A Novel Approach to the Stereocontrolled Synthesis of Steroid Side Chains Including the CD-Ring System: The First Total Synthesis of (+)-8α-(Phenylsulfonyl)-des-AB-cholestane and Its Efficient Conversion into Grundmann's Ketone and Vitamin D_3†

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A new stereocontrolled approach to steroid CD-ring system including side chain starting from an optically active indenedione **6** is described. The application of this finding allows for the asymmetric synthesis of des-AB-cholestane **3** and 8α-(phenylsulfonyl)-des-AB-cholestane **37**; from the latter Grundmann's ketone **25** and vitamin D_3 (**27**) were synthesized efficiently.

In the total synthesis of biologically important steroidal compounds, the stereocontrolled construction of the CD-ring system and side chain is a major problem, and a number of investigations into a solution to this problem have been reported to date. Namely, catalytic hydrogenation[1] of $\Delta^{17(20)}$-, $\Delta^{20(22)}$-, or $\Delta^{20(21)}$-olefins, [3,3]-sigmatropic[2a-g] and [2,3]-Wittig[2h,i] rearrangements, substitution reactions of π-allylpalladium intermediates,[3] boron intermediates,[4] and allyl alcoholic esters,[5] addition reactions of allylic epoxides[6] and enones,[7] ene reactions,[8] cycloaddition reactions,[9] and radical cyclization reactions[10] have been used as key stereodirecting processes. The use of the conformational rigidity of bicyclo[2.2.1]heptane derivatives[11] has also led to an interesting solution to this problem. Although various types of reaction exemplified above have been used to explore an efficient route for stereoselective construction of steroid side chain including CD-ring system, a direct and practical process still remains to be developed for bringing totally synthesized, biologically important steroidal compounds to market. Accordingly, a program for the total synthesis of steroidal CD-ring compounds having appropriate side chains in optically pure form was undertaken. This paper describes the stereocontrolled synthesis of (−)-des-AB-8-oxacholest-14-en-9-one (**3**) and the first total synthesis of (+)-8α-(phenylsulfonyl)-des-AB-cholestane **37**, both in optically pure forms. Compound **37** was then converted into Grundmann's ketone (**25**) and vitamin D_3 (**27**).

Synthetic Plan for (−)-Des-AB-8-oxacholest-14-en-9-one (3). The first target compound was (−)-des-AB-8-oxacholest-14-en-9-one (**3**) because des-AB-cholestan-9-one (**1**) and its ester derivative (**2**), both of which had been prepared from **3**,[7b] were known to be flexible intermediates for annelative elaboration into cholestane-like steroids or for transformation into members of the vitamin D series.[12] The starting material should be readily available in large quantities and also optically pure form for our concept to be viable, and the indenedione **6**[13] seemed to be an ideal candidate for this purpose. The overall plan is summarized in Scheme I[16] wherein the selective bond scission in cyclohexane ring of the indanedione **5**, which could be prepared from **6**, would give the cyclopentane **4a** which is redrawn as **4** for convenience. Reduction of the carboxylic acid to a methyl group, homologation of the X portion, and then cyclization of **4** would provide the initial target compound **3**. The most significant feature of this plan is that the chiral centers at C(13), C(17), and C(20) (steroid numbering) are incorporated in compound **5** as the most stable isomeric form.

Results. The reaction[17] of the optically pure (−)-indenedione **6** with paraformaldehyde and thiophenol in triethanolamine afforded the sulfide **7** (Scheme II), which was then oxidized (MCPBA) to give the sulfone **8**, in 39%

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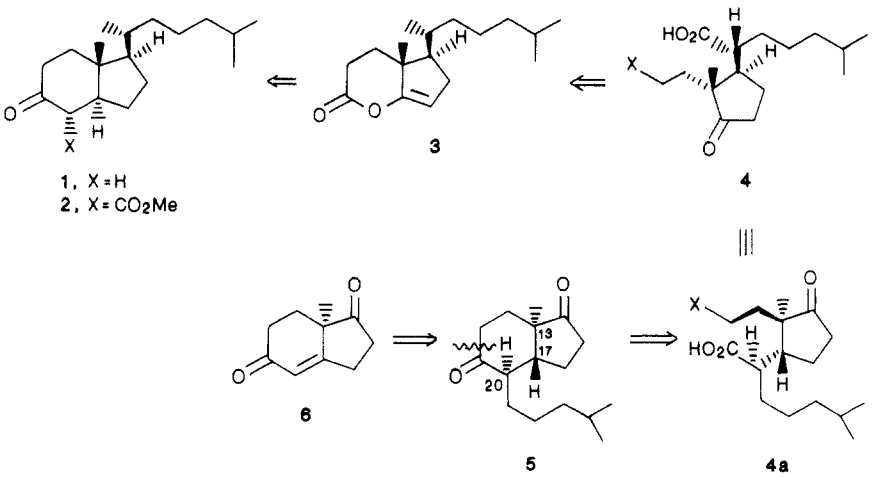
0022-3263/86/1951-5311$01.50/0

Scheme I



overall yield from **6**. Base-catalyzed elimination of the trans sulfone **9**, obtained in 71% yield by catalytic hydrogenation (H_2, Pd–C) of **8**, furnished the methylene ketone **10**[18] in 98% yield. Next, the isoamyl group was added in a 1,4-fashion to **10** by using isoamylmagnesium bromide in THF under CuI/BF_3·Et_2O catalysis[20] to give a 73% yield of the dione **5**, m/z 250 (M^+). The enol acetylation (isopropenyl acetate, *p*-TsOH) of **5** afforded the dienol diacetate **11**, m/z 334 (M^+), and the enol monoacetate **12**, m/z 292 (M^+), in a ratio of 2:1 in 94% yield, and the diacetate **11** was found to be hydrolyzed (LiOH, aqueous THF) selectively to give the monoacetate **12** in 86% yield. The keto acid **13** which was obtained by the ozonolysis (O_3, CH_2Cl_2; Me_2S) of **12**, followed by a hydrolysis (LiOH, aqueous THF) of the resulting acid anhydride, was converted as usual ($HOCH_2CH_2OH$, camphorsulfonic acid) into the acetal carboxylic acid **14**, in 70% yield. The transformation of **14** into the methyl derivative **18** was straightforward as described below. The carboxylic acid **14** was subjected to reduction ($LiAlH_4$) to the diol **15**, m/z 314 (M^+), which was converted (*p*-TsCl, TEA, DMAP) into the monotosylate **16**, m/z 468 (M^+), in 62% overall yield from **14**. The compound **17**, m/z 512 (M^+), prepared in 84% yield by the protection (MOMCl, Hünig base) of **16**, was then subjected to reduction ($LiAlH_4$) to give the methyl derivative **18**, m/z 342 (M^+), in 92% yield. Selective deprotection (10% HCl, acetone) of the acetal group of **18** afforded the aldehyde **19**, in 92% yield, and then this was transformed into the ester **21**, in 72% yield, via the enol ether **20**, m/z 326 (M^+), by a Wittig reaction[21] ($MeOCH_2POPh_2$, LDA; then NaH) followed by oxidation[22] (PCC) of the resulting enol ether **20**. The lactone **22**, m/z 266 (M^+), [prepared by deprotection (10% HCl, acetone) of the ester **21**] was hydrolyzed (LiOH, aqueous THF) and then oxidized (Jones' reagent) to afford in 81% overall yield from **21** the keto carboxylic acid **24**, which was identical by IR (neat) and ^1H NMR ($CDCl_3$, 300 MHz) spectral comparison with an authentic sample.[7b] The keto carboxylic acid **24** thus obtained was transformed into the enol lactone **3**, $[\alpha]_D$ – 32.5°, according to the known procedure.[7b]

Thus, the synthetic strategy described above provides a new method for stereoselective construction of the steroid CD-ring system and side chain.

Synthesis of Vitamin D_3. Because of the important therapeutic value of vitamin D in treating disorders of calcium and phosphorus metabolism, considerable attention has been directed toward the chemistry of vitamin D leading to the discovery of vitamin D derivatives possessing high biological activity and increased activity.[8b,d,11b,c,d,12,24] In Scheme III is illustrated the synthetic approach to these compounds by Julia's olefin synthesis, namely the reductive elimination of β-alkoxy sulfone **27**, (prepared by condensation of sulfone **25** with aldehyde **26**), which gives stereoselectively vitamin D_4 (**28**).[25a] This has provided a limited entry to the vitamin D series mainly because of the difficulty in obtaining the starting sulfone **25** (synthesis of which requires several steps from the corresponding 8-keto derivative). These facts and the desirable feature that the trans-fused sulfone **25** does not epimerize the corresponding cis-fused sulfone under basic conditions in which Grundmann's ketone could be epimerized to the corresponding cis-isomer stimulated us to develop a direct and efficient method for synthesis of 8α-(phenylsulfonyl)-des-AB-cholestane (**30**) and its application to the synthesis of vitamin D_3.

Synthetic Plan. The overall synthetic plan of **30** summarized in Scheme IV is inherently the same as for that of **3** in Scheme I except for the stereoselective hydrogenation of **34**, which could be prepared from **5**, giving the keto sulfone **33** and the intramolecular alkylation of **31**, which could be obtained from **33** via **32a** (**32**) by bond scission of **33**, followed by reduction of the carboxyl group to a methyl group and homologation of the X portion of the resulting compound **32a** (**32**).

Certainly the most provocative feature of this plan is that all the chiral centers at C(13), C(14), C(17), and C(20) (steroid numbering) required for the synthesis of **30** are incorporated in compound **33** as the most stable isomeric form since the chirality at C(8) could be generated selec-

