Total Synthesis of Furanocembranolides. 3. A Concise Convergent Route to Acerosolide[1,2]

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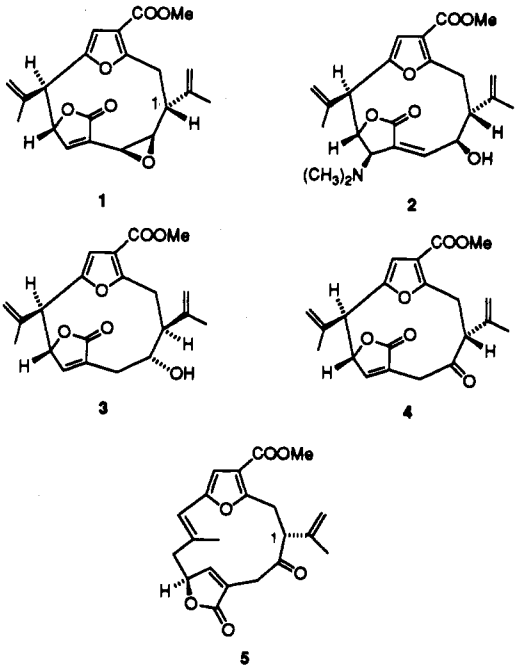
The first synthesis of a 14-membered furanocembranolide has been achieved. The target molecule, acerosolide, contains two stereogenic cetners whose relative and absolute configuration have not previously been assigned. MM2 calculations performed during the course of the present work suggest their configuration to be 1(*S**),10(*R**). The synthesis began by $SnCl_2$-promoted condensation of allylstannane **6** to aldehyde **7** so as to achieve regioreversed condensation and formation of the extended allylic alcohol **9**. Acid-catalyzed lactonization and 2-fold oxidation via the bis-selenide gave butenolide **11** and subsequently the derived bromide **12b**. Palladium(0)-catalyzed condensation of **12b** with vinylstannane **13** provided *seco*-cembrane **14**. Following the elaboration of **14** into bromo aldehyde **16**, macrocyclization was effected with chromous chloride. The single homoallylic alcohol produced by this means underwent oxidation to give acerosolide, as deduced by proper spectral comparison with the natural product.

The potent biological activity and complex chemistry of marine furanocembranolide diterpenes has attracted considerable attention from the world's community of synthetic organic chemists.[3] Structurally, the vast majority of these secondary metabolites feature either a 12- or 14-membered carbocyclic framework into which a substituted furan ring and a butenolide subunit (or an epoxidized equivalent) have become embedded. Certain of them such as pseudopterolide (**1**) are doubly activated Michael acceptors of unusual type.[4] When exposed to dimethylamine at room temperature, **1** is rapidly transformed into tobagolide **2**[5] in a process that can be easily reversed.[6]

Recently, the dihydropseudopterolide **3** and gorgiacerone (**4**)[7] were reported to be the first furanocembranolides to yield to total synthesis.[1] This achievement required the development of new methodology and a carefully designed cyclization strategy based upon intramolecular Cr(II)-promoted reductive coupling. The fact that no viable route had yet been developed to the larger-ring cembranoids[8] prompted us to direct attention to a stereocontrolled synthesis of acerosolide (**5**).[9] The relative stereochemistry of **5** at C-1 cannot be unequivocally ascertained by advanced NMR techniques and was left unassigned by the original discoverers. This configurational facet of the problem will be accorded specific attention later.



As in our earlier investigations, a trifunctionalized furan derivative was to serve as the pivotal building block to which the 7(*E*)-trisubstituted double bond and an appropriate butenolide subunit were to be serially appended.[2]

The previously described allylstannane **6** is known to respond well to BF_3-promoted condensation with aldehydes.[1] Particularly notable is the preponderance of erythro selectivity that operates without regard for the *E* or *Z* geometry of the double bond during the ensuing allylic rearrangement.[10] *Branched* homoallylic alcohols result. In the present context, our requirements are that a *linear* homoallylic alcohol be produced instead. Several examples of this desired regioreversal have been observed previously.[10a,11] Two fundamental factors conspire to over-

