Stereospecific Synthesis and Ring Closure of a Racemic Actinospectose Equivalent: A Concise Route to the Spectinomycin Series

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Abstract: A new route to the spectinomycin series has been developed. The approach involves exchange of a β-methoxy enone with a cyclitol to produce a substituted enone (cf. **11** → **12** and **16** → **17**). The enones are silylated to afford the activated butadienes bearing a cyclitoloxy group at the 1-position (cf. **12** → **13** and **17** → **18**). After cycloaddition of the dienes with a suitable aldehyde, oxidative cyclization leads to a tricyclic spectinomycin analogue (see formations **23**, **24**, and **27**). The facial sense of the cycloaddition reactions and the sense of diastereotopic formation of tricyclic product are considered.

Background and Synthetic Strategies

The novel antibiotic spectinomycin (**1**)[1] can be perceived in formal terms to be a condensation product of the aminocyclitol actinamine (**2**) with the 4,6-dideoxyhexose spectinose (**3**), alternatively called actinospectose[1c] (Figure 1). Actinamine is a well-known degradation product of spectinomycin.[2] It has also been obtained by totally synthetic methods.[3] In contrast, and not surprisingly, the term spectinose is, at the present writing, an abstraction, since compound **3** is unknown. The well-known lability of even the tricyclic spectinomycin vis-à-vis benzilic acid type rearrangement[2] calls into question the viability of any synthetic strategy which would involve the use of spectinose, per se, as a building block.

The only two efforts which have culminated in total syntheses of spectinomycin[4,5] involved the glycosylation of a suitably protected actinamine (**2b**) by a glucose (D or L) derivative. After glycosylation at the required carbon (5) of the actinamine, the functionalities within the hexose were adjusted, producing sequentially keto oxidation levels at carbons 2′ and 3′. At the stage where the $C_{3'}$ keto group is actually unveiled, the formal keto group at $C_{2'}$ has already been engaged in a protective hemiacetal linkage with the hydroxyl group at C_4 (i.e., the R center) of the cyclitol.

The plan described herein centered on the synthesis of a diene such as **6** which, upon cyclocondensation with acetaldehyde, would give rise to **7**. We deliberately left unspecified the precise structure of **8**. It was recognized that any of several two-electron oxidation products of **7** (vide infra) could serve as a latent α-diketone at $C_{2'}$ and $C_{3'}$. It was anticipated that conditions could be found under which system **8** would react with a C_4 hydroxyl group, unveiled on the cyclitol, to give the tricyclic hemiacetal signified as **9**. *Thus, it was hoped to create, through a cyclocondensation–oxidation process, a usable equivalent of the elusive spectinose (3), glycosidically linked to the cyclitol.*

Diene **6** would be derived by enol silylation of acetoxy enone **5**, which would in turn arise from an exchange reaction[6] of suitably protected actinamine **2b** and the known[7] enone **4**. For the scheme to be successful, it would be necessary to distinguish the C_5 hydroxyl group of actinamine for participation in the exchange reaction.

Results

Before embarking on the nontrivial objective of uniquely exposing the C_5 hydroxyl group of the actinamine for the exchange reaction, it was appropriate to examine the feasibility of some of the central tenets of the plan, i.e., the cycloaddition reaction, the oxidation process, and the formation of the tricyclic system in the manner indicated in Figure 2. Toward this end we employed as starting materials for the exchange reaction the secondary alcohols **11** and **16**, prepared as shown (Figure 3, see Experimental Section for details). In each case, the exchange reaction with acetoxy enone **4** under the influence of pyridinium *p*-toluenesulfonate (PPTS) worked smoothly, producing enones **12** and **17**, respectively. Enol silylation using *tert*-butyldimethylsilyl triflate[8] in the presence of triethylamine afforded dienes **13** and **18**.

The feasibility of the cycloaddition could now be evaluated. The issue of diastereofacial selectivity arose in the cycloaddition reaction of diene **13**. The assessment of the sense and extent of this selectivity was of considerable interest in envisioning the extension of this scheme to unsymmetrical analogues of actinamine.

No such issue of diastereofacial selectivity was relevant to the cycloaddition reaction of symmetric diene **18**. In this instance, attacks on the two faces are enantiotopically distinct. However, with cycloadducts derived from diene **19**, the issue of "folding"[9] in the final cyclization step must be confronted (vide infra).

Reaction of diene **13** with acetaldehyde was carried out in hexane at room temperature in the presence of 5–10 mol % Eu(fod)$_3$[10] (Figure 4). A 60% yield of a 5.7:1 ratio of two adducts was obtained.[11] The components were separable by HPLC. At this stage the assignment of stereochemistry to these adducts was far from a simple matter. Instead, efforts were directed toward cyclization of the adducts to produce spectinomycin congeners. The major product, in retrospect known to be **19**, was subjected to the action of *m*-chloroperoxybenzoic acid (mCPBA) in a two-phase (methylene chloride/aqueous sodium bicarbonate) system. The product was of only marginal stability, and attempted purification was only partially successful. Instead, the adduct was treated with aqueous HF/THF. The hydroxyl group, thus exposed at C_4,[12] cyclized to $C_{2'}$ to afford a 54% yield of the tricyclic product

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(5) (a) Hanessian, S.; Roy, R. *Can. J. Chem.* **1985**, *63*, 163. (b) Hanessian, S.; Roy, R. *J. Am. Chem. Soc.* **1979**, *101*, 5839.

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(9) By "folding", we refer to the tendency of one of the two diastereotopic hydroxyl groups of actinamine (at C_4 and C_6) to engage in stereoselective hemiacetal formation. For a discussion, see: White, D. R.; Birkenmeyer, R. D.; Thomas, R. C.; Mizsak, S. A.; Wiley, V. H. In *Aminocyclitol Antibiotics*; Rinehart, K. L., Suami, T., Eds.; ACS Symposium Series 125; American Chemical Society: Washington, DC, **1980**; pp 111–120.

