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Total Synthesis of *ent*-Cholesterol via a Steroid C,D-Ring Side-Chain Synthon

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For the first time, one of the two enantiomers of cholesterol (*ent*-cholesterol) has been synthesized by a synthetic route that starts from a precursor containing the D-ring and entire side chain of cholesterol. As part of the reported synthetic route, a method of general utility for the large scale (>10 g) preparation of each enantiomer of [1α(*R**),7aα]-1-(1,5-dimethylhexyl)-1,2,3,6,7,7a-hexahydro-7a-methyl-5*H*-inden-5-one, C,D ring-side chain synthons that can be used for the synthesis of enantiomers of vitamin D_3, cholesterol, and their analogues was also developed. Using the enantiomer of the C,D-ring side-chain synthon that leads to *ent*-cholesterol, the A- and B-rings were elaborated from a linear fragment that is sequentially cyclized to form the steroid B- and A-rings. Using this route, *ent*-cholesterol was prepared in 23 steps from the methyl ester of (1α,5α,6α)−(±)-6-methyl-2-oxo-bicyclo[3.1.0]hexane-1-carboxylic acid in a total yield of 2.6%.

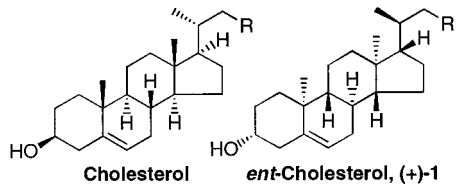
Introduction

The enantiomer of natural cholesterol, *ent*-cholesterol ((+)-**1**, Chart 1), was first synthesized in 1992 by Mickus and Rychnovsky.[1] It was used by them to study the enantioselectivity of cholesterol interactions with amphotericin B.[2] In a more recent study, these investigators and their colleagues also used *ent*-cholesterol to study the molecular recognition of cholesterol stereoisomers by a monoclonal antibody raised and selected against crystals of cholesterol monohydrate.[3]

We are interested in the importance of the absolute configuration of cholesterol for its biological functions either as a modulator of cell membrane properties or as a ligand for cellular proteins that bind, transport, or enzymatically transform cholesterol. In this regard, we found that the monolayer interactions of cholesterol and *ent*-cholesterol with egg yolk sphingomyelin are different.[4] We have also found that the absolute configuration of cholesterol affects the transport of daunomycin by the multidrug resistance transporter P-glycoprotein (Pgp) in human HepG and Chinese hamster ovary (CHO) cells.[5] Most recently, we found that the nematode *Caenorhabditis elegans*, a cholesterol auxotroph, does not thrive on *ent*-cholesterol.[6]

To expand upon our earlier studies, as well as to undertake additional studies, we continue to explore new synthetic routes for the synthesis of *ent*-cholesterol. Of particular interest to us is a method of *ent*-cholesterol preparation that can be adapted readily for the efficient synthesis of A- or B-ring ^{13}C-labeled forms of *ent*-cholesterol. Current synthetic routes to *ent*-cholesterol proceed via the initial construction of the steroid ring system followed by the subsequent introduction of the C-17 side chain.[1,6,7] A similar approach that has been used to construct the cholesterol side chain on the steroid ring system could also be used for the synthesis of *ent*-cholesterol from an *ent*-steroid precursor.[8] However, these synthetic routes are not optimal for preparing the desired ^{13}C-labeled *ent*-cholesterols because the isotopic labels have to be incorporated before the multiple steps involved in construction of the side chain are initiated. The alternative strategy of preparing *ent*-cholestenone and then opening the A-ring so that ^{13}C-labels can be incorporated into the A-ring of *ent*-cholesterol is clearly unattractive, as it makes no sense to first construct the entire C_{27}-steroid and then lose more than 70% of it by opening the A-ring to incorporate ^{13}C-labels.[9]

CHART 1[a]



[a] R = isopentyl.