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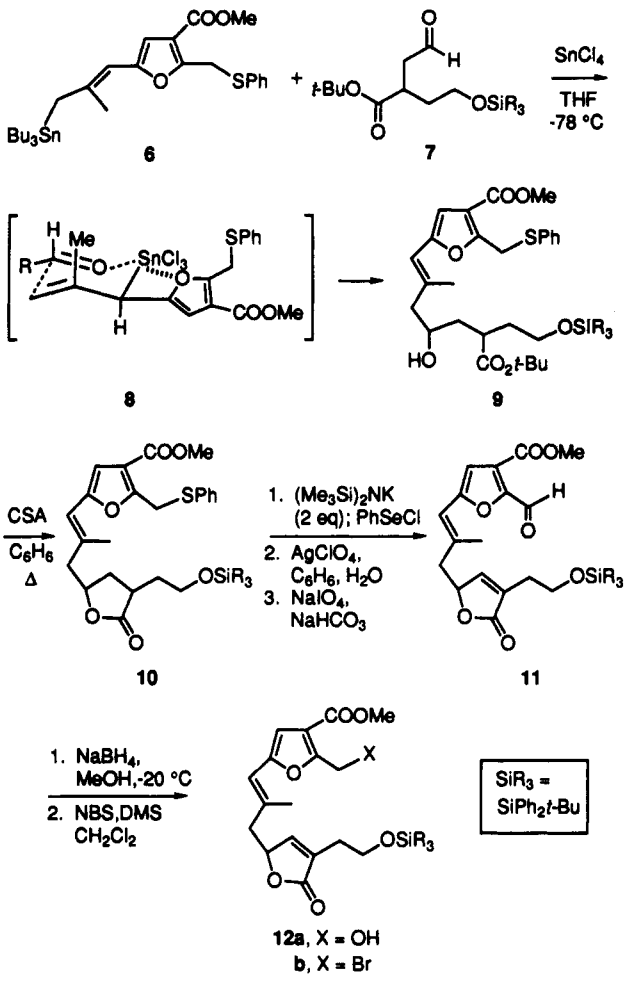
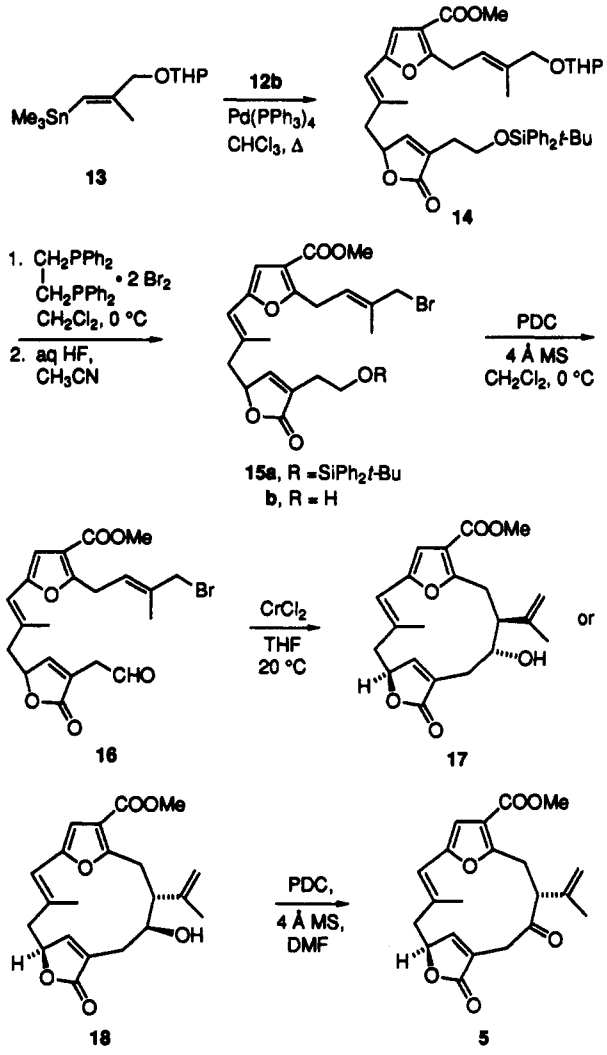
0022-3263/93/1958-0165$04.00/0

Scheme I



Scheme II



come the normal propensity for C–C bonding. In the first, ligand exchange intervenes with accompanying 1,3-transposition prior to the actual condensation reaction.[12] Equally important, the newly formed organometallic reagent must possess latent metallo–ene reactivity substantially more elevated than that of its stannane precursor.

