oxyphenoxy)-1,2-propanediol, 93-14-1; 3-(3-methoxyphenoxy)propylene 1,2-oxide, 2210-75-5; 3-methoxyphenol, 150-19-6; 3-(3-methoxyphenoxy)-1,2-propanediol, 17131-51-0; 3-(4-methoxyphenoxy)propylene 1,2-oxide, 2211-94-1; 4-methoxyphenol, 150-76-5; 3-(4-methoxyphenoxy)-1,2-propanediol, 17131-52-1; 3-((1-naphthyl)oxy)propylene 1,2-oxide, 2461-42-9; 1-naphthol, 90-15-3; 3-((1-naphthyl)oxy)-1,2-propanediol, 36112-95-5; 8-hydroxyquinoline, 148-24-3; 3-chloro-1,2-propanediol, 96-24-2; 3-((8-quinolinyl)oxy)-1,2-propanediol, 56469-01-3; benzoyl chloride, 98-88-4; 4-methoxybenzoyl chloride, 100-07-2; 4-nitrobenzyl chloride, 122-04-3; 3-(4-allyl-2-methoxyphenoxy)propylene 1,2-oxide, 36014-34-3; eugenol, 97-53-0; 3-(4-allyl-2-methoxyphenoxy)-1,2-propanediol, 398-58-3; Na^+, 17341-25-2; K^+, 24203-36-9.

Total Synthesis of the Hypocholesterolemic Agent Compactin

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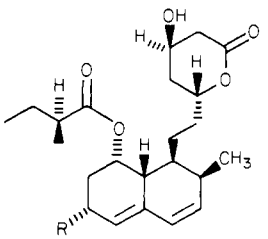
Abstract: A total synthesis of (+)-compactin (ML-236B) (**1a**), a potent inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A reductase, is presented. The key chiral hexahydronaphthalene intermediate, **3**, was efficiently synthesized in 70% overall yield from the optically active diol (−)-**6**. In turn, (−)-**6** was obtained via microbiological reduction of the racemic dione (±)-**5**. (+)-Compactin (**1a**) was prepared in 14 steps from **3** in 0.8% yield.

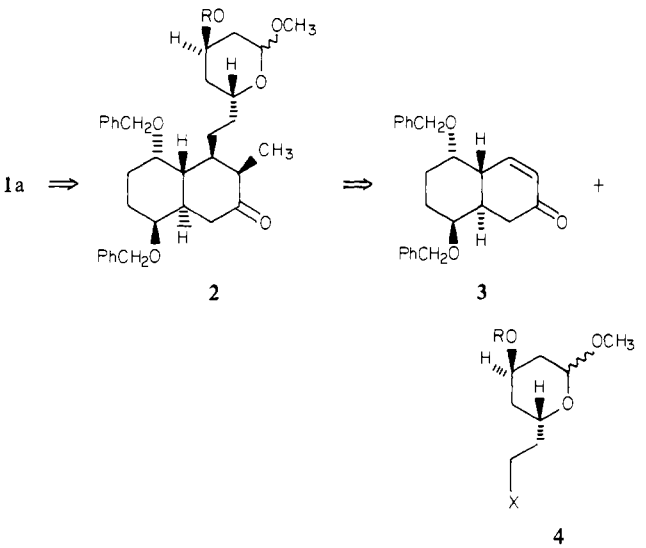
In 1976, an important new class of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors was discovered. The first member of this family, compactin (**1a**), was isolated from



1a, R = H
1b, R = CH_3

Penicillium brevicompactum[1] by the Beecham group as an antifungal metabolite. Later, this same metabolite, designated as ML-236B,[2] and other derivatives were isolated from *Penicillium citrinum* by the Sankyo group as hypocholesterolemic agents. Subsequently, Monacolin K[3] (**1b**) or Mevinolin[4] was discovered by two independent groups from cultures of *Monascus ruber* and *Aspergillus terreus*, respectively. All of these compounds are potent competitive inhibitors of HMG-CoA reductase,[2-5] the rate-limiting enzyme in cholesterol biosynthesis,[6] with **1b** being the most potent. However, the pharmacology of **1a** is the most extensively studied. Compactin effectively reduced plasma cholesterol levels in a number of animal species including dogs,[7a] monkeys,[7b] and humans.[7c] Further, it has been investigated

Scheme I



clinically as a hypocholesteremic drug with encouraging results. It can selectively reduce the low-density lipoprotein (LDL) without affecting the desirable high-density lipoprotein (HDL).[8] On the other hand, it is possible that these compounds will produce unexpected side effects and that new chemical variants will have to be developed to further enhance the therapeutic efficacy.

Compactin is a challenging synthetic target owing to the presence of seven asymmetric centers, a high degree of functionalization, and the highly sensitive β-hydroxy-δ-lactone, which is essential for biological activity. In recent years, extensive synthetic studies have resulted in the syntheses of the hexahydronaphthalene nucleus,[9] the lactone moiety,[10] and the simpler

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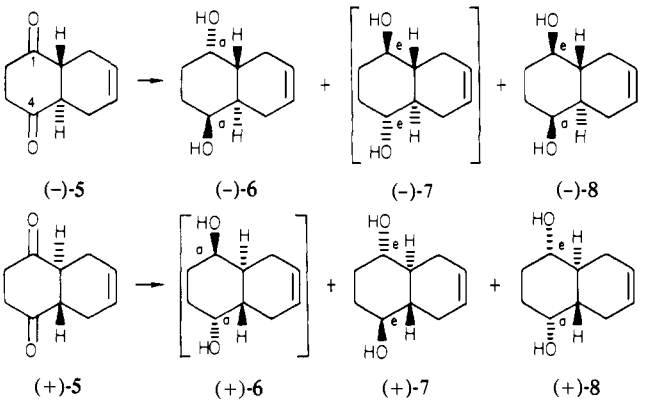
Scheme II



lactone analogues.[11] In 1981, we reported the first total synthesis of this molecule,[12] and now we describe the experimental details of our synthetic explorations.

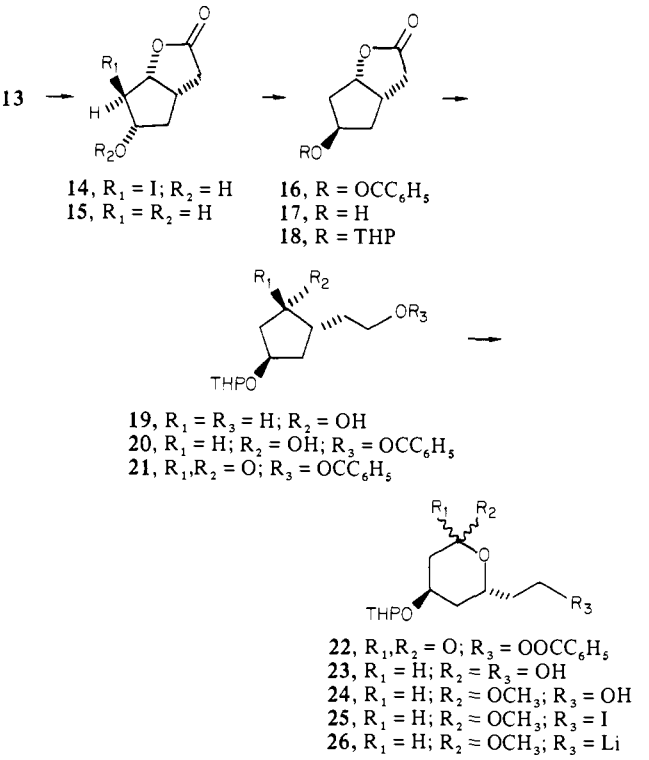
Our initial planned synthetic strategy entailed the dissection of **1a** as outlined in Scheme I. We envisaged that compactin (**1a**) might be prepared from the intermediate **2**, which contains strategically situated latent functionalities for the elaboration of the transoid conjugated diene. Compound **2** in turn might be constructed by vicinal dialkylation via conjugate addition of the cuprate derived from **4** to the enone **3** and trapping of the resulting kinetic enolate with a suitable electrophile, culminating in a highly convergent approach to **1a**.

The enone **3** could be derived from the readily available (±)-trans-dione **5**.[13] By taking advantage of the inherent symmetry element (C_2) of **6**, we eliminated the regiochemical problem associated with the subsequent functionalization of the double bond. Because chemical reduction of **5** with diisobutylaluminum hydride or sodium borohydride gave a statistical mixture of racemic diastereomers, we decided to effect the reduction of (±)-**5** into (−)-**6** using microbial methods.

The stereospecificity of microbiological reduction of alicyclic ketones had been investigated in considerable detail by the Prelog school.[14] It was reported[15] that *Curvularia falcata* transformed (±)-**5** into five products, but the desired diol (−)-**6** was only formed in low yields. However, oxidoreductases are widely distributed in nature, and different microorganisms, or even different strains of the same species, can differ markedly in their "substrate stereospecificity" and "product stereospecificity".[4] These differences may be due to the presence of several different enzymes in the cells and/or due to the fact that single enzymes react with enantiomeric substrates at different rates. In theory, microbiological reduction of (±)-**5** could give rise to three *dl* pairs of diastereomeric diols as shown in Scheme II.

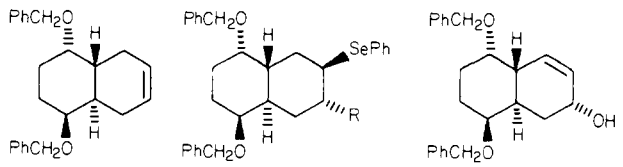
In fact, most of the microorganisms we examined did metabolize (±)-**5** to yield the three diastereomeric alcohols **6**, **7**, and **8**. But the optical purities of the resulting diols were rather moderate. On the other hand, the fungus *Aureobasidium pullulans* was uniquely suited for this transformation. It converted (±)-**5** to give (−)-**6** in 33% yield, accompanied by (+)-**7** (22%) and (±)-**8** (42%). These diastereomeric diols were readily separated by silica gel column chromatography and were then oxidized with Jones reagent back to the dione **5**. The optical purities of these resulting

Scheme III



diones were then determined by comparison of their optical rotations with the known (−)-**5** (−396°) and (+)-**5** (+396°). From these experiments, it is noteworthy that neither (+)-**6** nor (−)-**7** was produced in any significant quantities during this microbial transformation, as evidenced by the optical purities of both products, (−)-**6** and (+)-**7**, being greater than 98% enantiomeric excess. On the other hand, the (±)-**8** diol consisted of a 6:4 mixture of (+)-**8** and (−)-**8**, respectively. This pattern of microbial reduction has been commonly observed and falls under the category of type IV reaction (substrate nonstereospecific; product nonstereoselective).[16]

Treatment of (−)-**6** with 2 equiv of NaH in Me_2SO at 25 °C, followed by the addition of $C_6H_5CH_2Cl$[17] afforded **9** (99%) as



an oil, which was reacted with phenylselenenyl bromide to furnish **10**. Hydrolysis of **10** afforded **11** (89%). Oxidation of **11** gave the selenoxide intermediate, which underwent smooth elimination upon heating at 55 °C for 2 h to yield the allylic alcohol **12**. Jones oxidation of **12** gave **3** (71% from **9**). The corresponding segment **4** may be prepared from 5-norbornen-2-one (**13**) via the following sequence of reactions (Scheme III): reaction of **13** with $H_2O_2/NaOH/KI_3/I_2$ afforded the iodo lactone[18] **14**, which was reduced with $(n\text{-}Bu)_3SnH$[19] to give **15**. Epimerization of the hydroxyl function was effected by treating **15** with diethyl azodicarboxylate[20] in the presence of benzoic acid to yield **16**. After

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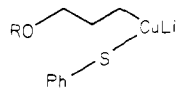
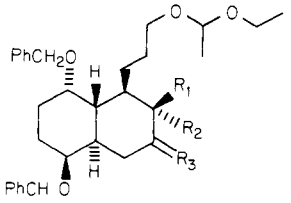
cleavage of the benzoate ester, **17** was converted into the tetrahydropyranyl ether **18**. The lactone ring of **18** was reduced with $NaBH_4$, and the resulting diol **19** was selectively benzoylated to give **20**. After oxidation of the secondary alcohol with pyridinium chlorochromate, the ketone **21** was reacted with *m*-chloroperbenzoic acid to give lactone **22**, which was reduced to lactol **23** by using DiBAL-H. Treatment of **23** with Ag_2O/CH_3I in ether gave acetal **24**, which was first tosylated and then treated with LiI to give iodide **25**. The overall yield of this reaction sequence for the preparation of **25** and **13** was reasonably high (18%). Further, it is noteworthy that iodo lactone **14** may be easily prepared in its optically active form.[18]

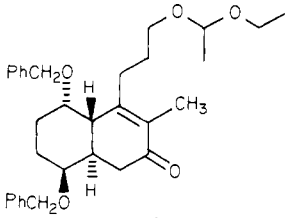
Having the desired acetal **25** in hand, we proceeded to examine the experimental procedures required for C–C coupling of **25** to enone **3**. Although reaction of **25** with lithium metal at 0 °C did afford the desired lithio derivative **26**, much to our disappointment, **26** was found to be too unstable even at −20 °C for further experimentation as evidenced by the ease with which a solution of **26** turned to a dark black color after a few minutes. Likewise, the Grignard derivative of **25** also decomposed readily at −20 °C. This unexpected turn of events forced us to the utilization of a less convergent approach for the incorporation of the lactone ring into the bicyclic enone **3** through the use of mixed cuprate[21] **27**.