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(1) Rychnovsky, S. D.; Mickus, D. E. *J. Org. Chem.* **1992**, *57*, 2732.
(2) Mickus, D. E.; Levitt, D. G.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1992**, *114*, 359.
(3) Geva, M.; Izhaky, D.; Mickus, D. E.; Rychnovsky, S. D.; Addadi, L. *ChemBioChem.* **2001**, *2*, 265.
(4) (a) Lalitha, S.; Kumar, A. S.; Covey, D. F.; Stine, K. J. *Chem. Commun. (Cambridge, U. K.)* **2001**, *13*, 1192. (b) Lalitha, S.; Kumar, A. S.; Stine, K. J.; Covey, D. F. *J. Supramol. Chem.* **2001**, *1*, 53−61.
(5) Luker, G. D.; Pica, C. M.; Kumar, A. S.; Covey, D. F.; Piwnica-Worms, D. *Biochemistry* **2000**, *39*, 7651.
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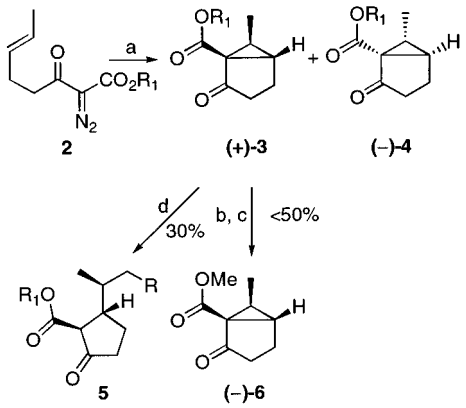
SCHEME 1[a]



[a] Reagents and conditions: (a) Cu(I) catalyst, benzene, reflux, 20 h; (b) 15% aq KOH, MeOH, reflux, 3 h; (c) MeI, K_2CO_3, acetone, reflux, 5 h; (d) Mg, CuI, 1-bromo-4-methylpentane, THF, −15 °C to 25 °C. R = isopentyl; R_1 = (*R*)-Pantolactone.

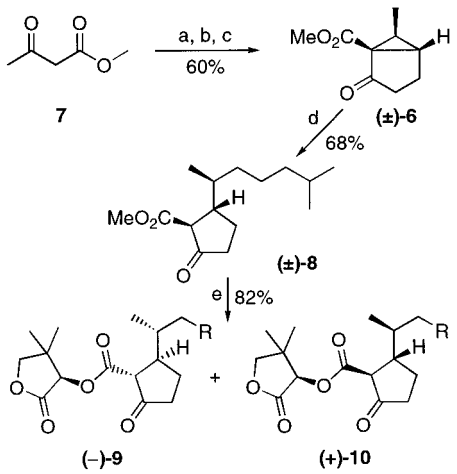
Herein, we report the total synthesis of *ent*-cholesterol by a route which starts with construction of the sterol D-ring containing the cholesterol side chain and then proceeds via elaboration of the sterol C, B, and A rings, respectively. The early steps of the synthesis involve modifications of recent synthetic work carried out by He et al.[10]

Results and Discussion

A method originally developed by He et al. (Scheme 1) was initially explored as a way to prepare the sterol C,D-rings containing the cholesterol side chain.[10] In this method, a Cu(I) catalyst containing an enantiopure ligand is used for the cyclopropanation of α-diazo ester **2** containing the (*R*)-pantolactone group as a chiral auxiliary. Compound (+)-**3** and its diastereomer compound (−)-**4** were obtained in an 85:15 ratio with a reported yield of 53%. At this point, the authors removed the (*R*)-pantolactone group and replaced it with a methyl group to yield compound (−)-**6** prior to introducing the cholesterol side chain. Since the ester exchange proceeds in only modest yield (<50%), we were puzzled as to why the side chain was not directly introduced into compound (+)-**3**. Experimentation showed the reason to be that the bulky (*R*)-pantolactone group of compound (+)-**3** prevents its efficient conversion to *β*-keto ester **5** (30% yield).

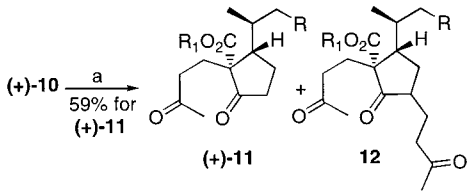
Additionally, when R_1 = Me for compound **5**, He et al. reported that this *β*-keto ester could be readily methylated at C-1 and then decarbomethoxylated in high yield to give the D-ring synthon, 3-(1,5-dimethylhexyl)-2-methylcyclopentanone. This synthon could not be efficiently prepared from compound **5** (R_1 = pantolactone) by the same reaction sequence because the pantolactone ester in the C-1 methylated product was resistant to removal by treatment with either NaCN, HMPA, or strong bases. Consequently, we modified the He et al. methodology to avoid various low yield transformations at the outset of the synthesis.