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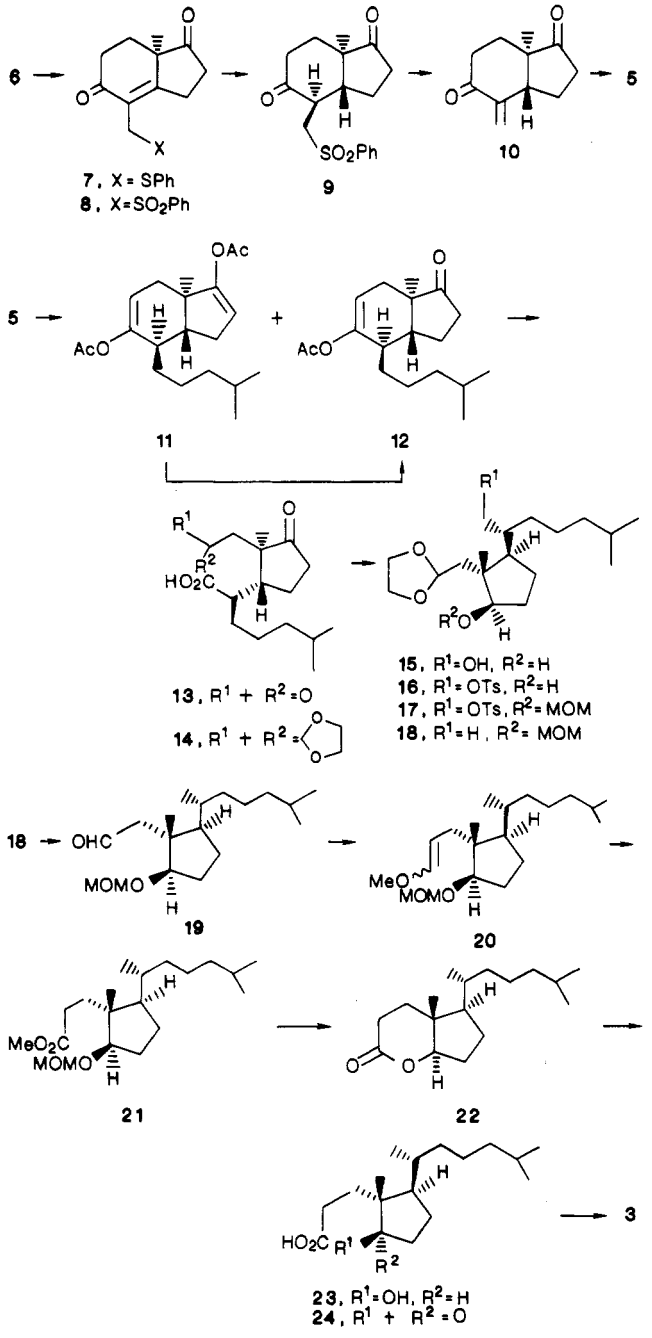
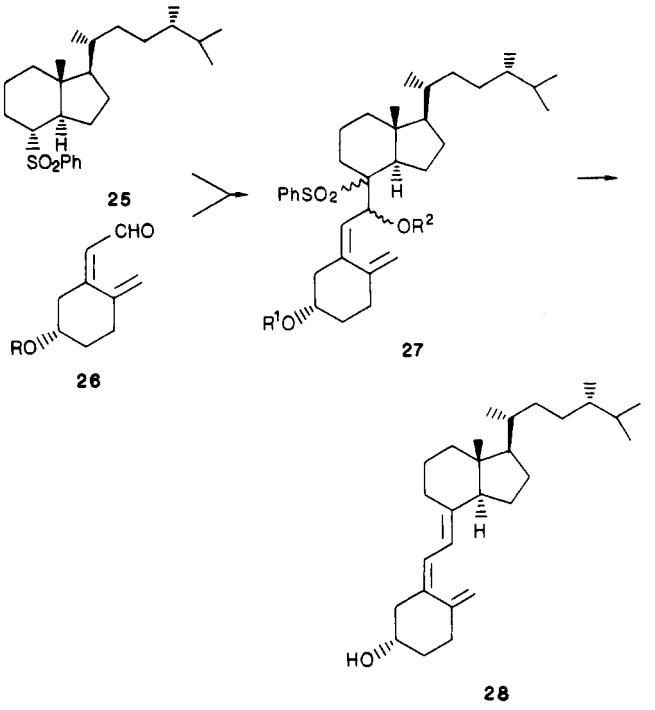
Scheme II



Scheme III



tively under thermodynamically controlled conditions. Finally, by following the same sequence of reactions shown in Scheme III, the sulfone **30** could be converted into vitamin D_3 (**29**).

Results. As shown in Scheme V, the monoketal (**35**), obtained in 85% yield by a selective ketalization ($HOCH_2CH_2OH$, *p*-TsOH) of the diketone **5**, was subjected to a Wittig reaction[25b] ($PhSCH_2PO(OEt)_2$, NaH) affording the vinyl sulfide **36**, *m/z* 400 (M^+), in 95% yield as a mixture of *E*/*Z* isomers. Oxidation (MCPBA) gave the corresponding vinyl sulfone **37** as a separable mixture of *Z* (**37a**) and *E* (**37b**) isomers, *m/z* 432 (M^+), in 80% total yield. Hydrogenation (H_2, Pd–C, 10% HCl, MeOH) of **37** afforded stereoselectively in 72% yield the keto sulfone **33**, *m/z* 390 (M^+), followed by enol acetylation (isopropenyl acetate, *p*-TsOH) to furnish the enol acetate **38**, *m/z* 432 (M^+), in 98% yield. Successive reaction of **38**, namely, ozonolysis (O_3, CH_2Cl_2; Me_2S), hydrolysis (LiOH, aqueous THF), and then acetalization ($HOCH_2CH_2OH$, camphorsulfonic acid) formed the acid acetal (**39**), *m/z* 466 (M^+), in 73% overall yield. The alcohol **40**, *m/z* 452 (M^+), obtained in 72% yield by reduction ($LiAlH_4$) of **39**, was then converted into the methyl derivative **42**, *m/z* 436 (M^+), in 95% yield via tosylation (*p*-TsCl, pyridine, DMAP) followed by reduction ($LiAlH_4$). The final stage of this synthesis involved a one-carbon homologation and intramolecular alkylation. To accomplish this, acetal **42** was hydrolyzed (10% HCl, acetone) to the aldehyde **43**, *m/z* 392 (M^+), in 95% yield. The intramolecular alkylation was achieved by two different routes. Thus, in the first sequence epoxide **44** obtained in 31% yield by the epoxidation ($Me_3S^+I^-$, *n*-BuLi) of aldehyde **43**, was subjected to the intramolecular cyclization (LDA, THF) giving the alcohols **45a** and **46a** in 30% and 50% yields, respectively. In the ^1H NMR spectrum, the signals observed at 3.55–3.76 ppm as multiplet due to methylene protons of hydroxymethylene moiety in the compound **45a** were shifted to 3.80–4.21 ppm in its acetoxy derivative **45b**. The α-configuration of a phenylsulfonyl group at C-8 in **46a** was deduced from the coupling constants (3.02 ppm, d,d,d, *J* = 12, 12, 4 Hz) of C-8H in the NMR spectrum. This was eventually confirmed by conversion of **46a** into the target compound **30**, $[\alpha]_D$ +0.06°, in 70% overall yield via the mesylate **46b** and olefins **47** by successive treatment (MsCl, pyridine; LiBr, Li_2CO_3; H_2, Pd–C). Because of the low yield of the epoxidation step and the lack of regioselectivity in the intramolecular cyclization of the epoxide **44** thus obtained, a second pathway to **30** was investigated. Thus, the aldehyde **43** was subjected to Peterson's olefin synthesis (Me_3SiCH_2MgCl; NaH), affording the olefin **48**, *m/z* 390 (M^+), in 81% yield. The alcohol **49**, *m/z* 408 (M^+), obtained in 92% yield by hydroboration–oxidation (BF_3·SMe_2; 30% H_2O_2, NaOH) of **47** was first mesylated (MsCl, pyridine) to give mesylate **50** in 98% yield and then subjected to intramolecular alkylation (LDA) to furnish the target compound **30** in 84% yield. This was identical with the authentic sample prepared above in all aspects including optical rotation and was converted by oxidation[26]

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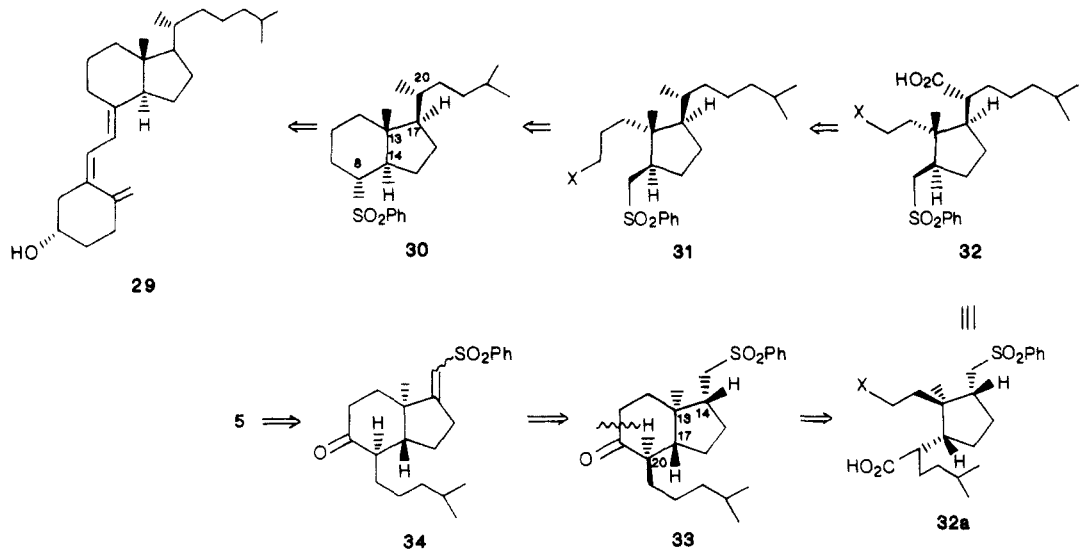
Scheme IV



[oxodiperoxymolybdenum–pyridine–hexamethylphosphoric triamide (MoOPH),[27] LDA] in 62% yield into Grundmann's ketone **51** which was identical with an authentic sample.[28] By this conversion to **51**, it was confirmed that all the chiral centers except C-8 of the compound **30** were introduced correctly. To this end, the compound **30** was converted into vitamin D_3 as follows. The sulfone was metalated (LDA) and then condensed with the ring A component **53**, obtained by oxidation (MnO_2) of the corresponding allyl alcohol **52**.[29] Treatment of the reaction mixture with acetyl chloride gave a mixture of diastereoisomeric β-acetoxysulfones **54**. This mixture was reduced (5% Na–Hg) to the triene **55**, whose desilylation (n-$Bu_4N^+F^-$) gave vitamin D_3 (**29**) in 51% overall yield. The 3,5-dinitrobenzoate **56** of the synthetic vitamin D_3 (mp 129–130 °C, $[\alpha]^{20}_D$ +95.9°) was identical with the authentic vitamin D_3 3,5-dinitrobenzoate (lit.[30] mp 128–129 °C, lit.[31] $[\alpha]^{20}_D$ +97°) in mixed melting point test and spectral (IR and ^1H NMR) comparisons.

A direct and efficient method for the synthesis of 8α-(phenylsulfonyl)-des-AB-cholestane (**30**) in an optically pure form has been disclosed. We have also demonstrated the versatility of **30** in the synthesis of vitamin D analogues by converting it into Grundmann's ketone (**51**) and vitamin D_3 (**29**). The methodology described above opens up many fascinating possibilities in the asymmetric synthesis of biologically important steroids.

Experimental Section

All melting points were uncorrected. Infrared (IR) spectra were recorded on a Hitachi 260-10 spectrophotometer. Nuclear magnetic resonance (NMR) spectra were measured on JEOL-PMX-60 and JEOL-PS-100 spectrometer. Chemical shifts were reported as δ values relative to internal tetramethylsilane (Me_4Si). Mass spectra were taken on Hitachi RMU-7, Hitachi M-52G, and JEOL-JMS-OISG-2 spectrometers. All optical rotations were measured in chloroform solution on a JASCO DIP-4 polarimeter using a 1-dm cell.