Since the α face of the double bond in **3** was substantially hindered by the bulky axial benzyloxy substituent, it was expected that the cuprate addition should take place preferentially from the opposite face. However, the stereochemical outcome of the subsequent methylation was not safely predictable. When **3** was reacted with **27**, followed by the addition of excess methyl iodide (DME[22]), **28** was obtained. To define the stereochemistry of the



27, R = $CHCH_3OC_2H_5$





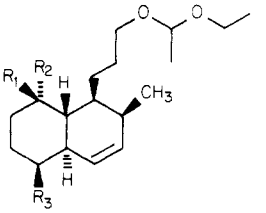
33

28, R_1 = H; R_2 = CH_3; R_3 = O
29, R_1 = H; R_2 = CH_2OH; R_3 = O
30, R_1 = CH_2OH; R_2 = H; R_3 = O
31, R_1,R_2 = CH_2; R_3 = O
32, R_1 = CH_3; R_2 = H; R_3 = O
34, R_1 = CH_3; R_2 = H; R_3 = $=NNHO_2SH_4C_6CH_3$

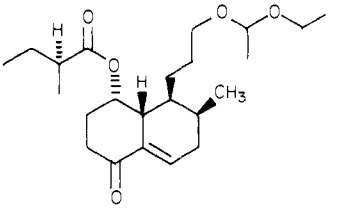
newly introduced methyl substituent, we repeated the conjugate addition, but the intermediary copperlithium enolate was alkylated with a slight excess of gaseous formaldehyde to give a mixture of **29** and **30**. This mixture was mesylated, and the crude mesylate was subjected to elimination to yield **31**. When **31** was hydrogenated, two epimers (**32** and **28**) were formed (75% yield) in 55:45 ratio, accompanied by 25% of **33**. These products were separated by silica gel column chromatography using benzene–ethyl acetate (93:7) as the eluent. In the presence of sodium methoxide in methanol, both epimers equilibrated to give a 9:1 mixture of **28** and **32**. Accordingly, it seemed reasonable to assign the thermodynamically more stable equatorial configuration to the methyl group in **28**.

Because **31** has a strong tendency to undergo isomerization on the surface of palladium metal to lead to the enone **33**, a series of hydrogenation experiments were conducted to minimize this undesirable side reaction. It was found that when the hydrogenation was carried out in the presence of either pyridine[23] or triethylamine in benzene, not only was the formation of **33** suppressed but also the desired axial epimer **32** was preferentially formed in 78% yield and the undesired equatorial epimer **28** diminished to 10%. Although one may envisage that the function of pyridine is to inhibit the isomerization of the double bond as had been observed in the area of steroidal ketones, the mechanism for the preferential formation of the axial epimer **32** is not yet understood at this time. One plausible explanation is that the palladium metal is deactivated by pyridine to form a complex with enhanced selectivity. The selective formation of **32** was also found to be solvent dependent, for the formation of **28** and **33** was enhanced when ethyl acetate or ethanol was substituted for benzene.

Condensation of **32** with *p*-toluenesulfonylhydrazide gave **34**, which after removal of the solvent was treated with 10 equiv of LDA to yield **35**. Debenzylation of **35** went smoothly to give



35, R_1 = H; R_2 = R_3 = OCH_2Ph
36, R_1 = H; R_2 = R_3 = OH
37, R_1 = H; R_2 = OH; R_3 = $O_2CCH(CH_3)C_2H_5$
38a, R_1,R_2 = O; R_3 = $O_2CCH(CH_3)C_2H_5$
38b, R_1,R_2 = O; R_3 = OH
39, R_1 = H; R_2 = R_3 = $O_2CCH(CH_3)C_2H_5$
40, R_1 = H; R_2 = $O_2CCH(CH_3)C_2H_5$; R_3 = OH



41

36 in quantitative yield. A series of experiments was conducted in an attempt to acylate selectively one of the two hydroxyl functions of **36**. However, no satisfactory acylation was achieved with (*S*)-2-methylbutyric chloride in Et_3N, (*S*)-2-methylbutyrylimidazole[24] in THF, or (*S*)-2-methylbutyric acid in the presence of 1-methyl-2-chloropyridinium iodide and betaine.[25] On the other hand, when **36** was treated with 2 equiv of (*S*)-2-methylbutyric anhydride (MBA), the monoacylate **37** was isolated as the major product. The position of the ester grouping was assigned by the oxidation of **37** with pyridinium chlorochromate to the ketone **38a**, which exhibited a band at 1710 cm^{-1} indicative of cyclohexanone. Treatment of **38a** with NaOEt/EtOH afforded **38b**, which exhibited no UV absorption. Reaction of **36** with a large excess of MBA gave the diester **39**. When the latter was hydrolyzed, **40** (63%), **37** (6.6%), residual **39** (6.5%), and a trace of **36** were formed. **40** was oxidized with pyridinium chlorochromate to further confirm our structural assignment, and the product was then treated with NaOEt/EtOH. In this case, an UV absorbing ketone (λ_{max} 244 nm (log ϵ 3.87)) **41** was obtained; its infrared spectrum also exhibited a band at 1680 cm^{-1}, characteristic of a conjugated ketone chromophore. These observations clearly indicate that the C-4 position is less hindered than the C-1 position in both **36** and **39** for esterification and hydrolysis, respectively. Mesylation of **40** followed by elimination furnished **42**. After removal of the ethoxyethoxy protecting group by acidic

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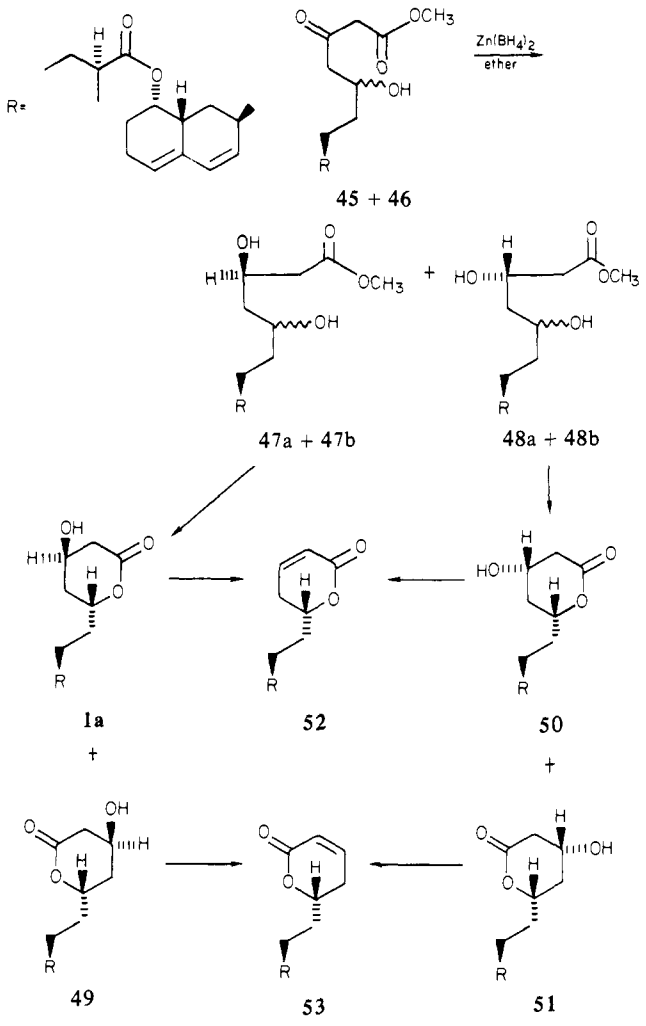
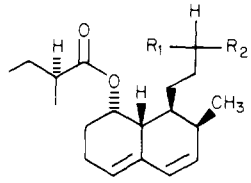
Scheme IV



hydrolysis, **43** was oxidized to the aldehyde **44** by using pyridinium chlorochromate.



42, $R_1 = OCHCH_3OC_2H_5$; $R_2 = H$
43, $R_1 = OH$; $R_2 = H$
44, $R_1, R_2 = O$
45, $R_1 = OH$; $R_2 = CH_2(CO)CH_2CO_2CH_3$
46, $R_1 = CH_2(CO)CH_2CO_2CH_3$; $R_2 = OH$

With the completion of the bicyclic nucleus of compactin, the synthesis devolved to the construction of the highly functionalized lactone ring. This was accomplished by reacting **44** with the dianion of methyl acetoacetate[26] to yield two diastereomeric alcohols **45** and **46**. Because this mixture resisted separation by TLC and HPLC, these two δ-hydroxy-β-keto esters were reduced with excess $Zn(BH_4)_2$ to two pairs of β,δ-dihydroxy esters (Scheme IV). The less polar pair of the β,δ-dihydroxy esters (R_f 0.48, **47a** and **47b**) can be separated from the more polar pair (R_f 0.42, **48a** and **48b**) by TLC using EtOAc/hexane (3:2) or by column chromatography over silica gel using acetone/chloroform (1:9) as eluent. Several attempts were made to lactonize **47a** and **47b** by using Lewis acids: BCl_3 in CH_2Cl_2[27] at −25 °C to 0 °C afforded only recovered starting material, and $AlCl_3$–$(CH_3)_2S$[28] in CH_2Cl_2 at 0 °C resulted in partial aromatization of the bicyclic system. However, lactonization of **47a** and **47b** proceeded cleanly with the use of *p*-toluenesulfonic acid in benzene at 25 °C to yield two β-hydroxy lactones, **1a** and **49**, which were isolated by HPLC. The retention times of **1a** and **49** were 14.8 and 21.8 min, respectively. The synthetic specimen **1a** was found to be identical (IR, HPLC, ^1H NMR, ^{13}C NMR, MS) with natural (+)-compactin. Likewise, the more polar pair of β,δ-dihydroxy esters, **48a** and **48b**, was lactonized and separated by HPLC into two lactones, **50** and **51**, with retention times of 16.4 and 24.4 min, respectively.

To define the absolute stereochemistry of the two newly generated asymmetric centers of the lactone-ring portion of the molecule in **49**, **50**, and **51**, we made the following correlations: Treatment of either natural (+)-compactin or **50** with $KHSO_4$[1] afforded anhydrocompactin (**52**), whereas under the same dehydrating conditions, **49** and **51** were transformed into anhydroisocompactin (**53**). Hence, **1a** and **50** as well as **49** and **51** differ only in the configuration of the β-hydroxyl group as illustrated in Scheme IV. This assignment is in agreement with the similarities of ^1H NMR of **1a** to **49** and **50** and **51**. Having established the absolute stereochemistry of these three diastereomers, it is now possible to analyze the stereoselectivity of the reactions used for the construction of the lactone ring. Since the ratio of **1a** and **50** to **49** and **51** is approximately 1:1, no selectivity was obtained in the aldol condensation of **44**, as expected. On the other hand, the ratio of **1a** and **49** to **50** and **51** approaches (2:1), indicating that $Zn(BH_4)_2$ reduction gave the axial alcohol preferentially.