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(11) A trace of a third compound was also isolated but in insufficient quantity for further characterization.

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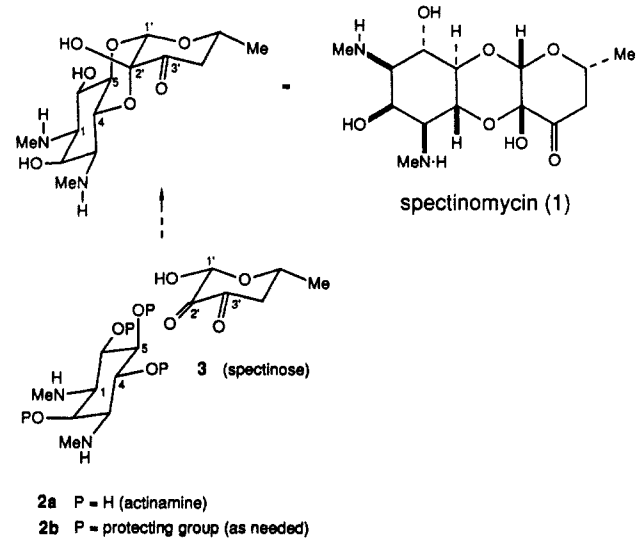


Figure 1.

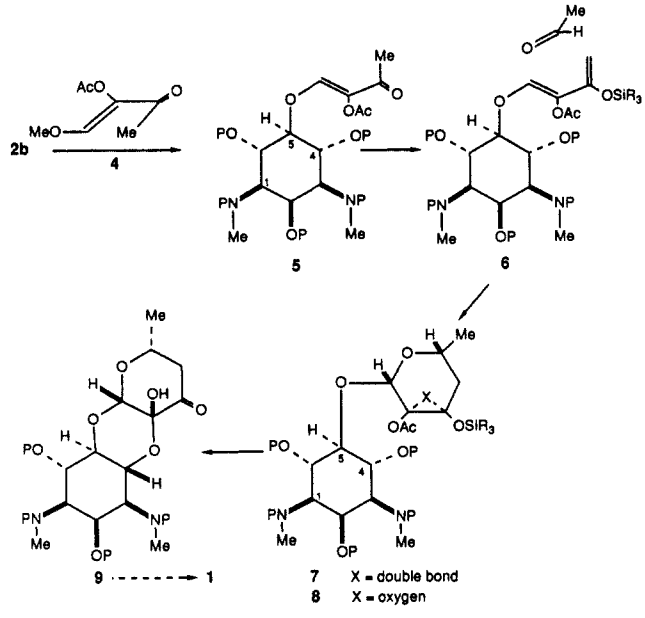


Figure 2.

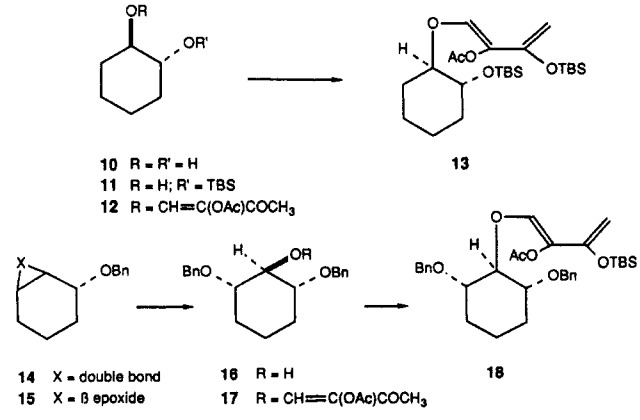
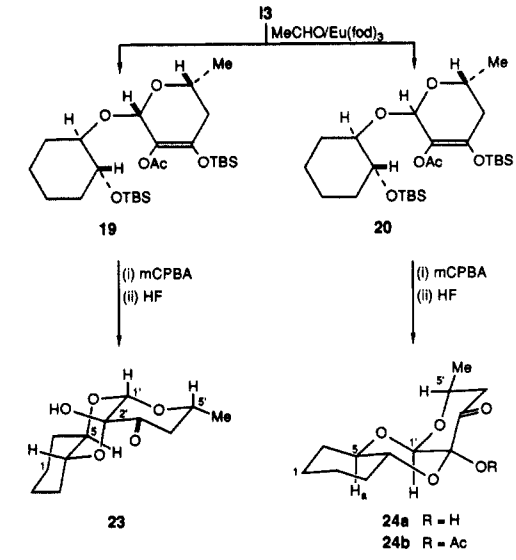


Figure 3.

23. The cis stereochemistry at $C_{5'}$ relative to $C_{1'}$ was deduced by a 10% Nuclear Overhauser Enhancement (NOE) of the relevant protons in the 500-MHz NMR spectrum of **23**. The absence of any corresponding enhancement between the protons at C_5 and $C_{1'}$ suggested an anti backbone relationship at these centers. The negative NOE result gained added significance from comparison with the products derived from compound **20** (vide infra). The backbone stereochemistry of **23** corresponded to that which has been derived for spectinomycin.[16] The stereochemistry at the hemiacetal center ($C_{2'}$) was not known with certainty. The assignment was consistent with that deduced for spectinomycin and is the one expected to be the most stable, given the fixed backbone relationships. Compound **23** proved unstable and did not provide an acetate on attempted acetylation (acetic anhydride, triethylamine, and (dimethylamino)pyridine). Its instability, like that of spectinomycin, arose from its propensity to undergo benzilic acid type rearrangement.



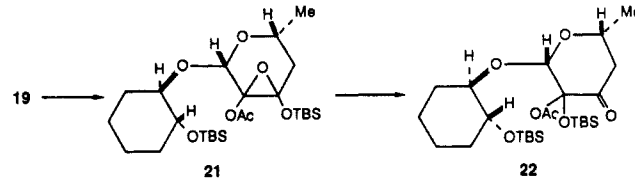


Figure 4.