As illustrated in Scheme I, $SnCl_4$ (1.5 equiv) in THF at −78 °C presumably acts on **6** to promote the desired rapid conversion to **8**. The subsequent introduction of aldehyde **7**[1] resulted in the formation of **9** as a single double bond isomer (55%). Comparison experiments showed $CoCl_2$ only to induce destannylation and $AlCl_3$–isopropyl alcohol to be substantially less effective (15% of **9**). None of the double-bond stereoselectivity is compromised during the cyclization to **10** (90%) with camphorsulfonic acid in hot benzene. The spectral properties of this intermediate are especially conducive to NOE studies. Thus, the *E* stereochemistry of its double bond was confirmed by double irradiation of the vinyl proton signal (δ 6.02). Integral enhancement of the allylic proton absorptions (δ 2.55–2.35) was seen, but the vinyl methyl singlet (δ 1.95) was not similarly affected. Conversely, irradiation of this methyl peak had no effect on the vinyl proton resonance.

The $-CH_2SPh$ substituent in **10** was now required to play its role as precursor to the reactive bromomethyl group in **12b**. Since introduction of the butenolide double bond also had to be accomplished, the strategy of concurrent oxidation of both side chains[1] was adopted. The facility with which **10** can be transformed into a dianion is noteworthy. Following the introduction of phenylselenenyl chloride, the bis-selenide was isolated in 55% yield. Chemospecific hydrolysis of the selenothioacetal with $AgClO_4$[13] unmasked the carboxaldehyde group. Due to their intrinsic lability, this and the ensuing 2-furyl aldehydes were not purified.

Gratifyingly, the use of sodium metaperiodate for selenoxide generation and the formation of PhSeOH via elimination were tolerated very well, thus allowing for highly satisfactory conversion to **11**. Clean reduction of the aldehyde carbonyl in **11** was possible with sodium borohydride. Functionalization of the hydroxyl group in **12a** as the bromide was accomplished with facility via the *N*-bromosuccinimide–dimethyl sulfide protocol.[14]

Side-chain extension as mediated by palladium(0)-catalyzed coupling[15] of **12b** to vinylstannane **13**[1] was next considered. Initial experiments, performed in refluxing benzene or dimethoxyethane solution, afforded **14** (Scheme II) in less than 30% yield. Fortunately, however, this reaction proved to be unusually solvent-dependent. A

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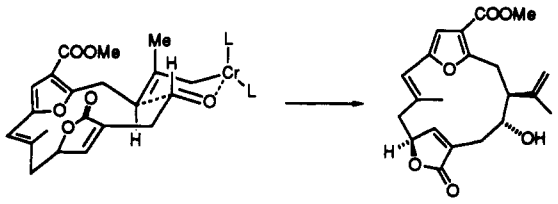
change to chloroform was particularly beneficial. In this medium, yields of 50–60% could be routinely achieved at loadings of 0.5 mmol or less. *seco*-Cembrane **14** was most conveniently transformed into bromide **15a** by exposure to 1,2-bis(diphenylphosphino)ethane tetrabromide[16] in CH_2Cl_2 solution. Desilylation with aqueous HF in acetonitrile[17] then led to **15b**.

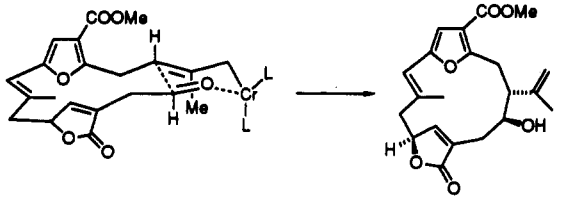
Oxidation of alcohol **15b** with pyridinium dichromate in the presence of 4-Å molecular sieves[18] proceeded without incident, affording the key intermediate **16**. For unknown reasons, however, this oxidant system among several that were examined stood alone in its ability to accomplish this particular transformation with reasonable efficiency.

The macrocyclization of **16** could best be realized by exposure to the chromous chloride reagent produced upon reduction of $CrCl_3$ with lithium aluminum hydride.[19] Commercial samples of $CrCl_2$ gave no ring-closure product(s), while the species obtained by $CrCl_3$ reduction with zinc dust gave evidence of modest levels (<10%) of ring closure. In the last process, many side products resulted as well, presumably because of the Lewis-acidic nature of the $ZnCl_2$ generated simultaneously. The absence of dimeric contaminants was ascertained by mass spectrometry at this stage and subsequently.

The success of the Nozaki reaction[19,21] in the present context is further testimony to its serviceability in the construction of medium-to-large rings.[22] Notwithstanding the presence of a butenolide double bond in **16**, only low levels of product contamination with the dihydro derivative were observed. Furthermore, only one of the two possible homoallylic alcohols **17** and **18** was produced via transition state **A** or **B**, respectively. Unfortunately, no distinction between them could be made on the basis of the available high-field ^1H NMR data.