(–)-(7a*R*)-4-[(Phenylthio)methyl]-5,6,7,7a-tetrahydro-7a-methylindan-1,5-dione (7). To a stirred solution of indenedione[13] **6** (50 g, 304.9 mmol) in triethanolamine (100 mL) was added 80% paraformaldehyde (14 g) at 60 °C, and stirring was continued for 20 min at the same temperature. To it was added dropwise thiophenol (34.4 mL), and the mixture was stirred for additional 24 h at the same temperature. The reaction mixture was then poured into water (300 mL) and extracted with ether (300 mL × 3). The combined extracts were washed with saturated NaCl solution and dried (Na_2SO_4). Removal of the solvent afforded a crude product which was chromatographed on silica gel (300 g) using hexane–ethyl acetate (4:1 v/v) as an eluant to give 38.4 g (44%) of the sulfide **7** as colorless prisms: mp 101–102 °C (MeOH); IR ($CHCl_3$) 1750, 1680 cm^{-1}; NMR ($CDCl_3$) δ 1.15 (3 H, s, CH_3), 3.63 (2 H, s, CH_2S), 7.00–7.30 (5 H, m, Ar H); mass spectrum, m/z 286 (M^+); $[\alpha]^{20}_D$ –227° (c 0.47). Anal. Calcd for $C_{17}H_{18}O_2S$: C, 71.29; H, 6.34; S, 11.20. Found: C, 71.13; H, 6.21; S, 11.04.

(–)-(7a*R*)-4-[(Phenylsulfonyl)methyl]-5,6,7,7a-tetrahydro-7a-methylindan-1,5-dione (8). To a stirred solution of the sulfide **7** (728 mg, 2.55 mmol) in CH_2Cl_2 (20 mL) was added in portions 70% m-chloroperbenzoic acid (1.26 g, 5.1 mmol) at room temperature. After stirring for 3 h at the same temperature, the reaction mixture was washed with saturated $NaHCO_3$ and NaCl solutions, and dried (Na_2SO_4). The residue resulting from evaporation of the solvent was chromatographed on silica gel (20 g) using hexane-ethyl acetate (3:2 v/v) as an eluant to afford 710 mg (88%) of the sulfone **8** as colorless needles: mp 164.5–165 °C (MeOH); IR ($CHCl_3$) 1750, 1680 cm^{-1}; NMR ($CDCl_3$) δ 1.33 (3 H, s, CH_3), 4.05, 4.35 (2 H, each d, J = 14 Hz, CH_2SO_2), 7.33–7.97 (5 H, m, Ar H); mass spectrum, m/z 318 (M^+); $[\alpha]^{20}_D$ –212° (c 0.33). Anal. Calcd for $C_{17}H_{18}O_4S$: C, 64.13; H, 5.70; S, 10.07. Found: C, 63.85; H, 5.69; S, 10.45.

(–)-(3a*R*,4*R*,7a*R*)-4-[(Phenylsulfonyl)methyl]-3a,4,5,6,7,7a-hexahydro-7a-methylindan-1,5-dione (9). A mixture of **8** (6.2 g, 19.5 mmol), 5% palladium on carbon (700 mg), AcOH (45 mL), 10% HCl (2.3 mL), and MeOH (160 mL) was stirred under an atmosphere of hydrogen at room temperature. Hydrogenation was completed within 4 h. The solution was then filtered to remove the catalyst, and the catalyst was washed with MeOH. The filtrate and washing were combined and evaporated to leave a residue, which was dissolved in benzene (200 mL). The organic layer was washed with water and dried (Na_2SO_4). The removal of the solvent afforded 4.42 g (71%) of **9** as colorless prisms: mp 118–119 °C (MeOH); IR ($CHCl_3$) 1740, 1720 cm^{-1}; NMR ($CDCl_3$) δ 1.23 (3 H, s, CH_3), 4.00 (2 H, dd, J = 5 Hz and 13 Hz, CH_2SO_2), 7.45–8.00 (5 H, m, Ar H); mass spectrum, m/z 320 (M^+); $[\alpha]^{20}_D$ –96.7° (c 0.24). Anal. Calcd for $C_{17}H_{20}O_4S$: C, 63.72; H, 6.29; S, 10.01. Found: C, 63.35; H, 6.16; S, 10.10.

(–)-(3a*R*,7a*R*)-4-Methylene-3a,4,5,6,7,7a-hexahydro-7a-methylindan-1,5-dione (10). To stirred solution of **9** (1 g, 3.1 mmol) in benzene (40 mL) was added dropwise 1,8-diazabicyclo[5.4.0]undec-7-ene (0.5 g) at room temperature, and stirring was continued for 30 min at the same temperature. The reaction

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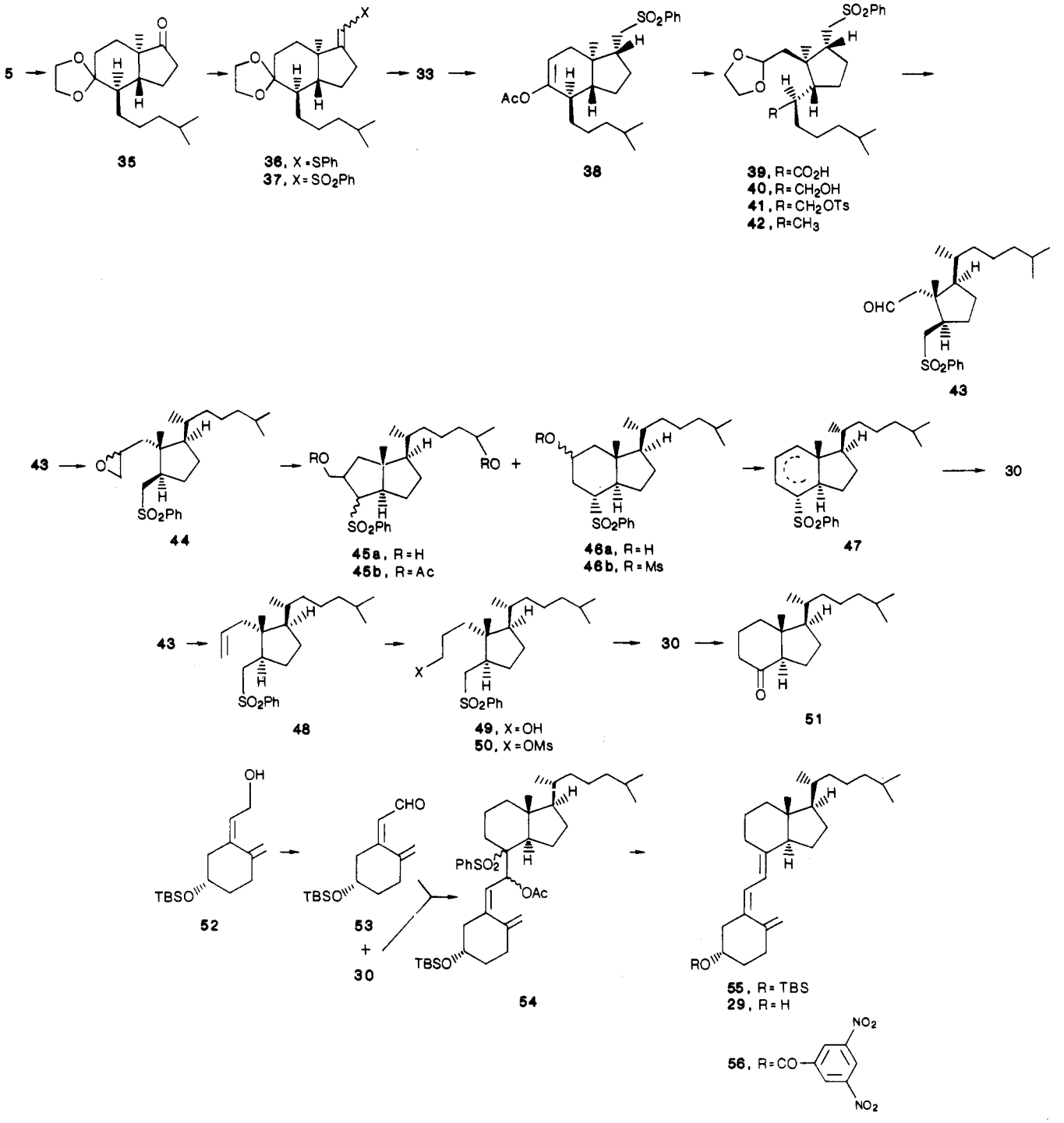
Scheme V



mixture was washed with 10% HCl solution and saturated NaCl solution and dried (Na_2SO_4). Removal of the solvent afforded a crude product which was chromatographed on silica gel (20 g) by using hexane–ethyl acetate (4:1 v/v) as an eluant to give 545 mg (98%) of **10** as a colorless oil: IR ($CHCl_3$) 1740, 1680 cm^{-1}; NMR (CCl_4) δ 0.87 (3 H, s, CH_3), 5.10 (1 H, d, J = 2 Hz, C=CH_2), 5.93 (1 H, d, J = 2 Hz, C=CH_2); mass spectrum, m/z 178 (M^+); $[\alpha]^{20}_D$ −130° (c 0.45). Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 73.68; H, 7.92.

(−)-(3a*R*,4*R*,7a*R*)-4-(4-Methylpentyl)-3a,4,5,6,7,7a-hexahydro-7a-methylindan-1,5-dione (5). To a stirred suspension of CuI (5.13 g, 26.9 mmol) in THF (40 mL) was added dropwise isoamylmagnesium bromide [prepared from Mg (665 mg, 27.4 mmol) and isoamyl bromide (4.06 g, 26.9 mmol)] in THF (40 mL) at −30 °C under an atmosphere of nitrogen. Stirring was continued for 30 min at the same temperature. To this mixture was then added dropwise $BF_3{\cdot}Et_2O$ (3.3 mL) at −78 °C. After stirring was continued for 5 min at room temperature, a solution of **10** (4.79 g, 26.9 mmL) in THF (15 mL) was added dropwise and stirred for 10 min at the same temperature. The reaction mixture was quenched with saturated NH_4Cl solution and extracted with ether (200 mL × 3). The combined extracts were washed with water, saturated $Na_2S_2O_3$, and saturated NaCl solution and dried (Na_2SO_4). The removal of the solvent left a residue, which was chromatographed on silica gel (50 g) by using hexane–ethyl acetate (9:1 v/v) as an eluant to afford 4.9 g (73%) of the diketone **5** as a colorless oil: IR ($CHCl_3$) 1740, 1710 cm^{-1}; NMR ($CDCl_3$) δ 0.83 (6 H, d, J = 6 Hz, $CH(CH_3)_2$), 1.12 (3 H, s, CH_3); mass spectrum, m/z 250 (M^+); $[\alpha]^{20}_D$ −95.8° (c 1.23). Anal. Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 76.53; H, 10.05.

Enol Acetylation of 5. A mixture of **5** (3.37 g, 13.5 mmol), p-toluenesulfonic acid (450 mg), and isopropenyl acetate (80 mL) was condensed to 10 mL in 2 h under atmospheric pressure. After refluxing was continued for 4 h, the reaction mixture was diluted

with ethyl acetate (200 mL), washed with ether, saturated $NaHCO_3$, and NaCl solution, and dried (Na_2SO_4). The residue resulting from the evaporation of the solvent was chromatographed on silica gel (50 g). From the fraction of hexane–ethyl acetate (19:1 v/v), 3.06 g (68%) of **(−)-(3a*R*,4*R*,7a*R*)-1,5-diacetoxy-4-(4-methylpentyl)-3a,4,7,7a-tetrahydro-7a-methyl-1-indene (11)** was obtained as a colorless oil: IR ($CHCl_3$) 1755 cm^{-1}; NMR ($CDCl_3$) δ 0.88 (6 H, d, J = 6 Hz, $CH(CH_3)_2$), 1.00 (3 H, s, CH_3), 2.05 (3 H, s, $OCOCH_3$), 2.10 (3 H, s, $OCOCH_3$), 5.25 (1 H, dd, J = 3 and 6 Hz, C-6H), 5.55 (1 H, t, J = 2 Hz, C-2H); mass spectrum, m/z 334 (M^+); $[\alpha]^{20}_D$ −35.2° (c 0.47); exact mass calcd for $C_{20}H_{30}O_4$ 334.2142, found 334.2129.