The intermediate oxidation product of **19** with mCPBA was also unstable, and pure material was not obtained at this stage. Spectroscopic data would favor its formulation as the Rubottom "rearrangement product", **22**. However, our data did not exclude the presence of epoxide **21** in the material.

The minor adduct from the cyclocondensation reaction (now known to be **20**, vide infra) was subjected to the same two-step sequence. Compound **24a**, thus obtained in 78% yield, underwent smooth acetylation to provide **24b**. By contrast with compound **23**, no NOE was observed between the signals for the protons at $C_{1'}$ and $C_{5'}$. However, a significant NOE (ca. 10%) was observed for the protons at C_5 and $C_{1'}$. Accordingly, we formulated this series to be that shown in expression **24**, i.e., opposite to spectinomycin in both the C_5–$C_{1'}$ and the $C_{1'}$–$C_{5'}$ backbone relationships.

The issue of diastereofacial selectivity in the Lewis acid catalyzed diene–aldehyde cyclocondensation reaction arises in the reaction of diene **13** with acetaldehyde. Given the eventual formation of tricyclic products **23** and **24**, the structures of the primary adducts must be formulated as **19** and **20**, respectively.

(12) The numbering system employed is that used in spectinomycin. For the sake of consistency this numbering is retained even in the modified cyclitols employed here.

(13) Cram, D. J.; Abd Elhafez, F. A.; Weingerten, H. *J. Am. Chem. Soc.* **1953**, *75*, 2293.

(14) Cf.: (a) Franck, R. W.; Argade, S.; Subramaniam, C. S.; Frechet, D. M. *Tetrahedron Lett.* **1985**, *26*, 3187. (b) Charlton, J. L. *Tetrahedron Lett.* **1985**, *26*, 3413. (c) Ito, Y.; Amino, Y.; Nakatsuka, M.; Saegusa, T. *J. Am. Chem. Soc.* **1983**, *105*, 1586.

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(16) Hasegawa, A.; Kobayoski, T.; Kiso, M. *Agric. Biol. Chem.* **1980**, *44*, 165.

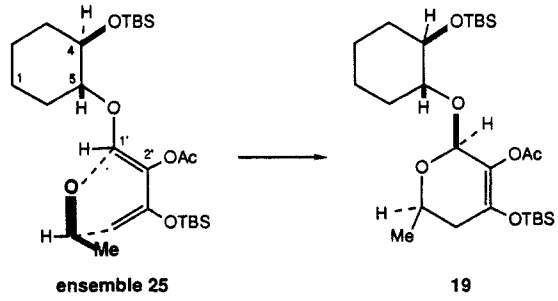

Figure 5.

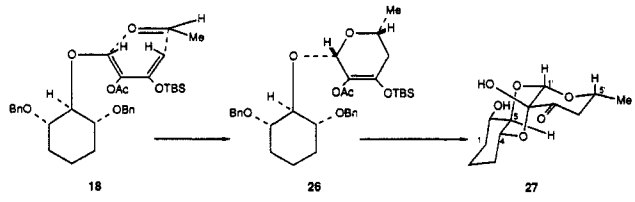

Figure 6.

The major component, **19**, apparently arises from endo addition. In ensemble **25** (Figure 5), the C_1–oxygen bond of the diene is placed antiperiplanar to the substituted bond of the cyclohexane with the C_1–$C_{2'}$ bond anti to the bond leading from the cyclohexyl auxiliary to the dienyl oxygen. Attack syn to the smallest group (hydrogen) leads to the observed product, **19**. This view would find enough analogy with the original Cram rule[13] formulation for additions of nucleophiles to ketones. We emphasize that the experimental data do not allow us to go beyond the purely formal accounting implied in ensemble **25**. It is, however, interesting to note that in the minor product **20** the topography of attack changes to exo as the diastereofacial sense of reaction of the diene is reversed. An understanding of the factors responsible for this connectivity is not possible from the limited data at hand.[14]

We turned next to the cyclocondensation of diene **18** with acetaldehyde. In this instance, the symmetry of the auxiliary rendered the two faces of the diene enantiotropic. The only significant stereochemical question in the cycloaddition reaction was that of endo vs. exo topography. In the event, reaction occurred in $CDCl_3$ in the presence of 10 mol % $Eu(fod)_3$. There was obtained substantially a single product, though NMR analysis of the reaction mixture suggested the possibility of a minor product to the extent of ca. 6% of the major substance. The isolated yield of cycloadduct was ca. 50%. A substantial part of diene **19** suffered conversion to enone **17**. On the basis of the two steps, and taking recovered enone into account, the yield of cycloadduct from **17** was ca. 75%. That the structure of the cycloadduct was, in fact, **26** could only be confirmed after oxidation and cyclization (Figure 6).

Treatment of **26** with mCPBA as before again gave rise to a difficulty characterizable product which deteriorated upon attempted purification. The crude material (see Experimental Section for spectral data) was subjected to the action of hydrogen under catalysis by $Pd(OH)_2$[15] in ethyl acetate. The material resulting from this reaction was then treated with HF/THF at room temperature. Workup afforded a 62% yield (over three steps) of an oily, but substantially homogeneous, product, whose structure was assigned to be **27**. Rapid chromatography produced a 48% (overall) yield of product, mp 124–127 °C.

The stereochemical assignment shown in **27** was based on its high-field NMR spectrum. In compounds **23** and **24**, the proton at $C_{5'}$ was clearly axial and cis to the $C_{1'}$ proton, as shown by a 10% NOE. The spectinomycin-type folding[9] was indicated by the absence of a corresponding enhancement between the $C_{1'}$ proton and that at C_5. This cis hemiacetal arrangement would be the more stable, given the backbone relationship, and was in accord with that deduced for spectinomycin.