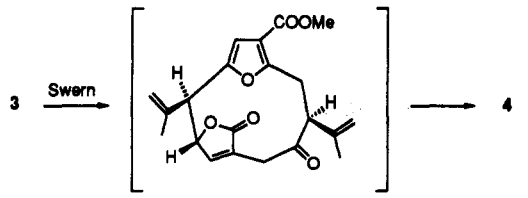


A **17**



B **18**

Oxidation of the carbinol with pyridinium dichromate *in dimethylformamide*[23] furnished **5**, identical by FTIR and 300-MHz ^1H NMR to authentic acerosolide.[24] When advancing into consideration of the relative stereochemistry of **5**, one must be mindful of the fact that Swern oxidation of **3** proceeds with in situ epimerization of intermediate ketone **19**.[1] An analogous scenario could well develop in the present series.[25] For this reason, our



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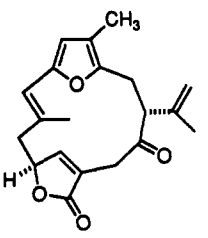
successful completion of the synthetic undertaking was followed by an assessment of the energies of structures **20–22** (CH_3 replacing COOMe for simplification purposes) by means of the MODEL program (version KS 2.96).[26] The multiconformer mode of this software package was used to generate a set of possible ring conformations. Further minimization refinements resulted in arrival at the most thermodynamically favored structure in each instance. Relevantly, **20** (E_S = 33.8, E_T = 39.0 kcal/mol) exists at a lower energy minimum than does **21** (E_S = 36.2, E_T = 41.5 kcal/mol), and both β,γ-unsaturated ketones are more stable than their conjugated counterpart **22** (E_S = 38.7, E_T = 43.0 kcal/mol).[27] The latter structure



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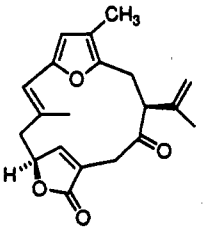

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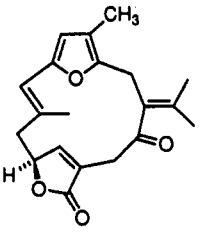

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undoubtedly suffers from the presence of yet another trigonal carbon in an already strained macrocycle.

Since **20** finds itself at the lowest energy point, the expectation is that **5** is either produced directly from **18** or generated from **17** via the β-isopropenyl epimer which

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(24) Authentic spectra were provided by Prof. Stewart McLean (University of Toronto) and Dr. Percy Manchand (Hoffmann-LaRoche).
(25) For yet another example of this behavior, see: Walba, D. M.; Thurmes, W. N.; Haltiwanger, R. C. *J. Org. Chem.* **1988**, *53*, 1046.
(26) We thank Prof. W. C. Still (Columbia) for making his program available for use, and Prof. K. Steliou (Montreal) for providing us with updates of his software package.
(27) E_S and E_T are acronyms for strain energy and total energy. These terms are outputed by the MMX program which was utilized for final minimization.

was not observed. The excellent agreement between theory and experiment that was demonstrated in the pseudopterane series (e.g., **3**, **4**, etc.)[1] increases the level of confidence in our conclusion that acerosolide is indeed correctly represented as **5**. Notwithstanding, proof of the relative stereochemistry of acerosolide continues to be elusive and, strictly speaking, must be considered to be an unresolved issue.

Experimental Section

Melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 1320 spectrometer. ^{1}H NMR spectra were recorded at 300 MHz and the ^{13}C NMR data obtained at 75 MHz. Mass spectra were measured on a Kratos MS-30 instrument at The Ohio State University Chemical Instrumentation Center. Elemental analyses were performed at the Scandinavian Microanalytical Laboratory, Herlev, Denmark. All flash chromatographic separations were carried out on Merck silica gel 60 (60–200 mesh), and reactions were routinely performed under an inert atmosphere unless otherwise indicated. Solvents were reagent grade and dried prior to use.