SCHEME 2[a]



[a] Reagents and conditions: (a) NaH, *n*-BuLi, crotyl bromide, THF, 0 °C to 25 °C; (b) *p*-TsN_3, Et_3N, CH_3CN, 25 °C, 1 h; (c) bis(*N*-*tert*-butylsalicylaldiminato)copper(II), toluene, reflux, 3 h; (d) Mg, CuI, 1-bromo-4-methylpentane, THF, −15 °C, 3 h; (e) (*R*)-pantolactone, DMAP, toluene, reflux, 6 h. R = isopentyl.

SCHEME 3[a]



[a] Reagents and conditions: (a) methyl vinyl ketone, NaOMe-MeOH, 0 °C, 1 h. R = isopentyl; R_1 = (*R*)-Pantolactone.

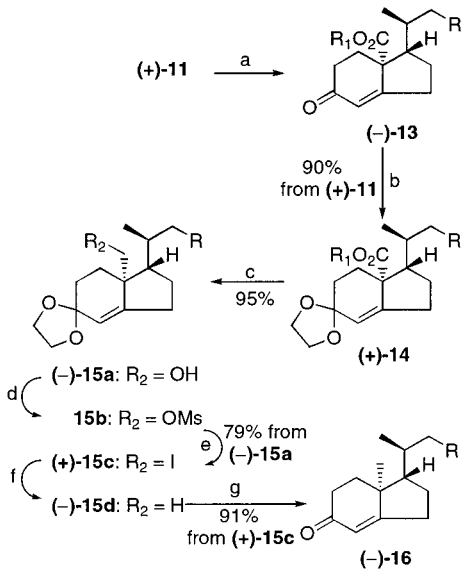
As shown in Scheme 2, we decided to abandon the diastereoselectivity achieved with the (*R*)-pantolactone group and chiral catalyst in the cyclopropanation step. Accordingly, methyl acetoacetate (**7**) was converted in three steps into racemic compound (±)-**6** using literature methods.[11] The addition of 4-methylpentylmagnesium bromide to *β*-keto ester (±)-**6** gave racemic product (±)-**8** in 68% yield.[12] At this point, transesterification of (±)-**8** with (*R*)-pantolactone was carried out to obtain the easily separated diastereomers (−)-**9** (40%) and (+)-**10** (42%).

Compound (+)-**10** was reacted with methyl vinyl ketone at 0 °C (Scheme 3) to give compound (+)-**11** (59%). Compound **12** (15%) and recovered compound (+)-**10** (10%) are also obtained. Raising the temperature of the reaction results in decreasing stereoselectivity for Michael addition of the methyl vinyl ketone at the C-1 position.

The next steps involve closing of what will become the C-ring, and also formation of the 18-methyl group, of *ent*-cholesterol (Scheme 4). Using *p*-TsOH as a catalyst,[13] compound (+)-**11** was initially cyclized to produce compound (−)-**13**, and then ethylene glycol was added for the in situ conversion of enone (−)-**13** to ketal (+)-**14**. The

(9) Yuan, S. S. *Steroids* **1982**, *39*, 279.
(10) He, M.; Tanimori, S.; Ohira, S.; Nakayama, M. *Tetrahedron* **1997**, *53*, 13307.
(11) (a) Tunemoto, D.; Araki, N.; Kondo, K. *Tetrahedron Lett.* **1977**, *18*, 109. (b) Taber, D. F.; Amedio, J. C.; Raman, K. *J. Org. Chem.* **1988**, *53*, 2984.
(12) The reaction time reported for this Grignard reaction in the literature[10] is only 5 min, but we found that 3−4 h were required for the reaction to reach completion.
(13) Miesch, M.; Mislin, G.; Franck-Neumann, M. *Tetrahedron Lett.* **1998**, *39*, 6873.

SCHEME 4[a]



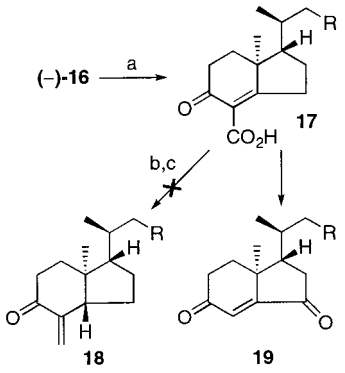
[a] Reagents and conditions: (a) *p*-TsOH, toluene, reflux, 5 h; (b) ethylene glycol, *p*-TsOH, toluene, reflux, 2 h; (c) $LiAlH_4$, THF, reflux, 2 h; (d) MsCl, Et_3N, CH_2Cl_2, 25 °C, 2 h; (e) LiI, $NaHCO_3$, 1,4-dioxane, reflux, 2 h; (f) Superhydride 1.0 M in THF, reflux, 3 h; (g) 2.0 N aqueous HCl in THF, 25 °C, 16 h. R = isopentyl; R_1 = (*R*)-Pantolactone.

overall yield for the two step conversion was 90%. The (*R*)-pantolactone group of compound (+)-**14** was then reduced using $LiAlH_4$ in refluxing THF to yield compound (−)-**15a** (95%). We note in passing that it is very difficult to saponify the (*R*)-pantolactone ester by conventional methods to obtain the corresponding carboxylic acid of (−)-**13** in more than trace amounts.

