Total Synthesis of (−)-Austalide B. A Generic Solution to Elaboration of the Pyran/*p*-Cresol/Butenolide Triad

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Received August 5, 1994[⊗]

Abstract: The toxic meroterpenoid (−)-austalide B has been prepared in its natural form by chemical modification of the readily available optically active enedione **11**. Following stereocontrolled Robinson annulation to give **13** and fully regiocontrolled gem-dimethylation of this intermediate, the highly functionalized tetracyclic ortho ester **22** was produced in four additional steps. At this point, it proved an easy matter to obtain **23** by Baeyer−Villiger oxidation. For the purpose of annealing rings E and F, carbomethoxy triflate **41** was prepared and coupled to **42** through the agency of $Pd_2(dba)_3$ and $(furyl)_3P$. With arrival at **49**, it proved possible by sequential intramolecular Claisen condensation, O-methylation, and modest warming to produce **50**. Deprotection of the secondary hydroxyl and inversion of its configuration delivered synthetic austalide B, which exhibited melting point, specific rotation, infrared, and NMR properties (^1H and ^{13}C) identical to the natural material obtained from South Africa.

Among the mixed polyketide−terpenoid (meroterpenoid) metabolites produced by the highly toxigenic strain MRC 1163 of *Aspergillus ustus*, austalide B (**1**) holds prominence as a key member of this fascinating group of natural products and one of the more important mycotoxins of its class.[1] In addition to the austalides, *A. ustus* is also recognized to be a source of the austamides,[2] the austocystins,[3] austdiol,[4] and austin.[5] The accomplishments in this area may have broad application to the problem of defining dietary sources of human illness. The strain identified above, for example, is often found in dried fish routinely consumed in the Middle East.

Austalide B (**1**) possesses an unusual molecular framework comprised of six rings, four of which are serially fused. Structurally defined in absolute terms by means of high-field ^1H and ^{13}C NMR studies, X-ray crystallographic analysis, and chemical interconversions,[1,6,7] the polycyclic array in **1** is recognized to be constituted of a bicyclic ortho ester subunit, a cyclohexane ring containing five contiguous stereogenic centers, and a pyran/*p*-cresol/butenolide triad in its eastern sector. The phthalide component is reminiscent of that found in mycophenolic acid.[8]

The biosynthesis of the austalides is believed to originate from 6-[(2*E*,6*E*)-farnesyl]-5,7-dihydroxy-4-methylphthalide (**2**).[9] In their original proposal, Horak and co-workers suggested that cyclization of **2** is initiated by stereospecific attack of the phenolic oxygen on the *Si* face of the proximal double bond to give rise to **3** (Scheme 1).[10] Ensuing oxygen-centered cyclization was thought to provide a reasonable route to austalide K (**7**), whose role it was to serve as precursor to the other austalides. However, later studies involving the feeding of deuterium-labeled mevalonolactones to *A. ustus* eliminated the depicted cascade cyclization and indicated that the biosynthetic pathway may involve instead the carbocation **4**.[7]

Although the precise biosynthetic origins of **1** remain unclear, the hazards posed by possible adoption of the tactics suggested in Scheme 1 in a research program aimed at the total synthesis of austalide B are worthy of mention. Cardinal among these are the remote oxidations mandated during the hypothetical conversion of **5** to **6** and of **7** to **1** for which methodology is seriously lacking. For this and related reasons associated with the difficulty of performing selected transformations in the austalide series,[11] we elected to approach **1** by constructing its alluring heterocyclic network in the reverse sense, viz. from west to east.

Retrosynthetic Analysis

A potentially serviceable disconnection of the austalide B structure is shown in Scheme 2. Should advanced assembly of this mycotoxin be based upon the annealing of rings E and F onto a preexisting tetracyclic dihydropyran or δ-lactone, viz. **8** or **9**, a level of convergency could be realized that would be expected to meaningfully simplify the synthetic problem at issue. Under these provisions, the western sector would be elaborated first. In this vein, dihydroxy diketone **10** was recognized to represent a key intermediate from which both **8** and **9** could be accessed. The secondary hydroxyl group in **10** is incorrectly oriented β because osmylation of the olefinic precursor was expected to occur under kinetic control from the sterically more accessible β surface. Although epimerization at C-13 would be required prior to arrival at **1**, the similarity in topography in

[⊗] Abstract published in *Advance ACS Abstracts,* November 15, 1994.

(1) Horak, R. M.; Steyn, P. S.; Van Rooyen, P. H.; Vleggaar, R.; Rabie, C. J. *J. Chem. Soc., Chem. Commun.* **1981**, 1265.

(2) (a) Steyn, P. S. *Tetrahedron* **1973**, *29*, 107. (b) Steyn, P. S.; Vleggaar, R. *Phytochemistry* **1976**, *15*, 355.

(3) Steyn, P. S.; Vleggaar, R. *J. Chem Soc., Perkin Trans. 1* **1974**, 2250.

(4) Vleggaar, R.; Steyn, P. S.; Nagel, D. W. *J. Chem. Soc., Perkin Trans. 1* **1974**, 45; Steyn, P. S.; Vleggaar, R. *J. Chem. Soc., Perkin Trans. 1* **1976**, 204.

(5) Chexal, K. K.; Springer, J. P.; Clardy, J.; Cole, R. J.; Kirksey, J. W.; Dorner, J. W.; Cutler, H. G.; Strawter, B. J. *J. Am. Chem. Soc.* **1976**, *98*, 6748.

(6) Horak, R. M.; Steyn, P. S.; Vleggaar, R.; Rabie, C. J. *J. Chem. Soc., Perkin Trans. 1* **1985**, 345.

(7) Dillen, J. L. M.; Horak, R. M.; Maharaj, V. J.; Marais, S. F.; Vleggaar, R. *J. Chem. Soc., Chem. Commun.* **1989**, 393.

(8) (a) Bowen, L.; Clifford, K. H.; Phillips, G. T. *J. Chem. Soc., Chem. Commun.* **1977**, 949, 950. (b) Colombo, L.; Gennari, C.; Potenza, D.; Scolastico, C.; Aragozzini, F. *J. Chem. Soc., Chem. Commun.* **1979**, 1021.

(9) Canonica, L.; Kroszczynski, W.; Ranzi, B. M.; Rindone, B.; Santaniello, E.; Scolastico, C. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2639.

(10) de Jesus, A. E.; Horak, R. M.; Steyn, P. S.; Vleggaar, R. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2253.

(11) Horak, R. M.; Steyn, P. S.; Vleggaar, R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 357.

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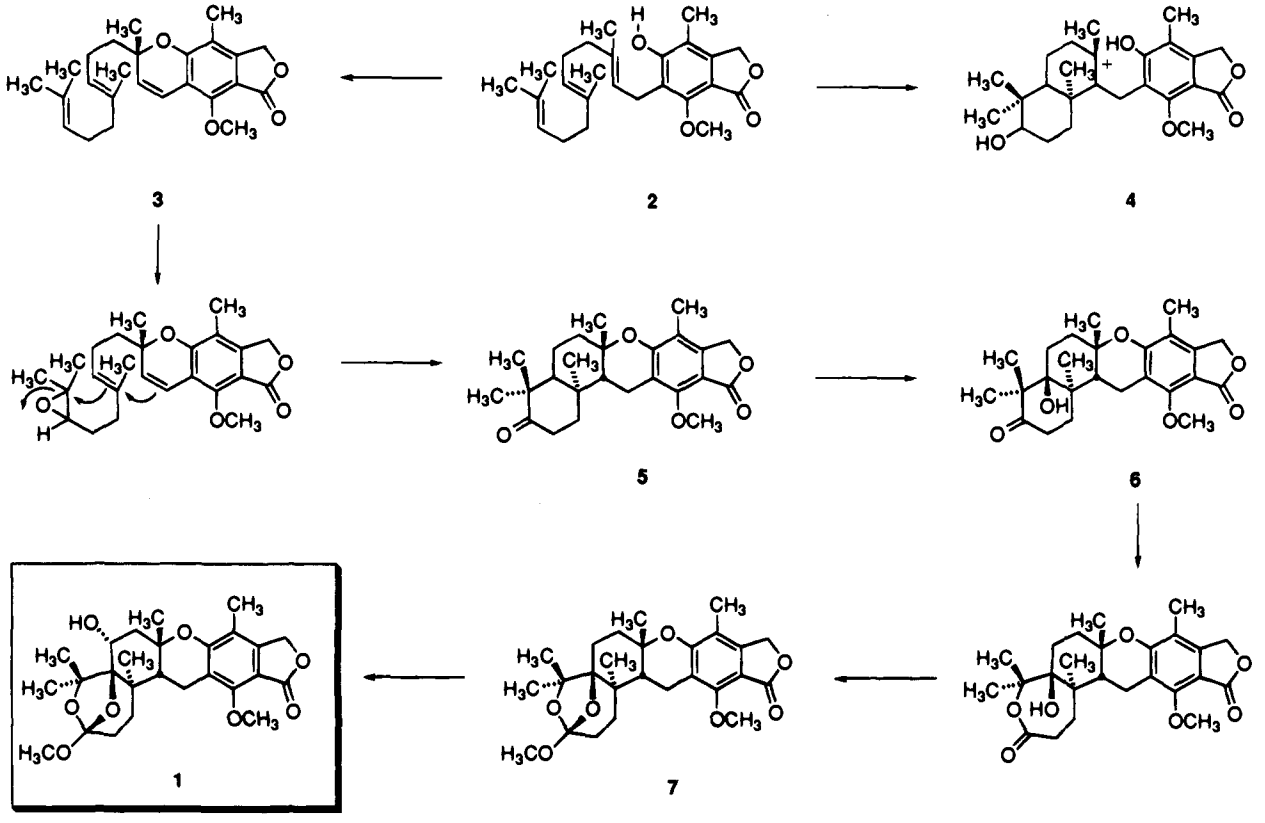
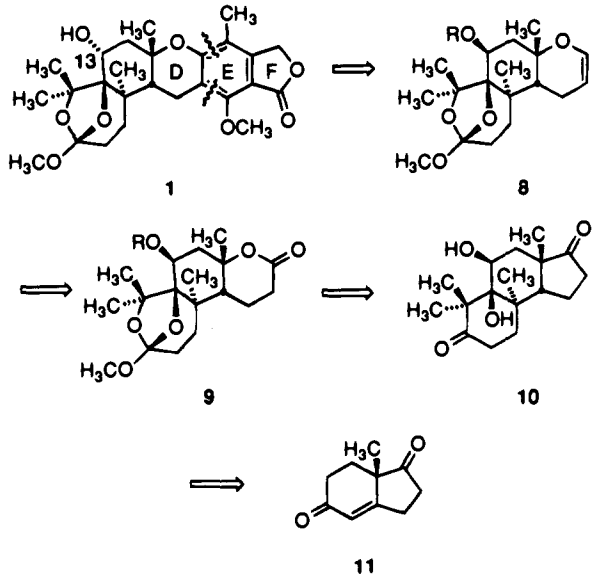
Scheme 1



Scheme 2



this region of both molecules suggested that this goal would be easily realized. Continued retrosynthetic projection led us back to ketone **11**, which is readily available in 98% ee.[12]

As will be discussed, it was not a priori possible to predict with any reasonable degree of confidence which of several tactics would constitute a general means for the attachment of rings E and F. However, the exhaustive substitution of the benzenoid ring and the diverse nature of the pendant groups would require an assembly tolerant of their presence. For our purposes, the total enterprise had also to be expedient and general.[13]

(12) Hajos, Z.; Parrish, D. R. *Organic Syntheses*; Wiley: New York, 1990; Collect. Vol. VII, p 363.

Construction of the Western Sector

Following established protocols, the optically active diketone **11** was regioselectively ketalized,[14] subjected to dissolving metal reduction in order to establish the desired cis ring fusion,[15] and monomethylated[16] to arrive at **12** (Scheme 3). The obvious possibility for reaching **13** involved a Robinson annulation. However, the often-used base-promoted variants of this ring-forming process proved unsuitable in the present context.[17] Alternatively, an acid-catalyzed variant involving the use of 4-chloro-2-butanone as developed by Zoretic[19] was found to proceed stereoselectively. Although **13** was formed reproducibly, its isolated yield averaged only 30%.

For this reason, an alternative route from readily available **14**[20] was briefly evaluated. Following condensation with ethyl vinyl ketone in acetic acid solution, an asymmetric cyclization was effected with L-valine as catalyst.[21] However, under the most favorable conditions utilized by us, the enantiomeric excess inherent in **15** did not exceed 75%. This level of optical purity was, of course, not improved following catalytic hydrogenation

(13) Preliminary communication: Paquette, L. A.; Wang, T.-Z.; Sivik, M. R. *J. Am. Chem. Soc.* **1994**, *116*, 2665.

(14) Bauduin, G.; Pietrasanta, Y. *Tetrahedron* **1973**, *29*, 4225.

(15) Stork, G.; Rosen, P.; Goldman, N.; Coombs, R. V.; Tsuji, J. *J. Am. Chem. Soc.* **1965**, *87*, 275.

(16) Smith, H. A.; Huff, B. J. L.; Powers, W. J., III; Caine, D. *J. Org. Chem.* **1967**, *32*, 2851.

(17) Base-promoted variants of the Robinson annulation fared no better. Recourse to methyl α-(trimethylsilyl)vinyl ketone[18a,b] and (*E*)-4-iodo-2-(trimethylsilyl)-2-butene[18c] did not improve matters.

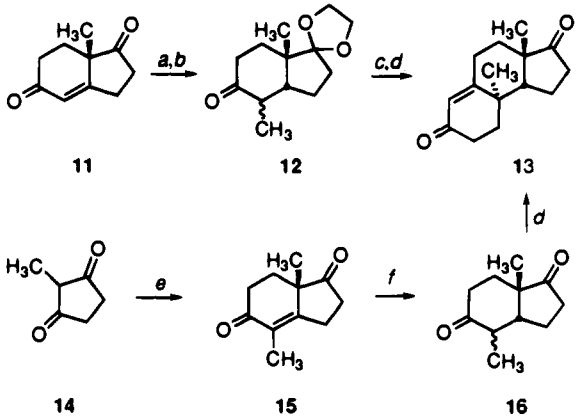
(18) (a) Stork, G.; Ganem, B. *J. Am. Chem. Soc.* **1973**, *95*, 6152. (b) Boeckman, R. K., Jr. *J. Am. Chem. Soc.* **1973**, *95*, 6867. (c) Stork, G.; Jung, M. E. *J. Am. Chem. Soc.* **1974**, *96*, 3682.

(19) Zoretic, P. A.; Branchaud, B.; Maestrone, T. *Tetrahedron Lett.* **1975**, 527.

(20) Meister, P. G.; Sivik, M. R.; Paquette, L. A. *Org. Synth.* **1991**, *70*, 226.

(21) Banerjee, D. K.; Kasturi, T. R.; Sarkar, A. *Proc. Indian Acad. Sci. (Chem. Sci.)* **1983**, *92*, 181.

Scheme 3[a]



[a] (*a*) $CH_3C(OCH_2CH_2O)CH_2CH_3$, TsOH; (*b*) Li, NH_3; MeI, ether; (*c*) H_3O^+; (*d*) $CH_3C(O)CH_2CH_2Cl$, TsOH, C_6H_6, Δ; (*e*) $CH_2{=}CHC(O)$-CH_2CH_3, HOAc; L-valine, $HClO_4$, CH_3CN; TsOH, C_6H_6; (*f*) H_2, 10% Pd−C, EtOAc.

to produce **16** as an 8:1 mixture of α/β epimers[22] and low-yield conversion to **13** in the predescribed manner.