In summary, (+)-compactin (**1a**) was synthesized in 0.8% yield in 14 steps from the key intermediate **3**, which was prepared in 70% overall yield from **6**.

Experimental Section

Melting points were determined on a Thomas-Hoover Unimelt apparatus and are uncorrected. ^1H NMR spectra were recorded on a Bruker HXE-90 spectrometer in deuteriochloroform solution with tetramethylsilane as the internal standard. Chemical shifts are reported in δ (peak multiplicity, coupling constant if appropriate, number of protons). When peak multiplicities are reported, the following abbreviations are used: s, singlet, d, doublet; t, triplet; q, quartet; m, multiplet; br, broadened. ^{13}C NMR spectra were obtained on a Jeol FX-90Q spectrometer operating at a frequency of 22.5 MHz. Infrared spectra were obtained on a Perkin-Elmer Model 599B spectrophotometer as a neat liquid or chloroform solution between sodium chloride plates. Data are given in cm^{-1} by using the following convention: w, weak; m, medium; s, strong; sh, shoulder. Ultraviolet spectra were recorded on a Cary 14 UV-VIS spectrophotometer in methanol. High-resolution mass spectroscopy was performed on an AEI MS-9 double-focusing mass spectrometer. Elemental analyses were performed by Galbraith Laboratories. Optical rotations were measured with a Hitachi Perkin-Elmer Model 241C instrument in ethanol unless otherwise stated. The designation *c* refers to concentration in grams per milliliter.

All solvents were purified before use: Benzene, toluene, CH_3CN, CH_2Cl_2, and DMF were distilled from CaH_2 and kept over 4-Å molecular sieves. Ether and THF were distilled from LAH. Me_2SO and pyridine were distilled in vacuo from BaO and kept over 4-Å molecular sieves. Et_3N was distilled from NaOH, and EtOH was dried over Mg and distilled prior to use. HMPA was distilled in vacuo from NaOH. Acetone was stirred with anhydrous $CaCl_2$ overnight and then distilled from BaO. Column chromatography was performed by using MN-Keiselgel 60 (0.05–0.2 mm/70–270 mesh, Brinkmann). All chromatography solvents were distilled prior to use. Preparative thin layer chromatography (TLC) was performed on 20 × 20 cm (EM) plates coated with 0.25-, 0.50-, and 2-mm thickness of silica gel containing PF254 indicator (Brinkmann).

Microbiological Reduction of (±)-1,4,5,8,9,10-*trans*-Hexahydronaphthalene-1,4-dione (5). The surface growth from a 1-week old agar slant of *Aureobasidium pullulans* NRRL Y-12610 was suspended in 5 mL of saline (0.85%) solution. Portions (2 mL) of this suspension were used to inoculate 50 mL of the Vogel's medium [yeast extract, 5 g; casamino acids, 5 g; dextrose, 40 g; trisodium citrate–5.5-water, 3 g; KH_2PO_4, 5 g; NH_4NO_3, 2 g; $CaCl_2 \cdot 2H_2O$, 0.1 g; $MgSO_4 \cdot 7H_2O$, 0.2 g;

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trace element solution (citric acid–1-water, 5 g; $ZnSO_4 \cdot 7H_2O$, 5 g; $Fe(NH_4)_2(SO_4)_2 \cdot 6H_2O$, 1 g; $CuSO_4 \cdot 5H_2O$, 0.25 g; $MnSO_4 \cdot 1H_2O$, 0.05 g; H_3BO_3, 0.05 g; $Na_2MoO_4 \cdot 2H_2O$, 0.05 g per 100 mL), 0.1 mL; distilled water to 1 L, pH 5.6] held in 250-mL Erlenmeyer flasks (F-1 stage). The flasks were incubated at 25 °C on a rotary shaker (250 cycles/min; 2-in. radius) for 24 h, after which a 10% volume transfer was made to each of four 2-L Erlenmeyer flasks (F-2 stage) containing 500 mL of the Vogel's medium. After 24 h of inoculation on a rotary shaker, 1.5 g of finely ground powder of (±)-**5** was dispersed to each flask. A total of 38 F-2 stage flasks were then incubated for an additional 72 h under the conditions used in the incubation of the F-1 stage flasks.

The cells were removed by filtration through Celite. The supernatant was adjusted to pH 3.0 with 6 N HCl and was continuously extracted with chloroform for 3 days. After evaporation of the chloroform in vacuo, 65 g of crude residue was obtained. This residue was mixed with 200 g of silica gel, made into a slurry with acetone/$CHCl_3$ (35:65), and was charged onto a column (9.5-cm inside diameter) containing 3 kg of silica gel. After the column was washed with 4 L of the above solvent system, 200-mL fractions were collected. Fractions 19–34 (17.7 g) contained pure (−)-**6**: mp 169–170 °C; $[\alpha]^{25}_D$ −3.93° (*c* 10.87). Fractions 35–38 contained a 1:1 mixture (1.93 g) of (−)-**6** and (+)-**7** (estimated by TLC). Fractions 39–43 contained 5.6 g of pure (+)-**7**: mp 170–171 °C; $[\alpha]^{25}_D$ +170.6° (c 2.61). Fractions 44–47 consisted of a mixture (1 g) of (+)-**7** containing 5% of (±)-**8** whereas fractions 48–55 contained 9.8 g of a mixture of (+)-**7** and (±)-**8** in a ratio of 1:1. Fractions 56–70 (7.8 g) contained mostly (±)-**8** contaminated with less than 5% of (+)-**7**. Finally, pure (±)-**8** (11.8 g) [mp 167–171 °C; $[\alpha]^{25}_D$ +13.74° (c 2.97)] was obtained in fractions 71–110.

Further purification of fractions 48–55 and 56–70 by crystallization from acetone gave 11.9 g of pure (±)-**8**. The total yields obtained were as follows: (−)-**6**, 18.67 g (33%); (+)-**7**, 12.8 g (22.5%); and (±)-**8**, 23.7 g (41.6%). The TLC R_f values with acetone/$CHCl_3$ (2:3) as solvent were as follows: (−)-**6**, 0.58; (+)-**7**, 0.42; and (±)-**8**, 0.38. Jones oxidation of (−)-**6** afforded (−)-**5** [mp 89–90 °C; $[\alpha]^{25}_D$ +393° (c 0.72)], and (+)-**7** gave (+)-**5** [mp 89–90 °C; $[\alpha]^{25}D$ −393° (c 0.24)].

1β,4α-Bis(benzyloxy)-1,2,3,4,4aβ,5,8,8aα-octahydronaphthalene (9). A 500-mL three-neck flask was charged under N_2 with 120 mL of dried Me_2SO and NaH (8.2 g, 60% oil dispersion, 205 mmol) prewashed with pentane twice. After the mixture was stirred for 15 min, a solution of diol **6** (8.05 g, 47.9 mmol) in 50 mL of Me_2SO was added dropwise under vigorous stirring at room temperature. After 30 min, a solution of benzyl chloride (34.35 mL, 298 mmol) in 75 mL of Me_2SO was added dropwise over a 2-h period. After the addition was complete, the contents were stirred for an additional 3 h at room temperature. The contents were poured into ice water and extracted with ether (3 × 150 mL). The ethereal layer was washed with water and brine. After drying over $MgSO_4$, the filtered extracts were concentrated in vacuo to give 17 g (99%) of **9** as an oil, which was used directly for the subsequent step.

A small sample was further purified by silica gel chromatography to afford pure **9**: $[\alpha]^{24}_D$ +32.4° (*c* 1.49, $CHCl_3$); IR ($CHCl_3$) 3090 (w), 3070 (w), 3030 (w), 3010 (m), 2940 (s), 2910 (ns), 2865 (s), 2850 (s), 1658 (w), 1499 (m), 1456 (m), 1441 (m), 1397 (w), 1354 (m), 1338 (m), 1320 (w), 1200 (m), 1167 (m), 1128 (m), 1093 (s), 1070 (s), 1030 (m), 942 (m), 702 (m), 665 (w) cm^{-1}; ^1H NMR δ 3.49 (br s, 2 H), 4.50 (ABq, *J* = 12, 14 Hz, 4 H), 5.60 (br s, 2 H). Anal. Calcd for $C_{24}H_{28}O_2$: C, 82.72; H, 8.10. Found: C, 82.69; H, 8.07.

7α-Acetoxy-1β,4α-bis(benzyloxy)-6β-(phenylselenyl)-4aβ,8aα-decahydronaphthalene (10). To a stirred solution 4.8 g (30 mmol) of bromine in 100 mL of acetic acid was added 9.6 g (30.7 mmol) of diphenyl diselenide in one portion. After the resulting dark red solution was stirred for 10 min at room temperature, 20.9 g (60 mmol) of **9** in 20 mL of acetic acid was added, followed by 12 g (122 mmol) of anhydrous potassium acetate. The reaction mixture was stirred at 25 °C for an additional hour, and the pale-yellow suspension was then poured into 200 mL of water and extracted with ether (3 × 150 mL). The combined ethereal extracts were successively washed with water, saturated $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$, and the solvent was removed in vacuo to yield a viscous liquid (32 g), which was subjected to hydrolysis directly.

A small portion (200 mg) of crude **10** was chromatographed over 6 g of silica gel. Elution of the column with hexane–ethyl acetate furnished pure **10**: $[\alpha]^{25}_D$ +22.4° (*c* 6.53, $CHCl_3$); IR (liquid film) 3090 (w), 3065 (w), 3035 (w), 2935 (m), 2865 (m), 1736 (s), 1581 (w), 1498 (w), 1457 (m), 1441 (m), 1372 (m), 1356 (m), 1338 (w), 1315 (w), 1241 (s), 1204 (m), 1122 (sh), 1091 (m), 1074 (m), 1028 (br), 948 (w), 902 (w), 740 (m), 700 (m) cm^{-1}; ^1H NMR δ 2.03 (s, 3 H), 3.39 (br s, 2 H), 3.66 (br s, 1 H), 5.19 (br s, 1 H). Exact mass calcd for $C_{32}H_{36}O_4{}^{80}Se$: 564.1778. Found: 564.1771.

1β,4α-Bis(benzyloxy)-7α-hydroxy-6β-(phenylselenyl)-4aβ,8aα-decahydronaphthalene (11). A solution containing 56.2 g (99.7 mmol) of **10**, 230 mL of 4% methanolic KOH, and 70 mL of ether was stirred at 25 °C for 2 h. The contents were poured into 400 mL of water, and the organic layer was separated. The aqueous layer was extracted with ether (2 × 300 mL), and the combined organic extracts were washed with water and brine. After the organic layer was dried with $MgSO_4$, the solvent was concentrated in vacuo to give an oil, which was chromatographed over 2 kg of silica gel. Elution of the column with ethyl acetate–hexane (1:4), and then increased to (2:3), afforded 37 g (88%) of **11** as a pale yellow liquid: TLC (hexane–ethyl acetate, 7:3) R_f 0.51; $[\alpha]^{25}_D$ +38° (*c* 1.87, $CHCl_3$); IR (liquid film) 3700–3180 (m), 3090 (w), 3065 (m), 3030 (m), 2930 (s), 2860 (s), 1581 (m), 1498 (m), 1480 (m), 1455 (m), 1440 (m), 1395 (w), 1355 (m), 1338 (m), 1219 (m), 1201 (m), 1175 (m), 1122 (sh), 1090 (m), 1070 (s), 1029 (m), 1004 (m), 955 (w), 937 (m), 904 (w), 870 (w), 750 (s), 700 (m) cm^{-1}; ^1H NMR δ 3.30 (br s, 2 H), 3.46 (br s, 1 H), 4.06 (m, 1 H). Exact mass calcd for $C_{30}H_{34}O_3{}^{80}Se$: 522.1672. Found: 522.1673.

