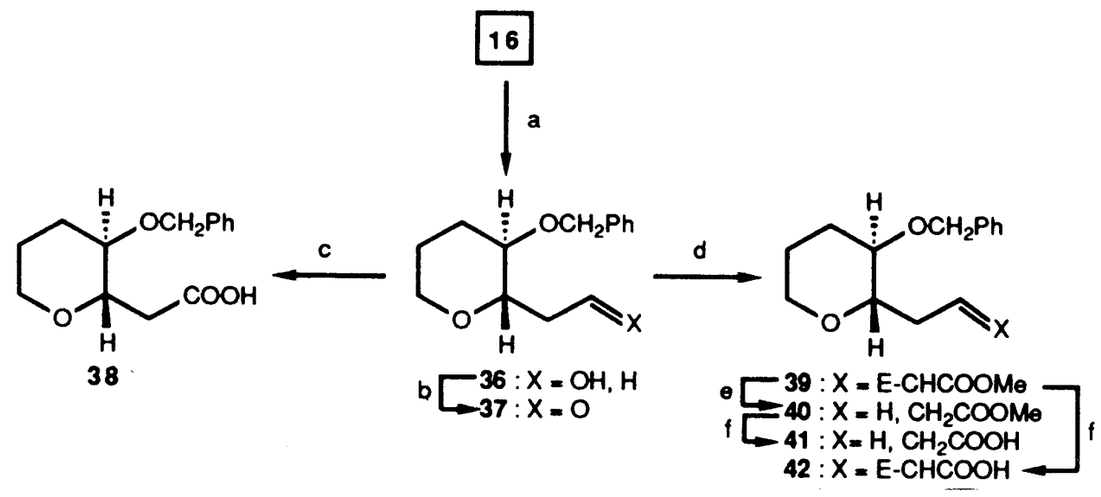
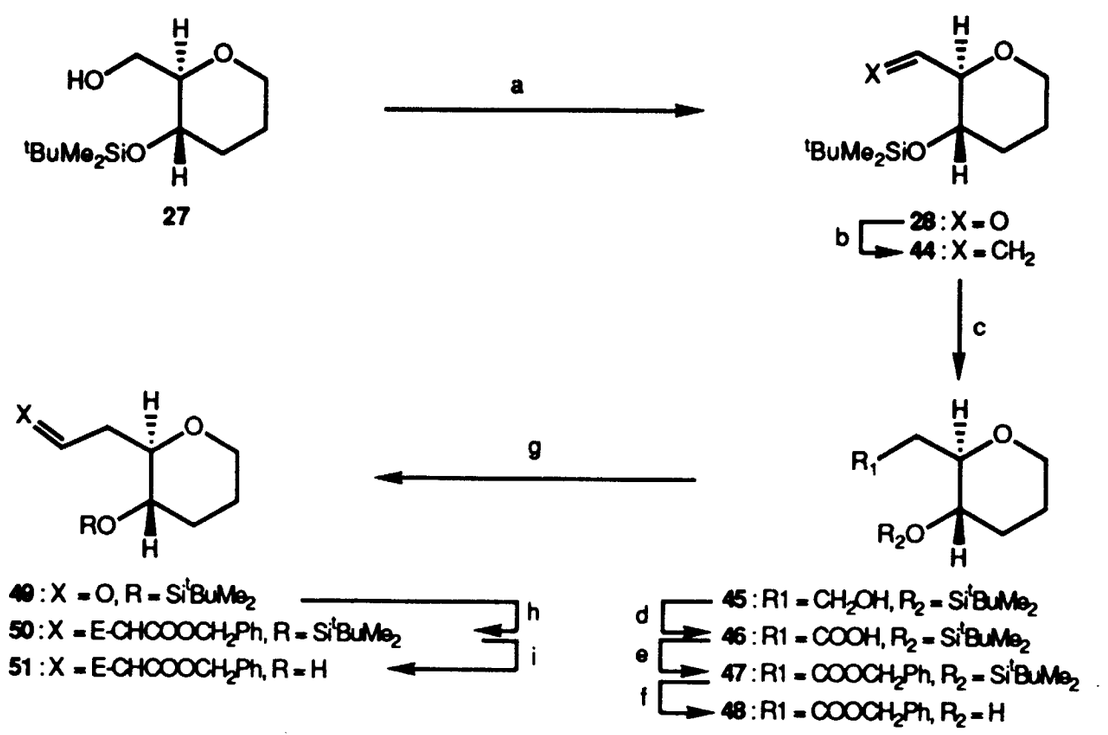
Scheme X[a]



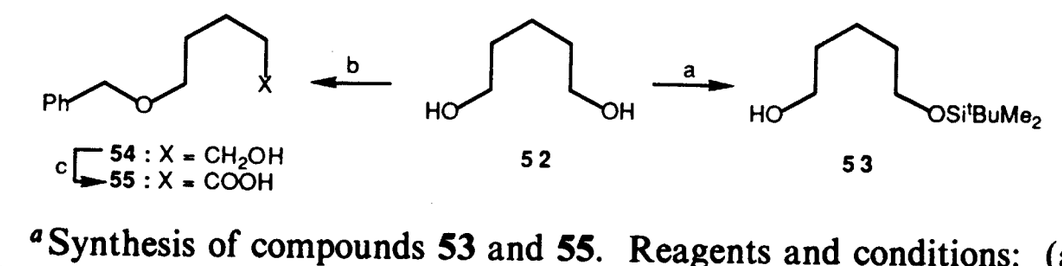
[a] Synthesis of compounds **38**, **41**, and **42**. Reagents and conditions: (a) 1.5 equiv of 9-BBN, THF, 0 °C, 3 h, then excess 3 N NaOH, excess 30% H_2O_2, 92%; (b) 1.5 equiv of $(COCl)_2$, 2.0 equiv of DMSO, CH_2Cl_2, −78 °C, 30 min, then 4.0 equiv of Et_3N, 98%; (c) Jones' reagent, acetone, 0 °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]



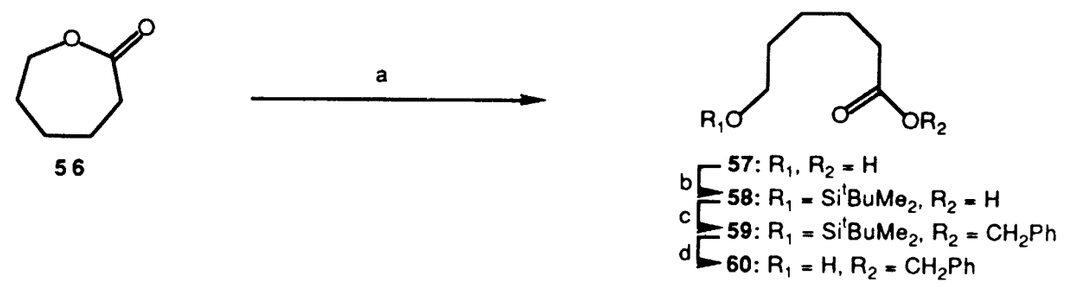
[a] Synthesis of compounds **48** and **51**. Reagents and conditions: (a) 1.5 equiv of $(COCl)_2$, 2.0 equiv of DMSO, CH_2Cl_2, −78 °C, 30 min, then 4.0 equiv of Et_3N, 95%; (b) 1.2 equiv of $Ph_3P{=}CH_2$, THF, 0 °C, 1 h, 82%; (c) 1.5 equiv of 9-BBN, THF, 0 °C, 3 h, then excess 3 N NaOH, excess H_2O_2, 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 $^nBu_4NF$, 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 $^tBuMe_2SiCl$, 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 $^tBuMe_2SiCl$, 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%.