In practice, the bond construction **11** → **12** → **13** provides adequate quantities of the tricyclic intermediate. Furthermore, the requirement that **13** be amenable to clean, regioselective methylation was conveniently met in 67% yield (Scheme 4). With compound **17** in hand, the stereochemical course of electrophilic attack at its endocyclic double bond was next examined. When this enedione was reacted with excess *m*-chloroperoxybenzoic acid buffered with sodium bicarbonate, 3-fold oxidation occurred to deliver the epoxy dilactone **18**. The high crystallinity of this substance allowed its stereochemical features to be corroborated by X-ray crystallographic analysis. The oxirane ring was noted to be β-oriented as expected. Since peracids generally act on trisubstituted π-bonds at rates faster than those operative during Baeyer−Villiger oxidation of hindered cyclopentanones and cyclohexanones, it was provisionally assumed that epoxidation occurred prior to lactone ring formation. Barring some special reactivity effect, osmylation would be expected to proceed analogously.

Within 2 h of mixing **17** with 15 mol % of OsO_4, an intense green color developed that persisted until sodium dithionite was introduced upon workup. The colored intermediate was successfully isolated when a ratio of OsO_4:**17**:NMO of 1:2:1 was utilized. The identification of **19** by crystallography and the mechanistic implications of this finding have been detailed elsewhere.[23]

After the conversion to diol **20a** had been satisfactorily achieved, the secondary SEM ether **20b** was selectively prepared. Further oxidation was now required in order to realize the regiospecific introduction of an oxygen atom into both of the outer rings. The suitability of epoxy dilactone **18** for being channeled into the synthetic scheme had earlier been dismissed. Its epoxide functionality proved unresponsive to regiocontrolled cleavage under nucleophilic and electrophilic conditions.[24] In addition, proper chemical differentiation of its lactone carbonyls in a chemoselective manner was not easily won.

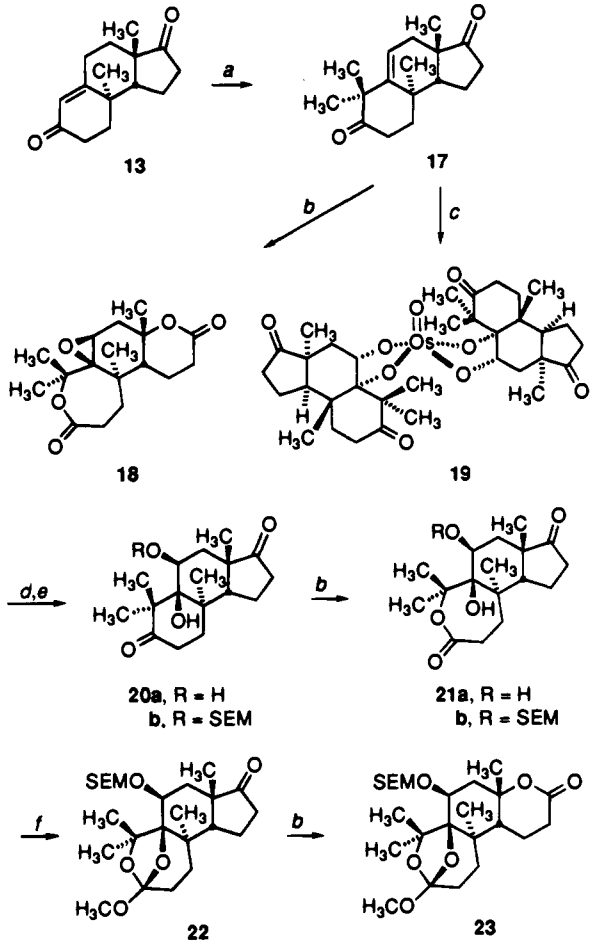
When the peracid oxidation of **20a** and **20b** was probed, we immediately recognized that ring expansion materialized only in the cyclohexanone sector. The recalcitrance of **21a** and **21b** to undergo second-stage Baeyer−Villiger oxidation was confirmed by further individual treatment with trifluoroperacetic

(22) This ratio was determined by integration of the ^1H NMR signals at δ 1.04 and 1.11, respectively, as determined in $CDCl_3$ at 300 MHz.

(23) Sivik, M. R.; Gallucci, J. C.; Paquette, L. A. *J. Org. Chem.* **1990**, *55*, 391.

(24) Sivik, M. R. Ph.D. Thesis, The Ohio State University, 1991.

Scheme 4[a]



[a] (*a*) KO*t*-Bu, *t*-BuOH, CH_3I; (*b*) MCPBA, $NaHCO_3$, CH_2Cl_2; (*c*) OsO_4, NMO, aq acetone; (*d*) $Na_2S_2O_4$; (*e*) SEMCl, $(i\text{-}Pr)_2NEt$; (*f*) $Me_3O^+BF_4^-$, 4-methyl-2,6-di-*tert*-butylpyridine, CH_2Cl_2, room temperature.

acid under more forcing conditions. Our past experience with **17** and the behavior of **22** that is detailed below suggest that the close proximity of the tertiary hydroxyl group to the six-ring ketone may be responsible for this significant rate difference.

The transformation of **21b** into ortho lactone **22** was accomplished by O-methylation with trimethyloxonium tetrafluoroborate[25] in the presence of 4-methyl-2,6-di-*tert*-butylpyridine. Once this issue had been addressed, oxidation of the cyclopentanone subunit with peracid provided the pivotal intermediate **23** in good yield.

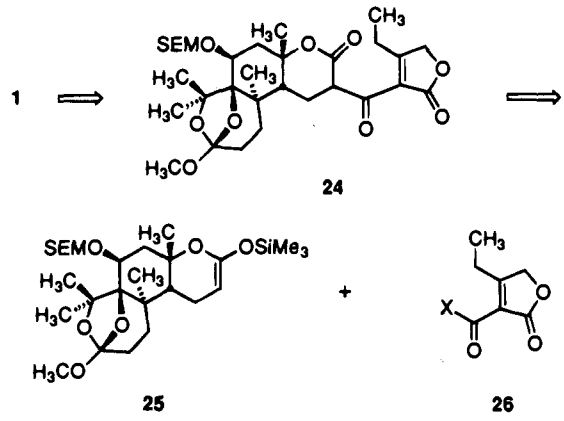
Appraisal of Routes for Annulating the Phthalide Subunit

With successful completion of the western sector of austalide B, several tactical approaches for elaborating the pyran/*p*-cresol/butenolide triad of the mycotoxin were considered. As illustrated in Scheme 5, one means for the rapid assembly of this system could involve the coupling of **23** as its *O*-trimethylsilyl ketene acetal **25** to an activated acylating agent of type **26**. If **24** were to be formed in this manner, this intermediate could presumably be cyclized[26] to give the *p*-cresol from which **1** could be crafted.

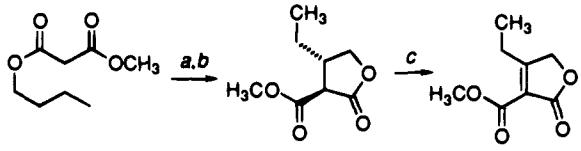
A procedure was soon developed to arrive at the butenolide ester **29** (Scheme 6). Acylation of *n*-butyl alcohol with methyl

(25) Meerwein, H.; Borner, P.; Fuchs, O.; Sasse, H. J.; Schrodt, H.; Spille, J. *Chem. Ber.* **1956**, *89*, 2060.

Scheme 5



Scheme 6[a]

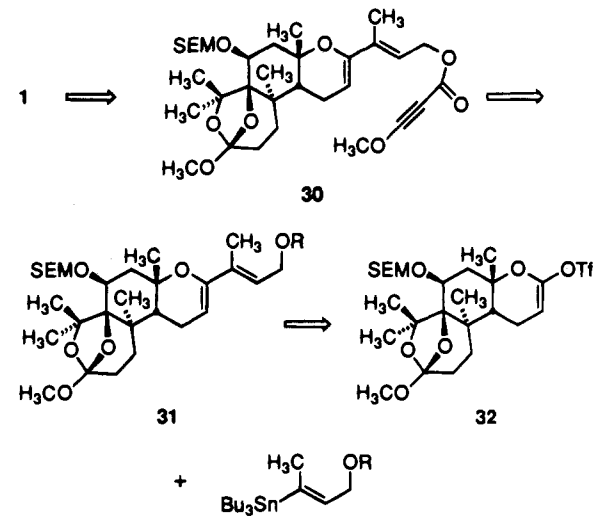


[a] (*a*) TsN_3, Et_3N, CH_3CN; (*b*) $Rh_2(OAc)_4$ (cat.), CH_2Cl_2; (*c*) NaH, PhSeCl, DME; H_2O_2, CH_2Cl_2.

malonyl chloride provided **27**, which underwent efficient diazo transfer from tosyl azide in the presence of triethylamine.[27] Treatment of the diazo intermediate with a catalytic quantity of rhodium(II) acetate dimer[28] promoted carbenoid insertion and formation of **28**. The double bond, which was introduced by organoselenium technology,[29] was exceptionally reactive to a variety of reagents. For example, an intense royal blue color develops when **29** is treated under mild conditions with lithium hydroxide in methanol, triethylamine in ether, or DBN in benzene. The species responsible for this color was not characterized. Acidic hydrolysis conditions also met with failure. Since it did not prove possible to activate **29** as in **26**, the alternative plan that follows was pursued.

The possibility of elaborating the aromatic ring in austalide B by means of an intramolecular Diels–Alder reaction[30] involving **30** was investigated (Scheme 7). The arrangement of the unsaturated centers in this ester is conducive to the transition state demands of the [4 + 2] cycloaddition process. The facial sense of approach of the acetylene to the conjugated diene is of no consequence because the E ring is destined to become aromatic. The projected need to acquire **31** was to be satisfied by palladium(0)-catalyzed coupling[31] of triflate **32** to a suitably elaborated vinylstannane.One obvious means for reaching **35** involved adaptation of the stannyl cuprate chemistry of Piers and Morton[32] to methyl 2-butynoate. Reduction of **34** with Dibal-H was followed by protection as the *tert*-butyldimethylsilyl ether to give **35** (Scheme 8). In a parallel experiment, lactone **23** was deprotected with LDA and the resulting enolate

Scheme 7



was exposed to *N*-phenyltriflimide to give enol triflate **32** in good yield. The coupling of **32** to **35**, initially carried out with tetrakis(triphenylphosphine)palladium(0) and lithium chloride in line with the original Stille protocol,[33] did furnish **31a** but in low yield (~30%). The serious competing side reaction was the transfer of a butyl group. When recourse was made instead to the trimethyltin analogue of **35**, the preference for methyl transfer was overwhelmingly favored; in fact, no vinylation product was detected. This would appear to be a consequence of steric shielding of the tin center in **35** since a probe reaction involving **32** and tributylvinylstannane resulted in much more rapid conversion (1.5 h instead of 72 h) to the simple vinylated product which was isolated in 87% yield!

An attempt to adapt Murai's cuprate coupling alternative[34] for the construction of **31a** failed, principally because of the instability of the organometallic intermediate under the reaction conditions. As will be discussed below, these complications can be conveniently skirted by substituting $(2\text{-furyl})_3P$[35] as a more well-suited ligand for the palladium as $Pd_2(dba)_3$.

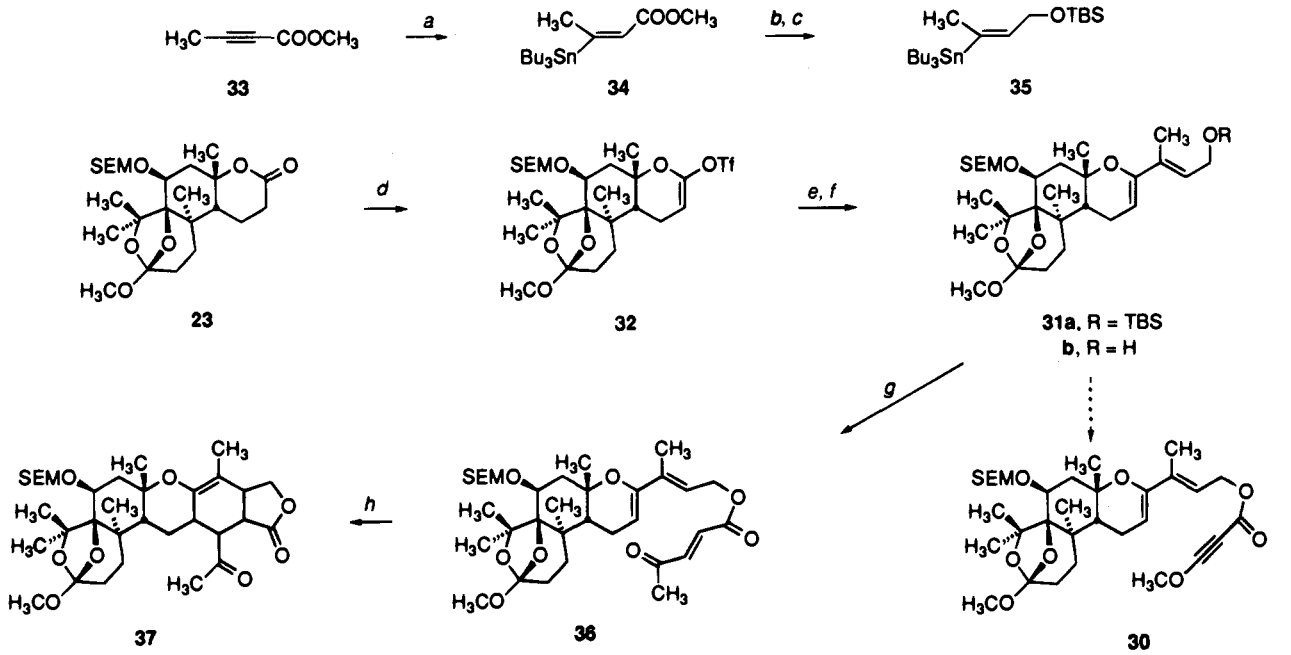
With **31a** in hand, the proclivity of this diene for intermolecular Diels–Alder cycloaddition to methyl 2-butynoate was first probed. Under a variety of conditions including high pressure, unreacted **31a** was invariably recovered. At elevated temperatures, decomposition ensued. The high level of substitution in the diene is evidently sufficient to exert significant kinetic retardation. The intramolecular cycloaddition option clearly had to be followed, and alcohol **31b** could be readily accessed for tethering purposes.

The obvious best choice of reaction partner was methoxypropynoic acid since the acquisition of **30** and its ensuing cyclocondensation would require no further chemical manipulation other than oxidation to finalize construction of the entire eastern sector. Although the methyl ester of methoxypropynoic acid has been reported,[36] we have failed to obtain this material because of the extreme sensitivity to thermal shock of its methoxyacetylene precursor.