Several methods were tried for conversion of the hydroxymethyl group of compound (−)-**15a** into the methyl group of compound (−)-**15d** before a satisfactory method was established. Trying to convert the hydroxyl group to an iodo group by using either Ph_3P/I_2 or methyltriphenoxyphosphonium iodide as iodinating reagents gave only low yields of compound (+)-**15c**. Alcohol (−)-**15a** was readily transformed to the mesylate **15b**, but hydride displacement using $LiB(Et)_3H$ in THF (Superhydride) or $LiAlH_4$ gave compound (−)-**15d** in only 40% yield. Finally, we converted mesylate **15b** to iodide (+)-**15c** by refluxing it with LiI in 1,4-dioxane[14] for 2 h. To avoid the partial loss of the ketal protecting group and the formation of other byproducts during the reaction, solid $NaHCO_3$ was added to the reaction mixture. The overall yield of compound (+)-**15c** obtained from alcohol (−)-**15a** by this method was 79%. Hydride displacement of the iodo group from (+)-**15c** using Superhydride gave a product, which after removal of the ketal protecting group, yielded the desired C,D ring-side chain fragment, indenone (−)-**16**, in high yield (91% from (+)-**15c**). Because the indenone enantiomer (+)-**16** is of general utility as a synthon for the preparation of vitamin D_3 and its analogues,[10,15] we also converted (*R*)-pantolactone ester (−)-**9** to indenone (+)-**16** (see Supporting Information for spectroscopic properties of (+)-**16**).

(14) Ireland, R. E.; Liu, L.; Roper, T. D. *Tetrahedron* **1997**, *53*, 13221.

SCHEME 5[a]



[a] Reagents and conditions: (a) 2.0 M MMC−DMF, 125 °C, 2 h; (b) MeOH, 5% Pd/$BaSO_4$, H_2, 200 psi, 0 °C, 1 h; (c) 37% aqueous HCHO, piperidine, DMSO, 25 °C, 1 h. R = isopentyl.

The first attempts to proceed further with the synthesis of *ent*-cholesterol by adding an exocyclic double bond to indenone (−)-**16** to obtain product **18** (Scheme 5), so that the sterol A and B rings could be subsequently formed, were based on procedures used for the synthesis of either 19-nortestosterone[16] or *ent*-testosterone.[1,17] This seemed a reasonable approach since only the side chain of indenone (−)-**16** (C_8 cholesterol side chain versus *tert*-butyl ether group) is different in the literature precedents. Accordingly, compound (−)-**16** was heated with 2.0 M magnesium methyl carbonate (MMC) in DMF to give compound **17**. However, attempts to purify this product by extracting it into aqueous NaOH, as is done for the literature precedents, failed. This is due to the increased hydrophobicity of the C_8 side chain present in indenone **17**. Another unexpected complication was also encountered. When indenone **17** was partially purified in low yield by flash column chromatography, we found that upon standing overnight at room temperature it was partly oxidized to compound **19** by air. Last, when we attempted to convert unpurified indenone **17** directly to product **18**, we obtained a complex mixture of products. These synthetic difficulties with the preparation of compound **18** led us to abandon further attempts to prepare this compound.

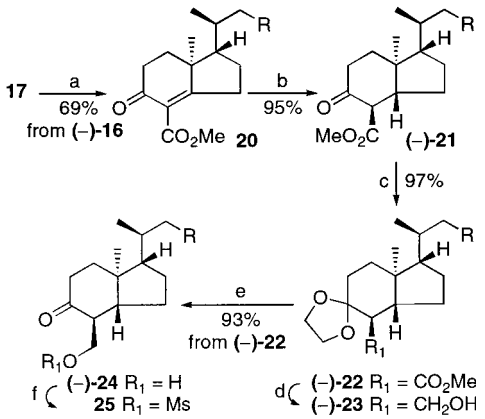
Compound **25** was selected as a synthetic target to take the place of compound **18** in the synthetic route to *ent*-cholesterol (Scheme 6). To stabilize keto acid **17**, it was converted into keto ester **20** by reaction with diazomethane in ether at 0 °C. This product was readily purified (yield from (−)-**16** after purification, 69%), and when it was hydrogenated using 5% Pd/$BaSO_4$, it gave only saturated keto ester (−)-**21** as a product (95%). The axial configuration of 3a-H of compound (−)-**21** was