Again, cycloaddition producing compound **26** occurred with high endo selectivity. This topography defined the critical C_1–$C_{5'}$ backbone relationship which had previously[4,5] been dealt with through glycosylation reactions. The C_5–$C_{1'}$ relationship was produced through diastereoselection in the formation of the hemiacetal. The stereospecific formation of **27**, in the spectinomycin sense, even in the absence of the substituents at carbons 1–3 established that these groups were not necessarily crucial in determining the mode of the folding.

The results described herein establish the feasibility of the new approach, wherein an equivalent of spectinose is fashioned through cycloaddition–oxidation rather than through manipulations of carbohydrates. Unsolved, at the present time, is the significant problem of generating a version of **2b** which is suitable for the exchange reaction.[6] This matter will be the subject of a continuing investigation.

Experimental Section

Preparation of (1β,2α)-2-([Dimethyl(1,1-dimethylethyl)silyl]oxy)-1-cyclohexanol (11). To a solution of diol **10** (2.5 g, 21.5 mmol) and triethylamine (5 mL, 36 mmol) in 100 mL of methylene chloride (CH_2Cl_2) at −78 °C under nitrogen was slowly added *tert*-butyldimethylsilyl trifluoromethanesulfonate (5.8 g, 22 mmol) via syringe. The reaction mixture was allowed to stir for 2 h at −78 °C and then warmed to room temperature. The reaction was quenched with 40 mL of saturated sodium bicarbonate solution ($NaHCO_3$) and the mixture transferred to a separatory funnel. The organic layer was washed once with $NaHCO_3$ solution and dried over magnesium sulfate ($MgSO_4$). Evaporation in vacuo and purification by flash chromatography on silica gel eluting with 25% ethyl acetate/hexane gave **11**: 2.8 g, 58%; ^1H NMR ($CDCl_3$, 90 MHz) δ 3.16–3.30 (m, 2 H), 2.39 (s, 1 H), 1.00–2.10 (m, 8 H), 0.90 (s, 9 H), 0.08 (s, 3 H); IR ($CHCl_3$) 3460 (br, OH), 2940, 1255, 1085, 840 cm^{-1}; MS, *m/e* 230 (M^+).

Preparation of (*Z*)-2-Acetoxy-1-([(1β,2α)-2-([dimethyl(1,1-dimethylethyl)silyl]oxy)-1-cyclohexyl]oxy)-1-buten-3-one (12). A solution of enone **4** (1.8 g, 11.4 mmol), alcohol **11** (2.4 g, 10.4 mmol), and pyridinium *p*-toluenesulfonate (PPTS) (0.30 g, 1.2 mmol) in benzene (50 mL) was refluxed for 30 h with continuous removal of methanol by using a Dean-Stark trap containing 4-Å molecular sieves. The reaction mixture was concentrated in vacuo and chromatographed on silica gel eluting with 30% ethyl acetate/hexane to give **12**: 2.6 g, 70%; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.38 (s, 1 H), 3.50–3.80 (m, 2 H), 2.20 (s, 3 H), 2.18 (s, 3 H), 1.10–2.10 (m, 8 H), 0.88 (s, 9 H), 0.07 (s, 3 H), 0.04 (s, 3 H); IR ($CHCl_3$) 2960, 1762, 1648, 1268, 1090, 841 cm^{-1}; MS, *m/e* 356 (M^+).

Preparation of (*Z*)-2-Acetoxy-1-([(1β,2α)-2-([dimethyl(1,1-dimethylethyl)silyl]oxy)-1-cyclohexyl]oxy)-3-([dimethyl(1,1-dimethylethyl)silyl]oxy)-1,3-butadiene (13). To a solution of enone **12** (320 mg, 0.90 mmol) and triethylamine (1.0 mL, 7.2 mmol) in ether (50 mL) at 0 °C under nitrogen was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (280 mg, 1.06 mmol). The reaction mixture was stirred for 1 h at 0 °C and then allowed to warm to room temperature. The reaction mixture was diluted with an addition 10 mL of ether and the reaction quenched with 10 mL of saturated $NaHCO_3$ solution. The mixture was transferred to a separatory funnel, and the organic layer was washed once with $NaHCO_3$ solution and dried over $MgSO_4$. Evaporation of solvent in vacuo gave diene **13**: 340 mg, 80%; ^1H NMR ($CDCl_3$, 250 MHz) δ 6.59 (s, 1 H), 4.24 (s, 1 H), 4.11 (s, 1 H), 3.40–3.70 (m, 2 H), 2.20 (s, 3 H), 1.1–2.1 (m, 8 H), 0.98 (s, 9 H), 0.89 (s, 9 H), 0.21 (s, 6 H), 0.07 (s, 3 H), 0.05 (s, 3 H).

Preparation of 2-(Phenylmethoxy)-7-oxabicyclo[4.1.0]heptane (15). To a solution of 5.00 g of 3-(benzyloxy)cyclohexene (**14**)[16] (0.0266 mol) in 100 mL of CH_2Cl_2 was added at 0 °C 5.93 g of *m*-chloroperoxybenzoic acid in 25 mL of CH_2Cl_2. The solution was allowed to warm to room temperature and stirred vigorously overnight. The resulting suspension was filtered, and the solute was washed with 2 × 10 mL of saturated sodium bisulfite, 2 × 10 mL of saturated $NaHCO_3$, and finally 1 × 10 mL of brine. The solution was dried (Na_2SO_4) and concentrated in vacuo to afford an oil which was purified by silica gel chromatography (eluent 1:9 ethyl acetate/hexanes). There was obtained 2.23 g of the desired trans epoxide as a clear oil (41%, R_f 0.73, 1:3 ethyl acetate/hexanes): ^1H NMR (90 MHz, $CDCl_3$) δ 7.32 (br s, 5 H), 4.60 (s, 2 H), 3.68 (m, 1 H), 3.16 (br s, 2 H), 1.12–2.08 (m, 6 H); IR (neat) 2950, 2900, 1460, 1360, 1080 cm^{-1}; MS (20 eV), *m/e* (relative intensity) 204 (M^+, 0.2%), 92 (100%). Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.42; H, 8.01. The corresponding cis isomer was also obtained (1.13 g, 21%, R_f 0.60, 1:3 ethyl acetate/hexanes): ^1H NMR (90 MHz, $CDCl_3$) δ 7.30 (br s, 5 H), 4.60 (s, 2 H), 3.74 (m, 1 H), 3.22 (br s, 2 H), 1.10–1.82 (m, 6 H).