Since maleic anhydride reacts with **31a** to give two [4 + 2] adducts, the strategy reappraisal forced upon us incorporated this important precedent. DCC-promoted esterification of **31b** with 4-oxo-2-pentenoic acid provided **36** in high yield. Heating **36** in toluene at 100 °C resulted in the formation of two isomers of **37**. The stereochemistry of the individual diastereomers was

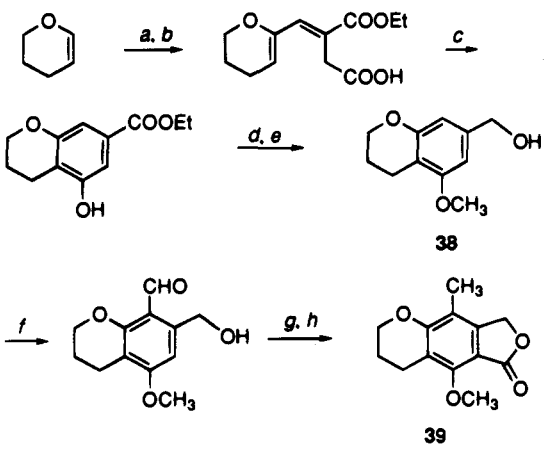
(26) For related methods of phthalide construction, see: (a) Auricchio, S.; Ricca, A.; Vajna de Pava, O. *J. Org. Chem.* **1983**, *48*, 602. (b) Yamaguchi, M.; Shibato, K.; Nakashima, H.; Minami, T. *Tetrahedron* **1988**, *44*, 4767. (c) Asaoka, M.; Miyake, K.; Takei, H. *Chem. Lett.* **1977**, 167.
(27) Review: Regitz, M. *Synthesis* **1972**, 351.
(28) (a) Taber, D. F.; Ruckle, R. E., Jr. *Tetrahedron Lett.* **1985**, *26*, 3059. (b) Taber, D. F.; Petty, E. H. *J. Org. Chem.* **1982**, *47*, 4808. (c) Taber, D. F.; Raman, K. *J. Am. Chem. Soc.* **1983**, *105*, 5935. (d) Wenkert, E.; Davis, L. L.; Mylari, B. L.; Solomon, M. F.; daSilva, R. R.; Shulman, S.; Warnet, R. J.; Ceccherelli, P.; Curini, M.; Pellicciari, R. *J. Org. Chem.* **1982**, *47*, 3242. (e) Cane, D. E.; Thomas, P. J. *J. Am. Chem. Soc.* **1984**, *103*, 5295.
(29) Reich, H. J.; Wollowitz, S. *Org. React.* **1993**, *44*, 1.
(30) Ciganek, E. *Org. React.* **1984**, *32*, 1.
(31) Review: Ritter, K. *Synthesis* **1993**, 735.
(32) Piers, E.; Morton, H. E. *J. Org. Chem.* **1980**, *45*, 4263.
(33) Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033.
(34) Tsushima, K.; Araki, K.; Murai, A. *Chem. Lett.* **1989**, 1313.
(35) Farina, V.; Baker, S. R.; Benigni, D. A.; Hauck, S. I.; Sapino, C., Jr. *J. Org. Chem.* **1990**, *55*, 5833.
(36) Gupta, I.; Yates, P. *J. Chem. Soc., Chem. Commun.* **1982**, 1227.

Scheme 8[a]



[a] (*a*) Bu_3SnCu; (*b*) Dibal-H, CH_2Cl_2; (*c*) TBSCl, imid, DMF; (*d*) LDA, THF, HMPA; $PhNTf_2$; (*e*) **35**, $Pd(PPh_3)_4$, LiCl, THF; (*f*) TBAF, THF; (*g*) $CH_3COCH{=}CHCOOH$, DCC, DMAP, CH_2Cl_2; (*h*) toluene, 100 °C.

Scheme 9[a]



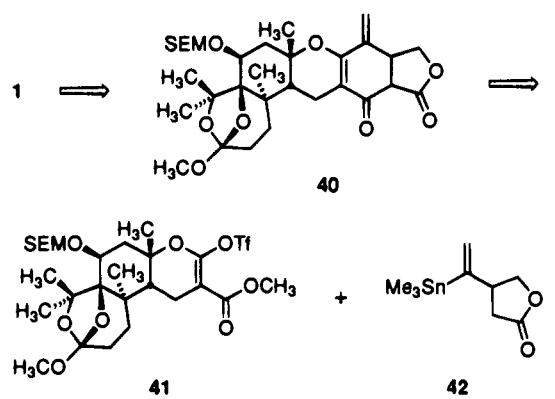
[a] (*a*) *t*-BuLi, pentane, −78 °C → 0 °C; DMF −78 °C; (*b*) $Ph_3P{=}C(COOEt)CH_2COOH$, C_6H_6, rt → 55 °C; (*c*) $(COCl)_2$, CH_2Cl_2, Δ; (*d*) NaH, CH_3I, THF; (*e*) $LiAlH_4$. (*f*) *n*-BuLi; C_6H_6, rt; DMF; (*g*) H_2NNH_2, K_2CO_3, diethylene glycol, Δ; (*h*) *n*-BuLi (2 equiv), TMEDA, ether, rt; CO_2, −30 °C.

not established because of the pending aromatization of the E ring. Unfortunately, we were singularly unsuccessful in a variety of ventures designed to achieve dehydrogenation of the cyclohexene ring in **37**.

In light of this development, a model study was pursued for the purpose of elaborating the pyran/*p*-cresol/butenolide triad in a manner that would ultimately be applied to **8**. This successful tactic, outlined in Scheme 9, has been detailed elsewhere.[37] The lessons learned from the synthesis of **39** include the requirement that metalation of the dihydropyran and of **38** requires *tert*- or *n*-butyllithium at 0 °C to room temperature. These demanding conditions could not be applied to **8** without degradative consequences.

As a result of the above, recourse, was made to a more interesting tactic, the basis of which again resided in Stille

Scheme 10



coupling. As shown in Scheme 10, the pyran was now to carry a carbomethoxy substituent whose ultimate role it was to become the methoxyl-substituted carbon in austalide B. In this way, coupling of **41** to vinylstannane **42** was to generate an intermediate, which on Claisen condensation would provide a workable route to **40**.

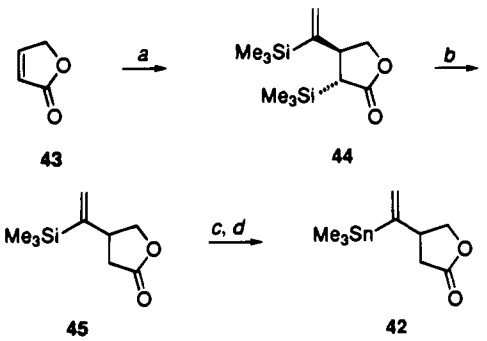
In order to produce **42**, the Cu(I)-catalyzed 1,4-addition of [1-(trimethylsilyl)vinyl]magnesium bromide to 5(2*H*)-furanone was investigated. Conventional reaction conditions delivered the desired conjugate addition product in approximately 5% yield, presumably because of the base sensitivity of **43**. To resolve this complication, excess trimethylsilyl chloride was introduced at the outset in order to trap the enolate as it was formed. Under these conditions, the unexpected C-silylated lactone **44** resulted (Scheme 11). Following chemoselective desilylation to produce **45**, this vinylsilane was transformed via the vinyl bromide into stannane **42**.

The conversion of **23** to **41** was next addressed. Although C-alkylation with methyl cyanoformate proceeded as expected,[38] it was necessary to delineate the regioselectivity with which a β-lactonic ester would engage in O-triflation. To our knowledge, no precedent relating to this question has been published. In the event, condensation of the enolate anion of **46** with

(37) (a) Paquette, L. A.; Schulze, M. M. *Tetrahedron Lett.* **1993**, *34*, 3235. (b) Paquette, L. A.; Schulze, M. M.; Bolin, D. G. *J. Org. Chem.* **1994**, *59*, 2043.

(38) Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, *24*, 5425.

Scheme 11[a]



[a] (*a*) $Me_3SiC(=CH_2)MgBr$, $CuBr{\cdot}Me_2S$, Me_3SiCl; (*b*) HF, CH_3CN, H_2O; Br_2; $Bu_4N^+F^-$; (*d*) $(Me_3Sn)_2$, $Pd(PPh_3)_4$.

N-phenyltriflimide gave rise in good yield to a single triflate. Proof that **41** had been formed was gained by Dibal-H reduction of this product in CH_2Cl_2 at −78 °C. That the resultant alcohol was the primary carbinol **48** (Scheme 12) was clearly evident by ^1H NMR analysis (see the Experimental Section).

Steric retardation was also evident during the attempted coupling of **41** with **42**. When the conversion to **49** was effected with $Pd(Ph_3P)_4$ and LiCl in THF at 60 °C, the extent of reaction never exceeded 10%. Accordingly, the reaction was carried out in the presence of $(2\text{-furyl})_3P$ and $Pd_2(dba)_3$. After 21 h of reflux, the result was formation of the dienyl ester as a 1:1 mixture of two diastereomers in 71% yield. Actuation of the necessary ring closure was achieved by exposure of **49** to potassium hexamethyl disilazide in THF at −78 °C. This treatment resulted in smooth conversion to **40a** and **40b** in 89% yield. While these cis-fused diastereomers could be readily separated by chromatography on silica gel, neither showed any tendency to aromatize when heated with $RhCl_3$, $Pd(OAc)_2$, or DBU in xylene or benzene. The resistance to aromatization is attributed to the high energy barrier associated with the transformation of two rather conformationally rigid tetrahedral carbons (see Figure 1) into sp^2-hybridized centers in one operation. To facilitate crafting of the benzene ring, a stepwise procedure was adopted. Once O-methylation had been accomplished, it proved an easy matter to effect [1,3] hydrogen sigmatropy simply by heating the pair of ethers in benzene for 15 min. By this means, **50** was obtained in 46% overall yield. In this sequence, both base and solvent are important. When K_2CO_3 was employed, very little methoxy product was isolated; in turn KH caused reduction of the dienone system. The replacement of HMPA with DMSO led to formation of a substantial amount of C-methylated material.

Following removal of the SEM protecting group,[39] the β-alcohol was subjected to perruthenate oxidation[40] to provide ketone **51**. This ketone is known, having been generated by the CSIRO group in Pretoria via Jones oxidation of austalide B.[6] While the spectroscopic features of their material and ours were superimposable, the reported optical rotation ($[\alpha]^{24}_D$ −79.2° (*c* 1.00, $CHCl_3$)) was more elevated than that determined experimentally in this work ($[\alpha]^{23}_D$ −69.3° (*c* 0.9, $CHCl_3$)) and brought on cause for concern about optical purity, at least temporarily. The treatment of **51** with sodium borohydride in methanol at 0 °C afforded a product whose spectral properties clearly revealed it to be austalide B. Indeed, direct comparison of synthetic **1** with the natural material showed them to exhibit *identical* $[\alpha]^{22}_D$ values of −46.2° in $CHCl_3$ solution. The possibility of a typographical error for the $[\alpha]_D$ value of **51** seems most likely since synthetic **1** is enantiopure.

(39) Good temperature control is necessary. HMPA as solvent accelerates the rate of deprotection.

(40) Review: Griffith, W. P.; Ley, S. V. *Aldrichim. Acta* **1990**, *23*, 13.

Summary. Austalide B is the first member of the meroterpenoid class produced by *Aspergillus ustus* to yield to total synthesis. Stereocontrolled assembly of a cyclic ortho ester early en route to this target was shown to be compatible with subsequent attachment of the eastern sector. A key element of the construction was the use of a Stille coupling reaction for advancing assembly of the DEF ring triad. This methodology could constitute a generic solution to elaboration of the pyran/*p*-cresol/butenolide triad in phthalides of this general type. In achieving the annulation, it was possible to incorporate the entire butenolide unit as a single entity. The logic of preparing a fully substituted benzene ring in this manner enabled the convergent scheme leading to **1** to be accomplished in 16 steps.

Experimental Section

Melting points were determined in open capillaries with a Thomas-Hoover apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 1320 instrument. ^1H NMR spectra were recorded at 300 MHz and ^{13}C spectra at 75 MHz on a Bruker AC-300 instrument as denoted. Mass spectra were recorded at The Ohio State University Chemical Instrument Center. Elemental analyses were performed by Scandinavian Microanalytical Laboratory, Herlev, Denmark. All solvents were predried by standard methods. All reactions involving nonaqueous solutions were performed under an inert atmosphere. Unless otherwise indicated, all separations were carried out under flash chromatography conditions on silica gel 60 (230−400 mesh, 60 Å) using the indicated solvents. The organic extracts were dried over anhydrous magnesium sulfate. The purity of all compounds was shown to be ≥95% by high-field ^1H NMR analysis. Optical rotations are based on concentrations of g/100 mL.

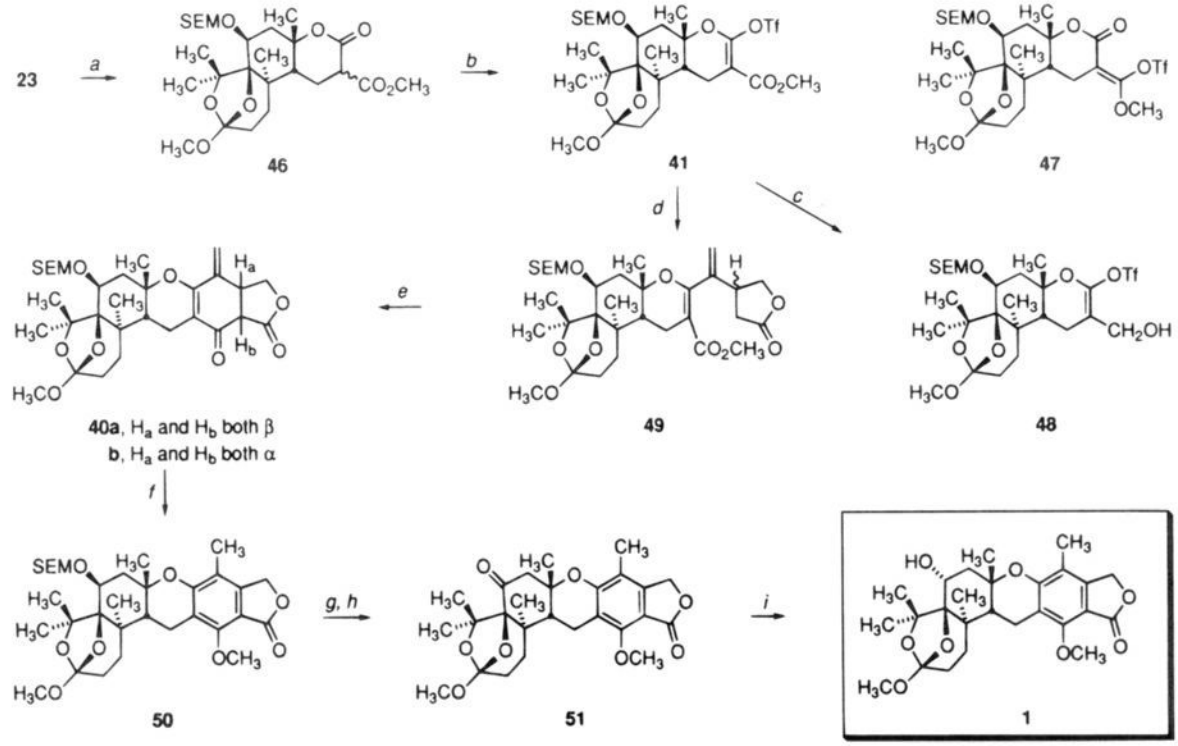
(3a*R*,7a*S*)-Tetrahydro-4′,7′a-dimethylspiro[1,3-dioxolane-2,1′-indan]-5′(4′*H*)-one (12). Ethylene glycol (2 mL) and *p*-toluenesulfonic acid (800 mg) were added to a solution of **11** (10.0 g, 61 mmol) in 100 mL of 2-ethyl-2-methyl-1,3-dioxolane. The mixture was stirred for 2 days, and triethylamine (2 mL) was added. The solution was diluted with benzene (100 mL) and washed with water (50 mL) and then brine (50 mL). Each aqueous washing was extracted with benzene (2 × 50 mL). The combined extracts were dried and concentrated. The resultant brown oil was purified by column chromatography on silica gel (elution with 30% ethyl acetate in petroleum ether) to give 10.10 g (80%) of the ketal as a pale yellow oil: $[\alpha]^{20}_D$ +8.2° (*c* 2.1, $CHCl_3$); IR (neat, cm^{-1}) 1660, 1460, 1320; ^1H NMR (300 MHz, $CDCl_3$) δ 5.70 (s, 1 H), 3.87 (m, 4 H), 2.55−1.25 (series of m, 8 H), 1.18 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 198.4, 173.9, 122.9, 117.3, 65.5, 64.7, 47.5, 32.8, 31.4, 26.6, 26.3, 19.8; MS *m/z* (M^+) calcd 208.1099, obsd 208.1109.