Furthermore, from the fraction of hexane–ethyl acetate (9:1 v/v), 1.03 (26%) of **(−)-(3a*R*,4*R*,7a*R*)-5-acetoxy-4-(4-methylpentyl)-3a,4,7,7a-tetrahydro-7a-methylindan-1-one (12)** was obtained as a colorless oil: IR ($CHCl_3$) 1755, 1740 cm^{-1}; NMR ($CDCl_3$) δ 0.90 (6 H, d, J = 6 Hz, $CH(CH_3)_2$), 1.00 (3 H, s, CH_3), 2.06 (3 H, s, $OCOCH_3$), 5.30 (1 H, dd, J = 3 and 5 Hz, C-6H); mass spectrum, m/z 292 (M^+); $[\alpha]^{20}_D$ −71.3° (c 0.49); exact mass calcd for $C_{18}H_{28}O_3$ 292.2038, found 292.2033.

Hydrolysis of 11. A mixture of **11** (1.7 g, 5.1 mmol), LiOH (214 mg, 8.9 mmol), water (6 mL), and THF (20 mL) was stirred for 3 h at room temperature. The reaction mixture was diluted with water (20 mL) and extracted with ether (50 mL × 3). The combined extracts were washed with saturated NaCl solution and dried (Na_2SO_4). The residue resulting from the evaporation of the solvent was chromatographed on silica gel (20 g) by using hexane–ethyl acetate (9:1 v/v) as an eluant. Evaporation of the first fraction afforded 1.28 g (86%) of **12**, and 130 mg (10%) of **5** was obtained from the second fraction.

(−)-6-Methyl-2(*R*)-[2-((2,5-dioxacyclopentyl)methyl)-2-(*R*)-methyl-3-oxo-1(*R*)-cyclopentyl]heptanoic Acid (14). Through a stirred solution of **12** (579 mg, 1.98 mmol) in CH_2Cl_2 (20 mL) was passed O_3 at −78 °C for 30 min. The reaction mixture was then treated with dimethyl sulfide (0.2 g, 3.2 mmol) at the same temperature, washed with water, and dried (Na_2SO_4). The residue resulted from the evaporation of the solvent was dissolved in THF (20 mL) and water (2 mL). To this solution was added LiOH (67 mg, 2.79 mmol), and stirring was continued for 1 h at room temperature. The reaction mixture was then acidified with 1% HCl solution and extracted with ether (50 mL × 3). The combined extracts were washed with saturated NaCl solution and dried (Na_2SO_4). Evaporation of the solvent gave 550 mg of a crude keto acid **13**: IR ($CHCl_3$) 1740, 1730, 1710 cm^{-1}; NMR ($CDCl_3$) δ 0.88 (6 H, d, J = 6 Hz, $CH(CH_3)_2$), 0.96 (3 H, s, CH_3), 9.00–9.30 (1 H, m, CO_2H), 9.42 (1 H, br s, CHO). This crude **13** was used for the next reaction without further purification because of its instability.

A mixture of the crude **13** (550 mg) obtained above, ethylene glycol (370 mg, 6 mmol), a catalytic amount of camphorsulfonic acid (CSA), and benzene (50 mL) was refluxed in a flask fitted with a Dean–Stark trap. After 1.5 h the reaction mixture was cooled, washed with water, and dried (Na_2SO_4). Evaporation of the solvent gave a crude product which was chromatographed on silica gel (20 g) using hexane–ethyl acetate (3:2 v/v) as an eluant to afford 452 mg (70%) of **14** as a colorless oil: IR ($CHCl_3$) 1740, 1710 cm^{-1}; NMR ($CDCl_3$) δ 0.87 (6 H, d, J = 6 Hz, $CH(CH_3)_2$), 0.93 (3 H, s, CH_3), 3.62–4.00 (4 H, m, OCH_2CH_2O), 5.15 (1 H, dd, J = 4 and 8 Hz, OCHO), 10.30 (1 H, br s, CO_2H); mass spectrum, m/z 326 (M^+); $[\alpha]^{20}_D$ −17.6° (c 1.3). Anal. Calcd for $C_{18}H_{30}O_5$: C, 66.23; H, 9.26. Found: C, 65.99; H, 8.88.

(+)-[1(*R*)-Methyl-2(*R*)-hydroxy-5(*R*)-(1(*R*)-((tosyloxy)methyl)-5-methylhexyl)cyclopentyl]acetaldehyde Ethylene Acetal (16). To a stirred suspension of $LiAlH_4$ (486 mg, 12.79 mmol) in THF (70 mL) was added dropwise a solution of **14** (1.39 g, 4.3 mmol) in THF (7 mL) at 0 °C, and then stirring was continued for 6 h at room temperature. The reaction mixture was treated successively with aqueous THF (3 mL), 15% NaOH solution (0.5 mL), and then water (1 mL). Evaporation of the filtrate, obtained by passing the reaction mixture through Celite, gave 1.06 g of **15** as a colorless oil: IR ($CHCl_3$) 3450 cm^{-1}; NMR ($CDCl_3$) δ 0.87 (3 H, s, CH_3), 0.87 (6 H, d, J = 6 Hz, $CH(CH_3)_2$), 3.63–4.10 (4 H, m, OCH_2CH_2O), 4.97 (1 H, dd, J = 7 and 2 Hz, OCHO); mass spectrum, m/z 314 (M^+).

A mixture of crude **15** (1.06 g), Et_3N (1.3 mL), p-toluenesulfonyl chloride (700 mg, 3.67 mmol), a catalytic amount of 4-(dimethylamino)pyridine, and CH_2Cl_2 (50 mL) was stirred for 8 h at room temperature. The reaction mixture was then washed with 10% HCl and saturated NaCl solution and dried (Na_2SO_4). The residue resulted from the evaporation of the solvent was chromatographed on silica gel (20 g) by using hexane–ethyl acetate (3:2 v/v) as an eluant to afford 1.24 g (62%) of **16** as a colorless oil: IR ($CHCl_3$) 3500 cm^{-1}; NMR ($CDCl_3$) δ 0.80 (3 H, s, CH_3), 0.84 (6 H, d, J = 6 Hz, $CH(CH_3)_2$), 2.45 (3 H, s, CH_3), 3.70–4.10 (6 H, m, OCH_2CH_2O, CH_2OTs), 4.94 (1 H, dd, J = 2 and 7 Hz, OCHO), 7.28 (2 H, d, J = 8 Hz, Ar H), 7.73 (2 H, d, J = 7 Hz, Ar H); mass spectrum, m/z 468 (M^+); $[\alpha]^{20}_D$ +21.5° (c 0.73). Anal. Calcd for $C_{25}H_{40}O_6S$: C, 64.07; H, 8.60; S, 6.84. Found: C, 64.45; H, 8.42; S, 7.07.

(+)-[1(*R*)-Methyl-2(*R*)-((methoxymethyl)oxy)-5(*R*)-(1-(*R*)-((tosyloxy)methyl)-5-methylhexyl)cyclopentyl]acetaldehyde Ethylene Acetal (17). To a solution of **16** (626 mg, 1.34 mmol) and *N,N*-diisopropylethylamine (0.47 mL) in CH_2Cl_2 (10 mL) was added dropwise methoxymethyl chloride (0.12 mL) at room temperature, and stirring was continued for 10 h at the same temperature. The reaction mixture was diluted with water (5 mL) and extracted with CH_2Cl_2 (30 mL × 3). The combined extracts were washed with saturated NaCl solution and dried ($MgSO_4$). Evaporation of the solvent afforded a residue which was chromatographed on silica gel (20 g) by using hexane–ethyl acetate (3:1 v/v) to give 576 mg (84%) of **17** as a colorless oil: NMR ($CDCl_3$) δ 0.77 (3 H, s, CH_3), 0.85 (6 H, d, J = 6 Hz, $CH(CH_3)_2$), 2.47 (3 H, s, CH_3), 3.30 (3 H, s, OCH_3), 3.60–4.10 (6 H, m, OCH_2CH_2O, CH_2OTs), 4.57 (2 H, s, OCH_2O), 4.88 (1 H, t, J = 5 Hz, OCHO), 7.33 (2 H, d, J = 8 Hz, Ar H), 7.80 (2 H, d, J = 8 Hz, Ar H); $[\alpha]^{20}_D$ +11.1° (c 0.83). Anal. Calcd for $C_{27}H_{44}O_7S$: C, 63.25; H, 8.65; S, 6.25. Found: C, 62.84; H, 8.42; S, 6.68.

(+)-[1(*R*)-Methyl-2(*R*)-((methoxymethyl)oxy)-5(*R*)-(1-(*R*),5-dimethylhexyl)cyclopentyl]acetaldehyde Ethylene Acetal (18). To a stirred suspension of $LiAlH_4$ (50 mg, 1.32 mmol) in THF (25 mL) was added dropwise a solution of **17** (679 mg, 1.28 mmol) in THF (2 mL) at room temperature. The solution was then refluxed for 1 h, after which the reaction mixture was treated successively with aqueous THF (2 mL), 15% NaOH (0.1 mL), and water (0.1 mL). The mixture was then passed through Celite to remove inorganics. The filtrate thus obtained was evaporated to leave a crude product which was chromatographed on silica gel (20 g) by using hexane–ethyl acetate (9:1 v/v), affording 419 mg (92%) of **18** as a colorless oil: NMR ($CDCl_3$) δ 0.84 (3 H, s, CH_3), 0.89 (6 H, d, J = 6 Hz, $CH(CH_3)_2$), 3.30 (3 H, s, OCH_3), 3.68–4.05 (4 H, m, OCH_2CH_2O), 4.57 (2 H, s, OCH_2O), 4.95 (1 H, t, J = 5 Hz, OCHO); mass spectrum, m/z 342 (M^+); $[\alpha]^{20}_D$ +26.0° (c 0.89); exact mass calcd for $C_{20}H_{38}O_4$ 342.2768, found 342.2742.

(+)-[1(*R*)-Methyl-2(*R*)-((methoxymethyl)oxy)-5(*R*)-(1-(*R*),5-dimethylhexyl)cyclopentyl]acetaldehyde (19). A solution of **18** (76 mg, 0.22 mmol) in acetone (8 mL) and 10% HCl (3 drops) was stirred for 2 h at room temperature. After evaporation of the solvent, the residue was treated with water (10 mL) and extracted with ether (50 mL × 3). The combined extracts were washed with saturated NaCl solution and dried (Na_2SO_4). Removal of the solvent left a crude product which was chromatographed on silica gel (5 g) by using hexane–ethyl acetate (9:1 v/v) as an eluant to give 61 mg (92%) of **19** as a colorless oil: IR ($CHCl_3$) 1710 cm^{-1}; NMR ($CDCl_3$) δ 0.87 (6 H, d, J = 6 Hz, $CH(CH_3)_2$), 0.97 (3 H, s, CH_3), 2.17 (1 H, dd, J = 4 and 14 Hz, CH_2CHO), 2.56 (1 H, dd, J = 2 and 14 Hz, CH_2CHO), 3.25 (3 H, s, OCH_3), 4.47 (2 H, s, OCH_2O), 9.72 (1 H, dd, J = 2 and 4 Hz, CHO); mass spectrum, m/z 267 (M^+ − 31); $[\alpha]^{20}_D$ +10.9° (c 0.64).