1β,4α-Bis(benzyloxy)-7-oxo-1,2,3,4,4aβ,7,8,8aα-octahydronaphthalene (3). To a solution of 37 g (70.9 mmol) of **11** in 200 mL of THF was added dropwise 35 mL of 30% H_2O_2. The mixture was stirred at 25 °C for 2.5 h and then refluxed for 2 h. After cooling, the contents were diluted with 100 mL of acetone. The brown solution was cooled in an ice bath, and 108 mL of Jones reagent was added over a period of 15 min. Water (600 mL) was then added, and the aqueous mixture was extracted with ethyl acetate (3 × 800 mL). The combined organic phases were washed with water and brine. After the organic layer was dried over Na_2SO_4, the solvent was evaporated in vacuo to furnish an oil (24.5 g), which was chromatographed over 1 kg of silica gel. Elution of the column with hexane–ethyl acetate (4:1) gave 20.6 g of **3** (80%) as a white solid. Recrystallization from petroleum ether–ether (1:1) gave an analytical sample: mp 73–74 °C; $[\alpha]^{25}_D$ +38.3° (*c* 8.95, $CHCl_3$); IR ($CHCl_3$) 3090 (w), 3070 (w), 3030 (m), 3010 (m), 2945 (m), 2875 (m), 1672 (s), 1499 (m), 1457 (m), 1392 (m), 1356 (m), 1339 (m), 1271 (m), 1253 (m), 1199 (m), 1169 (w), 1153 (m), 1125 (m), 1088 (s), 1071 (s), 1052 (m), 1030 (m), 955 (w), 916 (m), 859 (m), 700 (m), 601 (w) cm^{-1}; ^1H NMR δ 3.53 (br s, 1 H), 3.83 (br s, 1 H), 5.98 (dd, *J* = 10, 2.5 Hz, 1 H), 6.78 (d, *J* = 10 Hz, 1 H); mass spectrum, *m/e* 363 ($M^+ + H$), 362 (M^+). Anal. Calcd for $C_{24}H_{26}O_3$: C, 79.53; H, 7.23. Found: C, 79.47; H, 7.09.

2α,4α-Dihydroxy-3β-iodocyclopentane-1α-acetic Acid γ-Lactone (14). A solution of 5-norbornen-2-one (**13**, 70.2 g, 0.65 mol) in 272 mL of ether was mixed with 260 mL of water containing 32 g of NaOH. The two-phase system was cooled in an ice bath and rapidly stirred while 260 mL of 30% H_2O_2 was added over a 40-min period. The aqueous phase was then separated, washed with ether, and then neutralized with 4 N HCl. To this aqueous solution was added 0.5 g of $NaHCO_3$, followed by KI (270 g, 1.63 mol) and I_2 (413 g, 1.63 mol). After stirring at 4 °C for 16 h, the reaction mixture was treated wtih a solution of $Na_2S_2O_3$ until colorless. The contents were then extracted with ethyl acetate (3 × 400 mL). The extract was washed successfully with $Na_2S_2O_3$, water, and brine and then dried over Na_2SO_4. The solvent was then evaporated in vacuo to yield 110 g (63%) of **14** as a white solid: ^1H NMR δ 3.34 (s, 1 H), 4.51 (br s, 1 H), 5.26 (d, *J* = 6.6 Hz, 1 H). This compound was used in the next step without further purification.

2α,4α-Dihydroxycyclopentane-1α-acetic Acid γ-Lactone (15). To 610 mL of dry benzene were added 181 g (0.675 mol) of **14** and 317 g (1.09 mol) of tributyltin hydride. After the mixture was heated at 70 °C for 1 h, benzene was evaporated under reduced pressure, and the residue was dissolved in 300 mL of acetonitrile, which was washed with hexane (5 × 100 mL). The CH_3CN layer was then concentrated in vacuo to give a grayish oil. Crystallization from benzene afforded 89 g (93%) of **15** as prisms: mp 82–84 °C; TLC (acetone–$CHCl_3$, 35:65) R_f 0.38; ^1H NMR δ 2.72 (d, *J* = 9.6 Hz, 1 H), 3.04 (m, 1 H), 4.42 (br s, 1 H), 5.06 (t, *J* = 6 Hz, 1 H). Anal. Calcd for $C_7H_{10}O_3$: C, 66.65; H, 7.99. Found: C, 66.49; H, 7.83.

2α-Hydroxy-4β-benzoylcyclopentane-1α-acetic Acid γ-Lactone (16). To a solution containing 10 g (70 mmol) of **15**, 37.2 g (142 mmol) of triphenylphosphine, and 17.3 g (142 mmol) of benzoic acid were added under N_2 24.6 g (142 mmol) of diethyl azodicarboxylate in 70 mL of THF over a period of 1.5 h. The reaction mixture was then stirred for 3 h and concentrated in vacuo. The residue was triturated with ethyl acetate–hexane (1:4) to remove most of the triphenylphosphine oxide. The filtrate was concentrated in vacuo, and the residue was chromatographed over 400 g of silica gel. Elution of the column with ethyl acetate–hexane (1:9 to 1:1) afforded 14.26 g (74%) of **16**: TLC (hexane–ethyl acetate, 1:1) R_f 0.54; ^1H NMR δ 5.10 (m, *J* = 4.5 Hz, 1 H), 5.53 (m, *J* = 4.5 Hz, 1 H), 7.53 (t, *J* = 9 Hz, 3 H), 7.98 (dd, *J* = 7.5 Hz, 2 H). Anal. Calcd for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 68.10; H, 5.67.

3α,4β-Dihydroxycyclopentane-1α-acetic Acid γ-Lactone (17). A solution of 1.5 L of CH_3OH containing 58.6 g (0.214 mol) of **16** and 2.9

g (53.7 mmol) of sodium methoxide was stirred for 16 h. The reaction mixture was neutralized with acetic acid and was then concentrated in vacuo. The residue was chromatographed over 600 g of silica gel. Elution of the column with acetone–chloroform (3:7) gave 30.3 g (100%) of **17** as a viscous oil: TLC (acetone–$CHCl_3$, 35:65) R_f 0.35; ^1H NMR δ 2.60 (br s, 1 H), 2.73 (d, J = 9.6 Hz, 1 H), 3.10 (m, 1 H), 4.48 (m, J = 4.8 Hz, 1 H), 5.06 (m, J = 4.5 Hz, 1 H). Anal. Calcd for $C_7H_{10}O_3$: C, 66.65; H, 7.99. Found: C, 66.57; H, 7.78.

1β-[3α-Hydroxy-4α-(2-hydroxyethyl)cyclopentyl] 2-Tetrahydropyranyl Ether (19). To a solution of 220 mL of CH_2Cl_2 containing 42 g (0.296 mol) of **17** and 0.4 g (2.1 mmol) of *p*-toluenesulfonic acid was added dropwise 30 g (0.35 mol) of dihydropyran at 0 °C under stirring. After completion of the addition, the contents were stirred at 25 °C for 1.5 h. The reaction mixture was then diluted with 300 mL of CH_2Cl_2 and washed with 5% $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo to give **18** as a viscous oil: TLC (hexane–ethyl acetate, 1:1) R_f 0.41; ^1H NMR δ 2.68 (d, J = 9 Hz, 1 H), 3.00 (m, 1 H), 3.65 (m, 2 H), 4.38 (m, J = 4.8 Hz, 1 H), 4.58 (br s, 1 H), 5.02 (m, 1 H). The crude **18** (67.8 g, 0.3 mol) was dissolved in 1 L of absolute ethanol and was then treated with 18.5 g (0.48 mol) of $NaBH_4$ at 25 °C. After the mixture was stirred for 16 h, the contents were diluted with 800 mL of water and then extracted with ethyl acetate (3 × 500 mL). After concentration of the solvent in vacuo, the residue was chromatographed over 1 kg of silica gel. Elution of the column with acetone–$CHCl_3$ (3:7) gave 57.5 g (85%) of **19** as an oil: TLC (acetone–$CHCl_3$, 2:3) R_f 0.31; ^1H NMR δ 3.64 (m, 4 H), 4.32 (m, 1 H), 4.56 (br s, 1 H). Anal. Calcd for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63. Found: C, 62.49; H, 9.58.

2-(1β-(2β-Hydroxy-4α-(2-tetrahydropyranyloxy))cyclopentyl)ethyl Benzoate (20). To a solution of 57.5 g (0.25 mol) of **19** in triethylamine (1.5 L) at 0 °C was added dropwise benzoyl chloride (64.6 g, 0.46 mol). After the addition was complete, the reaction mixture was stirred at 4 °C for 24 h. The resultant precipitate was filtered off and washed with ether. The filtrate was washed with water and brine and was evaporated under reduced pressure. The residue was redissolved in ether, washed successively with Na_2CO_3, H_2O, and brine, and then dried over Na_2SO_4. After concentrating in vacuo, the residue was chromatographed over 1.5 kg of silica gel. Elution of the column with ethyl acetate–hexane (1:1) afforded 80.2 g (96%) of **20** as an oil: TLC (hexane–ethyl acetate, 1:1) R_f 0.39; IR (liquid film) 3640–3120 (m), 2940 (s), 2878 (m), 1718 (s), 1613 (w), 1602 (w), 1586 (w), 1469 (sh), 1453 (m), 1440 (sh), 1385 (w), 1345 (w), 1317 (m), 1278 (s), 1202 (w), 1180 (w), 1158 (w), 1134 (sh), 1117 (m), 1073 (m), 1022 (m), 985 (sh), 871 (w), 812 (w), 717 (m) cm^{-1}; ^1H NMR δ 2.44 (br s, 1 H), 4.39 (t, J = 7.5 Hz, 2 H), 7.45 (m, 3 H), 8.05 (dd, J = 7.5 Hz, 2 H); mass spectrum, m/e 334 (M^+), 316 ($M^+ - H_2O$). Exact mass calcd for $C_{19}H_{26}O_5$: 334.1780. Found: 334.1782.

2-(1β-(2-oxo-4α-(2-tetrahydropyranyloxy))cyclopentyl)ethyl Benzoate (21). To a solution of **20** (59.8 g, 0.179 mol) in 1.5 L of CH_2Cl_2 were added small portions of pyridinium chlorochromate (57.8 g, 0.268 mol) and sodium acetate (18 g, 0.22 mol) with stirring at room temperature. After 2 h, ether (2 L) was added and the upper layer was decanted. The black residue was washed with ether (3 × 500 mL). The combined ethereal extracts were passed through a short column of Florisil. The solvents were concentrated under reduced pressure, and the residue was chromatographed over 1.5 kg of silica gel. Elution of the column with hexane–ethyl acetate (1:1) gave 67 g (84%) of **21** as an oil: TLC (hexane–ethyl acetate, 1:1) R_f 0.60; IR ($CHCl_3$) 2998 (w), 2940 (m), 2850 (w), 1740 (s), 1710 (s), 1600 (w), 1581 (w), 1462 (w), 1450 (m), 1440 (w), 1385 (m), 1339 (m), 1313 (m), 1272 (s), 1174 (m), 1150 (m), 1113 (m), 1069 (m), 1030 (sh), 1023 (m), 1004 (m), 971 (m), 903 (w), 866 (w), 707 (m) cm^{-1}; ^1H NMR δ 4.39 (t, J = 7.5 Hz, 2 H), 7.48 (m, 3 H), 8.03 (dd, J = 7.5 Hz, 2 H); mass spectrum, m/e 332 (M^+). Exact mass calcd for $C_{19}H_{24}O_5$: 332.1624. Found: 332.1621.