Lithium wire (60 mg, 8.6 mmol) was dissolved in 60 mL of liquid ammonia at -78 °C. To the resultant blue solution was added dropwise a solution of the ketal (1.00 g, 4.8 mmol) and *tert*-butyl alcohol (229 mg, 3.1 mmol) in 30 mL of dry ether. The mixture was stirred for 2 h at −33 °C, at which point methyl iodide (1.50 mL, 3.40 g; 24 mmol) was added. After 1 h of stirring at −33 °C, the ammonia was distilled off. The solution was diluted with ether (125 mL), and the reaction mixture was washed with saturated aqueous NH_4Cl solution (30 mL) and then brine (50 mL). Each washing was sequentially extracted with ether (2 × 30 mL). The combined extracts were dried and concentrated. The concentrate was purified by MPLC on silica gel (elution with 20% ethyl acetate in petroleum ether) to afford 0.70 g (65%) of a 2:1 mixture of the methyl epimers of **12**. The ratio was determined by the weight of the isolated isomers, each obtained as a colorless oil.

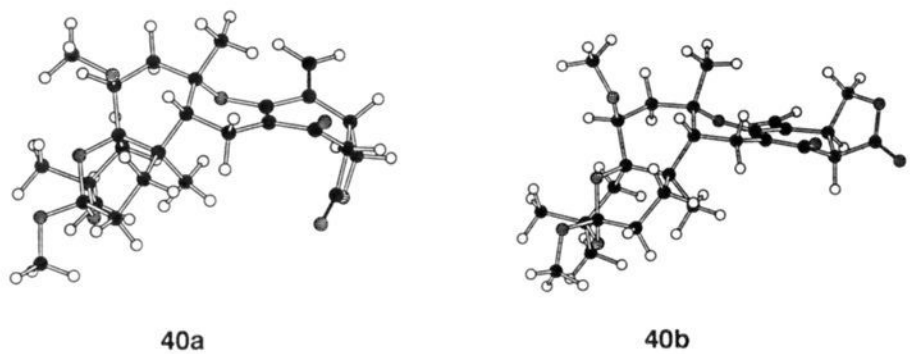
For the major isomer (0.47 g, 44%): IR (neat, cm^{-1}) 1735; ^1H NMR (300 MHz, C_6D_6) δ 3.51−3.35 (m, 4 H), 2.25−2.12 (m, 1 H), 2.10−1.97 (m, 2 H), 1.80−1.67 (m, 1 H), 1.62−1.46 (m, 3 H), 1.44−1.40 (m, 1 H), 1.16−1.05 (m, 1 H), 1.03 (s, 3 H), 1.00−0.86 (m, 1 H), 0.92 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 219.7, 110.2, 65.5, 64.0, 49.7, 47.3, 36.5, 36.0, 30.7, 26.7, 20.4, 18.9, 11.1; MS *m/z* (M^+) calcd 224.1412, obsd 224.1416.

For the minor isomer (0.23 g, 21%): IR (neat, cm^{-1}) 1710; ^1H NMR (300 MHz, C_6D_6) δ 3.52−3.38 (m, 4 H), 3.26−2.19 (m, 1 H), 2.17−1.90 (m, 2 H), 1.89−1.49 (m, 3 H), 1.48−1.26 (m, 3 H), 1.05−0.95 (m, 1 H), 0.94 (d, *J* = 6.4 Hz, 3 H), 0.78 (s, 3 H); ^{13}C NMR (75 MHz,

Scheme 12[a]



[a] (*a*) LiN(*i*-Pr)$_2$, $NCCO_2CH_3$, THF; (*b*) KN(SiMe$_3$)$_2$, THF; $PhNTf_2$; (*c*) Dibal-H; (*d*) 42, $Pd_2(dba)_3$, (furyl)$_3$P, LiCl, THF, 60 °C; (*e*) KN(SiMe$_3$)$_2$, THF, −78 °C; (*f*) KN(SiMe$_3$)$_2$, HMPA, Me_2SO_4; C_6H_6, 80 °C; (*g*) $Bu_4N^+F^-$, HMPA, 45 °C; (*h*) TPAP, CH_2Cl_2, 0 °C; (*i*) $NaBH_4$, MeOH, 0 °C.



40a **40b**

Figure 1. Conformational depictions of **40a** and **40b** as deduced by molecular mechanics calculations.

C_6D_6) ppm 218.8, 110.2, 65.1, 64.6, 49.4, 49.5, 40.2, 33.0, 31.9, 29.3, 24.3, 21.9, 12.4; MS *m/z* (M^+) calcd 224.1412, obsd 224.1455.

(3a*R*,7a*S*)-Tetrahydro-4,7a-dimethyl-1,5(4*H*)-indandione (16). Hydrogenation of 15. To a pressure bottle which had been rinsed with a 0.3 N solution of potassium hydroxide in ethanol was added 100 mL of absolute ethanol, enedione **15** (17.7 g: 99.1 mmol), and 300 mg of 10% palladium on carbon. The bottle was placed under 45 psi of hydrogen and shaken in a Paar hydrogenator for 24 h. The catalyst was filtered off and the fitrate was concentrated *in vacuo*. The concentrate was taken up in 300 mL of ether and washed with brine. The washing was extracted with ether, and the combined extracts were dried and concentrated to give an 8:1 mixture of methyl epimers (α; β as shown by the integration of the epimeric methyl ^{1}H NMR signals at 1.04 and 1.11 ppm, respectively) of **16** as a pale yellow oil (17.28 g; 97%): bp 160 °C (0.5 mmHg); IR (neat, cm^{-1}) 1736, 1710; α-isomer ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.79 (qd, *J* = 6.8, 6.4 Hz, 1 H), 2.53−2.39 (m, 2 H), 2.33 (dt, *J* = 7.1, 6.1 Hz, 1 H), 2.25−2.12 (m, 1 H), 2.02 (m, 1 H), 1.87 (td, *J* = 13.7, 4.6 Hz, 1 H), 1.58 (dt, *J* = 14.0, 4.6 Hz, 1 H), 1.33 (m, 1 H), 1.31 (s, 3 H), 1.11−1.03 (m, 1 H), 1.04 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 219.6, 211.4, 51.5, 47.4, 42.6, 36.9, 35.3, 30.1, 21.3, 19.6, 11.1; MS *m/z* (M^+) calcd 180.1450, obsd 180.1410.

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.38; H, 9.02.

B. Hydrolysis of 12. To a solution of **12** (2.86 g, 12.8 mmol) in 6 mL of 50% aqueous acetone was added *p*-toluenesulfonic acid (0.22 g), and the mixture was stirred for 8 h. The solution was diluted with ether (80 mL) and washed with water (30 mL) and then brine (2 × 20 mL). Each aqueous phase was sequentially extracted with ether (2 × 15 mL). The combined extracts were dried and concentrated to give 2.02 g (88%) of an epimeric mixture of **16**, spectroscopically identical to that obtained in part A except for the isomer distribution (now 2:1).

(3a*S*,9a*R*,9b*R*)-4,5,8,9,9a,9b-Hexahydro-3a,9a-dimethyl-1*H*-benz[*e*]indene-3,7(2*H*,3a*H*)-dione (13). A. Starting from 16. To a 500 mL round-bottomed flask equipped with a Dean−Stark trap was added dione **16** (17.0 g, 94.3 mmol), dry benzene (250 mL), 4-chloro-2-butanone (16.2 g, 0.15 mol), and *p*-toluenesulfonic acid (1.1 g, 5.8 mmol). The mixture was heated at reflux under a N_2 atmosphere for 10 days. Benzene (200 mL) was added, and the orange solution was washed with saturated aqueous $NaHCO_3$ solution (200 mL) and then brine (200 mL). The aqueous washings were sequentially extracted with benzene (3 × 150 mL), and the combined organic phases were dried and concentrated. The concentrate was passed through a 25 cm × 7 cm column of silica gel (elution with 30% ethyl acetate in petroleum ether), and the fractions containing starting material and product were separately concentrated. Kugelrohr distillation of the product gave 4.65 g (21%) of **13** as a highly viscous yellow oil,[22] bp 190 °C at 0.6 mm (oven temp). Short-path distillation of the recovered

starting material returned 6.80 g (40%) of **16** as a pale yellow oil. The corrected yield for **13** is 35%; $[\alpha]^{20}_D$ +100° (*c* 1.10, $CHCl_3$); IR (neat, cm^{-1}) 1730, 1665, 1620; ^1H NMR (300 MHz, $CDCl_3$) δ 5.79 (s, 1 H), 2.75−2.20 (series of m, 6 H), 1.95 (m, 4 H), 1.75−1.10 (series of m, 3 H), 1.08 (s, 3 H), 1.00 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 220.5, 198.5, 169.7, 124.3, 52.9, 48.9, 38.3, 35.9, 34.5, 33.6, 30.1, 29.2, 26.5, 20.9, 19.1; MS *m/z* (M^+) calcd 232.1463, obsd 232.1470.

B. Beginning with 12. To a 100 mL round-bottomed flask equipped with a Dean−Stark trap was added the diketone derived from **12** (2.00 g, 11.1 mmol), dry benzene (25 mL), 4-chloro-2-butanone (1.77 g, 16.6 mmol), and *p*-toluenesulfonic acid (2.10 mg, 1.10 mmol). The mixture was refluxed under a nitrogen atmosphere for 10 days. Ethyl acetate (50 mL) was added, and the solution was washed with saturated aqueous $NaHCO_3$ solution (30 mL) and then brine (30 mL). The pooled aqueous washings were extracted with ethyl acetate (2 × 40 mL), and the combined extracts were dried and concentrated to leave a residual oil which was purified by elution through a 3 cm x 10 cm column of silica gel (elution with 30% ethyl acetate in petroleum ether). Kugelrohr distillation of the purified product gave 0.40 g (16%) of **13** as a highly viscous yellow oil, bp 190° at 0.6 mmHg (oven temp); $[\alpha]^{20}_D$ = +129° (*c* 1.10, $CHCl_3$). This material of 94% ee exhibited a ^1H NMR spectrum identical with that of the previously obtained diketone having 75% ee.

(3a*S*,9a*R*,9b*R*)-4,6,8,9,9a,9b-Hexahydro-3a,6,6,9a-tetramethyl-1*H*-benz[*e*]indene-3,7(1*H*,3a*H*)-dione (17). Potassium hexamethyl disilazide (0.5 M in toluene, 155 mL, 77.5 mmol) was added to *tert*-butyl alcohol (70 mL) at 20 °C and stirred for 30 min before a solution of **13** (8.7 g, 37.5 mmol) in *tert*-butyl alcohol (45 mL) was introduced. The reaction mixture was stirred for 2 h, quenched with saturated NH_4Cl solution, and extracted with ether. The combined organic phases were washed with brine, dried, and evaporated. Chromatography of the residue on silica gel (elution with 15% ethyl acetate in petroleum ether) afforded 6.5 g (67%) of **17** as a viscous, colorless oil which solidified on standing: mp 60−62 °C; $[\alpha]^{20}_D$ +154.1° (*c* 1.45, $CHCl_3$); IR (neat, cm^{-1}) 1735, 1710, 1665; ^1H NMR (300 MHz, $CDCl_3$) δ 5.69 (dd, *J* = 2.3, 6.8 Hz, 1 H), 2.48−2.24 (m, 5 H), 2.21−2.04 (m, 2 H), 2.16−1.78 (m, 4 H), 1.26 (s, 6 H), 1.15 (s, 3 H), 0.91 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 222.7, 215.6, 147.8, 119.3, 52.6, 49.2, 47.8, 36.9, 35.3, 34.6, 32.7, 29.4, 27.7, 27.2, 25.7, 21.6, 21.3; MS *m/z* (M^+) calcd 260.1762, obsd 260.1792.

(5a*R*,6a*S*,7a*S*,11a*R*,11b*R*)-Hexahydro-5,5,7a,11b-tetramethyl-5*H*,6a*H*-oxepino[4,3-*f*]oxireno[*g*][1]benzopyran-3,9(2*H*,10*H*)-dione (18). A mixture of **17** (300 mg, 1.15 mmol), sodium bicarbonate (2.03 g, 24.2 mmol), and *m*-chloroperbenzoic acid (2.79 g, 16.1 mmol) in CH_2Cl_2 (100 mL) was stirred for 24 h, diluted with chloroform (50 mL), and treated with water (70 mL). The mixture was stirred for 30 min, and the organic phase was separated and washed with brine. The combined extracts were dried and concentrated to leave a white solid which was purified by chromatography on silica gel (elution with 60% ethyl acetate in petroleum ether) to give 201 mg (57%) of **18** as colorless crystals, mp 141−142 °C; $[\alpha]^{20}_D$ +133° (*c* 1.7, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) 1720, 1450, 1292; ^1H NMR (300 MHz, $CDCl_3$) δ 2.98 (d, *J* = 3.9 Hz, 1 H), 2.92 (td, *J* = 14.0, 5.3 Hz, 1 H), 2.70−2.45 (m, 4 H), 2.30−2.15 (m, 2 H), 2.10−1.65 (series of m, 4 H), 1.53 (s, 3 H), 1.36 (s, 3 H), 1.33 (s, 3 H), 1.25 (s, 3 H); ^{13}C NMR (20 MHz, $CDCl_3$) ppm 173.3, 171.7, 84.0, 78.1, 66.0, 55.7, 43.5, 39.1, 37.8, 36.4, 31.3, 30.1, 29.3, 26.3, 24.2, 21.0, 16.0; MS *m/z* ($M^+ - C_3H_6O$) calcd 250.1249, obsd 250.1258.

(3a*S*,5*S*,5a*S*,9a*R*,9b*R*)-Octahydro-5,5a-dihydroxy-3a,6,6,9a-tetramethyl-1*H*-benz[*e*]indene-3,7(2*H*,3a*H*)-dione (20a). To a solution of **17** (4.9 g, 18.8 mmol) in a mixture of acetone (50 mL), water (10 mL), and *tert*-butyl alcohol (5 mL) was added sequentially 4-methylmorpholine *N*-oxide (3.3 g, 28.2 mmol) and osmium tetraoxide (1.0 g, 3.9 mmol). The dark green mixture was stirred at room temperature for 6 days before a solution of sodium dithionite (4.0 g) in water (40 mL) was introduced. The reaction mixture was stirred for an additional 7 h, diluted with ethyl acetate, and filtered through a Celite pad. The filtrate was washed twice with brine, dried, and concentrated to leave a pale yellow solid. Recrystallization of this material from ethyl acetate afforded **20a** as white crystals (3.3 g), mp 178−179 °C. Chromatography of the mother liquor concentrates on silica gel (elution with 40% ethyl acetate in petroleum ether) furnished an additional 1.0 g (78% total) of **20a**: $[\alpha]^{20}_D$ +124° (*c* 1.33, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) 3610, 1740, 1695, 1210; ^1H NMR (300 MHz, $CDCl_3$) δ 3.94 (dd, *J* = 21.1, 6.1 Hz, 1 H), 2.90−2.79 (m, 1 H), 2.47−1.65 (series of m, 11 H), 1.56 (dd, *J* = 11.0, 13.0 Hz, 1 H), 1.33 (s, 3 H), 1.28 (s, 3 H), 1.08 (s, 3 H), 0.64 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 220.8, 217.8, 79.5, 68.0, 52.5, 50.4, 49.0, 41.5, 35.3, 34.1, 33.6, 33.1, 27.4, 25.4, 23.0, 18.6, 18.1; MS *m/z* (M^+) calcd 294.1831, obsd 294.1831.

Anal. Calcd for $C_{17}H_{26}O_4$: C, 69.36; H, 8.90. Found: C, 69.24; H, 8.84.