Preparation of (1α,2β,6β)-2,6-Bis(phenylmethoxy)-1-cyclohexanol (16). A suspension of 60% sodium hydride in mineral oil (3.97 g, 0.099 mol) was washed with pentane, suspended in 50 mL of dry dimethyl-

formamide (DMF), and cooled to 0 °C. To this solution was added dropwise 10.0 g of benzyl alcohol, followed by a solution of 6.32 g of epoxide **15** in 10 mL of DMF. The mixture was heated to 100 °C for 10 h, cooled, and partitioned between water (100 mL) and ether (100 mL). The aqueous layer was extracted with 2 × 30 mL of ether, and the organic layers were combined, washed with 1 × 30 mL of water, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on silica gel (20% ethyl acetate/hexanes) to yield 6.32 g of **16** as a yellow semisolid (65%). Recrystallization from pentane gave the title compound as white crystals: mp 52–54 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 7.34 (m, 10 H), 4.65 (AB quartet, J = 11.8 Hz, $\Delta\nu$ = 14.3 Hz, 4 H), 3.53 (t, J = 8.8 Hz, 1 H), 3.25 (m, 2 H), 2.81 (s, 1 H), 2.03 (m, 2 H), 1.10–1.33 (m, 4 H); IR ($CHCl_3$) 3580, 3000, 2960, 2870, 1455, 1070, 700 cm^{-1}; MS (20 eV), m/e (relative intensity) 221 ($M^+ - C_7H_7$, 11.2%), 91 (100%). Anal. Calcd for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74. Found: C, 77.04; H, 7.74.

Preparation of (*Z*)-2-Acetoxy-1-([(1α,2β,6β)-2,6-bis(phenylmethoxy)-1-cyclohexyl]oxy)-1-buten-3-one (17). A dry 50-mL round-bottom flask equipped with a Dean-Stark trap filled with 4-Å molecular sieves was charged with a solution of 1.120 g of alcohol **16** (3.59 mmol), 0.852 g of 2-acetoxy-1-methoxy-1-buten-3-one (**4**) (5.38 mmol), and 0.180 g of pyridinium *p*-toluenesulfonate (0.718 mmol) in ca. 25 mL of benzene. The mixture was stirred at reflux for 20 h, cooled, and concentrated in vacuo. The residue was chromatographed on silica gel (1:4 ethyl acetate/hexane) to obtain 1.129 g of enone **17** as a white powder (72%): mp 111–112 °C after recrystallization from ether/ethyl acetate; ^1H NMR (250 MHz, $CDCl_3$) δ 7.45 (s, 1 H), 7.28 (m, 10 H), 4.57 (AB quartet, J = 11.4 Hz, $\Delta\nu$ = 6.6 Hz, 4 H), 3.77 (t, J = 9.0 Hz, 1 H), 3.41 (m, 2 H), 2.28 (s, 3 H), 2.12 (m, 2 H), 1.96 (s, 3 H), 1.28 (m, 4 H); IR ($CDCl_3$) 2940, 2850, 1760, 1640, 1440, 1250, 1230, 1060 cm^{-1}; MS (20 eV), m/e (relative intensity) 438 (M^+, 0.5%), 91 (100%). Anal. Calcd for $C_{24}H_{28}O_4$: C, 71.21; H, 6.90. Found: C, 71.05; H, 6.98.

Preparation of *cis*-3-Acetoxy-4-([dimethyl(1,1-dimethylethyl)silyl]oxy)-2-([1β,2α)-2-([dimethyl(1,1-dimethylethyl)silyl]oxy)-1-cyclohexyl]oxy)-6-methyl-5,6-dihydro-2*H*-pyran (19) and *trans*-3-Acetoxy-4-([dimethyl(1,1-dimethylethyl)silyl]oxy)-2-([(1β,2α)-2-([dimethyl(1,1-dimethylethyl)silyl]oxy)-1-cyclohexyl]oxy)-6-methyl-5,6-dihydro-2*H*-pyran (20). A solution of diene **13** (420 mg, 0.89 mmol), freshly distilled acetaldehyde (0.32 mL, 5.70 mmol), and tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium(III) ($Eu(fod)_3$) (116 mg, 0.11 mmol) in hexane (1 mL) was reacted at room temperature for 48 h. The reaction was monitored by ^1H NMR spectroscopy and TLC for disappearance of the starting diene **13**. The reaction mixture was concentrated in vacuo and chromatographed on silica gel eluting with 10% ethyl acetate/hexane to give a mixture of three products (285 mg, 62%). Purification by HPLC (SiO_2, 2% ethyl acetate/hexane) gave the major enol ether **19** and the minor enol ether **20** in a 5.7:1 ratio and a trace of a third cycloadduct.

Major cycloadduct **19**: mp 82–84 °C; ^1H NMR ($CDCl_3$, 250 MHz) δ 5.45 (t, J = 2.25 Hz, 1 H), 3.90–4.10 (m, 1 H), 3.71 (br dd, J = 8.12, 5.00 Hz, 1 H), 3.55 (br dd, J = 8.12, 5.00 Hz, 1 H), 1.40–2.40 (m, 13 H, includes 2.15 (s, 3 H)), 1.30 (d, J = 6.25 Hz, 3 H), 0.93 (s, 9 H), 0.90 (s, 9 H), 0.07 (s, 6 H), 0.06 (s, 6 H); IR ($CHCl_3$) 2925, 1748, 1700, 1365, 1085, 839 cm^{-1}; MS, m/e 514 (M^+).