Transformation of 21 into 22. To a solution of **21** (10.04 g, 30.3 mmol) in 200 mL of CH_2Cl_2 were added 12.1 g (59.6 mmol) of *m*-chloroperbenzoic acid and 16.15 g (193 mmol) of anhydrous sodium bicarbonate. After the reaction mixture was stirred in the dark for 20 h at 25 °C, 75 mL of 10% $Na_2S_2O_3$ was added, and the contents were diluted with 400 mL of CH_2Cl_2. The mixture was then washed with 5% $NaHCO_3$ (3 × 100 mL), water, and brine and dried over Na_2SO_4. The solvents were concentrated in vacuo, and the residue was chromatographed on 250 g of silica gel. Elution of the column with ethyl acetate–hexane (1:1) gave 9.2 g (87.5%) of **22**. Crystallization from ethyl acetate–petroleum ether afforded pure **22** as needles: mp 74–78 °C; TLC (hexane–ethyl acetate, 1:1) R_f 0.36; IR ($CHCl_3$) 3010 (w), 2950 (m), 2860 (w), 1735 (sh), 1720 (s), 1603 (w), 1586 (w), 1468 (w), 1455 (m), 1444 (w), 1381 (w), 1342 (w), 1319 (m), 1280 (s), 1256 (sh), 1210 (sh), 1180 (m), 1158 (w), 1120 (m), 1073 (m), 1036 (m), 1029 (m), 995 (sh), 976 (w), 937 (w), 872 (w), 712 (m), cm^{-1}; ^1H NMR δ 2.66 (d, J = 9 Hz, 1 H), 2.74 (d, J = 9 Hz, 1 H), 4.29 (m, 1 H), 4.53 (t, J = 6 Hz, 2 H), 7.46 (m, 3 H), 8.05 (dd, J = 7.0 Hz, 2 H); mass spectrum, m/e 348 (M^+). Exact mass calcd for $C_{19}H_{24}O_6$: 348.1573. Found: 348.1569.

Reduction of 22 with Diisobutylaluminum Hydride. To a solution containing 18.86 g (54.2 mmol) of **22** in 850 mL of dry toluene at −78 °C under N_2 was added diisobutylaluminum hydride (103 mL of 25 wt % solution in toluene, Aldrich) over a 10-min period. After the reaction mixture was stirred for 1.5 h at −78 °C, 450 mL of methanol was added and the temperature was slowly raised to 25 °C. Another 500 mL of methanol was then added, and the resultant solution was stirred for 2 h. A white precipitate appeared, which was removed by filtration. The filtrate was concentrated in vacuo, and the residue was chromatographed over 600 g of silica gel. Elution of the column with acetone–chloroform (1:1) yielded 13.33 g (100%) of **23** as an oil: TLC (acetone–$CHCl_3$, 1:1) R_f 0.38; ^1H NMR δ 3.72 (t, J = 6 Hz, 2 H), 4.60 (br s, 1 H), 5.05 (m, 1 H).

Methylation of 23. A reaction mixture containing **23** (360 mg, 1.46 mmol), Ag_2O (580 mg, 2.5 mmol), and CH_3I (2.26 g, 15.9 mmol) in 25 mL of anhydrous ether was refluxed under N_2 for 40 h. After cooling, a white precipitate was formed, which was removed by filtration. The filtrate was concentrated to dryness under reduced pressure, and the residue was purified by column chromatography on silica gel (10 g). Elution of the column with acetone–$CHCl_3$ (2:3) gave 323 mg (90%) of **24** as an oil: TLC (acetone–$CHCl_3$, 1:3) R_f 0.40; IR (liquid film) 3700–3100 (m), 2940 (s), 2872 (m), 1469 (w), 1445 (m), 1391 (m), 1355 (sh), 1340 (m), 1325 (sh), 1285 (w), 1260 (w), 1215 (m), 1185 (m), 1145 (m), 1119 (m), 1090 (m), 1079 (m), 1041 (s), 1025 (sh), 1002 (m), 957 (w), 919 (m), 872 (m), 815 (w), 735 (w) cm^{-1}; ^1H NMR δ 2.61 (br s, 1 H), 3.46 (s, 3 H), 3.77 (t, J = 6 Hz, 2 H); mass spectrum, m/e 260 (M^+), 228 ($M^+ - CH_3OH$), 211 ($M^+ - H_2O - CH_3O$). Exact mass calcd for $C_{13}H_{24}O_5$: 260.1624. Found: 260.1620.

Conversion of 24 into 25. To a solution of **24** (2.8 g, 11 mmol) in dry pyridine (150 mL) was added *p*-toluenesulfonyl chloride (2.52 g, 13.2 mmol) at 0 °C. The reaction mixture was stirred at 4 °C for 24 h and poured into ice water. The aqueous phase was extracted with ether (2 × 100 mL), and the organic layer was successively washed with 1 N HCl, $NaHCO_3$, H_2O, and brine. After the extract was dried over Na_2SO_4, the solvent was concentrated in vacuo to give an oil, which was dissolved in 130 mL of dry benzene and then refluxed with NaI (4 g, 26.6 mmol) for 14 h under N_2. The cooled reaction mixture was concentrated in vacuo, and the residue was dissolved in ether. After the organic layer was washed with H_2O, $NaHCO_3$ and brine, it was dried over Na_2SO_4. Evaporation of the solvent under reduced pressure afforded 3.05 g (77%) of **25** as an oil, which was purified by being passed through a short silica gel column. Elution of the column with hexane–ethyl acetate (1:1) gave a pure sample: TLC (hexane–ethyl acetate, 1:1) R_f 0.65; IR (liquid film) 2938 (s), 2870 (m), 2845 (m), 1468 (w), 1443 (m), 1392 (m), 1350 (sh), 1337 (m), 1303 (w), 1281 (w), 1261 (m), 1232 (w), 1203 (m), 1183 (m), 1155 (m), 1138 (m), 1117 (m), 1079 (m), 1036 (s), 1025 (sh), 1000 (m), 962 (w), 932 (w), 907 (w), 872 (m), 815 (w) cm^{-1}; ^1H NMR δ 3.29 (t, J = 7.5 Hz, 2 H), 3.50 (s, 3 H); mass spectrum, m/e 370 (M^+), 338 ($M^+ - CH_3OH$). Exact mass calcd for $C_{13}H_{23}O_4I$: 370.0643. Found: 370.0641.

(4aα,8aβ)-5β,8α-Bis(benzyloxy)-2α-methyl-3-oxo-1β-[3-(1-ethoxyethoxy)propyl]decahydronaphthalene (28). The mixed cuprate **27** was prepared by the addition of 2 mL (1.0 mmol) of the lithium reagent [prepared by reacting ethyl-3-bromopropyl acetaldehyde acetal with lithium metal (1% Na, 50% mineral oil, Alfa, washed with pentane three times) in anhydrous ether under argon according to Eaton et al.[21]] to a suspension of phenylthiocopper (138 mg, 0.08 mmol) in 5 mL of dry THF at −20 °C under N_2. After the addition was complete, the colorless solution was stirred at −20 °C for 10 min and a solution of the enone **3** (200 mg, 0.55 mmol) in 1 mL of dry THF was added via a syringe. The reaction mixture was stirred at −20 °C for 30 min. The solvent was then removed in vacuo (temperature was maintained below 0 °C), and 5 mL of DME was added. To this dark slurry was injected quickly 2 mL of CH_3I (4.56 g, 32 mmol), and the resulting green solution was stirred at −20 °C for 20 min. Water was then added, and the aqueous solution was extracted with ether (3 × 20 mL). The organic layer was washed with brine and then dried over Na_2SO_4. Evaporation of the solvent afforded an oily residue, which was chromatographed over 10 g of silica gel. Elution of the column with $CHCl_3$–acetone (95:5) gave 224 mg (80%) of **28**: TLC (benzene–methanol, 9:1) R_f 0.68; IR (liquid film) 3065 (w), 3030 (w), 2975 (m), 2935 (m), 2875 (m), 1710 (s), 1498 (w), 1454 (m), 1379 (m), 1354 (m), 1338 (m), 1234 (m), 1195 (m), 1132 (m), 1088 (m), 1064 (s), 1030 (m), 959 (w), 876 (w), 735 (m), 701 (m) cm^{-1}; ^1H NMR δ 1.00 (d, J = 6.8 Hz, 3 H), 1.20 (t, J = 7 Hz, 3 H), 1.29 (d, J = 5.2 Hz, 3 H), 4.67 (q, J = 6 Hz, 1 H). Exact mass calcd for ($M^+ - C_2H_5O$) $C_{30}H_{39}O_4$: 463.2849. Found: 463.2802.

(4aα,8aβ)-5β,8α-Bis(benzyloxy)-2-(hydroxymethyl)-3-oxo-1β-[3-(1-ethoxyethoxy)propyl]decahydronaphthalenes (29 and 30). To a stirred

suspension of phenylthiocopper (5.5 g, 32 mmol) in 90 mL of dry THF at −20 °C was added under N_2 70 mL of the lithium reagent, prepared as described above. After the completion of the addition (5 min), the colorless (sometimes slightly pink depending on the quality of phenylthiocopper) solution was stirred at −20 °C for 10 min, and a solution of **3** (8 g, 22 mmol) in 40 mL of dry THF was quickly added via syringe. The greenish yellow solution was stirred at −20 °C for 30 min and then cooled to −78 °C. A stream of gaseous formaldehyde, generated by heating paraformaldehyde (0.99 g) at 170 °C and carried by a gentle flow of N_2 gas, was passed into the solution. The reaction was quenched by the addition of 200 mL of a saturated solution of NH_4Cl, and the mixture was then extracted with ethyl acetate (3 × 300 mL). The combined organic phases were washed with brine and then dried over Na_2SO_4. Evaporation of the volatiles under reduced pressure afforded an oil, which was chromatographed over 500 g of silica gel. Elution of the column with $CHCl_3$–acetone (5:1) gave 7.73 g (67%) of a mixture of the alcohols **29** and **30** as a colorless liquid: IR (liquid film) 3690–3155 (m), 3090 (w), 3065 (w), 3035 (m), 2975 (s), 2935 (s), 2875 (s), 1700 (s), 1609 (w), 1498 (m), 1454 (m), 1379 (m), 1354 (m), 1338 (m), 1231 (m), 1202 (m), 1182 (m), 1130 (s), 1090 (s), 1060 (s), 1029 (s), 982 (m), 951 (m), 927 (m), 873 (m), 858 (w), 732 (m), 700 (m) cm^{-1}; ^1H NMR δ 1.19 (t, J = 7 Hz, 3 H), 1.30 (d, J = 5 Hz, 3 H), 3.19–3.96 (m, 8 H); mass spectrum, m/e 479 ($M^+ - C_2H_5O$), 461 ($M^+ - C_2H_5O - H_2O$).

(4aα,8aβ)-5β,8α-Bis(benzyloxy)-2-methylene-3-oxo-1β-[3-(1-ethoxyethoxy)propyl]decahydronaphthalene (31). To a mixture of **15** and **16** (30.7 g, 58.5 mmol) in 280 mL of CH_2Cl_2 at −5 °C was added 17.4 mL of triethylamine followed by methanesulfonyl chloride (10.5 g, 91.7 mmol). After stirring for 30 min, the reaction mixture was diluted with 100 mL of CH_2Cl_2, washed with water and brine, and then dried over Na_2SO_4. Evaporation of the volatiles under reduced pressure gave 38 g of an oil, which was subjected to elimination as follows: the crude mesylates obtained above were dissolved in 350 mL of dry benzene and 12.5 g (82.1 mmol) of 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) was added. After the mixture was stirred at 25 °C for 1 h, the contents were concentrated in vacuo to 35 mL. After dilution with 350 mL of ethyl acetate, the resulting solution was washed with water and brine. After the organic layer was dried over Na_2SO_4, the solvents were concentrated in vacuo to give an oil, which was chromatographed over 1.2 kg of silica gel. Elution of the column with hexane–ethyl acetate (6:4) yielded 28.09 g (95%) of **31** as a colorless liquid: IR ($CHCl_3$) 3090 (w), 3070 (w), 305 (m), 2940 (s), 2872 (m), 1691 (s), 1606 (m), 1498 (w), 1465 (sh), 1454 (m), 1395 (m), 1382 (m), 1354 (m), 1339 (m), 1305 (w), 1270 (w), 1238 (w), 1200 (w), 1130 (s), 1088 (s), 1064 (s), 1030 (m), 949 (m), 873 (w), 700 (m), 663 (w), 601 (w) cm^{-1}; ^1H NMR δ 1.17 (t, J = 6 Hz, 3 H), 1.27 (d, J = 5 Hz, 3 H), 3.20–3.87 (m, 6 H), 5.19 (br s, 1 H), 5.92 (br s, 1 H); mass spectrum, m/e 434 ($M^+ - C_4H_8O$).