(3a*S*,5*S*,5a*S*,9a*R*,9b*R*)-Octahydro-5,5a-dihydroxy-3a,6,6,9a-tetramethyl-5-[[2-(trimethylsilyl)ethoxy]methoxy]-1*H*-benz[*e*]indene-3,7(2*H*,3a*H*)-dione (20b). To a solution of **20a** (3.76 g, 12.8 mmol) in CH_2Cl_2 (60 mL) was added diisopropylethylamine (3.3 g, 25.9 mmol) and SEM chloride (3.3 g, 19.8 mmol). The reaction mixture was refluxed for 3 h, cooled, and treated with saturated $NaHCO_3$ solution. The separated aqueous phase was extracted with CH_2Cl_2, and the combined organic layers were washed with brine, dried, and concentrated. Chromatography of the residue on silica gel (elution with 20% ethyl acetate in petroleum ether) delivered 5.2 g (96%) of **20b** as a powdery, white solid: mp 89−90 °C; $[\alpha]^{20}_D$ +87.4° (*c* 1.67, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) 2920, 1730, 1700, 1200; ^1H NMR (300 MHz, $CDCl_3$) δ 4.82 (d, *J* = 6.4 Hz, 1 H), 4.72 (d, *J* = 6.4 Hz, 1 H), 3.78 (dd, *J* = 5.9, 10.6 Hz, 1 H), 3.66 (dd, *J* = 7.7, 16.6 Hz, 2 H), 2.90−2.79 (m, 1 H), 2.54 (dd, *J* = 5.9, 13.4 Hz, 1 H), 2.47−1.99 (series of m, 5 H), 1.80−1.66 (m, 3 H), 1.55−1.34 (m, 5 H), 1.29 (s, 3 H), 1.28 (s, 3 H), 0.96 (dd, *J* = 7.7, 9.0 Hz, 2 H), 0.66 (s, 3 H), 0.03 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 220.1, 217.4, 93.3, 79.7, 74.2, 66.5, 16.6, 52.6, 50.3, 48.4, 41.5, 33.9, 33.5, 32.9, 31.6, 27.6, 25.1, 22.3, 18.5, 18.0, −1.5; FAB MS *m/z* (M^+) calcd 424.26, obsd 424.27.

Anal. Calcd for $C_{23}H_{40}O_5Si$: C, 65.05; H, 9.49. Found: C, 65.07; H, 9.46.

(5a*R*,6*S*,7a*S*,10*R*,10b*R*)-Octahydro-5a,6-dihydroxy-5,5,7a,10b-tetramethyl-1*H*-indeno[5,4-*c*]oxepin-3,8(2*H*,5*H*)-dione (21a). To a mixture of **20a** (72 mg, 0.24 mmol) and sodium bicarbonate (11 mg, 1.2 mmol) in CH_2Cl_2 (3 mL) was added *m*-chloroperbenzoic acid (17 mg, 0.97 mmol). The resultant slurry was stirred for 2 days, diluted with 4 mL of CH_2Cl_2, and washed twice with 3 mL of saturated K_2CO_3 solution. Each washing was extracted with 4 mL of CH_2Cl_2, and the combined organic extracts were washed with 6 mL of brine, dried, and concentrated. The concentrate was purified on 3 g of TLC-grade silica gel (elution with 70% ethyl acetate in petroleum ether) to give 30 mg (40%) of **21a** as a crystalline solid: mp 210−211 °C; $[\alpha]^{20}_D$ +35° (*c* 1.5, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) 3600, 3450, 1730; ^1H NMR (300 MHz, $CDCl_3$) δ 3.77 (br m, 1 H), 2.93−2.59 (m, 1 H), 2.57−2.07 (series of m, 8 H), 2.04−1.81 (m, 2 H), 1.69−1.50 (m, 2 H), 1.52 (s, 3 H), 1.45 (s, 3 H), 1.06 (s, 3 H), 0.99 (s, 3 H); ^{13}C NMR (75 MHz, $CHCl_3$) ppm 219.4, 172.8, 91.5, 80.4, 67.7, 48.6, 48.1, 40.7, 34.7, 33.8, 31.7, 30.9, 30.5, 27.1, 26.9, 19.4, 19.2; MS *m/z* ($M^+ - C_3H_6O - H_2O$) calcd 234.1256, obsd 234.1289.

Anal. Calcd for $C_{17}H_{26}O_5$: C, 65.78; H, 8.44. Found: C, 65.52; H, 8.55.

(5a*R*,6*S*,7a*S*,10a*R*,10b*R*)-Octahydro-5a-hydroxy-5,5,7a,10b-tetramethyl-6-[[2-(trimethylsilyl)ethoxy]methoxy]-1*H*-indeno[5,4-*c*]oxepin-3,8(2*H*,5*H*)-dione (21b). To a solution of **20b** (5.0 g, 11.8 mmol) in CH_2Cl_2 (140 mL) was added $NaHCO_3$ (3.85 g, 45.8 mmol) and *m*-chloroperbenzoic acid (6.15 g, 35.6 mmol). The mixture was stirred at room temperature for 24 h, diluted with CH_2Cl_2, and washed three times with water. After drying and concentration, the crude product was purified by silica gel chromatography (elution with 50% to 75% ethyl acetate in petroleum ether). There was isolated 3.8 g (73%) of **21b** and 0.3 g (8%) of **21a**.

For **21b**: colorless solid; mp 107−109 °C; $[\alpha]^{20}_D$ +23° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) 3450, 2920, 1730; ^1H NMR (300 MHz, $CDCl_3$) δ 4.78 (d, *J* = 6.7 Hz, 1 H), 4.74 (d, *J* = 6.7 Hz, 1 H), 3.80 (dd, *J* = 4.4, 6.01 Hz, 1 H), 3.64 (ddd, *J* = 2.3, 5.1, 11.8 Hz, 2 H), 2.82−2.71 (m, 1 H), 2.62−1.55 (series of m, 11 H), 1.49 (s, 3 H), 1.47 (s, 3 H), 1.11 (s, 3 H), 1.01 (s, 3 H), 0.92 (m, 2 H), 0.01 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 220.0, 171.9, 94.2, 91.6, 79.5, 74.2, 66.5, 47.9, 47.8, 40.4, 33.8, 30.9, 30.4, 29.8, 27.1, 26.6, 19.7, 19.0, 18.1, −1.4 (1 carbon not seen); FAB MS *m/z* ($M^+ + 1$) calcd 441.27, obsd 441.26.

Anal. Calcd for $C_{23}H_{40}O_6Si$: C, 62.69; H, 9.15. Found: C, 62.60; H, 9.07.

(3*S*,5a*R*,6*S*,7a*S*,10a*R*,10b*R*)-Decahydro-3-methoxy-5,5,7a,10b-tet-

ramethyl-3,6-bis[[2-(trimethylsilyl)ethoxy]methoxy]-5*H*,3,5a-epoxy-8*H*-indeno[5,4-*c*]oxepin-8-one (22). To a suspension of trimethyloxonium tetrafluoroborate (3.8 g, 25.8 mmol) in dry CH_2Cl_2 (60 mL) was added a solution of **21b** (6.87 g, 15.3 mmol) and 2,5-di-*tert*-butyl-4-methylpyridine (7.7 g, 37.6 mmol) in CH_2Cl_2 (50 mL). The mixture was stirred at room temperature for 10 h, quenched with saturated $NaHCO_3$ solution, and diluted with CH_2Cl_2. The organic phase was separated, washed with brine, dried, and concentrated. The residue was chromatographed on silica gel (elution with 15% ethyl acetate in petroleum ether) to give 4.5 g (63%) of **22** as a viscous oil that crystallized on standing: mp 99−100 °C; $[\alpha]^{25}_D$ −12.4° (*c* 2.5, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) 2970, 2930, 2900, 2870, 1730, 1260; ^1H NMR (300 MHz, $CDCl_3$) δ 4.78 (d, J = 6.6 Hz, 1 H), 4.73 (d, J = 6.6 Hz, 1 H), 3.91−3.50 (m, 3 H), 3.45 (s, 3 H), 2.54−1.50 (series of m, 7 H), 1.52 (s, 3 H), 1.51 (s, 3 H), 1.30−0.80 (series of m, 6 H), 1.14 (s, 3 H), 0.82 (s, 3 H), 0.02 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 220.8, 118.3, 94.4, 88.9, 88.4, 71.1, 65.9, 56.9, 48.9, 47.4, 45.9, 41.4, 34.3, 33.4, 32.3, 27.1, 25.6, 19.0, 18.2, 18.0, 15.1, −1.5; MS *m/z* (M^+ − C_3H_6O − $Me_3SiCH_2CH_2OCH_2$) calcd 265.1439, obsd 265.1489.

Anal. Calcd for $C_{24}H_{42}SiO_6$: C, 63.40; H, 9.31. Found: C, 63.16; H, 9.28.

(4a*S*,6a*R*,9*S*,11a*R*,11b*R*)-Octahydro-9-methoxy-4a,7,7,11a-tetramethyl-6-[[2-(trimethylsilyl)ethoxy]methoxy]-5*H*-3,5a-epoxy-8*H*-indeno[5,4-*c*]oxepin-8-one (23). A mixture of **22** (2.2 g, 4.84 mmol), $NaHCO_3$ (2.0 g, 23.8 mmol), and *m*-chloroperbenzoic acid (2.5 g, 14.5 mmol) in CH_2C_2 (50 mL) was stirred at room temperature for 72 h, diluted with ether, and washed twice with brine prior to drying and concentration. The residue was chromatographed on silica gel (elution with 40% to 70% ethyl acetate in petroleum ether) to return 0.2 g of unreacted **22** and to afford 1.21 g (58%) of **23** in addition to 140 mg (10%) of the desilylated lactone.

For **23**: colorless viscous oil that crystallized on standing, mp 87−89 °C; $[\alpha]^{20}_D$ −55° (*c* 0.5, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) 2960, 2930, 2900, 2885, 1760, 1260, 1250; ^1H NMR (300 MHz, $CDCl_3$) δ 4.70 (d, J = 6.6 Hz, 1 H), 4.62 (d, J = 6.6 Hz, 1 H), 4.13−3.97 (m, 1 H), 3.90−3.74 (m, 2 H), 3.71−2.81 (m, 2 H), 3.45 (s, 3 H), 2.60−2.53 (m, 2 H), 2.41−2.37 (m, 1 H), 2.31−0.83 (series of m, 6 H), 1.56 (s, 3 H), 1.54 (s, 3 H), 1.50 (s, 3 H), 1.10−1.04 (m, 2 H), 1.04 (s, 3 H), 0.02 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 172.4, 118.3, 95.0, 89.1, 85.0, 82.5, 71.0, 66.0, 57.2, 49.2, 42.3, 41.8, 37.9, 32.5, 30.6, 29.7, 27.0, 25.6, 19.6, 18.1, 17.1, −1.4; MS *m/z* (M^+) calcd 470.2699, obsd 470.6771.

Anal. Calcd for $C_{24}H_{42}SiO_7$: C, 61.24; H, 8.99. Found: C, 61.19; H, 8.98.

For the desilylated product: colorless solid, mp 198−199.5 °C; IR ($CHCl_3$, cm^{-1}) 3570, 2990, 1740; ^1H NMR (300 MHz, $CDCl_3$) δ 4.04 (dd, J = 5.8, 4.7 Hz, 1 H), 3.43 (s, 3 H), 2.63 (ddd, J = 17.6, 6.2, 3.7 Hz, 1 H), 2.47 (m, 2 H), 2.29 (dd, J = 14.8, 5.8 Hz, 1 H), 2.12−1.62 (series of m, 7 H), 1.55 (s, 3 H), 1.53 (s, 3 H), 1.51 (s, 3 H), 1.05 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 172.7, 118.9, 87.5, 85.1, 81.6, 64.5, 49.1, 43.8, 40.7, 39.2, 32.2, 31.0, 30.6, 30.1, 38.6, 24.8, 19.9, 18.7; MS *m/z* (M^+) calcd 340.1886, obsd 340.1904.

Butyl Methyl Propanedioate (27). Methylmalonyl chloride (15.5 g, 113 mmol) was added dropwise to a chilled (0 °C) solution of 1-butanol (16.9 g, 228 mmol) and pyridine (18.4 mL, 228 mmol) in dry CH_2Cl_2 (100 mL). After 1 h of stirring at 0 °C, the mixture was allowed to come to room temperature, stirred for an additional 11 h, and diluted with 75 mL of 1 N H_2SO_4. The separated aqueous phase was extracted with 50 mL of CH_2Cl_2, and the combined organic solutions were washed with brine, dried, and concentrated. Purification was accomplished by passing the concentrate through silica gel with petroleum ether to give 19.3 g (94%) of **27** as a colorless oil: IR (neat, cm^{-1}) 2970, 1755, 1740; ^1H NMR (300 MHz, $CDCl_3$) δ 4.12 (t, J = 6.6 Hz, 2 H), 3.71 (s, 3 H), 3.34 (s, 2 H), 1.65−1.55 (m, 2 H), 1.41−1.29 (m, 2 H), 0.90 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 167.0, 166.5, 65.3, 52.3, 41.3, 30.4, 18.9, 13.5; MS *m/z* (M^+) calcd 175.0970, obsd 175.097.

Anal. Calcd for $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found C, 55.26; H, 8.15.

Butyl Methyl 2-Diazopropanedioate. *p*-Toluenesulfonyl azide (1.14 g, 5.77 mmol) was added to a solution of *n*-butyl methyl malonate (1.00 g, 5.72 mmol) and triethylamine (0.59 g, 5.83 mmol) in 5 mL of acetonitrile and stirred at room temperature for 24 h. The mixture was concentrated under house vacuum at 40 °C, and the resultant solid was triturated with 12 mL of ether. The ethereal solution was washed with 0.7 g of KOH in 12 mL of water. The organic phase was separated, and the aqueous phase was saturated with Na_2SO_4 and extracted with a 12 mL portion of ether. The combined extracts were washed with brine (10 mL) and dried to give 0.92 g (80%) of the diazo compound: IR (neat, cm^{-1}) 1760, 1730; ^1H NMR (300 MHz, $CDCl_3$) δ 4.22 (t, J = 6.6 Hz, 2 H), 3.81 (s, 3 H), 1.75−1.60 (m, 2 H), 1.43−1.31 (m, 2 H), 0.91 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 161.5, 160.9, 77.2, 65.4, 52.4, 30.6, 18.9, 13.5.

Methyl 4-Ethyl-2-oxotetrahydro-3-furancarboxylate (28). Rhodium(II) acetate dimer (30 mg) was added to a stirred solution of the above diazo compound (0.92 g, 4.6 mmol) in 20 mL of dry CH_2Cl_2. After vigorous gas evolution ceased, the emerald green solution was diluted with 10 mL of 4% aqueous HCl solution and the organic phase was separated. The aqueous phase was extracted with an additional 18 mL of CH_2Cl_2, and the combined extracts were washed with 10 mL of brine, dried, and concentrated. The concentrate was purified by column chromatography using TLC-grade silica gel (20 g) and elution with 20% ethyl acetate in petroleum ether to give lactone **28** as a colorless oil (0.62 g, 78%): IR (neat, cm^{-1}) 2950, 1780, 1745; ^1H NMR (300 MHz, $CDCl_3$) δ 4.51 (dd, J = 8.9, 7.8 Hz, 1 H), 3.92 (t, J = 8.5 Hz, 1 H), 3.81 (s, 3 H), 3.24 (d, J = 8.6 Hz, 1 H), 2.96−2.84 (m, 1 H), 1.66−1.52 (m, 2 H), 0.95 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 171.8, 168.1, 71.6, 52.7, 52.0, 41.5, 25.0, 11.0; MS *m/z* (M^+) calcd 172.0736, obsd 172.0790.

Anal. Calcd for $C_8H_{12}O_4$: C, 55.81; H, 7.02. Found C, 55.74; H, 7.12.