5-[(1*E*)-8-(*tert*-Butyldiphenylsiloxy)-6-carboxy-4-hydroxy-2-methyl-1-octenyl]-2-[(phenylthio)methyl]-3-furoic Acid, 6-*tert*-Butyl Methyl Ester (9). To a solution of allylstannane **6** (5.91 g, 10 mmol) in THF (100 mL) at −78 °C was added $SnCl_4$ (15.0 mL of 1.0 M solution in CH_2Cl_2, 15 mmol). After 5 min, aldehyde **7** (4.42 g, 10 mmol) in THF (20 mL) precooled to −78 °C was introduced, and the reaction mixture was allowed to stir at room temperature for 90 min prior to careful quenching with saturated $NaHCO_3$ solution (100 mL). The mixture was extracted with ether (4 × 200 mL) and the combined organic extracts were washed with saturated $NaHCO_3$ solution (150 mL), water (2 × 150 mL), and brine (200 mL) prior to drying and concentration. The residue was chromatographed on silica gel (elution with 20–30% ethyl acetate in petroleum ether) to give 4.08 g (55%) of **9** as a colorless oil: IR (neat, cm^{-1}) 3500, 1720, 1600; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (m, 4 H), 7.40 (m, 8 H), 7.20 (m, 3 H), 6.42 (s, 1 H), 6.02 (s, 1 H), 4.41 (s, 2 H), 3.82 (m, 1 H), 3.72 (s, 3 H), 3.68 (m, 2 H), 2.80 (m, 1 H), 2.65 (m, 1 H), 2.50 (br m, 2 H), 1.95–1.50 (m, 4 H), 1.93 (s, 3 H), 1.40 (s, 9 H), 1.04 (s, 9 H); MS *m/z* ($M^+ - OC(CH_3)_3$) calcd 669.2706, obsd 669.2628.

Anal. Calcd for $C_{43}H_{54}O_7SSi$: C, 69.51; H, 7.32. Found: C, 69.22; H, 7.32.

Methyl 5-[(1*E*)-3-[4-[2-(*tert*-Butyldiphenylsiloxy)ethyl]-tetrahydro-5-oxo-2-furyl]-2-methylpropenyl]-2-[(phenylthio)methyl]-3-furoate (10). A solution of hydroxy ester **9** (4.08 g, 5.50 mmol) in benzene (400 mL) was heated to reflux under Dean-Stark conditions for 1 h. Recrystallized 10-camphorsulfonic acid (0.45 g) was added, and heating was resumed for an additional 2 h. The benzene was removed, and the residue was chromatographed on silica gel (elution with 30% ethyl acetate in petroleum ether) to give lactone **10** (3.31 g, 90%) as a colorless foam: IR (neat, cm^{-1}) 1770, 1720, 1600; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (m, 4 H), 7.38 (m, 8 H), 7.25 (m, 3 H), 6.41 (s, 1 H), 6.02 (s, 1 H), 4.65 (m, 1 H), 4.41 (s, 2 H), 3.85 (m, 1 H), 3.72 (s, 3 H), 3.69 (m, 1 H), 2.85 (m, 1 H), 2.55–2.35 (m, 2 H), 2.20–2.05 (m, 2 H), 1.95 (s, 3 H), 1.60 (m, 2 H), 1.05 (s, 9 H); MS *m/z* (M^+) calcd 668.2628, obsd 668.2623.

Anal. Calcd for $C_{39}H_{44}O_6SSi$: C, 70.03; H, 6.63. Found: C, 70.16; H, 6.86.

2-Fold Selenenylation of 10. To **10** (5.50 g, 8.23 mmol) in THF (250 mL) at −78 °C was added potassium hexamethyldisilazide (36.0 mL of a 0.5 M solution in toluene, 18 mmol) and the resulting dark red solution was stirred for 45 min before introduction of a solution of phenylselenyl chloride (3.40 g, 18 mmol). The reaction mixture was stirred a further 2 h at −78 °C before being quenched with water (50 mL), diluted with ether (500 mL), and warmed to room temperature. The aqueous layer was extracted with ether (2 × 50 mL), and the combined organic layers were washed with water (150 mL) and brine (150 mL), dried, and concentrated. Chromatography of the residue on silica gel (elution with 15% ethyl acetate in petroleum ether) yielded 4.40 g (55%) of the bis-selenide as a pale yellow oil: IR (neat, cm^{-1}) 1760, 1720, 1580; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70–7.20 (m, 25 H), 6.38 (s, 1 H), 6.32 (s, 1 H), 5.95 (s, 1 H), 4.63 (m, 1 H), 4.05–3.85 (m, 2 H), 3.65 (s, 3 H), 2.60–2.30 (m, 4 H), 2.15–2.00 (m, 2 H), 1.95 (s, 3 H), 1.05 (s, 9 H); FAB MS *m/z* ($M^+ - SeC_6H_6$) calcd 823.20, obsd 823.20.