Minor cycloadduct **20**: ^1H NMR ($CDCl_3$, 250 MHz) δ 5.22 (s, 1 H), 4.20–4.40 (m, 1 H), 3.40–3.70 (m, 2 H), 1.30–2.40 (m, 13 H, includes 2.15 (s, 3 H)), 1.25 (d, J = 7.51 Hz, 3 H), 0.92 (s, 9 H), 0.90 (s, 9 H), 0.18 (s, 3 H), 0.17 (s, 3 H), 0.08 (s, 6 H); IR ($CHCl_3$) 2927, 1750, 1702, 1365, 1080, 841 cm^{-1}; MS, m/e 514 (M^+).

Trace cycloadduct: ^1H NMR ($CDCl_3$, 250 MHz) δ 5.41 (t, J = 2.4 Hz, 1 H), 3.68–3.80 (m, 1 H), 3.50–3.60 (m, 1 H), 1.4–2.4 (m, 13 H, includes 2.15 (s, 3 H)), 1.38 (d, J = 7.5 Hz), 0.92 (s, 9 H), 0.90 (s, 9 H), 0.16 (s, 3 H), 0.15 (s, 3 H), 0.08 (s, 3 H), 0.06 (s, 3 H).

Preparation of *cis*-3-Acetoxy-3-([dimethyl(1,1-dimethylethyl)silyl]oxy)-2-([(1β,2α)-2-([dimethyl(1,1-dimethylethyl)silyl]oxy)-1-cyclohexyl]oxy)-6-methyl-2,3,5,6-tetrahydro-4-pyrone (22). To a mixture of enol ethers primarily consisting of **19** and **20** (111 mg, 0.21 mmol) in 10 mL of CH_2Cl_2 at room temperature was added *m*-chloroperoxybenzoic acid (55 mg, 0.32 mmol). The reaction mixture was stirred at room temperature for 24 h and diluted with an additional 10 mL of CH_2Cl_2, and the reaction was quenched with 10 mL of saturated $NaHCO_3$ solution. The reaction mixture was transferred to a separatory funnel, and the organic layer was washed once with $NaHCO_3$ solution and dried over Na_2SO_4. Evaporation of the solvent in vacuo and chromatography on silica gel eluting with 5% ethyl acetate/hexane gave a mixture of products of which 38 mg (34%) could be obtained as a pure homogeneous product, **22**: ^1H NMR ($CDCl_3$, 250 MHz) δ 5.12 (s, 1 H), 3.90–4.10 (m, 1 H), 3.58–3.70 (m, 1 H), 3.35–3.50 (m, 1 H), 2.73 (dd, J = 13.5, 1.6 Hz, 1 H, 1.4–2.2 (m, 12 H, includes 2.05 (s, 3 H)), 1.26 (d, J = 5.4 Hz, 3 H), 0.88 (s, 9 H), 0.86 (s, 9 H), 0.08 (s, 6 H), 0.05 (s, 6 H); ^{13}C NMR ($CDCl_3$, 93.6 MHz) δ 194, 181, 99.2, 98.4, 97.9, 82.2, 73.0, 67.1, 49.7, 33.4, 31.2, 25.9, 25.6, 23.4, 27.9, 21.4, 20.3, 19.4, 18.1; IR ($CHCl_3$) 2948, 2870, 1778, 1760, 1260, 1200, 1065 cm^{-1}.

Preparation of (2α,4aβ,5aβ,9aα,10aβ)-4a-Hydroxy-2-methyldecahydro-4*H*-pyrano[2,3-*b*][1,4]benzodioxin-4-one (23). To a vigorously stirred solution of enol ether **19** (40 mg, 0.075 mmol) in 3 mL of CH_2Cl_2 at room temperature was added a saturated solution of $NaHCO_3$ (2 mL) and *m*-chloroperoxybenzoic acid (27 mg, 0.16 mmol). The resulting biphasic system was stirred at room temperature, and aliquots were monitored by ^1H NMR spectroscopy for the disappearance of **19**. After 7 h, no starting material remained, at which time 10 mL of additional CH_2Cl_2 was added. The reaction mixture was passed through a plug of Celite and dried over $MgSO_4$. Concentration in vauco gave an unstable oil to which was added tetrahydrofuran (5 mL) and approximately 6 drops of a 50% aqueous solution of hydrogen fluoride at room temperature. This solution was stirred at room temperature and monitored for the disappearance of starting material by TLC. After 12 h the reaction was complete, at which time triethylamine was added to adjust the pH of the reaction mixture to approximately 8. The mixture was filtered through a plug of Celite, silica gel, and $MgSO_4$ and the plug washed with ethyl acetate. The organics were combined, concentrated in vacuo, and purified by HPLC (SiO_2, 30% ethyl acetate/hexane) to give the tricyclic compound **23**: 11 mg, 60%; ^1H NMR ($CDCl_3$, 500 MHz) δ 4.65 (s, 1 H), 4.17–4.27 (m, 1 H), 4.05–4.15 (m, 1 H), 3.70–3.85 (m, 1 H), 2.84 (dd, J = 14.6, 12.1 Hz, 1 H), 2.48 (dd, J = 14.6, 3.34 Hz, 1 H), 1.20–2.20 (m, 11 H, includes 1.42 (d, J = 7.5 Hz, 3 H)); IR ($CHCl_3$) 2950, 1739, 1177, 1067 cm^{-1}; high-resolution MS (20 eV), m/e calcd for $C_{12}H_{18}O_5$ 242.1154, found 242.1152. In the NOE difference spectrum, irradiation of the $C_{1'}$ "anomeric" proton at δ 4.76 gave a strong (approximately 10%) NOE with the $C_{5'}$ proton at δ 3.70–3.85 and no NOE with the C_5 proton at δ 4.05–4.15.