Methyl 4-Ethyl-2-oxo-3-(phenylselenenyl)tetrahydro-3-furancarboxylate. To a stirred, chilled (0 °C) suspension of sodium hydride (115 mg, 4.80 mmol) in freshly distilled 1,2-dimethoxyethane (10 mL) was added **28** (0.75 g, 4.36 mmol) as a solution in 10 mL of 1,2-dimethoxyethane. After 30 min of stirring at 0 °C, the solution was warmed to room temperature, stirred for 2 h more, cooled to −78 °C, treated with a solution of phenylselenyl chloride (0.92 g, 4.80 mmol) in 5 mL of 1,2-dimethoxyethane, warmed again to room temperature, and stirred for 3 h prior to dilution with ether (40 mL), washing with brine (20 mL), drying, and concentration. The residue was purified by column chromatography on silica gel (elution with 20% ethyl acetate in petroleum ether). The two isomeric phenyl selenides could be separated by MPLC on silica gel (elution with 10% ethyl acetate in petroleum ether) to give 640 mg (44%) of isomer A and 360 mg (25%) of isomer B.

Isomer A: IR (neat, cm^{-1}) 1780, 1738; ^1H NMR (300 MHz, $CDCl_3$) δ 7.69−7.29 (series of m, 5 H), 4.23 (dd, J = 8.7, 7.5 Hz, 1 H), 3.98 (t, J = 8.4 Hz, 1 H), 3.77 (s, 3 H), 2.57−2.47 (m, 1 H), 1.77−1.64 (m, 1 H), 1.37−1.22 (m, 1 H), 0.94 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 172.1, 167.2, 138.0, 130.1, 129.3, 125.2, 70.3, 57.8, 53.2, 46.8, 21.4, 11.5. MS *m/z* (M^+) calcd 328.0214, obsd 328.0217.

Isomer B: IR (neat, cm^{-1}) 1760, 1720; ^1H NMR (300 MHz, $CDCl_3$) δ 7.73−7.29 (series of m, 5 H), 4.33 (dd, J = 8.7, 7.7 Hz, 1 H), 3.82 (dd, J = 10.5, 8.7, 1 H), 3.76 (s, 3 H), 3.05−2.94 (m, 1 H), 1.97−1.85 (m, 1 H), 1.69−1.55 (m, 1 H), 0.99 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 170.8, 168.7, 138.1, 130.1, 129.1, 124.7, 70.1, 57.4, 53.5, 47.5, 21.8, 11.7.

Methyl 2,5-Dihydro-4-ethyl-2-oxo-3-furancarboxylate (29). To a cooled (0 °C) solution of the above selenides (9.24 g, 28.2 mmol) in 125 mL of CH_2Cl_2 was added 2.1 g of 50% hydrogen peroxide. After 1 h at 0 °C, the solution was warmed to room temperature, stirred for 2 h, diluted with 125 mL of CH_2Cl_2, and washed with brine (60 mL). The organic phase was dried and concentrated to give an oil which was purified by chromatography on silica gel (elution with 70% ethyl acetate in petroleum ether) to give 2.11 g (44%) of **29** as a viscous pale yellow oil: IR (neat, cm^{-1}) 1780, 1725, 1642; ^1H NMR (300 MHz, $CDCl_3$) δ 4.78 (s, 2 H), 3.80 (s, 3 H), 2.82 (q, J = 7.6 Hz, 2 H), 1.15 (t, J = 7.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) 179.7, 169.0, 161.4, 117.9, 70.5, 51.8, 21.8, 11.5; MS *m/z* (M^+) calcd 170.0579, obsd 170.0614.

(4a*S*,6*S*,6a*R*,11a*R*,11b*R*)-4a,5,6,9,10,11,11a,11b-Octahydro-9-methoxy-4a,7,7,11a-tetramethyl-6-[[2-(trimethylsilyl)ethoxy]methoxy]-7*H*-6a,9-epoxy-1*H*-pyrano[3,2-*g*][2]benzoxepin-3-yl Trifluoromethanesulfonate (32). To a cold (−78 °C) solution of diisopropylamine (0.23 mL, 1.64 mmol) in dry THF (5 mL) was added *n*-butyllithium (1.0

mL of 1.6 M in hexane, 1.6 mmol). After 20 min, a solution of **23** (528 mg, 1.12 mmol) in the same solvent (2.5 mL) was introduced dropwise, and the reaction mixture was stirred at −78 °C for 2 h before a solution of *N*-phenyltriflimide (585 mg, 1.6 mmol) and HMPA (0.3 mL, 1.67 mmol) in THF (3 mL) was added. The resultant mixture was stirred at −78 °C for 30 min, warmed to 0 °C for 2 h, and concentrated to leave a yellow oil which was extracted with hexanes (4 × 5 mL). The combined hexane solutions were evaporated, and the residue was chromatographed on silica gel (elution with 10% ethyl acetate in petroleum ether containing 0.5% triethylamine) to give 570 mg (85%) of **32** as a colorless oil: IR (neat, cm^{-1}) 1715, 1430; ^1H NMR (300 MHz, C_6D_6) δ 4.49 (d, J = 6.5 Hz, 1 H), 4.44 (d, J = 6.5 Hz, 1 H), 4.24 (m, 1 H), 4.10 (dd, J = 9.5, 6.6 Hz, 1 H), 3.66 (m, 1 H), 3.50 (s, 3 H), 3.46 (m, 1 H), 2.30 (m, 2 H), 1.91−1.70 (m, 5 H), 1.67 (s, 3 H), 1.50 (m, 1 H), 1.46 (s, 3H), 1.25 (m, 1 H), 1.05 (s, 3 H), 0.94 (m, 2 H), 0.90 (s, 3 H), 0.01 (s, 9 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 148.3, 118.7, 95.2, 90.2, 88.5, 84.9, 84.0, 70.8, 65.9, 49.0, 43.0, 41.9, 37.9, 34.1, 30.9, 30.4, 26.2, 25.3, 19.5, 18.2, 17.5, −1.4.

This material was generally used without further purification.

***tert*-Butyldimethyl[[(2*E*)-3-[(4a*S*,6*S*,6a*R*,9*S*,11a*R*,11b*R*)-4a,5,6,9,-10,11,11a,11b-octahydro-9-methoxy-4a,7,7,11a-tetramethyl-6-[[2-(trimethylsilyl)ethoxy]methoxy]-7*H*-6a,9-epoxy-1*H*-pyrano[3,2-*g*]-[2]benzoxepin-3-yl]-2-butenyl]oxy]silane (31a).** Lithium chloride (170 mg, 4.0 mmol) was weighed into a 15 mL round-bottomed flask and dried under vacuum at 120 °C. Tetrakis(triphenylphosphine)-palladium (60 mg, 0.052 mmol) was introduced, and a solution of **32** (450 mg, 0.75 mmol) and **35** (430 mg, 0.90 mmol) in THF (6 mL) containing HMPA (50 mg) was added. The yellow mixture was heated at gentle reflux for 72 h, cooled, diluted with ether, washed with 10% ammonium hydroxide solution, water, and brine, dried, and concentrated. Chromatography of the residue on silica gel (elution with 5% ethyl acetate in hexanes) gave 140 mg (30%) of **31a** and 70 mg (17%) of the butylated product.

For **31a**: colorless oil; $[\alpha]^{25}_D$ −79.1° (*c* 1.22, C_6H_6); ^1H NMR (300 MHz, C_6D_6) δ 6.40 (t, J = 6.3 Hz, 1 H), 4.79 (m, 1 H), 4.61 (d, J = 6.6 Hz, 1 H), 4.52 (d, J = 6.6 Hz, 1 H), 4.34 (d, J = 6.3 Hz, 2 H), 4.23 (m, 1 H), 3.77 (m, 1 H), 3.54 (s, 3 H), 3.52 (m, 1 H), 2.45 (d, J = 8.3 Hz, 2 H), 2.12−1.77 (series of m, 7 H), 1.72 (s, 3 H), 1.65 (s, 3 H), 1.56 (m, 2 H), 1.52 (s, 3 H), 1.15 (s, 3 H), 1.03 (s, 3 H), 1.00 (s, 9 H), 0.11 (s, 6 H), 0.04 (s, 9 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 151.2, 130.3, 125.6, 118.8, 98.7, 95.3, 90.8, 84.9, 75.8, 71.8, 65.8, 60.8, 48.9, 43.22, 43.20, 37.7, 34.2, 31.1, 30.7, 26.4, 26.2, 25.9, 20.6, 18.5, 18.4, 17.7, 12.7, −1.2, −4.8; MS *m/z* (M^+) calcd 638.4034, obsd 638.4081.

Anal. Calcd for $C_{34}H_{62}O_7Si_2$: C, 63.90; H, 9.78. Found: C, 63.95; H, 9.86.

For the butylated product: ^1H NMR (300 MHz, C_6D_6) δ 4.62 (d, J = 6.6 Hz, 1 H), 4.52 (d, J = 6.6 Hz, 1 H), 4.40 (m, 1 H), 4.28 (dd, J = 10.5, 5.5 Hz, 1 H), 3.73 (m, 1 H), 3.56 (s, 3 H), 3.52 (m, 1H), 2.42 (m, 2 H), 2.10 (d, J = 8.7 Hz, 1 H), 2.04−1.81 (series of m, 7 H), 1.75 (s, 3 H), 1.64 (m, 2 H), 1.56 (s, 3 H), 1.49−1.22 (m, 3 H), 1.20 (s, 3 H), 1.13 (s, 3 H), 0.93 (t, J = 8.0 Hz, 2 H), 0.87 (t, J = 7.3 Hz, 3 H), 0.01 (s, 9 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 152.8, 118.8, 95.9, 95.1, 90.8, 84.9, 75.5, 71.5, 65.9, 48.9, 43.4, 43.0, 37.6, 34.6, 34.2, 31.1, 30.7, 29.4, 26.42, 26.37, 22.7, 19.9, 18.3, 18.0, 14.1, −1.2; MS *m/z* (M^+) calcd 510.3377, obsd 510.3376.

(2*E*)-3-[(4a*S*,6*S*,6a*R*,9*S*,11a*R*,11b*R*)-4a,5,6,9,10,11,11a,11b-Octahydro-9-methoxy-4a,7,7,11a-tetramethyl-6-[[2-(trimethylsilyl)-ethoxy]methoxy]-7*H*-6a,9-epoxy-1*H*-pyrano[3,2-*g*][2]benzoxepin-3-yl]-2-buten-1-ol (31b). A solution of **31a** (300 mg, 0.47 mmol) in THF (6 mL) was treated with tetra-*n*-butylammonium fluoride (0.75 mL of 1.0 M in THF, 0.75 mmol), stirred for 40 min, diluted with ether, washed twice with brine, dried, and concentrated. Chromatography of the residue on silica gel (elution with 25% ethyl acetate in petroleum ether) gave 200 mg (81%) of **31b** as a colorless oil: $[\alpha]^{25}_D$ −102.2° (*c* 2.3, C_6H_6); IR (neat, cm^{-1}) 3480, 1660, 1635; ^1H NMR (300 MHz, C_6D_6) δ 6.35 (t, J = 6.5 Hz, 1 H), 4.78 (m, 1 H), 4.60 (d, J = 6.7 Hz, 1 H), 4.51 (d, J = 6.7 Hz, 1 H), 4.27 (m, 1 H), 4.09 (d, J = 6.6 Hz, 2 H), 3.76 (m, 1 H), 3.55 (s, 3 H), 3.52 (m, 1 H), 2.47 (d, J = 8.4 Hz, 2H), 2.12−1.77 (series of m, 5 H), 1.72 (s, 3 H), 1.59 (s, 3 H), 1.55 (m, 2 H), 1.52 (s, 3 H), 1.17 (s, 3 H), 1.04 (s, 3 H), 0.97 (t, J = 8.0 Hz, 2 H), 0.02 (s, 9 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 151.1, 131.1, 125.2, 118.8, 98.9, 95.2, 90.8, 84.9, 75.8, 71.6, 65.9, 59.6, 49.0, 43.2, 43.1, 37.7, 34.1, 31.1, 30.6, 26.4, 25.9, 20.6, 18.3, 17.7, 12.6, −1.3; MS *m/z* (M^+) calcd 524.3169, obsd 524.3134.

(2*E*)-3-[(4a*S*,6*S*,6a*R*,9*S*,11a*R*,11b*R*)-4a,5,6,9,10,11,11a,11b-Octahydro-9-methoxy-4a,7,7,11a-tetramethyl-6-[[2-(trimethylsilyl)-ethoxy]methoxy]-7*H*-6a,9-epoxy-1*H*-pyrano[3,2-*g*][2]benzoxepin-3-yl]-2-butenyl (2*E*)-4-Oxo-2-pentenoate (36). To a solution of **31b** (195 mg, 0.37 mmol), 4-oxo-2-pentenoic acid (84 mg, 0.73 mmol), and 4-(dimethylamino)pyridine (58 mg, 0.47 mmol) in CH_2Cl_2 (12 mL) at 0 °C was added dicyclohexylcarbodiimide (140 mg, 0.68 mmol) in CH_2Cl_2 (3 mL). The stirred reaction mixture was allowed to warm to room temperature during 20 min, diluted with CH_2Cl_2, washed with saturated $NaHCO_3$ solution and brine, dried, and evaporated. Chromatography of the residue on silica gel (elution with 15% ethyl acetate in petroleum ether) furnished 203 mg (88%) of **36** as a colorless oil: $[\alpha]^{25}_D$ −71.7° (*c* 1.6, C_6H_6); IR (neat, cm^{-1}) 1735, 1710, 1695; ^1H NMR (300 MHz, C_6D_6) δ 6.85 (d, J = 16.1 Hz, 1 H), 6.37 (m, 1 H), 6.32 (d, J = 16.1 Hz, 1 H), 4.83 (br s, 1 H), 4.75 (d, J = 7.1 Hz, 2 H), 4.58 (d, J = 6.6 Hz, 1 H), 4.48 (d, J = 6.6 Hz, 1 H), 4.22 (m, 1 H), 3.76 (m, 1 H), 3.54 (s, 3 H), 3.51 (m, 1 H), 2.46 (d, J = 7.3 Hz, 2 H), 2.11−1.75 (series of m, 6 H), 1.69 (s, 3 H), 1.65 (s, 3 H), 1.58 (s, 3 H), 1.49 (s, 3 H), 1.34 (m, 1 H), 1.14 (s, 3 H), 1.00 (s, 3 H), 0.98 (t, J = 8.2 Hz, 2 H), 0.04 (s, 9 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 195.9, 165.2, 150.7, 140.0, 135.0, 130.8, 118.8, 118.3, 100.5, 95.3, 90.7, 84.8, 76.1, 71.7, 65.9, 62.0, 48.9, 43.2, 37.6, 34.1, 31.1, 30.6, 27.3, 26.4, 25.9, 20.6, 18.3, 17.7, 12.7, −1.2; MS *m/z* (M^+) calcd 620.3381, obsd 620.3383.

(3*S*,5a*R*,6*S*,7a*S*,14a*R*,14b*R*)-13-Acetyl-1,2,3,6,7,7a,9a,10,12a,13,-13,14,14a,14b-tetradecahydro-3-methoxy-5,5,7a,9,14b-pentamethyl-6-[[2-(trimethylsilyl)-ethoxy]methoxy]-12*H*-3,5a-epoxy-5*H*-furo[3,4-*i*]oxepino[4,3-*a*]xanthen-12-one (37). A solution of **36** (203 mg, 0.33 mmol) in toluene (5 mL) was heated at 100 °C for 36 h, cooled, and concentrated. Chromatography of the residue on silica gel (elution with 30% ethyl acetate in hexanes) afforded 30 mg of the less polar isomer of **37** and 76 mg of its more polar isomer (combined yield 52%).