Methyl 5-(1*E*)-3-[4-[2-(*tert*-Butyldiphenylsiloxy)ethyl]-2,5-dihydro-5-oxo-2-furyl]-2-methylpropenyl]-2-(hydroxymethyl)-3-furoate (12a). To a vigorously stirred solution of the above diselenide (4.40 g, 4.48 mmol) in benzene (250 mL) and water (20 mL) was added silver perchlorate (3.30 g, 16.0 mmol) in small portions over 1 h. Stirring was continued for a further hour, whereupon the reaction mixture was diluted with 250 mL of ether and filtered through a pad of Celite. The filtrate was washed with 10% NH_4OH solution (2 × 100 mL), water (150 mL), and brine (150 mL) prior to drying and concentration.

This residue was taken up in methanol (200 mL), THF (50 mL), and water (30 mL). After the addition of $NaIO_4$ (3.20 g, 15.0 mmol) and $NaHCO_3$ (0.75 g, 9.0 mmol), the mixture was stirred vigorously for 5 h, concentrated, diluted with ether (500 mL), and washed with water (2 × 150 mL). The aqueous layers were extracted with ether (2 × 100 mL), and the combined organic phases were washed with brine (2 × 150 mL), dried, and concentrated.

The resultant residue was dissolved in methanol (150 mL) and THF (30 mL), cooled to −20 °C, and treated portionwise with $NaBH_4$ (0.30 g, 8.0 mmol) over 30 min. The reaction mixture was quenched with water (20 mL), warmed to room temperature, and freed of solvent. After dilution with ether (250 mL), the organic solution was washed with water (2 × 100 mL) and brine (150 mL) prior to drying and concentration. Flash chromatography of the residue on silica gel (elution with 30% ethyl acetate in petroleum ether) gave **12a** (1.30 g, 50% overall) as a colorless oil; IR (neat, cm^{-1}) 3460, 1760, 1720; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (m, 4 H), 7.45 (m, 6 H), 7.15 (d, J = 1.5 Hz, 1 H), 6.48 (s, 1 H), 6.12 (s, 1 H), 5.03 (dt, J = 1.5, 6 Hz, 1 H), 4.80 (d, J = 7 Hz, 2 H), 3.88 (m, 2 H), 3.88 (s, 3 H), 3.57 (br t, J = 7 Hz, 1 H), 2.50 (br m, 4 H), 2.05 (s, 3 H), 1.05 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 173.4, 165.0, 159.6, 151.3, 149.2, 135.5, 134.4, 133.5, 133.4, 131.9, 129.8, 127.7, 116.7, 116.1, 108.9, 79.7, 61.3, 57.4, 52.0, 44.6, 28.5, 26.8, 19.3, 19.2; MS *m/z* ($M^+ - C(CH_3)_3$) calcd 517.1682, obsd 517.1630.

Anal. Calcd for $C_{33}H_{38}O_7Si$: C, 68.96; H, 6.67. Found: C, 68.62; H, 6.78.

Methyl 2-(Bromomethyl)-5-[(1*E*)-3-[4-[2-(*tert*-butyldiphenylsiloxy)ethyl]-2,5-dihydro-5-oxo-2-furyl]-2-methylpropenyl]-3-furoate (12b). To a cooled (0 °C) suspension of *N*-bromosuccinimide (0.68 g, 3.84 mmol) in CH_2Cl_2 (16 mL) was added dimethyl sulfide (0.35 mL, 4.69 mmol) dropwise. After 5 min, alcohol **12a** (1.47 g, 2.56 mmol) was introduced, and the cooling bath was removed. After stirring had been continued for 2 h at room temperature, the reaction mixture was diluted with ether (100 mL) and washed with water (20 mL) and brine (20 mL). After filtration through a short pad of silica gel, concentration gave **12b** as a pale yellow oil (1.55 g, 95%): IR (neat, cm^{-1}) 1760, 1720, 1600; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (m, 4 H), 7.40 (m, 6 H), 7.16 (d, J = 1.5 Hz, 1 H), 6.51 (s, 1 H), 6.11 (s, 1 H), 5.04 (dt, J = 1.5, 6.8 Hz, 1 H), 4.90 (s, 2 H), 3.88 (m, 2 H), 3.87 (s, 3 H), 2.54 (br m, 4 H), 2.06 (s, 3 H), 1.05 (s, 9 H); MS *m/z* ($M^+ - C(CH_3)_3$) calcd 581.0778, obsd 581.0817.