Preparation of (2α,4aα,5aβ,9aα,10aα)-4a-Hydroxy-2-methyldecahydro-4*H*-pyrano[2,3-*b*][1,4]benzodioxin-4-one (24a). To a vigorously stirred solution of enol ether **20** (12 mg, 0.024 mmol) in 2 mL of CH_2Cl_2 at room temperature was added a saturated solution of $NaHCO_3$ (2 mL) and *m*-chloroperoxybenzoic acid (8 mg, 0.048 mmol). The resulting biphasic system was stirred at room temperature, and the reaction was monitored by TLC for the disappearance of **20**. After 16 h no starting material remained, at which time 6 mL of additional CH_2Cl_2 was added. The reaction mixture was passed through a plug of Celite and dried over $MgSO_4$. Concentration in vacuo gave an unstable oil to which was added tetrahydrofuran (1 mL) and approximately 4 drops of a 50% aqueous solution of hydrogen fluoride at room temperature. After 3 h the reaction was complete by TLC analysis and was quenched by the addition of 5 mL of ethyl acetate and $MgSO_4$. The reaction mixture was filtered through a silica plug, concentrated in vacuo, and chromatographed on silica gel eluting with 25% ethyl acetate/hexane to give **24a**: 4 mg, 70%; ^1H NMR ($CDCl_3$, 250) 4.92 (s, 1 H), 4.40–4.60 (m, 1 H), 3.30–3.60 (m, 2 H), 3.10–3.20 (m, 1 H) disappears upon addition of D_2O, 2.85 (dd, J = 14.6, 12.1 Hz, 1 H), 2.52 (dd, J = 14.5, 3.34 Hz, 1 H), 1.20–2.20 (m, 11 H includes 1.37 (d, J = 5.8 Hz, 3 H)); IR ($CHCl_3$) 2950, 1740, 1175, 1062 cm^{-1}; high-resolution MS (20 eV), m/e calcd for $C_{12}H_{18}O_5$ 242.1154, found 242.1156.

Preparation of (2α,4aα,5aβ,9aα,10aα)-4a-Acetoxy-2-methyldecahydro-4*H*-pyrano[2,3-*b*][1,4]benzodioxin-4-one (24b). To a stirred solution of alcohol **24a** (4 mg, 0.017 mmol) in 3 mL of CH_2Cl_2 was added triethylamine (50 μL, 0.36 mmol), acetic anhydride (10 μL, 0.11 mmol), and a catalytic amount of (dimethylamino)pyridine at room temperature. After 16 h no starting material remained by TLC analysis. The reaction mixture was concentrated in vacuo and chromatographed on silica gel eluting with 25% ethyl acetate/hexane to give the tricyclic acetate **24b**: 4 mg, 82%; mp 160–162 °C; ^1H NMR ($CDCl_3$, 500 MHz) δ 5.13 (s, 1 H), 4.30–4.50 (m, 1 H), 3.85–4.15 (m, 1 H), 3.30–3.50 (m, 1 H, 2.5–2.7 (m, 2 H), 2.18 (s, 3 H), 1.2–2.5 (m, 11 H includes 1.36 (d, J = 5.8 Hz, 3 H)); IR ($CHCl_3$) 3020, 2940, 1763, 1740, 1123, 1070 cm^{-1}; MS (20 ev), m/e 284 (M^+). In the NOE difference spectrum, irradiation of the $C_{1'}$ anomeric proton at δ 5.13 gave a strong (approximately 10%) NOE with the C_5 proton at δ 3.30–3.50 and no NOE with the $C_{5'}$ proton at δ 4.30–4.50.

Preparation of *cis*-3-Acetoxy-4-([dimethyl(1,1-dimethylethyl)silyl]oxy)-2-([(1α,2β,6β)-2,6-bis(phenylmethoxy)-1-cyclohexyl]oxy)-6-methyl-5,6-dihydro-2*H*-pyran (26). To a suspension of 1.120 g of enone **17** (2.58 mmol) in 5 mL of dry ether was added dropwise at 0 °C 1.31 g of triethylamine (12.9 mmol) followed by 1.36 g of *tert*-butyldimethylsilyl trifluoromethanesulfonate (5.16 mmol). After the mixture was stirred at 0 °C for 10 min, the yellow solution was decanted from the oily precipitate, and the residue salts were washed with 2 × 2 mL of ether. The combined ether portions were washed with 1 × 5 mL of saturated $NaHCO_3$ and 1 × 5 mL of brine and dried over Na_2SO_4. The solution was filtered and concentrated in vacuo to yield 1.406 g of diene

18 (99%), which was used without further purification: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.31 (m, 10 H), 6.86 (s, 1 H), 4.61 (AB quartet, J = 11.7 Hz, $\delta\nu$ = 32.8 Hz, 4 H), 4.24 (s, 1 H), 4.11 (s, 1 H), 3.60 (t, J = 8.8 Hz, 1 H), 3.32 (m, 2 H), 2.22 (s, 3 H), 1.98 (m, 2 H), 1.11–1.35 (m, 4 H), 0.88 (s, 9 H), 0.15 (s, 6 H).

The above diene was dissolved in ca. 2 mL of deuteriochloroform and treated with 0.336 g of freshly distilled acetaldehyde (7.62 mmol) and 0.263 g of Eu(fod)$_3$. The mixture was allowed to stand at room temperature for 36 h, at which time it was concentrated in vacuo and purified by silica gel chromatography (1:9 ether/hexane) to obtain 0.780 g of the oily pyran **26** (51% from **17**) as well as 0.362 g of recovered **17** (32%). Compound **26**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.30 (m, 10 H), 5.80 (t, J = 2.1 Hz, 1 H), 4.73 (AB quartet, J = 11.8 Hz, $\Delta\nu$ = 48.6 Hz, 2 H) 4.64 (AB quartet, J = 11.9 Hz, $\Delta\nu$ = 31.8 Hz, 2 H), 3.86 (m, 1 H), 3.71 (t, J = 8.3 Hz, 1 H), 3.37 (m, 2 H), 2.24 (m, 1 H), 2.00 (s, 3 H), 1.98 (m, 2 H), 1.64 (m, 3 H), 1.28 (m, 2 H), 1.10 (d, J = 6.2 Hz, 3 H), 0.89 (s, 9 H), 0.13 (s, 6 H); IR ($CDCl_3$) 2950, 2800, 1720, 1590, 1420, 1180, 1020 cm^{-1}; MS (20 eV), m/e 596 (M^+, 1%), 537 (12.8%). Anal. Calcd for $C_{34}H_{48}O_7Si$: C, 68.42; H, 8.11; Si, 4.71. Found: C, 68.58; H, 8.44; Si, 4.51. A peak is assigned to the anomeric diastereomer at δ 6.62, which integrated to ca. 6% of the corresponding proton in the major isomer.