For the less polar isomer: colorless oil; ^1H NMR (300 MHz, C_6D_6) δ 4.59 (d, J = 6.7 Hz, 1 H), 4.51 (d, J = 6.7 Hz, 1 H), 4.18 (dd, J = 11.5, 4.6 Hz, 1 H), 3.82 (m, 3 H), 3.52 (s, 3 H), 3.49 (m, 1 H), 3.32 (dd, J = 10.2, 8.5 Hz, 1 H), 2.73−2.05 (series of m, 6 H), 2.03 (s, 3 H), 2.00−1.73 (series of m, 3 H), 1.70 (s, 3 H), 1.60 (m, 1 H), 1.49 (s, 3 H), 1.36 (m, 2 H), 1.30 (d, J = 2.0 Hz, 3 H), 1.12 (s, 3 H), 0.98 (t, J = 8.1 Hz, 2 H), 0.93 (s, 3 H), 0.02 (s, 9 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 208.0, 176.3, 145.7, 118.7, 109.7, 95.2, 90.3, 84.7, 77.6, 72.2, 71.5, 65.7, 53.0, 48.9, 43.4, 43.1, 41.5, 39.6, 38.9, 34.2, 32.9, 32.4, 31.1, 30.0, 26.9, 26.4, 24.5, 20.6, 18.4, 12.9, −1.3.

For the more polar isomer: colorless solid, mp 134−136 °C; $[\alpha]^{25}_D$ +23.8° (*c* 0.73, C_6H_6); IR ($CHCl_3$, cm^{-1}) 1790, 1720; ^1H NMR (300 MHz, C_6D_6) δ 4.60 (d, J = 6.7 Hz, 1 H), 4.53 (d, J = 6.7 Hz, 1 H), 4.21 (dd, J = 11.5, 4.7 Hz, 1 H), 3.74 (m, 3 H), 3.51 (s, 3 H), 3.45 (m, 1 H), 3.17 (dd, J = 11.2, 8.0 Hz, 1 H), 2.79 (series of m, 8 H), 1.96 (s, 3 H), 1.93−1.76 (m, 2 H), 1.73 (s, 3 H), 1.55 (s, 3 H), 1.39 (m, 2 H), 1.30 (s, 3 H), 1.13 (s, 3 H), 1.00 (s, 3 H), 0.98 (t, J = 8.1 Hz, 2 H), 0.01 (s, 9 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 205.0, 174.2, 147.2, 118.7, 114.8, 95.0, 90.4, 84.7, 78.9, 71.3, 69.4, 65.7, 49.0, 48.6, 43.5, 43.4, 42.7, 39.1, 34.2, 31.7, 31.6, 31.1, 30.1, 26.6, 26.5, 23.7, 21.6, 18.4, 11.3, −1.3; MS *m/z* (M^+) calcd 620.3381, obsd 620.3377.

(4a*S*,6*S*,6a*R*,11a*R*,11b*R*)-4a,5,6,9,10,11,11a,11b-Octahydro-9-methoxy-4a,7,7,11a-tetramethyl-6-[[2-(trimethylsilyl)ethoxy]methoxy]-7*H*-6a,9-epoxy-1*H*-pyrano[3,2-*g*][2]benzoxepin (8, R = SEM). To a cold (-78 °C), magnetically stirred solution of **23** (160 mg, 0.34 mmol) in CH_2Cl_2 (8 mL) was added 0.5 mL of a 1.0 M solution of diisobutylaluminum hydride in hexane. The reaction mixture was stirred at −78 °C for 1 h and at −25 °C for 2 h, treated with methanol (0.5 mL), and warmed to room temperature. A 20% aqueous solution of Rochelle's salt was added, and the solution was stirred for 6 h and extracted with ether (3 × 10 mL). The combined organic extracts were dried, concentrated, and used directly.

To a chilled (0 °C), magnetically stirred solution of the above lactol in 5 mL of dry pyridine was added methanesulfonyl chloride (90 μL, 1.16 mmol). The mixture was stirred at 0 °C for 30 min, heated at 80 °C for 2 h, cooled, and diluted with ether (40 mL). The organic phase was washed with brine (20 mL), dried, and concentrated. The concentrate was purified by column chromatography on silica gel (elution with 10% ethyl acetate in petroleum ether containing 5% of

triethylamine) to give 102 mg (66% overall) of **8** (R = SEM) as a viscous colorless oil: ^{1}H NMR (300 MHz, C_6D_6) δ 6.19 (d, J = 6.2 Hz, 1 H), 4.62 (d, J = 6.6 Hz, 1 H), 4.54 (d, J = 6.6 Hz, 1 H), 4.56–4.49 (m, 1 H), 4.25 (dd, J = 10.1, 6.0 Hz, 1 H) 3.78–3.70 (m, 1 H), 3.54 (s, 3 H), 2.48–2.37 (m, 2 H), 2.11 (d, J = 8.7 Hz, 1 H), 1.96–1.77 (series of m, 3 H), 1.74 (s, 3 H), 1.71–1.55 (m, 1 H), 1.54 (s, 3 H), 1.52–1.30 (m, 1 H), 1.22 (s, 3 H), 1.11 (s, 3 H), 0.95 (t, J = 8.0 Hz, 4 H), −0.01 (s, 9 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 142.9, 118.8, 101.7, 95.2, 90.8, 84.9, 75.6, 71.6, 65.8, 49.0, 43.5, 43.1, 38.2, 34.2, 31.1, 30.5, 26.4, 19.1, 18.3, 18.1, −1.4; MS m/z ($M^+ - H_2O$) calcd 454.2750, obsd 454.2744 .

Dihydro-4-[1-(trimethylsilyl)vinyl]-2(3*H*)-furanone (45). The Grignard reagent prepared from 1-bromo-1-(trimethylsilyl)ethylene (10.7 g, 60.0 mmol) and magnesium turnings (1.45 g, 60.0 mmol) in THF (150 mL) was cooled to −78 °C and treated with the copper(I) bromide dimethyl sulfide complex (4.2 g, 20.4 mmol). The resulting suspension was warmed to −40 °C for 10 min, returned to −78 °C, and treated sequentially with chlorotrimethylsilane (8.5 mL, 67 mmol) and 5(2*H*)-furanone (4.1 g, 48.8 mmol). After being stirred for 45 min, the mixture was quenched with saturated NH_4Cl solution and filtered through a Celite pad. The filtrate was extracted with ether, and the combined organic phases were washed with brine, dried, and evaporated. The yellow liquid was dissolved in acetonitrile (70 mL) and water (5 mL), hydrofluoric acid (2 mL, 48%) was introduced, and the mixture was stirred for 9 h at room temperature prior to extraction with ether. The combined ethereal layers were washed with saturated $NaHCO_3$ solution and brine, dried, and evaporated. Purification of the product by chromatography on silica gel (elution with 15% ethyl acetate in hexanes) gave 3.9 g (44%) of **45** as a colorless oil: IR (neat, cm^{-1}) 1785; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.68 (t, J = 1.4 Hz, 1 H), 5.51 (br s, 1 H), 4.43 (dd, J = 8.8, 7.4 Hz, 1 H), 4.05 (dd, J = 8.8, 7.8 Hz, 1 H), 3.31 (m,1 H), 2.63 (dd, J = 17.2, 8.2 Hz, 1 H), 2.43 (dd, J = 17.2, 8.9 Hz, 1 H), 0.12 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 176.5, 149.8, 124.8, 72.9, 40.2, 34.4, −1.4; MS m/z (M^+) calcd 184.0919, obsd 184.0904.

Anal. Calcd for $C_9H_{16}O_2Si$: C, 58.65; H, 8.75. Found: C, 58.67; H, 8.76.

Dihydro-4-[1-(trimethylstannyl)vinyl]-2(3*H*)-furanone (42). A cold (−30 °C), magnetically stirred solution of **45** (4.0 g, 21.7 mmol) in CH_2Cl_2 (70 mL) was treated with a solution of bromine (3.8 g, 23.7 mmol) in CH_2Cl_2 (50 mL) during 10 min. The reaction mixture was warmed to room temperature during 20 min, washed with dilute $NaHSO_3$ solution and brine, dried, and concentrated to give a labile dibromide which was immediately dissolved in THF (40 mL) and added to a solution of dry tetra-*n*-butylammonium fluoride (5.8 g, 22.2 mmol) in THF (100 mL) at 0 °C. After being stirred for 30 min, the mixture was diluted with ether, washed twice with brine, dried, and concentrated. Chromatography of the residue (silica gel, elution with 30% ethyl acetate in hexanes) produced 3.9 g (94%) of vinyl bromide as a colorless oil: IR (neat, cm^{-1}) 1789, 1630; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.79 (d, J = 2.4 Hz, 1 H), 5.57 (d, J = 2.4 Hz, 1 H), 4.43 (dd, J = 9.2, 8.0 Hz, 1 H), 4.22 (dd, J = 9.2, 7.4 Hz, 1 H), 3.51 (m, 1 H), 2.69 (s, 1 H), 2.66 (d, J = 1.0 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 175.1, 131.5, 119.2, 71.0, 45.0, 33.4; MS m/z (M^+) calcd 189.9629, obsd 189.9627.

A solution of the vinyl bromide (1.25 g, 6.5 mmol), hexamethylditin (3.2 g, 9.7 mmol), and tetrakis(triphenylphosphine)palladium(0) (500 mg, 0.43 mmol) in THF (25 mL) was refluxed for 8 h under N_2, cooled, diluted with ether, washed with saturated NH_4Cl solution and brine, dried, and evaporated. Chromtography of the residue (silica gel, elution with 15% ethyl acetate in hexanes) afforded **42** (1.05 g, 58%) as a colorless oil: IR (neat, cm^{-1}) 1780; ^{1}H NMR (300 MHz, C_6D_6) δ 5.37 (br d, J = 1.4 Hz, 1 H), 5.02 (m, 1 H), 3.79 (m, 1 H), 3.54 (m, 1 H), 2.66 (m, 1 H), 2.12 (ddd, J = 17.0, 8.3, 1.8 Hz, 1 H), 1.96 (ddd, J = 17.1, 8.6, 1.3 Hz, 1 H), −0.01 (s, 9 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 175.1, 152.7, 125.9, 71.9, 45.5, 34.4, −9.1; MS m/z (M^+) calcd 274.0166, obsd 274.0177.

Anal. Calcd for $C_9H_{16}O_2Sn$: C, 39.32; H, 5.87. Found: C, 39.51; H, 5.94.

Methyl (4a*S*,6*S*,6a*R*,9*S*,11a*R*,11b*R*)-4a,5,6,9,10,11,11a,11b-Octahydro-3-hydroxy-9-methoxy-4a,7,7,11a-tetramethyl-3-oxo-6-[[2-(trimethylsilyl)ethoxy]methoxy]-7*H*-6a,9-epoxy-1*H*-pyrano[3,2-*g*]-[2]benzoxepine-2-carboxylate (46). To an LDA solution prepared from diisopropylamine (0.3 mL, 2.14 mmol) and *n*-butyllithium (0.85 mL of 2.5 M, 2.12 mmol) in THF (8 mL) was added a solution of **23** (450 mg, 0.96 mmol) in THF (3 mL) at −78 °C. After 90 min of stirring, HMPA (0.35 mL, 2.1 mmol) and methyl cyanoformate (0.16 mL, 2.0 mmol) were introduced sequentially. The mixture was stirred for 1 h before being quenched with saturated NH_4Cl solution and extracted several times with ether. Chromatography of the residue on silica gel (elution with 30% ethyl acetate in hexanes) furnished 60 mg of unreacted **23** and 378 mg (86% based on unconsumed starting material) of **46** as a foamy white solid: mp 51–53 °C; IR ($CHCl_3$, cm^{-1}) 1760, 1740; ^{1}H NMR (300 MHz, C_6D_6) δ 4.49 (d, J = 6.5 Hz, 1 H), 4.39 (d, J = 6.6 Hz, 1 H), 3.66 (m, 2 H), 3.51 (s, 3 H), 3.48 (s, 3 H), 3.44 (m, 1 H), 3.31 (m, 1 H), 2.30–2.00 (series of m, 3 H), 1.84–1.51 (series of m, 4 H), 1.46 (s, 3 H), 1.36 (m, 3 H), 1.27 (s, 3 H), 1.13 (s, 3 H), 0.92 (t, J = 8.2 Hz, 2 H), 0.83 (s, 3 H), −0.01 (s, 9 H); MS m/z (M^+) calcd 528.2755, obsd 528.2771.

Anal. Calcd for $C_{26}H_{44}O_9Si$: C, 59.07; H, 8.39. Found: C, 59.12; H, 8.45.

Methyl (4a*S*,6*S*,6a*R*,9*S*,11a*R*,11b*R*)-4a,5,6,9,10,11,11a,11b-Octahydro-3-hydroxy-9-methoxy-4a,7,7,11a-tetramethyl-6[[2-(trimethylsilyl)ethoxy]methoxy]-7*H*-6a,9-epoxy-1*H*-pyrano[3,2-*g*][2]-benzoxepin-2-carboxylate Trifluoromethanesulfonate (41). A solution of **46** (380 mg, 0.72 mmol) in THF (7 mL) at −78 °C was admixed with potassium hexamethyl disilazide (1.9 mL of 0.5 M in toluene, 0.95 mmol), stirred for 20 min, and treated with a solution of HMPA (0.5 mL, 2.8 mmol) and *N*-phenyltriflimide (360 mg, 1.0 mmol) in THF (2 mL). The mixture was stirred at room temperature for 20 h, quenched with saturated NH_4Cl solution, and extracted with ether. The combined organic phases were washed with brine, dried, and concentrated to leave a residue that was purified chromatographically on silica gel. Elution with 15% → 30% ethyl acetate in hexanes led to the recovery of unreacted **46** (100 mg) and the isolation of **41** (320 mg, 91% based on recovered starting material): colorless oil; $[\alpha]^{25}_D$ −62.7° (c 1.25, C_6H_6); ^{1}H (300 MHz, C_6D_6) δ 4.58 (d, J = 6.7 Hz, 1 H), 4.52 (d, J = 6.7 Hz, 1 H), 4.14 (dd, J = 8.9, 7.2 Hz, 1 H), 3.78 (m, 1 H), 3.60 (s, 3 H), 3.59 (s, 3 H), 3.55 (m, 1 H), 2.56 (d, J = 18.6 Hz, 1 H), 2.36 (m, 3 H), 2.14 (d, J = 8.4 Hz, 1 H), 1.84 (m, 3 H), 1.73 (s, 3 H), 1.49 (s, 3 H), 1.44 (m, 1 H), 1.05 (s, 3 H), 1.03 (m, 2 H), 0.93 (s, 3 H), 0.01 (s, 9 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 164.5, 152.1, 118.8, 95.7, 95.3, 89.9, 86.1, 84.8, 70.8, 65.8, 51.5, 48.9, 43.1, 41.6, 37.9, 33.9, 32.3, 30.8, 30.3, 26.0, 25.4, 21.8, 18.2, 17.5, −1.5; MS m/z ($M^+ - CH_3$) calcd 645.2013, obsd 645.2016.

(4a*S*,6*S*,6a*R*,9*S*,11a*R*,11b*R*)-4a,5,6,9,10,11,11a,11b-Octahydro-2-(hydroxymethyl)-9-methoxy-4a,7,7,11a-tetramethyl-6-[[2-(trimethylsilyl)ethoxy]-methoxy]-7*H*-6a,9-epoxy-1*H*-pyrano[3,2-*g*][2]-benzoxepin-3-yl Trifluoromethanesul-fonate (48). A solution of **41** (4 mg, 0.006 mmol) in CH_2Cl_2 (1 mL) at −78 °C was treated with Dibal-H (0.02 mL of 1.0 M in hexanes, 0.02 mmol), stirred for 20 min, allowed to warm to room temperature, diluted with ether, filtered through a small pad of silica gel, and concentrated. The crude product was purified by silica gel chromatography (elution with 40% ethyl acetate in hexanes) to give **48** as a colorless oil: ^{1}H NMR (300 MHz, C_6D_6) δ 4.51 (d, J = 6.6 Hz, 1 H), 4.45 (d, J = 6.6 Hz, 1 H), 4.12 (dd, J = 10.1, 6.0 Hz, 1 H), 3.94 (br d, J = 12.2 Hz, 1 H), 3.74 (br d, J = 12.3 Hz, 1 H), 3.69 (m, 1 H), 3.51 (s, 3 H), 3.45 (m, 1 H), 2.31 (m, 2 H), 2.01 (m, 1 H), 1.90 (d, J = 4.0 Hz, 2 H), 1.81 (m, 3 H), 1.67 (s, 3 H), 1.46 (s, 3 H), 1.32 (m, 2 H), 1.04 (s, 3 H), 0.93 (s, 3H), 0.91 (m, 2 H), 0.00 (s, 9 H).