Methyl 5-[(1*E*)-3-[4-[2-(*tert*-Butyldiphenylsiloxy)ethyl]-2,5-dihydro-5-oxo-2-furyl]-2-methylpropenyl]-2-[(2*E*)-3-methyl-4-[(tetrahydro-2*H*-pyran-2-yl)oxy]-2-butenyl]-3-furoate (14). A solution containing **12b** (0.11 g, 0.17 mmol) and **13** (64 mg, 0.2 mmol) in $CHCl_3$ (4 mL) was deoxygenated, treated with tetrakis(triphenylphosphine)palladium (20 mg), heated to reflux for 48 h under an atmosphere of nitrogen, and concentrated. The residue was transferred to a short column of silica gel with the aid of benzene and eluted with 20% ethyl acetate in petroleum ether to furnish **14** (80 mg, 65%) as a pale yellow oil: IR (neat, cm^{-1}) 1760, 1715, 1590; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (m, 4 H), 7.40 (m, 6 H), 7.15 (s, 1 H), 6.44 (s, 1 H), 6.05 (s, 1 H), 5.61 (br t, J = 7.2 Hz, 1 H), 4.98 (br t, J = 7.0 Hz, 1 H), 4.59 (m, 1 H), 4.14 (m, 1 H), 3.90–3.73 (m, 6 H), 3.83 (s, 3 H), 3.48 (m, 1 H), 2.55–2.44 (m, 4 H), 2.03 (s, 3 H), 1.85–1.25 (m, 6 H), 1.78 (s, 3 H), 1.03 (s, 9 H); MS *m/z* ($M^+ - C_5H_9O$) calcd 627.2637, obsd 627.2666.

Methyl 2-[(2*E*)-4-Bromo-3-methyl-2-butenyl]-5-[(1*E*)-3-[4-[2-(*tert*-butyldiphenylsiloxy)ethyl]-2,5-dihydro-5-oxo-2-furyl]-2-methylpropenyl]-3-furoate (15a). A solution of 1,2-bis(diphenylphosphino)ethane (0.35 g, 0.88 mmol) in CH_2Cl_2 (10 mL) at 0 °C was treated dropwise with bromine (86 μL, 1.67 mmol). After 5 min, a solution of **14** (0.42 g, 0.59 mmol) in the same solvent (4 mL) was introduced, and the reaction mixture was stirred for a further 2 h, diluted with ether (50 mL), washed with water (10 mL) and brine (10 mL), filtered through a short pad of silica gel, and concentrated. The residue was chromatographed on silica gel (elution with 20% ethyl acetate in petroleum ether) to give **5a** as a pale yellow oil (0.26 g, 64%): IR (neat, cm^{-1}) 1770, 1720, 1605; ^1H NMR (300 MHz, C_6D_6) δ 7.70 (m, 4 H), 7.21 (m, 6 H), 6.56 (s, 1 H), 6.41 (s, 1 H), 5.89 (s, 1 H), 5.52 (br t, J = 6 Hz, 1 H), 4.37 (dt, J = 1.5, 7.1 Hz, 1 H), 3.75 (m, 2 H), 3.65 (d, J = 7.1 Hz, 2 H), 3.51 (s, 2 H), 3.47 (s, 3 H), 2.41 (t, J = 6.2 Hz, 2 H), 2.03 (dd, J = 7.4, 14.0 Hz, 1 H), 1.89 (dd, J = 5.9, 14.0 Hz, 1 H), 1.73 (s, 3 H), 1.68 (s, 3 H), 1.12 (s, 9 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 172.5, 163.8, 151.6, 148.5, 135.9, 134.8, 133.9, 131.9, 130.1, 128.9, 128.1, 127.8, 124.7, 116.9, 115.1, 109.4, 79.3, 61.8, 51.0, 44.6, 40.3, 28.9, 27.2, 27.0, 19.4, 19.1, 14.7; FAB MS m/z (M^+ − t-Bu) calcd 633.13, found 633.08.