Hydrogenation of 31. A mixture containing 1 g of **31** and 100 mg of 10% Pd/C in 70 mL of absolute ethanol was hydrogenated under 1 atm of H_2 for 2 h. The progress of the reaction was monitored by TLC (benzene–ethyl acetate, 2:1). The reaction mixture was filtered through Celite, and the filtrate was evaporated in vacuo to yield an oily residue (980 mg). For identification, 30 mg of this crude residue was dissolved in $CHCl_3$, applied to a TLC plate (0.5 mm, 20 × 20 cm), and developed three times with a solvent mixture consisting of acetone–hexane (1:9). Three distinct UV absorbing bands were noted. Elution of the least polar band with $CHCl_3$ gave 8.3 mg of **28**; the middle band (8.4 mg) consisted of **32**: TLC (benzene–acetone, 9:1) R_f 0.59; IR (liquid film) 3065 (w), 3030 (w), 2975 (m), 2935 (s), 2875 (s), 1710 (s), 1498 (w), 1454 (m), 1378 (m), 1354 (m), 1339 (m), 1265 (m), 1195 (m), 1130 (m), 1090 (s), 1065 (s), 1030 (m), 739 (m), 702 (m) cm^{-1}; ^1H NMR δ 1.03 (d, J = 7 Hz, 3 H), 1.10 (t, J = 7 Hz, 3 H), 1.27 (d, J = 6 Hz, 3 H), 3.43 (br s, 1 H), 3.80 (br s, 1 H). Exact mass calcd for ($M^+ - C_2H_5O$) $C_{30}H_{39}O_4$: 463.2849. Found: 463.2802.

The most polar band (5.6 mg) was identified as **33**: ^1H NMR δ 1.18 (t, J = 6.5 Hz, 3 H), 1.29 (d, J = 5 Hz, 3 H), 1.82 (br s, 3 H), 3.24–3.80 (m, 5 H), 4.10 (br s, 1 H); mass spectrum, m/e 434 ($M^+ - C_4H_8O$).

Hydrogenation of 31 in the Presence of Pyridine. A solution containing **31** (15.63 g, 30.89 mmol) in 325 mL of dry benzene and dry pyridine (16.1 g, 204 mmol) with 1.013 g of 10% palladium on charcoal was stirred under hydrogen (1 atm) at 25 °C for 40 min. Under these same conditions, two other separate experiments were conducted by using 3.79 g and 8.67 g of **31**. The combined hydrogenated mixtures were filtered through a pad of Celite. The catalyst was washed with ethyl acetate (4 × 10 mL), and the combined filtrate and washings were concentrated in vacuo. The oily residue was chromatographed over 2.2 kg of silica gel. Elution of the column with ethyl acetate–hexane (3:7) gave 1.3 g of **28**, 5.8 g of **32**, and 20 g of a mixture. The latter was rechromatographed over 1.2 kg of silica gel. Elution of the column with benzene–ethyl acetate, initially (95:5) and then increased to (90:10), afforded 1.43 g of **28** (total yield 9.75%), pure **32** (16.02 g, total yield 78%), and 1.66 g (5.9%) of a mixture of **28** and **32**.

(4aα,8aβ)-5β,8α-Bis(benzyloxy)-2β-methyl-3-oxo-1β-[3-(1-ethoxyethoxy)propyl]decahydronaphthalene Tosylhydrazone (34). To a sample of **32** (8.78 g, 17.3 mmol) in 40 mL of absolute ethanol containing 10 drops of triethylamine were added 3.9 g (20.9 mmol) of *p*-toluenesulfonylhydrazide (pretreated with triethylamine in ethanol and dried in vacuo) and 4.5 g of anhydrous Na_2SO_4. The mixture was stirred at 25 °C for 7 h. Filtration followed by evaporation of the filtrate under reduced pressure left a glassy residue (**34**): IR ($CHCl_3$) 3030 (w), 2980 (sh), 2938 (m), 2875 (m), 1599 (w), 1495 (w), 1462 (sh), 1454 (m), 1380 (m), 1354 (m), 1338 (m), 1308 (w), 1167 (s), 1128 (m), 1092 (s), 1067 (s), 1030 (m), 950 (w), 922 (w), 814 (w), 701 (w), 661 (w) cm^{-1}; ^1H NMR δ 0.87 (d, J = 6.5 Hz, 3 H), 1.18 (t, J = 6.8 Hz, 3 H), 1.23 (d, J = 5.0 Hz, 3 H), 2.39 (s, 3 H), 3.15–3.88 (m, 6 H). This crude **34** was used directly for the subsequent transformation.

5β,8α-Dibenzyl-2β-methyl-1β-[3-(1-ethoxyethoxy)propyl]-1,2,4aα,5,6,7,8,8aβ-octahydronaphthalene (35). The crude **34** was dissolved in 50 mL of dry THF, and to this solution, maintained at −78 °C, was added under N_2 320 mL of lithium diisopropylamide solution (prepared from 140 mL of 1.55 M *n*-butyllithium in hexane and 22.3 g of diisopropylamine in 150 mL of dry THF). The mixture was warmed to 0 °C during a period of 1 h with stirring. When the temperature approached 0 °C, a brisk bubbling occurred. After the gas evolution subsided, the mixture was stirred at 0 °C for an additional 4 h. The reaction was quenched by adding 400 mL of a saturated NH_4Cl solution and worked up by extracting with ethyl acetate (3 × 500 mL). The combined extracts were washed with water and brine and then dried over Na_2SO_4. Concentration of the solvent in vacuo gave an oil, which was chromatographed over 40 g of silica gel. Elution of the column with acetone–hexane (1:3) afforded 5.3 g (62% from **32**) of the olefin **35**: mp 38–41 °C; IR (liquid film) 3095 (w), 3070 (m), 3030 (m), 3005 (s), 2930 (s), 2870 (s), 2780 (w), 1658 (w), 1609 (w), 1590 (w), 1499 (m), 1456 (m), 1395 (m), 1382 (m), 1372 (m), 1355 (m), 1341 (m), 1310 (m), 1235 (m), 1198 (m), 1140–1045 (s), 1031 (m), 986 (m), 945 (m), 920 (m), 877 (m), 851 (m), 821 (w), 701 (m), 609 (w) cm^{-1}; ^1H NMR δ 0.88 (d, J = 7 Hz, 3 H), 1.18 (t, J = 6.5 Hz, 3 H), 1.26 (d, J = 5 Hz, 1.5 H), 1.28 (d, J = 5 Hz, 1.5 H), 3.22–3.93 (m, 6 H), 5.31–5.96 (m, 3 H). Anal. Calcd for $C_{32}H_{44}O_4$: C, 78.01; H, 9.00. Found: C, 77.95; H, 9.17.

5β,8α-Dihydroxy-2β-methyl-1β-[3-(1-ethoxyethoxy)propyl]-1,2,4aα,5,6,7,8,8aβ-octahydronaphthalene (36). Lithium wire (172 mg, 24.7 mmol) was cut into pieces and added to 35 mL of liquid ammonia freshly distilled from sodium metal. To the deep-blue solution was added dropwise a solution of 1 g (2.03 mmol) of **35** in 12 mL of dry THF. After the addition was completed, the blue solution was stirred for 30 min. The reaction was quenched by slowly adding solid NH_4Cl until the color faded. At this stage, the ammonia was allowed to evaporate at ambient temperature, and to the residue was added 15 mL of water. The aqueous mixture was extracted with ethyl acetate (3 × 20 mL), and the organic layer was washed with water and then dried over $MgSO_4$. Evaporation of the solvent in vacuo gave 635 mg (100%) of **36** as a colorless liquid: TLC (hexane–ethyl acetate, 4:6) R_f 0.39; IR (liquid film) 3700–3110 (s), 3010 (m), 2975 (s), 2935 (s), 2880 (s), 1658 (w), 1530 (w), 1449 (m), 1379 (m), 1341 (m), 1300 (w), 1245 (m), 1198 (m), 1175 (m), 1133 (s), 1087 (s), 1062 (s), 1018 (m), 991 (m), 945 (m), 910 (m), 851 (w), 840 (w), 763 (m), 731 (m) cm^{-1}; ^1H NMR δ 0.87 (d, J = 7.2 Hz, 3 H), 1.22 (t, J = 6.4 Hz, 3 H), 1.31 (d, J = 6 Hz, 3 H), 3.98 (br s, 1 H), 4.16 (br s, 1 H), 4.69 (q, J = 5 Hz, 1 H), 5.40–6.10 (m, 2 H). Anal. Calcd for $C_{18}H_{32}O_4$: C, 69.19; H, 10.32. Found: C, 69.03; H, 10.15.

(*S*)-2-Methylbutyric Anhydride. To a stirred solution of (*S*)-2-methylbutyric acid (8.63 g, 84.57 mmol) in 85 mL of CH_2Cl_2 was added *N*,*N*′-dicyclohexylcarbodiimide (DCC) (9.6 g, 46.6 mmol) at 4 °C. A white precipitate appeared immediately after addition. After the mixture was stirred at 4 °C for 3 h, the contents were cooled with a dry ice–acetone bath and filtered. The white precipitate was washed with cold CH_2Cl_2. After evaporation of the solvent in vacuo, pure (*S*)-2-methylbutyric anhydride (8.2 g, 97%) was obtained by distillation: bp 60 °C (0.2 mm); $[\alpha]^{25}_D$ +30.2° (neat); ^1H NMR δ 0.98 (t, J = 7.5 Hz, 6 H), 1.20 (d, J = 7.5 Hz, 6 H), 1.60 (m, 4 H), 2.45 (m, 2 H).

Selective Monoacylation of 36. To a solution of the diol **36** (26 mg, 0.083 mmol) in 0.5 mL of dry pyridine at 25 °C were added 0.35 mg (0.188 mmol) of (*S*)-2-methylbutyric anhydride and 1.5 mg of (dimethylamino)pyridine. After the reaction mixture was stirred for 16 h at 25 °C, the contents were poured into cold water and extracted with ether (3 × 20 mL). After the organic layer was washed with water and brine, the solvent was dried over Na_2SO_4 and concentrated to dryness in vacuo. The oily residue was chromatographed on a TLC plate (0.5 mm, 20 × 20 cm) and developed with ethyl acetate–hexane (2:3). Elution of the major band (most polar) with chloroform afforded 10 mg of **37**: IR (liquid film) 3660–3105 (m), 3015 (sh), 2965 (s), 2935 (s), 2880 (s),

1730 (s), 1658 (w), 1456 (m), 1381 (m), 1341 (m), 1295 (m), 1264 (m), 1241 (m), 1185 (m), 1135 (m), 1084 (m), 1012 (m), 989 (m), 943 (m), 907 (m), 856 (w), 761 (w), 730 (m) cm^{-1}; ^1H NMR δ 0.83 (d, J = 6.5 Hz, 3 H), 0.88 (t, J = 7.5 Hz, 3 H), 1.12 (d, J = 6.2 Hz, 3 H), 1.20 (t, J = 7 Hz, 3 H), 1.30 (d, J = 5 Hz, 3 H), 3.26–3.82 (m, 5 H), 4.21 (br s, 1 H), 4.68 (q, J = 5 Hz, 1 H), 5.07–5.84 (m, 3 H). Approximately 1 mg of **40** (middle band) and 8 mg of the diester (**39**, least polar band) were also obtained.