Preparation of (2α,4aβ,5aβ,9α,9aα,10aβ)-4a,9-Dihyroxy-2-methyldecahydro-4*H*-pyrano[2,3-*b*][1,4]benzodioxin (27). To a vigorously stirred solution of 61 mg of *m*-chloroperoxybenzoic acid (0.30 mmol) in 2 mL of CH_2Cl_2 was added at room temperature 3 mL of saturated $NaHCO_3$, followed by a solution of 147 mg of **26** (0.25 mmol) in 1 mL of CH_2Cl_2. The resulting biphasic system was vigorously stirred for 10 h, at which time an additional portion of *m*-chloroperoxybenzoic acid (20 mg, 0.10 mmol) was added. After stirring an additional 6 h, the reaction mixture was diluted with 10 mL of CH_2Cl_2. The organic layer was separated and washed successively with 1 × 2 mL of saturated sodium bisulfite, 1 × 2 mL of saturated $NaHCO_3$, and 1 × 2 mL of brine. The reaction mixture was dried (Na_2SO_4) and concentrated in vacuo to afford an unstable oil which was used without further publication: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.32 (m, 10 H), 5.45 (s, 1 H), 4.48–4.93 (m, 4 H), 3.98 (m, 1 H), 3.75 (t, J = 8.8 Hz, 1 H), 3.44 (m, 2 H), 2.55 (dd, J = 14.0, 2.0 Hz, 1 H), 1.90–2.10 (m, 3 H), 1.72 (s, 3 H), 1.16–1.25 (m, 4 H), 0.85 (s, 9 H), 0.18 (s, 3 H), 0.17 s, 3 H); IR ($CDCl_3$) 2940, 2850, 1770, 1750, 1450, 1380, 1250, 1090 cm^{-1}.

To a solution of the above material in 5 mL of ethyl acetate was added a spatula tip of $Pd(OH)_2$ on carbon (10%). The above suspension was stirred at room temperature for 30 min under a balloon of hydrogen gas, at which time TLC analysis showed the formation of several new products. The suspension was filtered through Celite and concentrated in vacuo to afford an unstable oil which was used directly in the next step without further purification or characterization.

The above oil was dissolved in 10 mL of tetrahydrofuran. To this was added 10 drops of an approximately 50% aqueous solution of hydrogen fluoride, and the resultant solution was stirred at room temperature for 16 h. Triethylamine was added to adjust the pH of the reaction mixture to ca. 8, and the cloudy mixture was filtered through Celite, concentrated in vacuo, and rapidly filtered through a plug of silica gel with 2% methanol/chloroform as eluent. In this manner, 31 mg of the desired tricyclic **27** (48% from **26**) was obtained as a white powder: mp 124–127 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.67 (s, 1 H), 4.40 (s, 1 H), 3.90 (1 H), 3.87 (t, J = 10.3 Hz, 1 H, partially obscured), 3.74 (m, 1 H), 3.72 (m, 1 H), 2.81 (dd, J = 14.2, 11.8 Hz, 1 H), 2.45 (dd, J = 14.2, 2.0 Hz, 1 H), 2.38 (br s, 1 H), 2.01 (m, 1 H), 1.77 (m, 2 H), 1.55 (br s, 1 H), 1.41 (d, J = 6.1 Hz, 3 H), 1.23–1.35 (m, 2 H), irradiation of the singlet at δ 4.67 produced an approximately 10% NOE enhancement in the signal at δ 3.74 (determined by NOEDS at 500 MHz); ^{13}C NMR ($CDCl_3$, 93.6 Hz) δ 97.0, 90.8, 77.1, 70.4, 69.9, 67.9, 66.9, 44.6, 38.8, 31.8, 30.5, 29.2, 28.9, 24.5, 23.9, 23.0, 21.5, 20.2, 14.0; IR ($CDCl_3$) 3500, 3020, 1710, 1140, 1100, 1040, 1010 cm^{-1}; high-resolution MS (20 eV), m/e calcd for $C_{12}H_{18}O_6$ 258.1103, found 258.1085. Anal. Calcd for $C_{12}H_{18}O_6$: C, 55.80; H, 7.02. Found: C, 55.79; H, 7.14.

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Total Synthesis of (−)-Coriolin[1]

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Abstract: The first total synthesis of the diterpene coriolin in the enantiomerically pure (−)-form is described. The key step is the photochemical generation of the 3,3,6-trimethyltricyclo[3.3.0^{2,8}]octane-4,7-dione building blocks (−)-**12a** and (−)-**12b** in solutions of exceptionally high concentrations (≥20%). It involves the site selective oxadi-π-methane rearrangement of one β,γ-enone partial chromophore of the β,γ-unsaturated ϵ-diketones (−)-**9a** and (−)-**9b** which are obtained from bicyclo[2.2.2]oct-7-ene-2,5-dione, (±)-**7**, by optical resolution, in multigram batch preparations, via the tartrate monoacetals followed by trimethylation. (−)-Coriolin is thus accessible in 14 steps from (±)-**7**.

Coriolin,[2] a sesquiterpene with potent antitumor and antibacterial properties,[3] has attracted the attention of numerous synthetic groups over the recent years.[4,5] The challenge of building up the cis,anti,cis-fused tricyclo[6.3.0.0^{2,6}]undecane skeleton with an array

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