Methyl 2-[(2*E*)-4-Bromo-3-methyl-2-butenyl]-5-[(1*E*)-3-[2,5-dihydro-4-(2-hydroxyethyl)-5-oxo-2-furyl]-2-methylpropenyl]-3-furoate (15b). A solution of **5a** (0.26 g, 0.37 mmol) in acetonitrile (10 mL) was treated with a 5% solution of 48% aqueous HF in acetonitrile (5 mL) and the mixture stirred for 3 h. After this time, the reaction mixture was diluted with CH_2Cl_2 (50 mL) and washed with water (2 × 15 mL). The aqueous layers were extracted with CH_2Cl_2 (2 × 20 mL), and the combined organic phases were washed with brine (25 mL) prior to drying and concentration. The residue was chromatographed on silica gel (elution with 7:2:1 petroleum ether–ethyl acetate–2-propanol) to give **15b** (115 mg, 68%) as a pale yellow oil: IR (neat, cm^{-1}) 3480, 1760, 1715, 1605; ^1H NMR (300 MHz, C_6D_6) δ 6.57 (s, 1 H), 6.37 (s, 1 H), 5.89 (s, 1 H), 5.53 (br t, J = 6.5 Hz, 1 H), 4.38 (dt, J = 1.5, 6 Hz, 1 H), 3.65 (d, J = 7.2 Hz, 2 H), 3.53 (s, 2 H), 3.50 (m, 2 H), 3.48 (s, 3 H), 2.26 (m, 2 H), 1.96 (m, 2 H), 1.73 (s, 3 H), 1.68 (s, 3 H) (hydroxyl proton not observed); ^{13}C NMR (75 MHz, C_6D_6) ppm 173.3, 163.9, 158.7, 151.6, 134.8, 133.7, 132.1, 124.7, 177.0, 115.1, 109.4, 79.6, 60.3, 51.0, 44.3, 40.3, 29.1, 27.2, 19.2, 14.7; FAB MS m/z (M^+ + H) calcd 453.09, obsd 453.11.

Oxidation/Cyclization of 15b. To a solution of **15b** (0.11 g, 0.24 mmol) in CH_2Cl_2 (5 mL) was added crushed, activated 4-Å molecular sieves (500 mg), and the mixture was stirred under nitrogen for 15 min with cooling to 0 °C. Freshly prepared pyridinium dichromate (225 mg, 0.6 mmol) was added in one portion, and the reaction mixture was stirred vigorously for 3 h, diluted with dry ether (150 mL), and filtered through a short pad of Celite. Concentration of the filtrate furnished unstable aldehyde **16** as a pale yellow oil (50 mg, 46%), which was used directly in the next step.

A cooled (0 °C) suspension of chromium(III) chloride (250 mg, 1.58 mmol) in deoxygenated THF (100 mL) under nitrogen was treated portionwise with lithium aluminum hydride (30 mg, 0.75 mmol) over 20 min. After a further 20 min, the resultant dark green solution was warmed to room temperature and stirred for 30 min before introduction of the unpurified **16** in THF (20 mL). The reaction mixture was stirred at room temperature for 36 h, quenched slowly with water (10 mL), and concentrated to a volume of ca. 20 mL. Ether (50 mL) and water (10 mL) were introduced, and the aqueous layer was extracted with ether (3 × 20 mL). The combined organic phases were washed with brine (20 mL), dried, and concentrated. The residue was chromatographed on silica gel (elution with 25% acetone in petroleum ether) to afford macrocyclic alcohol **17** or **18** (8 mg, 20%) as a colorless oil: IR ($CHCl_3$, cm^{-1}) 3460, 1760, 1710, 1610; ^1H NMR (300 MHz, C_6D_6) δ 6.62 (s, 1 H), 6.27 (s, 1 H), 5.91 (s, 1 H), 4.78 (br s, 1 H), 4.73 (br s, 1 H), 4.33 (br t, J = 6 Hz, 1 H), 3.50 (s, 3 H), 3.42 (m, 2 H), 3.20 (m, 2 H), 2.40 (m, 2 H), 2.18 (m, 2 H), 1.72 (s, 3 H), 1.65 (s, 3 H) (hydroxyl proton not observed); MS m/z (M^+) calcd 372.1573, obsd 372.1582.

Acerosolide (5). A solution of the macrocyclic alcohol (2 mg, 5 mmol) in freshly distilled DMF (0.5 mL) was stirred for 15 min with crushed, activated 4-Å molecular sieves (10 mg) and treated with freshly prepared pyridinium dichromate (4 mg). After stirring for a further 2 h, the reaction mixture was diluted with water (1 mL), extracted with ether (6 × 2 mL), dried briefly, and concentrated. Residual DMF was removed at room temperature under high vacuum, and the residue was chromatographed on a short column of silica gel (elution with 12:2:1 petroleum ether–ethyl acetate–2-propanol) to yield **5** as a colorless oil (0.5 mg, 25%) identical by ^1H NMR, FTIR, and mass spectroscopy to authentic acerosolide.

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Supplementary Material Available: 300-MHz ^1H NMR spectra of the bis-selenide precursor to **11**, **12b**, **14**, **15a**, **15b**, **17** or **18**, and **5** (7 pages). This material is contained in 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.