Transformation of 36 into 39. To a solution of the diol **36** (720 mg, 2.3 mmol) in 12 mL of dry pyridine containing 4-(dimethylamino)-pyridine (48 mg, 0.393 mmol) was added (*S*)-2-methylbutyrl anhydride (2.4 g, 12.9 mmol). The reaction mixture was stirred at 25 °C under N_2 for 16 h and was then poured into 100 mL of water. The contents were extracted with ether (3 × 50 mL), and the organic layer was washed with water and brine. After drying over Na_2SO_4, the ether was evaporated in vacuo to yield an oil, which was chromatographed over 100 g of silica gel. Elution of the column with ethyl acetate–hexane (1:9) yielded 1.07 g (97%) of **39**: TLC (hexane–ethyl acetate, 9:1) R_f 0.33; IR (liquid film) 3015 (w), 2965 (s), 2935 (s), 2875 (s), 1730 (s), 1463 (m), 1380 (m), 1340 (m), 1297 (w), 1262 (m), 1240 (m), 1181 (s), 1149 (s), 1080 (m), 1012 (m), 988 (w), 932 (w), 909 (m), 750 (w), 730 (m) cm^{-1}; ^1H NMR δ 0.83 (d, J = 6.5 Hz, 3 H), 0.88 (t, J = 7.5 Hz, 3 H), 0.93 (t, J = 7.5 Hz, 3 H), 1.12 (d, J = 6.3 Hz, 3 H), 1.16 (d, J = 7 Hz, 3 H), 1.20 (t, J = 7 Hz, 3 H), 1.29 (d, J = 5 Hz, 3 H), 3.18–3.84 (m, 4 H), 4.64 (q, J = 5 Hz, 1 H), 5.20 (br s, 2 H), 5.28–5.87 (m, 2 H). Exact mass calcd for ($M^+ - C_2H_5O$) $C_{26}H_{43}O_5$: 435.3112. Found: 435.3160.

Hydrolysis of 39. A solution of **39** (0.634 g, 1.32 mmol) in 30 mL of absolute ethanol containing 3 g (53.6 mmol) of KOH was stirred at 25 °C for 18 h. The reaction mixture was diluted with 60 mL of ethyl acetate and was then washed with brine and dried over Na_2SO_4. After removal of the volatiles in vacuo, the oily residue (0.453 g) was chromatographed over 50 g of silica gel. Elution of the column with ethyl acetate–hexane (1:4) afforded 0.33 g (63%) of **40** [TLC (hexane–ethyl acetate, 6:4) R_f 0.56; IR (liquid film) 3650–3180 (m), 3010 (m), 2970 (s), 2935 (s), 2880 (s), 1730 (s), 1462 (m), 1450 (m), 1385 (m), 1343 (m), 1295 (w), 1266 (m), 1243 (m), 1188 (m), 1156 (m), 1135 (m), 1085 (m), 1065 (m), 1015 (m), 987 (m), 911 (w) cm^{-1}; ^1H NMR δ 0.88 (d, J = 6.5 Hz, 3 H), 0.92 (t, J = 7.5 Hz, 3 H), 1.16 (d, J = 7 Hz, 3 H), 1.20 (t, J = 7.5 Hz, 3 H), 1.29 (d, J = 5 Hz, 3 H), 3.10–3.77 (m, 5 H), 4.02 (br s, 1 H), 4.67 (q, J = 5 Hz, 1 H), 5.08–6.06 (m, 3 H). Exact mass calcd for ($M^+ - C_2H_5O$) $C_{21}H_{35}O_4$: 351.2536. Found: 351.2498], 0.034 g (6.5%) of **37** [IR (liquid film) 3660–3105 (m), 3015 (sh), 2965 (s), 2880 (s), 1730 (s), 1658 (w), 1456 (m), 1381 (m), 1341 (m), 1295 (m), 1264 (m), 1241 (m), 1185 (m), 1135 (m), 1084 (m), 1012 (m), 989 (m), 943 (m), 907 (m), 856 (w), 761 (w), 730 (m) cm^{-1}; ^1H NMR δ 0.83 (d, J = 6.5 Hz, 3 H), 0.88 (t, J = 7.5 Hz, 3 H), 1.12 (d, J = 6.2 Hz, 3 H), 1.20 (t, J = 7 Hz, 3 H), 1.30 (d, J = 5 Hz, 3 H), 3.26–3.82 (m, 5 H), 4.21 (br s, 1 H), 4.68 (q, J = 5 Hz, 1 H), 5.07–5.84 (m, 3 H). Exact mass calcd for ($M^+ - C_2H_5O$) $C_{21}H_{35}O_4$: 351.2536. Found: 351.2510], and 0.032 g (6.6%) of recovered **39**.

Oxidation of 37 with Pyridinium Chlorochromate. To a solution of **37** (73 mg, 0.18 mmol) in 2 mL of CH_2Cl_2 were added under vigorous stirring 90 mg (0.41 mmol) of pyridinium chlorochromate and 34 mg (0.42 mmol) of sodium acetate. After stirring at 25 °C for 2 h, the reaction mixture was passed over a Florisil column. Elution with ether gave a crude product, which was purified by chromatography over 5 g of silica gel. Elution of the column with hexane–ethyl acetate (2:1) afforded 52 mg (70%) of **38a**: IR ($CHCl_3$) 2995 (m), 2960 (s), 2923 (m), 2865 (m), 1720 (s), 1708 (s), 1659 (w), 1457 (m), 1442 (m), 1379 (m), 1338 (m), 1298 (m), 1260 (m), 1235 (m), 1178 (m), 1128 (s), 1076 (s), 1053 (m), 1035 (sh), 942 (m), 868 (w), 824 (w), 700 (w) cm^{-1}; ^1H NMR δ 0.88 (d, J = 7.2 Hz, 3 H), 0.92 (t, J = 7.2 Hz, 3 H), 1.16 (d, J = 7.2 Hz, 3 H), 1.20 (t, J = 7.2 Hz, 3 H), 1.30 (d, J = 6.5 Hz, 3 H), 3.53 (dt, J = 7.2 Hz, 1 H), 4.68 (q, J = 6 Hz, 1 H), 5.13–6.13 (m, 2 H).

Attempted isomerization of **38a** with sodium ethoxide (catalytic amount) in ethanol at 25 °C for 16 h resulted in the loss of the ester grouping to give **38b**: IR ($CHCl_3$) 3680–3120 (m), 3003 (m), 2965 (m), 2930 (m), 2875 (m), 1710 (s), 1655 (w), 1448 (m), 1381 (m), 1345 (w), 1314 (w), 1220 (br), 1130 (s), 1088 (s), 1058 (m), 955 (m), 870 (w), 830 (w) cm^{-1}; ^1H NMR δ 0.90 (d, J = 7.2 Hz, 3 H), 1.20 (t, J = 7.2 Hz, 3 H), 1.30 (d, J = 6.5 Hz, 3 H), 3.52 (dt, J = 7.2 Hz, 1 H), 4.03 (br s, 1 H), 4.67 (q, J = 6 Hz, 1 H), 5.32–6.17 (m, 2 H); mass spectrum, m/e 264 ($M^+ - C_2H_6O$), 246 ($M^+ - C_2H_6O - H_2O$).

Oxidation of 40. The monoester **40** (73 mg) was oxidized with pyridine chlorochromate and then isomerized overnight with catalytic quantities of sodium ethoxide in ethanol to yield **41**: IR ($CHCl_3$) 2995 (m), 2960 (s), 2925 (s), 2870 (m), 1720 (s), 1680 (s), 1614 (m), 1459 (m), 1380 (m), 1340 (w), 1251 (m), 1236 (sh), 1177 (s), 1150 (s), 1130 (s), 1080 (s), 1058 (m), 946 (w), 918 (w), 848 (w), 819 (w) cm^{-1}; ^1H NMR δ 0.80 (d, J = 5.4 Hz, 3 H), 0.89 (t, J = 5.6 Hz, 3 H), 1.12 (d, J = 7.2 Hz, 3 H), 1.20 (t, J = 7.5 Hz, 3 H), 1.30 (d, J = 5.0 Hz, 3 H), 3.16–3.87 (m, 4 H), 4.66 (q, J = 5.6 Hz, 1 H), 5.42 (br s, 1 H), 6.86 (m, 1 H); UV (MeOH) λ_{max} 244 nm (log ϵ 3.87); mass spectrum, m/e 349 ($M^+ - C_2H_5O$).

8α-[(*S*)-(2-Methylbutyryl)oxy]-2β-methyl-1β-[3-(1-ethoxyethoxy)-propyl]-1,2,6,7,8,8aβ-hexahydronaphthalene (42). To a solution of 2.2 g (5.55 mmol) of **40** in 44 mL of pyridine at 0 °C was added dropwise 6.54 g (57.1 mmol) of methanesulfonyl chloride. After stirring for 8 h at 0 °C, the mixture was poured into 100 mL of saturated $NaHCO_3$ solution. The aqueous mixture was extracted with ether (3 × 75 mL), and the combined extracts were washed with brine and then dried over Na_2SO_4. Evaporation of the solvent in vacuo yielded a viscous liquid (2.8 g), which was subjected to elimination as follows: the crude mesylate was dissolved in 88 mL of pyridine and heated with 8.1 g (53.2 mmol) of DBU at reflux for 3 h. The dark mixture was poured into water and extracted with ether (3 × 200 mL). The combined ethereal extracts were washed with water and brine and then dried over Na_2SO_4. The solvent was concentrated in vacuo to give a crude residue, which was chromatographed over 100 g of silica gel. Elution of the column with hexane–ethyl acetate (2:1) afforded 1.8 g (86%) of **42** as a pale yellow liquid: ^1H NMR δ 0.89 (d, J = 7 Hz, 3 H), 0.90 (t, J = 8 Hz, 3 H), 1.13 (d, J = 7.5 Hz, 3 H), 1.20 (t, J = 7 Hz, 3 H), 1.30 (d, J = 5 Hz, 3 H), 4.68 (q, J = 5 Hz, 1 H), 5.29 (br s, 1 H), 5.40–6.18 (m, 3 H).

8α-[(*S*)-(2-Methylbutyryl)oxy]-2β-methyl-1β-(3-hydroxypropyl)-1,2,6,7,8,8aβ-hexahydronaphthalene (43). A sample of 1.8 g (4.76 mmol) of the acetal (**42**) was dissolved in 30 mL of HOAc/THF/H_2O (3:2:1), and the resulting solution was stirred at 25 °C for 8 h. For preparative purposes, the solvent was removed by evaporation in vacuo, and the solid (1.44 g) obtained was used without further purification. An analytical sample of **43** was obtained by recrystallization of a portion of the solid (120 mg) from petroleum ether to give needles: mp 66–67 °C; $[\alpha]^{25}_D$ +347° (c 1.06, $CHCl_3$); UV (MeOH) λ_{max} 229, 236, 244 nm (log ϵ 4.35, 4.40, 4.26); IR ($CHCl_3$) 3670–3270 (m), 3005 (m), 2965 (s), 2935 (s), 2880 (m), 2842 (w), 1718 (s), 1649 (w), 1463 (m), 1451 (m), 1435 (w), 1386 (m), 1373 (m), 1296 (w), 1268 (m), 1242 (m), 1185 (m), 1159 (m), 1095 (m), 1083 (m), 1073 (m), 1032 (m), 1020 (m), 840 (m) cm^{-1}; ^1H NMR δ 0.88 (t, J = 7.5 Hz, 3 H), 0.90 (d, J = 7 Hz, 3 H), 1.13 (d, J = 7 Hz, 3 H), 3.60 (t, J = 5.4 Hz, 2 H), 5.34 (br s, 1 H), 5.40–6.12 (m, 3 H); mass spectrum, m/e 306 (M^+). Anal. Calcd for $C_{23}H_{34}O_5$: C, 74.47; H, 9.87. Found: C, 74.59; H, 9.95.