2(*R*)-Methyl-1(*R*)-[(methoxymethyl)oxy]-2-(3-methoxy-2-propenyl)-3(*R*)-(1(*R*),5-dimethylhexyl)cyclopentane (20). To a solution of (methoxymethyl)diphenylphosphine oxide (273 mg, 1.19 mmol) in THF (7 mL) was added dropwise a solution of LDA [prepared from diisopropylamine (103 mg, 1.02 mmol) and 0.65 mL (1.02 mmol) of *n*-butyllithium (100 mg/mL in hexane)] in THF (2 mL) at 0 °C under stirring. After 10 min, the reaction mixture was cooled to −78 °C, and a solution of **19** (276 mg, 0.93 mmol) in THF (2 mL) was added dropwise to this solution at the same temperature. The resulting mixture was raised to room temperature, quenched with saturated NH_4Cl solution (10 mL), and extracted with ether (50 mL × 3). The

combined extracts were washed with saturated NaCl solution and dried ($MgSO_4$). To a solution of the residue, resulting from the evaporation of the solvent, in THF (20 mL) was added 93 mg (2.33 mmol) of NaH (60% in oil), and stirring was continued for 20 h at room temperature. The reaction mixture was treated with saturated NH_4Cl solution and extracted with ether (50 mL × 3). The combined extracts were washed with saturated NaCl solution and dried ($MgSO_4$). Evaporation of the solvent left a residue which was chromatographed on silica gel (5 g) by using hexane–ethyl acetate (95:5 v/v) as an eluant to give 251 mg (83%) of **20** as a colorless oil: NMR ($CDCl_3$) δ 0.78 (3 H, s, CH_3), 0.88 (6 H, d, J = 6 Hz, $CH(CH_3)_2$), 3.27 (3 H, s, OCH_3), 3.49, 3.52 (3 H, each s, OCH_3), 4.48 (2 H, s, OCH_2O), 5.70–6.30 (2 H, m, CH=CHO); mass spectrum, m/z 326 (M^+), exact mass calcd for $C_{20}H_{38}O_3$ 326.2821, found 326.2843.

(+)-Methyl 3-[1(*R*)-Methyl-2(*R*)-((methoxymethyl)-oxy)-5(*R*)-(1(*R*),5-dimethylhexyl)cyclopentyl]propionate (21). To a stirred solution of **20** (45 mg, 0.14 mmol) in CH_2Cl_2 (2 mL) was added pyridinium chlorochromate (90 mg, 0.42 mmol), and stirring was continued for 20 h at room temperature. The reaction mixture was treated with Florosil and filtered through Celite. The residue resulting from evaporation of the filtrate was chromatographed on silica gel (1 g) by using hexane–ethyl acetate (9:1 v/v) as an eluant to afford 41 mg (87%) of **21** as a colorless oil: IR ($CHCl_3$) 1730 cm^{-1}; NMR ($CDCl_3$) δ 0.82 (3 H, s, CH_3), 0.87 (6 H, d, J = 6 Hz, $CH(CH_3)_2$), 3.27 (3 H, s, OCH_3), 3.59 (3 H, s, CO_2CH_3), 4.46 (1 H, d, J = 6 Hz, OCH_2O), 4.51 (1 H, d, J = 6 Hz, OCH_2O); mass spectrum, m/z 311 ($M^+ - 31$); $[\alpha]^{20}_D$ +1.3° (c 0.62). Anal. Calcd for $C_{20}H_{38}O_4$: C, 70.13; H, 11.18. Found: C, 69.90; H, 10.95.

(+)-Des-AB-8-oxacholestan-9-one (22). A solution of **21** (30 mg, 0.09 mmol) in acetone (5 mL) and 10% HCl solution (3 drops) was refluxed for 4 h. After evaporation of the solvent, the residue was diluted with water (5 mL) and extracted with ether (20 mL × 3). The combined extracts were washed with saturated NaCl solution and dried (Na_2SO_4). Removal of the solvent afforded the crude product which was chromatographed on silica gel (1 g) by using hexane–ethyl acetate (17:3 v/v) as an eluant to give 20 mg (86%) of **22** as a colorless oil: IR ($CHCl_3$) 1730 cm^{-1}; NMR ($CDCl_3$) δ 0.85 (3 H, s, CH_3), 0.90 (6 H, d, J = 6 Hz, $CH(CH_3)_2$), 4.20 (1 H, dd, J = 4 and 10 Hz, OCH); mass spectrum, m/z 266 (M^+); $[\alpha]^{20}_D$ +133.2° (c 0.62); exact mass calcd for $C_{17}H_{30}O_2$ 266.2246, found 266.2263.

(−)-3-[1(*R*)-Methyl-5(*R*)-(1(*R*),5-dimethylhexyl)-2-oxocyclopentyl]propionic Acid (24). A mixture of **22** (22 mg, 0.08 mmol), LiOH (2.5 mg, 0.10 mmol), water (0.1 mL), and THF (3 mL) was stirred for 1 h at room temperature. The reaction mixture was then acidified with 10% HCl solution and extracted with ethyl acetate (20 mL × 3). The combined extracts were washed with saturated NaCl solution and dried (Na_2SO_4). The residue resulted from the evaporation of the solvent was dissolved in acetone (3 mL) and Jones' reagent (2 drops) was added to this solution at 0 °C. After 10 min, the reaction mixture was treated with isopropyl alcohol and water successively and extracted with ethyl acetate (20 mL × 3). The combined extracts were washed with saturated NaCl solution and dried (Na_2SO_4). Evaporation of the solvent left the residue which was chromatographed on silica gel (1 g) by using hexane–ethyl acetate (1:1 v/v) as an eluant to give 20 mg (94%) of **24** as a colorless oil: IR ($CHCl_3$) 1740, 1710 cm^{-1}; NMR ($CDCl_3$) δ 0.88 (6 H, d, J = 6.6 Hz, $CH(CH_3)_2$), 0.94 (3 H, s, CH_3), 0.99 (3 H, d, J = 6.6 Hz, CH_3); mass spectrum, m/z 282 (M^+); $[\alpha]^{20}_D$ −42.3° (c 0.85). Anal. Calcd for $C_{17}H_{30}O_3 \cdot 0.1H_2O$: C, 71.84; H, 10.71. Found: C, 71.75; H, 10.52. The IR and NMR spectra of this sample were identical with those of an authentic sample.[7b]

(−)-Des-AB-8-oxacholest-14-en-9-one (3). A mixture of **24** (47 mg, 0.17 mmol), sodium acetate (13.6 mg, 0.17 mmol), and acetic anhydride (3 mL) was refluxed for 1.5 h. After evaporation of the acetic anhydride, the residue was treated with water and extracted with ether (50 mL × 3). The combined extracts were washed with saturated $NaHCO_3$ and NaCl solution successively and then dried (Na_2SO_4). Removal of the solvent afforded the crude product which was chromatographed on silica gel (1 g) by using hexane–ethyl acetate (19:1 v/v) as an eluant to give 35 mg (80%) of **3** as a colorless oil: IR ($CHCl_3$) 1770 cm^{-1}; NMR ($CDCl_3$) δ 0.88 (6 H, d, J = 6.6 Hz, $CH(CH_3)_2$), 0.93 (3 H, d, J = 6.3 Hz, CH_3), 1.10 (3 H, s, CH_3), 5.02 (1 H, dd, J = 3.3 and 1.2 Hz, C=CH); mass spectrum, m/z 264 (M^+); $[\alpha]^{20}_D$ −32.5° (c 0.63); exact mass calcd for $C_{17}H_{28}O_2$ 264.2087, found 264.2081.

(−)-(3a*R*,4*R*,7a*R*)-5,5-(Ethylenedioxy)-4-(4-methylpentyl)-3a,4,5,6,7,7a-hexahydro-7a-methylindan-1-one (35). A mixture of **5** (2.1 g, 8.4 mmol), ethylene glycol (730 mg, 11.77 mmol), a catalytic amount of *p*-toluenesulfonic acid, and benzene (200 mL) was refluxed in a flask fitted with a Dean–Stark trap. After 1.5 h the reaction mixture was cooled, washed with water, and dried (Na_2SO_4). Evaporation of the solvent gave a crude product which was chromatographed on silica gel (40 g) by using hexane–ethyl acetate (19:1 v/v) as an eluant to afford 2.1 g (85%) of **35** as a colorless oil: IR ($CHCl_3$) 1740 cm^{-1}; NMR ($CDCl_3$) δ 0.87 (6 H, d, J = 6 Hz, $CH(CH_3)_2$), 0.90 (3 H, s, CH_3), 3.87 (4 H, br s, OCH_2CH_2O); mass spectrum, m/z 294 (M^+); $[\alpha]^{20}_D$ −74.3° (c 1.27). Anal. Calcd for $C_{18}H_{30}O_3$: C, 73.43; H, 10.27. Found: C, 73.65; H, 10.46.

(3a*R*,4*R*,7a*R*)-5,5-(Ethylenedioxy)-1-[(phenylthio)-methylene]-4-(4-methylpentyl)-3a,4,5,6,7,7a-hexahydro-7a-methylindan (36). After a mixture of 0.47 g (11.75 mmol) of NaH (60% in oil), diethyl [(phenylthio)methyl]phosphonate (2.52 g, 9.7 mmol), and THF (5 mL) was refluxed for 30 min, a solution of the monoketone **35** (1.9 g, 6.5 mmol) in THF (5 mL) was added dropwise to this solution, and refluxing was continued for 5 h. To this end, the reaction mixture was treated with saturated NH_4Cl solution and extracted with ether (50 mL × 3). The combined extracts were washed with saturated NaCl solution and dried (Na_2SO_4). The residue resulting from the evaporation of the solvent was chromatographed on silica gel (50 g) by using hexane–ethyl acetate (19:1 v/v) as an eluant to give 2.46 g (95%) of **36** as a colorless oil: NMR ($CDCl_3$) δ 0.87 (6 H, d, J = 6 Hz, $CH(CH_3)_2$), 0.92, 1.03 (3 H, each s, CH_3), 3.83 (4 H, br s, OCH_2CH_2O), 5.57–5.90 (1 H, m, C=CHS), 6.97–7.43 (5 H, m, Ar H); mass spectrum, m/z 400 (M^+). Anal. Calcd for $C_{25}H_{36}O_2S$: C, 74.95; H, 9.06; S, 8.00. Found: C, 74.78; H, 8.90; S, 8.27.