Methyl (4a*S*,6*S*,6a*R*,9*S*,11a*R*,11b*R*)-4a,5,6,9,10,11,11a,11b-Octahydro-9-methoxy-4a,7,7,11a-tetramethyl-3-(tetrahydro-α-methylene-5-oxo-3-furyl)-6-[[2-(trimethylsilyl)ethoxy]methoxy]-7*H*-6a,9-epoxy-1*H*-pyrano[3,2-*g*][2]benzoxepine-2-carboxylate (49). Lithium chloride (90 mg, 2.1 mmol) was weighed into a flask and dried under vacuum with heating. After cooling, $Pd_2(dba)_3$ (40 mg, 0.043 mmol) and tris(2-furyl)phosphine (40 mg, 0.17 mmol) were introduced, and the solid mixture was treated with a solution of **41** (470 mg, 0.71 mmol) and **42** (260 mg, 0.94 mmol) in THF (8 mL). The reaction mixture was heated at reflux for 21 h, cooled, diluted with ether, washed with saturated NH_4Cl solution and brine, dried, and concentrated. Chromatography of the residue (silica gel, elution with 30% ethyl acetate in hexanes) gave **49** as a mixture of two epimers (315 mg, 71%): colorless, viscous oil; IR ($CHCl_3$, cm^{-1}) 1785, 1705, 1620; ^{1}H NMR (300 MHz, C_6D_6) δ 4.88 (2, 1 H), 4.70 (s, 1 H), 4.53 (dd, J = 11.3,

6.8 Hz, 1 H), 4.42 (dd, J = 6.7, 3.5 Hz, 1 H), 4.16−3.88 (m, 3 H), 3.77−3.65 (m, 1 H), 3.50 (s, 3 H), 3.49−3.40 (m, 1 H), 3.38 (s, 1.5 H), 3.37 (s, 1.5 H), 2.95−2.84 (m, 1 H), 2.55−2.24 (series of m, 5 H), 2.08 (m, 2 H), 1.88−1.74 (m, 3 H), 1.65 (s, 3 H), 1.53 (m, 1 H), 1.44 (s, 3 H), 0.93 (s, 1.5 H), 0.90 (m, 2 H), 0.89 (s, 1.5 H), 0.88 (s, 1.5 H), 0.87 (s, 1.5 H), 0.0 (s, 4.5 H), −0.01 (s, 4.5 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 175.4, 175.3, 167.9, 167.8, 160.9, 160.8, 144.5, 144.1, 118.8, 116.7, 116.5, 105.8, 105.7, 95.1, 90.23, 90.20, 84.8, 78.6, 78.4, 71.5, 71.1, 71.0, 65.90, 65.86, 50.8, 49.0, 43.30, 43.28, 42.2, 42.1, 40.0, 39.9, 37.3, 37.2, 34.2, 34.0, 33.1, 30.9, 30.5, 26.2, 25.8, 25.4, 21.4, 18.3, 17.6, −1.3; MS m/z (M^+) calcd 622.3173, obsd 622.3169.

Anal. Calcd for $C_{32}H_{50}O_{10}Si$: C, 61.71; H, 8.09. Found: C, 61.29; H, 8.09.

(3*S*,5a*R*,6*S*,7a*S*,9a*R*,12a*S*,14a*R*,14b*R*)-2,3,7,7a,9,9a,12a,14,14a,-14b-Decahydro-3-methoxy-5,5,7a,14b-tetramethyl-9-methylene-6-[[2-(trimethylsilyl)ethoxy]methoxy]-6*H*-3,5a-epoxy-5*H*-furo[3,4-*i*]-oxepino[4,3-*a*]xanthene-12,13-(1*H*,10*H*)-dione (40a) and (3*S*,5a*R*,6*S*,-7a*S*,9a*S*,12a*R*,14a*R*,14b*R*)-2,3,7,7a,9,9a,12a,14,14a,14b-Decahydro-3-methoxy-5,5,7a,14b-tetramethyl-9-methylene-6-[[2-(trimethylsilyl)-ethoxy]methoxy]-6*H*-3,5a-epoxy-5*H*-furo[3,4-*i*]oxepino[4,3*a*]-xanthene-12,13(1*H*,10*H*)-dione (40b). A cold (−78 °C), magnetically stirred solution of **49** (525 mg, 0.84 mmol) in THF (25 mL) was treated with potassium hexamethyl disilazide (4.2 mL of 0.5 M in toluene, 2.1 mmol). After 30 min, the reaction mixture was quenched with saturated NH_4Cl solution and extracted with ether. The combined organic phases were washed with brine, dried, and evaporated. Silica gel chromatography (elution with 50% ethyl acetate in hexanes) resulted in the separation of the less polar (**40a**, 210 mg) from the more polar isomer (**40b**, 233 mg) for an 89% combined yield.

For **40a**: colorless solid, mp 89−91 °C; $[\alpha]^{25}_D$ −201.1° (c 1.2, $CHCl_3$); ^{1}H (300 MHz, C_6D_6) δ 5.70 (s, 1 H), 4.67 (s, 1 H), 4.53 (d, J = 6.9 Hz, 1 H), 4.42 (d, J = 6.9 Hz, 1 H), 3.99 (t, J = 8.0 Hz, 1 H), 3.74 (m, 1 H), 3.61−3.43 (m, 3 H), 3.52 (s, 3 H), 2.91 (d, J = 8.4 Hz, 1 H), 2.57 (m, 1 H), 2.43−2.11 (series of m, 5 H), 1.76 (m, 3 H), 1.63 (s, 3 H), 1.39 (s, 3 H), 1.35 (m, 1 H), 0.93 (m, 2 H), 0.85 (s, 3 H), 0.50 (s, 3 H), 0.01 (s, 9 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 184.9, 170.2, 159.3, 133.1, 118.9, 117.4, 114.6, 95.4, 90.1, 84.7, 79.3, 71.5, 70.7, 65.8, 49.7, 48.9, 43.2, 42.4, 39.6, 36.8, 34.0, 30.9, 30.1, 26.2, 18.4, 18.3, 17.2, −1.3.

Anal. Calcd for $C_{31}H_{46}O_9Si$: C, 63.02; H, 7.85. Found: C, 62.86; H, 7.88.

For **40b**: colorless oil; $[\alpha]^{25}_D$ −57.1° (c 0.55, $CHCl_3$); IR (neat, cm^{-1}) 1795, 1750, 1665, 1635, 1600; ^{1}H (300 MHz, C_6D_6) δ 5.80 (s, 1 H), 4.77 (s, 1 H), 4.54 (d, J = 6.8 Hz, 1 H), 4.44 (d, J = 6.8 Hz, 1 H), 4.07 (dd, J = 8.8, 7.2 Hz, 1 H), 3.72 (m, 1 H), 3.59 (d, J = 6.8 Hz, 2 H), 3.49 (s, 3 H), 3.48 (m, 1 H), 3.10 (d, J = 8.5 Hz, 1 H), 2.72 (m, 1 H), 2.56 (d, J = 18.4 Hz, 1 H), 2.37−1.71 (series of m, 7 H), 1.64 (s, 3 H), 1.48 (m, 1 H), 1.42 (s, 3 H), 0.92 (t, J = 7.1 Hz, 2 H), 0.83 (s, 3 H), 0.75 (s, 3 H), 0.00 (s, 9 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 184.7, 170.1, 159.5, 133.9, 118.6, 116.2, 114.5, 95.0, 89.9, 84.4, 79.3, 71.1, 70.7, 65.6, 49.5, 48.7, 42.9, 42.1, 38.7, 36.5, 33.7, 30.6, 30.0, 26.1, 26.0, 18.1, 18.0, 17.1, −1.6; MS m/z (M^+) calcd 590.2911, obsd 590.2891.

(3*S*,5a*R*,6*S*,7a*S*,14a*R*,14b*R*)-1,2,3,6,7,7a,10,14,14a,14b-Decahydro-3,13-dimethoxy-5,5,7a,9,14b-pentamethyl-6-[[2-(trimethylsilyl)ethoxy]-methoxy]-12*H*-3,5a-epoxy-5*H*-furo[3,4-*i*]oxepino[4,9-*a*]xanthen-12-one (50). A solution of **40** (118 mg, 0.2 mmol) in HMPA (3 mL) was treated with potassium hexamethyl disilazide (0.5 mL of 0.5 M in toluene, 0.25 mmol). After 10 min, dimethyl sulfate (54 mg, 0.41 mmol) was introduced, and the mixture was stirred for 20 min, diluted with ether, washed with saturated NH_4Cl solution and brine, dried, and concentrated. The resulting yellow oil was dissolved in benzene (3 mL), refluxed for 15 min, and evaporated. The residue was purified by MPLC (silica gel, elution with 25% ethyl acetate in hexanes) to return 10 mg of unreacted **40** and afford 51 mg (48% based on recovered starting material) of **50** as an off-white foamy solid: mp 77−79 °C; $[\alpha]^{25}_D$ −97.3° (c 0.92, C_6H_6); IR ($CHCl_3$, cm^{-1}) 1755, 1615; ^{1}H (300 MHz, C_6D_6) δ 5.12 (s, 2 H), 4.74 (d, J = 6.8 Hz, 1 H), 4.65 (d, J = 6.8 Hz, 1 H), 4.19 (dd, J = 10.5, 5.5 Hz, 1 H), 4.12 (s, 3 H), 3.78 (m, 1 H), 3.58 (m, 1 H), 3.47 (s, 3 H), 2.83 (br d, J = 6.5 Hz, 2 H), 2.37 (m, 3 H), 2.04 (s, 3 H), 1.99−1.70 (m, 4 H), 1.54 (s, 6 H), 1.26 (s, 3 H), 0.98 (t, J = 8.3 Hz, 2H), 0.79 (s, 3 H), 0.05 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 169.3, 158.0, 155.3 145.5, 118.2, 115.6, 114.3, 107.5, 94.9, 90.3, 84.9, 70.7, 68.2, 65.9, 62.0, 49.1, 43.2, 42.3, 36.2, 33.6, 30.3, 30.1, 27.0, 25.9, 18.4, 18.2, 18.1, 10.6, −1.4; MS m/z (M^+) calcd 604.3067, obsd 604.3068.

(3*S*,5a*S*,7a*S*,14a*R*,14b*R*)-1,2,3,7,7a,14,14a,14b-Octahydro-3,13-dimethoxy-5,5,7a,9,14b-pentamethyl-6*H*-3,5a-epoxy-5*H*-furo[3,4-*i*]-oxepino[4,3-*a*]xanthene-6,12(10*H*)-dione (51). A solution of **50** (27 mg, 0.044 mmol) in HMPA (1.0 mL) was treated with tetra-*n*-butylammonium fluoride (0.06 mL of 1.0 M in THF, 0.06 mmol), heated at 45 °C for 4.5 h, cooled, diluted with ether, washed with saturated NH_4Cl solution and brine, dried, and evaporated. Chromatography of the residue on silica gel (elution with 50% ethyl acetate in hexanes) gave the alcohol (16 mg, 76%) as a white solid: mp 241−243 °C; $[\alpha]^{25}_D$ −76.5° (c 1.25, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) 3600, 1750, 1615; ^{1}H (300 MHz, $CDCl_3$) δ 5.12 (s, 2 H), 4.27 (m, 1 H), 4.11 (s, 3 H), 3.47 (s, 3 H), 2.84 (m, 2 H), 2.39 (m, 2 H), 2.13 (dd, J = 13.6, 11.4 Hz, 1 H), 2.03 (s, 3H), 1.94−1.76 (series of m, 5 H), 1.61 (s, 3 H), 1.60 (s, 3 H), 1.25 (s, 3 H), 0.79 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 169.4, 158.0, 155.3, 145.6, 118.4, 115.8, 114.4, 107.6, 89.9, 85.5, 77.2, 68.2, 64.7, 62.0, 49.1, 45.9, 42.7, 36.2, 33.8, 30.4, 30.1, 26.9, 26.2, 18.5, 17.7, 10.6; MS m/z (M^+) calcd 474.2254, obsd 474.2257.

To a cold (0 °C) solution of the above alcohol (13 mg, 0.027 mmol) in CH_2Cl_2 (2 mL) was added tetrapropylammonium perruthenate (11 mg, 0.035 mmol). After 5 min, the reaction mixture turned black, at which point a drop of methanol was added and ether (5 mL) was introduced. The ethereal solution was washed with saturated $NaHCO_3$ solution and brine, dried, and evaporated. Silica gel chromatography of the residue (elution with 30% ethyl acetate in hexanes) furnished 12 mg (94%) of **51** as a white solid: mp 221−222 °C; $[\alpha]^{25}_D$ −69.3° (c 0.9, $CHCl_3$); ^{1}H (300 MHz, C_6D_6) δ 5.11 (s, 2 H), 4.12 (s, 3 H), 3.46 (s, 3 H), 3.39 (d, J = 12.2 Hz, 1 H), 2.87 (m, 3 H), 2.68 (d, J = 12.2 Hz, 1 H), 2.07−1.99 (m, 2 H), 2.02 (s, 3 H), 1.97−1.77 (m, 2 H), 1.55 (s, 3 H), 1.38 (s, 3 H), 1.37 (s, 3 H), 0.67 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 204.2, 169.2, 157.3, 155.2, 145.7, 118.5, 114.7, 114.6, 107.8, 93.4, 82.6, 82.2, 68.2, 62.1, 51.3, 49.0, 47.1, 36.6, 30.3, 30.2, 30.0, 27.1, 24.5, 18.3, 16.2, 10.6. This material was identical to the product of Jones oxidation of austalide B (lit.[6] $[\alpha]^{24}_D$ −79.2° (c 1.0, $CHCl_3$)).

Austalide B (1). A solution of **51** (11 mg, 0.023 mmol) in methanol (1.5 mL) was cooled to 0 °C and treated with sodium borohydride (excess) in small portions until all of the starting material was consumed. Following the addition of saturated NH_4Cl solution, the product was extracted into ethyl acetate, and the combined organic phases were washed with brine, dried, and concentrated. The residue was chromatographed on silica gel (elution with 40% ethyl acetate in hexanes) to give 10 mg (91%) of **1** as a white solid: mp 242−243 °C; $[\alpha]^{23}_D$ −46.2° (c 0.95, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.13 (s, 2 H), 4.14 (s, 3 H), 4.11 (m, 1 H), 3.42 (s, 3 H), 2.91 (m, 2 H), 2.53 (d, J = 8.4 Hz, 1 H), 2.39 (m, 1 H), 2.34 (d, J = 3.3 Hz, 2 H), 2.04 (s, 3 H), 2.01−1.69 (m, 4 H), 1.65 (s, 3 H), 1.48 (s, 3 H), 1.27 (s, 3 H), 0.98 (s, 3 H). This material proved identical in all respects to authentic **1** derived from natural sources (lit.[6] mp 243−245 °C; $[\alpha]^{24}_D$ −46.2° (c 1.0, $CHCl_3$)).

Acknowledgment. This investigation was made possible by the financial support provided by the National Institutes of Health (Grant GM-30827) to whom we are most grateful. We particularly thank Prof. Robert Vleggaar of the University of Pretoria for generously providing a comparison sample of austalide B, James Lanter for the molecular mechanics calculations, and Noel D. Jones, John K. Swartzendruber, and Jack B. Deeter (Eli Lilly and Co.) for the X-ray crystallographic analysis of **18**.

Supplementary Material Available: Crystallographic experimental details, ORTEP diagrams, and tables of atom coordinates and temperature factors, bond lengths, bond angles, anisotropic temperature factors, and nonbonded distances for **18** (21 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.