8α-[(*S*)-(2-Methylbutyryl)oxy]-2β-methyl-1β-(3-oxopropyl)-1,2,6,7,8,8aβ-hexahydronaphthalene (44). The crude alcohol **43** (1.32 g, 4.3 mmol) in 30 mL of CH_2Cl_2 was stirred with 1.72 g (8.0 mmol) of pyridinium chlorochromate at 25 °C for 4 h. Ether (50 mL) was then added, and, after the brown suspension was stirred vigorously for 10 min, the mixture was filtered through a short column of Florisil. The column was flushed with ether (3 × 50 mL), and the eluents were combined. Evaporation of the solvent in vacuo afforded a viscous liquid, which was chromatographed over 100 g of silica gel. Elution of the column with hexane–ethyl acetate (5:1) gave 854 mg (65%) of the aldehyde **44** as a colorless oil: TLC (hexane–ethyl acetate, 4:1) R_f 0.52; $[\alpha]^{25}_D$ +332° (c 2.82, $CHCl_3$); UV (MeOH) λ_{max} 229, 237, 245 nm (log ϵ 4.04, 4.10, 3.91); IR (liquid film) 3020 (m), 2965 (s), 2935 (s), 2880 (s), 2840 (m), 2720 (m), 1726 (s), 1649 (w), 1461 (m), 1450 (m), 1433 (m), 1384 (m), 1375 (sh), 1295 (m), 1265 (m), 1241 (m), 1196 (sh), 1182 (m), 1157 (m), 1096 (m), 1082 (m), 1030 (sh), 1018 (m), 969 (w), 934 (w), 915 (w), 866 (w), 838 (m), 745 (w) cm^{-1}; ^1H NMR δ 0.89 (t, J = 6.5 Hz, 3 H), 0.90 (d, J = 7.0 Hz, 2 H), 1.13 (d, J = 7.0 Hz, 3 H), 5.37 (br s, 1 H), 5.47–6.12 (m, 3 H), 9.74 (t, J = 2 Hz, 1 H). Exact mass calcd for $C_{19}H_{28}O_3$: 304.2038. Found: 304.2038.

Condensation of 44 with Dianion of Methyl Acetoacetate. To a suspension of NaH (107 mg, 60% oil dispersion, 2.675 mmol) in 6 mL of THF at 0 °C under N_2 was added 280 mg (2.41 mmol) of methyl acetoacetate. After the colorless solution was stirred at 0 °C for 10 min, *n*-butyllithium (1.76 mL, 1.43 M in hexane, 2.51 mmol) was added dropwise. The resulting yellow to orange solution was stirred for another 10 min, and the aldehyde **44** (730 mg, 2.40 mmol) in 1 mL of THF was then added in one portion. After the mixture was stirred at 0 °C for 15 min, the contents were poured into a mixture of 20 mL of cold 1 N HCl and 20 mL of ethyl acetate. The aqueous layer was extracted with ethyl acetate (2 × 20 mL), and the combined organic layer was washed with aqueous $NaHCO_3$ (10 mL) followed by water (2 × 20 mL). The solution was dried over Na_2SO_4 and concentrated to dryness in vacuo to yield an oily residue, which was chromatographed over 40 g of silica gel. Elution of the column with ethyl acetate–hexane (2:3) afforded 581 mg (67.8% based on recovered **44**, 110 mg) of **45** and **46**. Numerous attempts to separate **45** and **46** using TLC and HPLC were unsuccessful. Hence, this mixture was used in the subsequent step without further purification.

Zinc Borohydride Reduction of 45 and 46. To a solution of β-keto esters **45** and **46** (80 mg, 0.19 mmol) in 5 mL of anhydrous ether was

added dropwise an ethereal solution of zinc borohydride (6 mL, 0.125 M, 4.25 mmol) at 0 °C under N_2. The reaction mixture was stirred at 25 °C for 60 min. The resulting white cloudy solution was carefully quenched with cold 0.4 N HCl until hydrogen gas evolution ceased and the solution turned clear. The aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with aqueous $NaHCO_3$, water, and brine. After the extracts were dried over Na_2SO_4, the solvents were concentrated in vacuo, and the residue was chromatographed on four TLC plates (0.5 mm, 20 × 20 cm) and developed three times in a solvent system consisting of hexane–ethyl acetate (65:35). Two UV absorbing bands were noted. Elution of the less polar band with ethyl acetate afforded 34 mg of two β-hydroxy esters **47a** and **47b**, and the polar band afforded 16 mg of the other two diastereomers **48a** and **48b**. The ratio of **47a** and **47b** to **48a** and **48b** was approximately 2.1:1, and the overall yield was 62.5%.

Lactonization of 47a and 47b. To a solution containing 135 mg (0.32 mmol) of **47a** and **47b** in 20 mL of benzene was added 23 mg (0.1 mmol) of *p*-toluenesulfonic acid monohydrate, and the reaction mixture was stirred at 25 °C for 15 min. The solution was concentrated in vacuo to give a residue, which was dissolved in 20 mL of dry benzene and stirred for another 15 min. The above procedure was repeated again until no more starting material was detectable as monitored by TLC. Powdered $NaHCO_3$ (20 mg) was then added and stirred for 2 min. The reaction mixture was diluted with 40 mL of ethyl acetate and washed with water and brine. After drying the solvent over Na_2SO_4, it was concentrated in vacuo to give an oily residue (110 mg), which was chromatographed over 5 g of silica gel. Elution of the column with ethyl acetate–hexane (3:2) afforded 73 mg (58.5%) of a mixture of **1a** and **49**.

HPLC separation of this mixture was achieved on a Waters radial compression module (RCM-100) with a radial-Pak 5-μm silica gel cartridge (0.8 × 10 cm) by using $CHCl_3$ as the mobile phase at a flow rate of 5 mL/min. The retention times of compactin (**1a**) and **49** were 14.8 and 21.8 min, respectively. Repeated injection of this mixture gave 32 mg of **1a** [mp 147–148 °C; $[\alpha]^{25}_D$ +283° (*c* 0.47, acetone); UV (MeOH) λ_{max} 229, 237, 246 nm (log ε 4.26, 4.32, 4.14); IR ($CHCl_3$) 3620–3120 (m), 2965 (m), 2935 (m), 2878 (m), 1720 (s), 1650 (w), 1462 (w), 1382 (w), 1263 (m), 1215 (m), 1182 (m), 1156 (m), 1708 (m), 1014 (w) cm^{-1}; ^{13}C NMR ($CDCl_3$, Me_4Si) 11.76, 13.92, 16.90, 21.02, 24.11, 26.33, 26.76, 30.99, 33.10, 36.30, 36.95, 37.71, 38.73, 41.77, 62.79, 67.66, 76.22, 123.68, 128.23, 132.67, 133.65, 170.11, 176.66. Exact mass calcd for $C_{23}H_{34}O_5$: 390.2406. Found: 390.2408] and 22 mg of **49** [UV (MeOH) λ_{max} 229, 236, 244 nm (log ε 4.29, 4.34, 4.18); IR ($CHCl_3$) 3620–3120 (m), 3025 (w), 3010 (w), 2965 (m), 2935 (m), 2878 (m), 1721 (s), 1650 (w), 1464 (m), 1450 (sh), 1435 (w), 1387 (m), 1355 (w), 1295 (sh), 1260 (m), 1247 (sh), 1218 (m), 1185 (m), 1159 (m), 1080 (m), 1040 (w), 1019 (w), 839 (w) cm^{-1}; ^1H NMR δ 0.88 (t, *J* = 7.5 Hz, 3 H), 0.89 (d, *J* = 7.2 Hz, 3 H), 1.12 (d, *J* = 7.0 Hz, 3 H), 4.39 (m, 1 H), 4.67 (m, 1 H), 5.34 (br s, 1 H), 5.47–6.17 (m, 3 H). Exact mass calcd for $C_{23}H_{34}O_5$: 390.2406. Found: 390.2432].

Lactonization of 48a and 48b. The mixture **48a** and **48b** (64 mg) was lactonized following the above procedure to yield 34 mg of a mixture of the lactones **50** and **51**, which were separated by using the same HPLC system. The retention times for **50** and **51** were 16.4 and 24.4 min, respectively. Repeated injections of the mixture yielded 5 mg of **50** [UV (MeOH) λ_{max} 229, 236, 244 nm (log ε 4.18, 4.25, 4.06); IR ($CHCl_3$) 3620–3120 (m), 3010 (w), 2968 (m), 2935 (m), 2880 (m), 1721 (s), 1650 (w), 1462 (m), 1450 (m), 1433 (w), 1385 (m), 1294 (m), 1262 (sh), 1240 (m), 1209 (sh), 1184 (m), 1159 (m), 1092 (sh), 1081 (m), 1038 (m), 1015 (w), 911 (w), 838 (w) cm^{-1}; ^1H NMR δ 0.89 (t, *J* = 7.2 Hz, 3 H), 0.90 (d, *J* = 7.2 Hz, 3 H), 1.12 (d, *J* = 7.2 Hz, 3 H), 3.90–4.46 (m, 2 H), 5.36 (br s, 1 H), 5.45–6.13 (m, 3 H). Exact mass calcd for $C_{23}H_{34}O_5$: 390.2406. Found: 390.2438] and 8 mg of **51** [UV (MeOH) λ_{max} 229, 236, 244 nm (log ε 4.19, 4.26, 4.07); IR ($CHCl_3$) 3620–3120 (m), 3100 (w), 2965 (m), 2934 (m), 2880 (m), 1721 (s), 1648 (w), 1461 (m), 1433 (w), 1383 (m), 1295 (sh), 1262 (m), 1240 (m), 1208 (sh), 1184 (m), 1158 (m), 1091 (sh), 1080 (m), 1035 (m), 1015 (w), 910 (w), 838 (w) cm^{-1}; ^1H NMR δ 0.89 (t, *J* = 7.5 Hz, 3 H), 0.90 (d, *J* = 7.5 Hz, 3 H), 1.12 (d, *J* = 7.0 Hz, 3 H), 3.92–4.50 (m, 2 H), 5.34 (br s, 1 H), 5.51–6.17 (m, 3 H). Exact mass calcd for $C_{23}H_{34}O_5$: 390.2406. Found: 390.2413].

Transformation of Compactin and 50 into Anhydrocompactin (52). The procedure of Brown et al.[1] was followed. Compactin (**1a**, 15 mg) was heated under reflux with 10 mg of potassium hydrogen sulfate in 0.1 mL of DMF for 6 h. After filtration, the solution was concentrated in vacuo to give an oily residue, which was chromatographed on 5 g of silica gel. Elution of the column with ethyl acetate–hexane (1:1) afforded 2.7 mg of anhydrocompactin (**52**): IR ($CHCl_3$) 3005 (w), 2965 (m), 2930 (m), 2878 (m), 1718 (s), 1462 (m), 1388 (m), 1262 (m), 1213 (sh), 1183 (m), 1155 (m), 1085 (br), 1040 (m), 1015 (m), 911 (w), 868 (w), 822 (m), 785–728 (m), 650 (w) cm^{-1}; ^1H NMR δ 0.88 (t, *J* = 6.5 Hz, 3 H), 0.91 (d, *J* = 7.5 Hz, 3 H), 1.12 (d, *J* = 7.0 Hz, 3 H), 4.33 (m, 1 H), 5.34 (br s, 1 H), 5.46–6.13 (m, 3 H), 6.04 (br s, 1 H), 6.85 (m, 1 H). The retention time of **52** was 9.7 min on a radial-Pak 5-μm silica gel cartridge (0.8 × 10 cm) with $CHCl_3$–hexane (2:3) as the mobile phase at a flow rate of 3 mL/min.

Dehydration of **50** under the same conditions afforded **52** also.

Dehydration of 49 and 51 into Anhydroisocompactin (53). With the procedure of Brown et al.,[1] **49** (15 mg) was converted into 3 mg of anhydroisocompactin (**53**): IR ($CHCl_3$) 3005 (w), 2965 (m), 2930 (m), 2878 (m), 1718 (s), 1462 (m), 1388 (m), 1262 (m), 1213 (sh), 1183 (m), 1155 (m), 1085 (br), 1040 (m), 1015 (m), 911 (w), 868 (w), 822 (m), 785–728 (m), 650 (w) cm^{-1}; ^1H NMR δ 0.89 (t, *J* = 7.2 Hz, 3 H), 0.90 (d, *J* = 7.5 Hz, 3 H), 1.13 (d, *J* = 7.0 Hz, 3 H), 4.38 (m, 1 H), 5.33 (br s, 1 H), 5.45–6.17 (m, 3 H), 6.05 (br s, 1 H), 6.86 (m, 1 H). The retention time of **53** was 10.8 min on the radial-Pak 5-μm silica gel cartridge (0.8 × 10 cm) with $CHCl_3$–hexane (2:3) as the mobile phase (flow rate was 3 mL/min).

Dehydration of **51** under these same conditions gave **53** also.

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