(+)-(3a*R*,4*R*,7a*R*)-5,5-(Ethylenedioxy)-1(*Z*)-[(phenylsulfonyl)methylene]-4-(4-methylpentyl)-3a,4,5,6,7,7a-hexahydro-7a-methylindan (37a) and (−)-(3a*R*,4*R*,7a*R*)-5,5-(Ethylenedioxy)-1(*E*)-[(phenylsulfonyl)methylene]-4-(4-methylpentyl)-3a,4,5,6,7,7a-hexahydro-7a-methylindan (37b). After a mixture of **36** (1 g, 2.5 mmol), saturated $NaHCO_3$ solution (20 mL), 1.24 g (5.03 mmol) of *m*-chloroperbenzoic acid (70%), and CH_2Cl_2 (20 mL) was stirred for 10 h at room temperature, the reaction mixture was diluted with CH_2Cl_2 (50 mL). The organic layer was washed with water and dried (Na_2SO_4). The residue resulting from the evaporation of the solvent was chromatographed on silica gel (20 g) by using hexane–ethyl acetate (4:1 v/v) as an eluant. Evaporation of the solvent of the first fraction afforded 423 mg (39%) of **37a** as a colorless oil: NMR ($CDCl_3$) δ 0.87 (3 H, d, J = 6 Hz, $CH(CH_3)_2$), 1.17 (3 H, s, CH_3), 3.88 (4 H, br s, OCH_2CH_2O), 5.97 (1 H, t, J = 2 Hz, C=$CHSO_2$), 7.40–7.97 (5 H, m, Ar H); mass spectrum, m/z 432 (M^+); $[\alpha]^{20}_D$ +25.9° (c 1.2). Anal. Calcd for $C_{25}H_{36}O_4S$: C, 69.41; H, 8.39; S, 7.41. Found: C, 69.77; H, 8.53; S, 7.39.

Furthermore, evaporation of the solvent of the second fraction gave 442 mg (41%) of **37b** as a colorless oil: NMR ($CDCl_3$) δ 0.87 (6 H, d, J = 6 Hz, $CH(CH_3)_2$), 0.90 (3 H, s, CH_3), 2.85 (4 H, br s, OCH_2CH_2O), 5.83 (1 H, t, J = 3 Hz, C=$CHSO_2$), 7.40–7.93 (5 H, m, Ar H); $[\alpha]^{20}_D$ −78.8° (c 1.56). Anal. Calcd for $C_{25}H_{36}O_4S$: C, 69.41; H, 8.39; S, 7.41. Found: C, 69.46; H, 8.69; S, 7.71.

(−)-(1*S*,3a*R*,4*R*,7a*S*)-1-[(Phenylsulfonyl)methyl]-4-(4-methylpentyl)-3a,4,5,6,7,7a-hexahydro-7a-methylindan-5-one (33). A mixture of **37** (1.3 g, 3 mmol), 5% palladium on carbon (100 mg), 10% HCl solution (0.4 mL), and MeOH (40 mL) was stirred under an atmosphere of hydrogen at room temperature and atmospheric pressure. Hydrogenation was completed within 5 h. The solution was then filtered to remove the catalyst. The residue resulted from the evaporation of the filtrate was dissolved in benzene. The benzene layer was washed with saturated NaCl solution and dried (Na_2SO_4). Removal of the solvent yielded a crude product, which was chromatographed on silica gel (20 g) by using hexane–ethyl acetate (17:3 v/v) as an eluant to give 845 mg (72%) of **33** as a colorless oil: IR ($CHCl_3$) 1710 cm^{-1}; NMR ($CDCl_3$) δ 0.87 (6 H, d, J = 6 Hz, $CH(CH_3)_2$), 0.88 (3 H, s, CH_3), 2.87–3.13 (2 H, m, CH_2SO_2), 7.40–7.97 (5 H, m, Ar H); mass spectrum, m/z 390 (M^+); $[\alpha]^{20}_D$ −26.0° (c 1.49). Anal. Calcd for

$C_{23}H_{34}O_3S$: C, 70.73; H, 8.77; S, 8.21. Found: C, 70.45; H, 8.95; S, 8.67.

(-)-(1*S*,3a*R*,4*R*,7a*S*)-5-Acetoxy-1-[(phenylsulfonyl)methyl]-4-(4-methylpentyl)-3a,4,7,7a-tetrahydro-7a-methylindan (38). A mixture of **33** (3.62 g, 9.3 mmol), *p*-toluenesulfonic acid (500 mg), and isopropenyl acetate (70 mL) was condensed to 10 mL in 2 h under an atmospheric pressure. After refluxing was continued for 10 h, the reaction mixture was diluted with ethyl acetate (200 mL), washed with water, saturated $NaHCO_3$, and NaCl solution, and dried (Na_2SO_4). The residue resulting from the evaporation of the solvent was chromatographed on silica gel (50 g) by using hexane–ethyl acetate (17:3 v/v) as an eluant to give 3.94 g (98%) of **38** as a colorless oil: IR ($CHCl_3$) 1740 cm^{-1}; NMR ($CDCl_3$) δ 0.73 (3 H, s, CH_3), 0.85 (6 H, d, J = 6 Hz, $CH(CH_3)_2$), 2.10 (3 H, s, CH_3), 5.10–5.37 (1 H, m, C=CH), 7.45–8.00 (5 H, m, Ar H); $[\alpha]^{20}_D$ –0.38° (*c* 2.1). Anal. Calcd for $C_{25}H_{36}O_4S$: C, 69.41; H, 8.39; S, 7.41. Found: C, 69.07; H, 8.34; S, 7.74.

(+)-6-Methyl-2(*R*)-[2-((2,5-dioxacyclopentyl)methyl)-2-(*S*)-methyl-3(*S*)-((phenylsulfonyl)methyl)-1(*R*)-cyclopentyl]heptanoic Acid (39). Through a stirred solution of **38** (787 mg, 1.82 mmol) in CH_2Cl_2 (30 mL) was passed O_3 at –78 °C for 30 min. To this end, the reaction mixture was treated with dimethyl sulfide (0.16 mL) at the same temperature, washed with water, and dried (Na_2SO_4). The residue resulting from the evaporation of the solvent was dissolved in THF (20 mL) and water (3 mL). To this solution was added LiOH (76 mg, 3.17 mmol), and stirring was continued for 2 h at room temperature. The reaction mixture was then acidified with 10% HCl solution and extracted with CH_2Cl_2 (50 mL × 3). The combined extracts were washed with saturated NaCl solution and dried ($MgSO_4$). Evaporation of the solvent gave 750 mg of the crude acid aldehyde: IR ($CHCl_3$) 1720, 1700 cm^{-1}; NMR ($CDCl_3$) δ 0.73 (3 H, s, CH_3), 0.83 (6 H, d, J = 6 Hz, $CH(CH_3)_2$), 7.40–8.00 (5 H, m, Ar H), 8.33–8.82 (1 H, m, CO_2H), 9.47 (1 H, t, J = 2.5 Hz, CHO). This crude sample was used for the next reaction without further purification because of its instability.

A mixture of the crude acid aldehyde (750 mg) obtained above, ethylene glycol (170 mg, 2.74 mmol), a catalytic amount of camphorsulfonic acid, and benzene (50 mL) was refluxed in a flask fitted with a Dean–Stark trap. After 2 h the reaction mixture was cooled, washed with water, and dried (Na_2SO_4). Evaporation of the solvent gave a crude product which was chromatographed on silica gel (20 g) by using hexane–ethyl acetate (7:3 v/v) as an eluant to afford 620 mg (73%) of **39** as a colorless oil: IR ($CHCl_3$) 1710 cm^{-1}; NMR ($CDCl_3$) δ 0.70 (3 H, s, CH_3), 0.83 (6 H, d, J = 6 Hz, $CH(CH_3)_2$), 3.45–3.83 (4 H, m, OCH_2CH_2O), 4.70 (1 H, dd, J = 3 and 7 Hz, OCHO) 7.40–8.03 (5 H, m, Ar H), 8.50–8.87 (1 H, m, CO_2H); mass spectrum, m/z 466 (M^+); $[\alpha]^{20}_D$ +0.79° (*c* 1.5); exact mass calcd for $C_{25}H_{38}O_6S$ 466.2390, found 466.2417.

(+)-[1(*S*)-Methyl-2(*S*)-((phenylsulfonyl)methyl)-5(*R*)-(1(*S*)-(hydroxymethyl)-5-methylhexyl)cyclopentyl]acetaldehyde Ethylene Acetal (40). To a stirred suspension of $LiAlH_4$ (122 mg, 3.2 mmol) in THF (20 mL) was added dropwise a solution of **39** (619 mg, 1.33 mmol) in THF (3 mL) at 0 °C, and then stirring was continued for 9 h at room temperature. The reaction mixture was treated successively with aqueous THF (2 mL), 15% NaOH solution (0.2 mL), and then water (1 mL). Evaporation of the filtrate, obtained by passing the reaction mixture through Celite, gave 435 mg (72%) of **40** as a colorless oil: IR ($CHCl_3$) 3460 cm^{-1}; NMR ($CDCl_3$) δ 0.63 (3 H, s, CH_3), 0.85 (6 H, d, J = 6 Hz, $CH(CH_3)_2$), 3.24–3.87 (6 H, m, OCH_2CH_2O, CH_2O), 4.55 (1 H, t, J = 4 Hz, OCHO), 7.37–7.97 (5 H, m, Ar H); mass spectrum, m/z 452 (M^+); $[\alpha]^{20}_D$ +0.88° (*c* 2.0). Anal. Calcd for $C_{25}H_{40}O_5S$: C, 66.33; H, 8.91; S, 7.08. Found: C, 66.61; H, 9.13; S, 7.17.

(-)-[1(*S*)-Methyl-2(*S*)-((phenylsulfonyl)methyl)-5(*R*)-(1(*S*)-((tosyloxy)methyl)-5-methylhexyl)cyclopentyl]acetaldehyde Ethylene Acetal (41). A mixture of **40** (190 mg, 0.42 mmol), *p*-toluenesulfonyl chloride (100 mg, 0.52 mmol), a catalytic amount of 4-(dimethylamino)pyridine, and pyridine (1 mL) was stirred for 5 h at room temperature. The reaction mixture was then diluted with water (5 mL) and extracted with ether (50 mL × 3). The combined extracts were washed with 10% HCl solution and saturated NaCl solution, and dried (Na_2SO_4). The residue resulting from the evaporation of the solvent was chromatographed on silica gel (5 g) by using hexane–ethyl acetate (7:3 v/v) as an eluant to give 237 mg (93%) of **41** as a colorless oil: NMR ($CDCl_3$) δ 0.58 (3 H, s, CH_3), 0.80 (6 H, d, J = 6 Hz, $CH(CH_3)_2$), 2.42 (3 H, s, CH_3), 3.52–3.83 (4 H, m, OCH_2CH_2O), 3.92 (2 H, d, J = 4 Hz, CH_2O), 4.52 (1 H, t, J = 5 Hz, OCHO), 7.23 (2 H, d, J = 8 Hz, Ar H), 7.68 (2 H, d, J = 8 Hz, Ar H), 7.42–7.95 (5 H, m, Ar H); mass spectrum, m/z 606 (M^+); $[\alpha]^{20}_D$ –3.1° (*c* 2.0). Anal. Calcd for $C_{32}H_{46}O_7S_2$: C, 63.33; H, 7.64; S, 10.57. Found: C, 63.33; H, 7.43; S, 10.64.

(-)-[1(*S*)-Methyl-2(*S*)-((phenylsulfonyl)methyl)-5(*R*)-(1(*R*),5-dimethylhexyl)cyclopentyl]acetaldehyde Ethylene Acetal (42). To a stirred suspension of $LiAlH_4$ (25 mg, 0.67 mmol) in THF (15 mL) was added dropwise a solution of **41** (405 mg, 0.67 mmol) in THF (3 mL) at room temperature. After stirring had been continued for 3 h under refluxing, the reaction mixture was treated successively with aqueous THF (1 mL), 15% NaOH solution (0.05 mL), and water (0.05 mL). The mixture was then passed through Celite to remove inorganics. The filtrate thus obtained was evaporated to leave a crude product, which was chromatographed on silica gel (10 g) by using hexane–ethyl acetate (17:3 v/v) as an eluant to give 276 mg (95%) of **42** as a colorless oil: NMR ($CDCl_3$) δ 0.67 (3 H, s, CH_3), 0.85 (6 H, d, J = 6 Hz, $CH(CH_3)_2$), 3.50–3.80 (4 H, m, OCH_2CH_2O), 4.67 (1 H, t, J = 4.5 Hz, OCHO), 7.77–8.00 (5 H, m, Ar H); mass spectrum, m/z 436 (M^+); $[\alpha]^{20}_D$ –12.0° (*c* 2.4). Anal. Calcd for $C_{25}H_{40}O_4S$: C, 68.76; H, 9.23; S, 7.34. Found: C, 68.44; H, 9.02; S, 7.71.

(-)-[1(*S*)-Methyl-2(*S*)-((phenylsulfonyl)methyl)-5(*R*)-(1(*R*),5-dimethylhexyl)cyclopentyl]acetaldehyde (43). A solution of **42** (306 mg, 0.7 mmol) in acetone (15 mL) and 10% HCl solution (1.5 mL) was stirred for 6 h at room temperature. After evaporation of the solvent, the residue was treated with water (10 mL) and extracted with ether (50 mL × 3). The combined extracts were washed with saturated NaCl solution and dried (Na_2SO_4). Removal of the solvent left a crude product, which was chromatographed on silica gel (5 g) by using hexane–ethyl acetate (9:1 v/v) as an eluant to give 261 mg (95%) of **43** as a colorless oil: IR ($CHCl_3$) 1720 cm^{-1}; NMR ($CDCl_3$) δ 0.73 (3 H, s, CH_3), 0.87 (6 H, d, J = 6 Hz, $CH(CH_3)_2$), 7.50–8.03 (5 H, m, Ar H), 9.63 (1 H, t, J = 3 Hz, CHO); mass spectrum, m/z 392 (M^+); $[\alpha]^{20}_D$ –19.3° (*c* 1.54); exact mass calcd for $C_{23}H_{36}O_3S$ 392.2383, found 392.2347.

2(*S*)-Methyl-3(*R*)-(1(*R*),5-dimethylhexyl)-1(*S*)-[(phenylsulfonyl)methyl]-2-(2,3-epoxypropyl)cyclopentane (44). To a stirred suspension of trimethylsulfonium iodide (39 mg, 0.19 mmol) in THF (1 mL) was added dropwise 0.135 mL (0.21 mmol) of *n*-butyllithium (100 mg/mL in hexane) at 0 °C. After 10 min, a solution of **43** (31 mg, 0.08 mmol) in THF (0.5 mL) was added to this solution, and stirring was continued for 30 min at the same temperature. The reaction mixture was then stirred for 1 h at room temperature and evaporated to leave a residue, which was treated with water (5 mL) and extracted with ether (20 mL × 3). The combined extracts were washed with water and dried (Na_2SO_4). Evaporation of the solvent afforded a crude product, which was chromatographed on silica gel (1 g) by using hexane–ethyl acetate (9:1 v/v) as an eluant to give 10 mg (31%) of **44** as a colorless oil: NMR ($CDCl_3$) δ 0.67 (3 H, s, CH_3), 0.84 (6 H, d, J = 6 Hz, $CH(CH_3)_2$), 2.29 (1 H, dd, J = 5 and 2.5 Hz, $\overline{OCCH}H$), 2.65 (1 H, dd, J = 5 and 4 Hz, $\overline{OCCH}H$), 2.66–2.94 (1 H, m, $\overline{OCHC}$), 7.48–7.98 (5 H, m, Ar H); mass spectrum, m/z 265 (M^+ – 141). Anal. Calcd for $C_{24}H_{38}O_3S{\cdot}0.2H_2O$: C, 70.27; H, 9.44; S, 7.82. Found: C, 70.00; H, 9.36; S, 8.08.

Intramolecular Cyclization of 44. To a stirred solution of LDA [prepared from diisopropylamine (13 mg, 0.13 mmol) and 0.08 mL (0.13 mmol) of *n*-butyllithium (100 mg/mL in hexane)] in THF (2 mL) was added a solution of **44** (26 mg, 0.06 mmol) in THF (0.5 mL) at –78 °C, and stirring was continued for 10 min at the same temperature. The reaction mixture was treated with saturated NH_4Cl solution and extracted with ether (20 mL × 3). The combined extracts were washed with saturated NaCl solution and dried (Na_2SO_4). Evaporation of the solvent yielded a crude product which was chromatographed on silica gel (1 g). From the fraction eluted with hexane–ethyl acetate (9:1 v/v), 8 mg (30%) of **45a** was obtained as a colorless oil: IR ($CHCl_3$) 3500 cm^{-1}; NMR ($CDCl_3$) δ 0.72 (3 H, s, CH_3), 0.83 (6 H, d, J = 6 Hz, $CH(CH_3)_2$),

3.04–3.36 (1 H, m, $CHSO_2$), 3.55–3.76 (2 H, m, CH_2O), 7.44–7.94 (5 H, m, Ar H); mass spectrum, m/z 406 (M^+); exact mass calcd for $C_{24}H_{38}O_3S$ 406.2542, found 406.2542.

Furthermore, from the fraction eluted with hexane–ethyl acetate (17:3, v/v), 13 mg (50%) of **45b** was obtained as a colorless oil: NMR ($CDCl_3$) δ 0.72 (3 H, s, CH_3), 0.85 (6 H, d, J = 6 Hz, $CH(CH_3)_2$), 3.04 (1 H, ddd, J = 12, 12, and 4 Hz, $CHSO_2$), 3.60–4.00 (1 H, m, CHO), 7.46–7.92 (5 H, m, Ar H); mass spectrum, m/z 265 (M^+ – 141); exact mass calcd for $C_{18}H_{33}O$ 265.2531 (M^+ – 141), found 265.2538.

Acetylation of 45a. After a mixture of **45a** (2 mg, 0.005 mmol), acetic anhydride (2 drops), and pyridine (0.05 mL) had been stirred for 2 h at room temperature, the reaction mixture was diluted with water (5 mL) and extracted with ether (5 mL × 3). The combined extracts were washed with saturated NaCl solution and dried (Na_2SO_4). The residue resulted from the evaporation of the solvent was chromatographed on silica gel (1 g) by using hexane–ethyl acetate (9:1 v/v) as an eluant to give 2 mg (91%) of **45b** as a colorless oil: IR ($CHCl_3$) 1730 cm^{-1}; NMR ($CDCl_3$) δ 0.72 (3 H, s, CH_3), 0.82 (6 H, d, J = 6 Hz, $CH(CH_3)_2$), 2.96–3.32 (1 H, m, $CHSO_2$), 3.80–4.20 (2 H, m, CH_2O), 7.40–7.92 (5 H, m, Ar H); mass spectrum, m/z 448 (M^+); exact mass calcd for $C_{26}H_{40}O_4S$ 448.2647, found 448.2657.

(+)-8α-(Phenylsulfonyl)-des-AB-cholestane (30). After a mixture of **45a** (3 mg, 0.08 mmol), mesyl chloride (1 drop), and pyridine (0.1 mL) was stirred for 1 h at 0 °C, the reaction mixture was diluted with water (5 mL) and extracted with ether (5 mL × 3). The combined extracts were washed with 10% HCl and saturated NaCl solution, and dried (Na_2SO_4). Evaporation of the solvent afforded a crude product, **46b**, which was used for the next reaction without further purification.

A mixture of the crude mesylate **46b** obtained above, LiBr (1 mg, 0.01 mmol), Li_2CO_3 (1 mg, 0.01 mmol), and *N*,*N*-dimethylformamide (0.5 mL) was stirred for 4 h at 150 °C. The reaction mixture was then diluted with water and extracted with ethyl acetate (5 mL × 3). The combined extracts were washed with water and dried (Na_2SO_4). Removal of the solvent yielded **47** as a crude product: NMR ($CDCl_3$) δ 0.68, 0.78 (3 H, each s, CH_3), 0.85 (6 H, d, J = 6 Hz, $CH(CH_3)_2$)), 3.20–3.68 (1 H, m, $CHSO_2$), 5.20–6.23 (2 H, m, CH=CH), 7.40–7.92 (5 H, m, Ar H); mass spectrum m/z 247 (M^+ – 141).

Next, a mixture of crude **47** prepared above and 5% palladium on carbon (1 mg) in ethyl acetate (1 mL) was stirred under an atmosphere of hydrogen at room temperature for 8 h. The solution was then filtered to remove the catalyst, and the filtrate was evaporated to leave a residue which was chromatographed on silica gel (1 g) by using hexane–ethyl acetate (9:1 v/v) as an eluant. Evaporation of the solvent yielded 2 mg (69%) of **30** as colorless needles: mp 116.5–118 °C (petroleum ether); NMR ($CDCl_3$) δ 0.69 (3 H, s, CH_3), 0.85 (6 H, d, J = 6 Hz, $CH(CH_3)_2$), 2.84–3.16 (1 H, m, $CHSO_2$), 7.44–7.92 (5 H, m, Ar H); mass spectrum, m/z 249 (M^+ – 141); $[\alpha]^{20}_D$ +0.06° (c 0.2). Anal. Calcd for $C_{24}H_{38}O_2S$: C, 73.39; H, 9.81; S, 8.21. Found: C, 73.62; H, 9.91; S, 8.43.

(–)-2(*S*)-Methyl-1(*S*)-[(phenylsulfonyl)methyl]-2-(2-propenyl)-3(*R*)-(1(*R*),5-dimethylhexyl)cyclopentane (48). To a solution of [(trimethylsilyl)methyl]magnesium chloride [prepared from 36 mg (1.48 mmol) of Mg and 182 mg (1.48 mmol) of (chloromethyl)trimethylsilane] in ether (8 mL) was added dropwise a solution of **43** (224 mg, 0.57 mmol) in ether (1 mL) at room temperature, and stirring was continued for 1 h at the same temperature. The reaction mixture was poured into saturated NH_4Cl solution, and extracted with ether (20 mL × 3). The combined extracts were washed with saturated $NaHCO_3$ and NaCl solution and dried (Na_2SO_4). The residue resulting from the evaporation of the solvent was dissolved in THF (20 mL). To this solution was added 24 mg (0.6 mmol) of NaH (60% in oil) under stirring. After refluxing had been continued for 12 h, the reaction mixture was poured into saturated NH_4Cl solution and extracted with ether (20 mL × 3). The combined extracts were washed with saturated NaCl solution and dried (Na_2SO_4). Evaporation of the solvent gave the residue, which was chromatographed on silica gel (5 g) by using hexane–ethyl acetate (19:1 v/v) as an eluant to afford 188 mg (81%) of **48** as a colorless oil: NMR ($CDCl_3$) δ 0.63 (3 H, s, CH_3), 0.85 (6 H, d, J = 6 Hz, $CH(CH_3)_2$), 4.70 (1 H, dd, J = 16 and 2 Hz, $CH=CH_2$), 4.83 (1 H, dd, J = 8 and 2 Hz, $CHCH_2$), 5.30–5.80 (1 H, m, $CH=CH_2$), 7.20–7.92 (5 H, m, Ar H); mass spectrum, m/z 390 (M^+); $[\alpha]^{20}_D$ –12.6° (c 1.4); exact mass calcd for $C_{24}H_{38}O_2S$ 390.2593, found 390.2593.

(–)-2(*S*)-Methyl-2-(3-hydroxypropyl)-1(*S*)-[(phenylsulfonyl)methyl]-3(*R*)-(1(*R*),5-dimethylhexyl)cyclopentane (49). To a stirred solution of **48** (159 mg, 0.4 mmol) in hexane (8 mL) was added BH_3·SMe_2 (0.013 mL) at 0 °C, and stirring was continued for 30 min at the same temperature. After stirring was continued for 1 h at room temperature, EtOH (8 mL) and 10% NaOH solution (0.054 mL) were added to this solution. The reaction mixture was cooled to 0 °C and then treated with 30% H_2O_2 solution (0.046 mL). After the mixture was stirred for 30 min at 0 °C, stirring was continued for 1 h at 50 °C. Finally, the reaction mixture was poured into ice–water (80 mL) and extracted with ether (20 mL × 3). The combined extracts were washed with saturated NaCl solution and dried (K_2CO_3). The residue resulting from the removal of the solvent was chromatographed on silica gel (5 g) by using hexane–ethyl acetate (7:3 v/v) as an eluant to give 153 mg (92%) of **49** as a colorless oil: IR ($CHCl_3$) 3500 cm^{-1}; NMR ($CDCl_3$) δ 0.63 (3 H, s, CH_3), 0.87 (6 H, d, J = 6 Hz, $CH(CH_3)_2$), 3.37–3.70 (2 H, m, CH_2O), 7.48–8.07 (5 H, m, Ar H); mass spectrum, m/z 408 (M^+); $[\alpha]^{20}_D$ –4.8° (c 1.17); exact mass calcd for $C_{24}H_{40}O_3S$ 408.2697, found 408.2667.

(–)-2(*S*)-Methyl-2-[3-(mesyloxy)propyl]-1(*S*)-[(phenylsulfonyl)methyl]-3(*R*)-(1(*R*),5-dimethylhexyl)cyclopentane (50). After a mixture of **49** (144 mg, 0.35 mmol), mesyl chloride (0.027 mL), and pyridine (1 mL) had been stirred for 1 h at 0 °C, the reaction mixture was diluted with water (10 mL) and extracted with ether (20 mL × 3). The combined extracts were washed with 10% HCl and saturated NaCl solution, and dried (Na_2SO_4). Evaporation of the solvent afforded a residue which was chromatographed on silica gel (5 g) by using hexane–ethyl acetate (7:3 v/v) as an eluant to give 168 mg (98%) of **50** as a colorless oil: NMR ($CDCl_3$) δ 0.63 (3 H, s, CH_3), 0.85 (6 H, d, J = 6 Hz, $CH(CH_3)_2$), 3.00 (3 H, s, OSO_2CH_3), 3.97–4.23 (2 H, m, CH_2O), 7.47–8.00 (5 H, m, Ar H); mass spectrum, m/z 390 (M^+ – 96); $[\alpha]^{20}_D$ –0.42° (c 0.96). Anal. Calcd for $C_{25}H_{42}O_5S_2$: C, 61.69; H, 8.70; S, 13.18. Found: C, 62.07; H, 8.98; S, 13.32.

Intramolecular Cyclization of 50. To a stirred solution of LDA [prepared from diisopropylamine (39 mg, 0.39 mmol) and 0.25 mL (0.39 mmol) of *n*-butyllithium (100 mg/mL in hexane)] in THF (10 mL) was added dropwise a solution of **50** (155 mg, 0.32 mmol) in THF (1 mL) at –78 °C, and stirring was continued for 30 min at the same temperature. After stirring had been continued for 30 min at room temperature, the reaction mixture was treated with saturated NH_4Cl solution and extracted with ether (20 mL × 3). The combined extracts were washed with saturated NaCl solution and dried (Na_2SO_4). The residue resulting from removal of the solvent was chromatographed on silica gel (5 g) by using hexane–ethyl acetate (9:1 v/v) as an eluant to give 105 mg (84%) of **30** as colorless needles: mp 116.5–118 °C, $[\alpha]^{20}_D$ +0.06° (c 1.4). This was identical with the sample prepared above.

Grundmann's Ketone (51). To a solution of **30** (10 mg, 0.026 mmol) in THF (3 mL) was added a solution of LDA [prepared from diisopropylamine (8.4 mg, 0.083 mmol) and 0.05 mL (0.08 mmol) of *n*-butyllithium (100 mg/mL in hexane)] in THF (1 mL) at –78 °C. After the mixture was stirred at the same temperature for 10 min, a solution of MoO_5·HMPA·pyridine[27] (37.8 mg, 0.09 mmol) in THF (1 mL) was added under stirring. The mixture was stirred for 20 min at –78 °C and then quenched with saturated Na_2SO_3 solution. The reaction mixture was poured into water (5 mL) and extracted with ether (10 mL × 3). The combined extracts were washed with 10% HCl and saturated NaCl solution and dried ($MgSO_4$). Evaporation of the solvent afforded a crude product, which was chromatographed on silica gel (1 g) by using hexane–ethyl acetate (10:1 v/v) as an eluant to give 4.2 mg (62%) of **51** as a colorless oil. This was identical with an authentic sample[28] in all aspects.

Vitamin D_3 (29). To a solution of **52** (50 mg, 0.18 mmol) in THF (10 mL) was added MnO_2 (500 mg, 3.5 mmol), and stirring was continued for 6 h at room temperature. After filtration of inorganics, the filtrate was evaporated to leave a residue, which was chromatographed on silica gel (2 g) by using hexane–ethyl acetate (19:1 v/v) as an eluant to give 39 mg of **53** as a colorless oil, which was used immediately for the next reaction because of its instability.

A solution of LDA [prepared from diisopropylamine (16 mg, 0.16 mmol) and 0.1 mL (0.16 mmol) of *n*-butyllithium (100 mg/mL in hexane)] in THF (1 mL) was added dropwise to a stirred solution of **30** (58 mg, 0.149 mmol) in THF (1 mL) at −78 °C. After stirring had been continued for 20 min, a solution of **53** (39 mg, 0.15 mmol) in THF (0.5 mL) was added to this solution, and the mixture was stirred for 1 h at the same temperature. The reaction mixture was then treated with acetyl chloride (0.011 mL), poured into water, and extracted with ether (10 mL × 3). The combined extracts were washed with saturated NaCl solution and dried (Na_2SO_4). The residue resulting from the evaporation of the solvent was chromatographed on silica gel (1 g) by using hexane–ethyl acetate (97:3 v/v) as an eluant to give 85 mg of **54** as a colorless oil, which was used immediately for the next reaction.

To a stirred solution of **54** (85 mg) in THF–MeOH (1:1) (3 mL) was added 5% sodium amalgam (300 mg) at −20 °C, and stirring was continued for 2 h at the same temperature. After stirring had been continued for 7 h at room temperature, the reaction mixture was poured into water and extracted with ether (20 mL × 3). The combined extracts were washed with saturated NaCl solution and dried (Na_2SO_4). The crude product, **55**, obtained by the evaporation of the solvent was dissolved in THF (2 mL), treated with 0.13 mL of *n*-Bu_4NF (1.0 M in THF), and stirred for 2 h at room temperature. The mixture was then poured into water and extracted with ether (20 mL × 3). The combined extracts were washed with saturated NaCl solution and dried (Na_2SO_4). The residue resulted from the evaporation of the solvent was chromatographed on silica gel (1 g) by using hexane–ethyl acetate (17:3 v/v) as an eluant to give 29.2 mg (51%) of vitamin D_3 (**29**) as a colorless oil: $[\alpha]^{20}_D$ +49.5° (*c* 0.5) [authentic sample, $[\alpha]^{20}_D$ +51.2° (*c* 0.63)]. This sample was identical with an authentic sample in spectral comparisons.

3,5-Dinitrobenzoate of Vitamin D_3. To a solution of triethylamine (0.08 mL) and 3,5-dinitrobenzoyl chloride (10 mg, 0.04 mmol) in CH_2Cl_2 (2 mL) was added a solution of **29** (5 mg, 0.013 mmol) and stirring was continued for 1 h at room temperature. The reaction mixture was then poured into water and extracted with ether (10 mL × 3). The combined extracts were washed with saturated NaCl solution and dried (Na_2SO_4). Evaporation of the solvent gave a crude product, which was chromatographed on neutral alumina (1 g) by using hexane–ethyl acetate (19:1 v/v) as an eluant to give 6 mg (80%) of **56** as yellow needles: mp 129–130 °C (acetone–MeOH); $[\alpha]^{20}_D$ +95.9° (*c* 0.34). This was identical with the authentic sample[30,31] in all aspects.

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α-Amino Acid Derivatives as Chiral Educts for Asymmetric Products. Synthesis of Sphingosine from α′-Amino-α,β-ynones

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The utility of α′-amino-α,β-ynones in the chirospecific synthesis of sphingosine is demonstrated. Thus, a protected L-serine isoxazolidide has been converted to sphingosine by two routes, both via α,β-ynones. The first route is very short and high yielding, merely involving two selective reductions after synthesis of the appropriate α,β-ynone. The second route involves alkylation of a β-unsubstituted ynone and illustrates the synthetic versatility of the α′-amino-α,β-ynone system. Further routes through conjugate 1,4 additions to ynones are demonstrated but are limited by the highly reactive nature of this system.

The chirospecific synthesis of natural products from simple, readily available components of the chiral pool as educts has become a major objective for organic chemists. Previous work from this laboratory has demonstrated the conversion of suitably protected amino acids into optically pure amino ketones by acylation of aromatic rings[1] and by reaction with organometallic reagents.[2] A modification of this methodology, using isoxazolidides, has produced optically pure α′-amino-α,β-ynones.[3] This modification was necessary because the less reactive organometallics derived from acetylenic precursors would not react with the carboxylate functionality of protected amino acids. The use of an isoxazolidide "activating" group gave good yields of the desired α,β-ynones.

To demonstrate the α′-amino-α,β-ynone system's utility, we have synthesized the amino lipid sphingosine (1). Presented here are two chirospecific routes to sphingosine from L-serine. Both routes involve the use of α′-amino-α,β-ynones and exploit the flexibility inherent in these synthetic intermediates. The carbon chain can be introduced directly via lithium pentadecyne, followed by a diastereoselective reduction of the ketone. This produces sphingosine (1) in five steps from CBZ-serine in an overall yield of 22% (Scheme I and II). An alternative path is to form an α,β-unsubstituted acetylenic ketone (**17**; Scheme III) using lithium acetylide. Reduction of the ketone followed by alkylation with 1-iodotridecane (Scheme IV) then leads to sphingosine (1).

Sphingosine has been the target of several syntheses in the past.[4] Recently, interest has greatly increased, with methodology centering on enantiospecific routes. Attempts have been made at utilizing the 2*S* stereochemistry of L-serine as a chiral precursor;[5] however, this route involves an intermediate α-amino aldehyde, whose chiral integrity is questionable.[6] Sphingosine has also been synthesized

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