(15) (a) Ziegler, F. E.; Mencel, J. J. *Tetrahedron Lett.* **1983**, *24*, 1859. (b) Desmaele, D.; Ficini, J.; Guingant, A.; Touzin, A. M. *Tetrahedron Lett.* **1983**, *24*, 3083. (c) Duhamel, P.; Dujardin, G.; Hennequin, L.; Poirier, J. M. *J. Chem. Soc., Perkin Trans. 1* **1992**, 387. (d) Pan, L. R.; Tokoroyama, T. *Tetrahedron Lett.* **1992**, *33*, 1473. (e) Marczak, S.; Wicha, J. *Tetrahedron Lett.* **1993**, *34*, 6627. (f) Grzywacz, P.; Marczak, S.; Wicha, J. *J. Org. Chem.* **1997**, *62*, 5293.

(16) Micheli, R. A.; Hajos, Z. G.; Cohen, N.; Parrish, D. R.; Portland, L. A.; Sciamanna, W.; Scott, M. A.; Wehrli, P. A. *J. Org. Chem.* **1975**, *40*, 675.

(17) Ohloff, G.; Maurer, B.; Winter, B.; Giersh, W. *Helv. Chim. Acta* **1983**, *66*, 192.

SCHEME 6[a]



[a] Reagents and conditions: (a) diazomethane, ether, 0 °C; (b) 5% Pd/$BaSO_4$, H_2, MeOH, 50 psi, 25 °C, 1.5 h; (c) ethylene glycol, benzene, *p*-TsOH, reflux, 14 h; (d) $LiAlH_4$, ether, reflux, 1.5 h; (e) 2 N HCl, acetone, 25 °C, 2 h; (f) MsCl, Et_3N, CH_2Cl_2, 25 °C, 2 h. R = isopentyl.

established from its ^{1}H NMR spectrum which contained a *trans*-diaxial coupling ($J_{3a-H,4-H}$ = 12.9 Hz) for 3a-H.

The carbomethoxy group of keto ester (−)-**21** was then converted into the CH_2OMs group of compound **25** in four steps so that the remaining rings of *ent*-cholesterol could be constructed. First, the keto group of indanone (−)-**21** was protected by converting it into the ketal group of compound (−)-**22** (97%). The carbomethoxy group of compound (−)-**22** was then reduced with $LiAlH_4$, and the ketal group was removed to give compound (−)-**24** (93%). The mesylate **25** was then prepared in the usual manner and used directly in the next reaction to prepare *ent*-cholestenone as shown in Scheme 7.

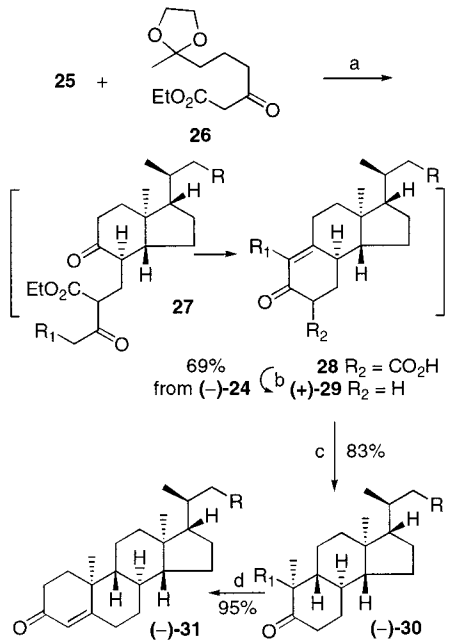
Displacement of the mesylate group of compound **25** by the anion formed from ethyl 2-methyl-*β*-oxo-1,3-dioxolane-2-hexanoate **26** led to unisolated intermediate **27**. In situ cyclization and saponification of intermediate **27** under alkaline conditions yielded uncharacterized intermediate **28**. Decarboxylation of intermediate **28** at 80 °C under high vacuum proceeded smoothly to afford tricyclic compound (+)-**29** (69% from compound (−)-**24**).

To introduce the C-19 methyl group of *ent*-cholesterol into precursor enone (+)-**29**, the enone is reduced with excess lithium in liquid ammonia/THF at −78 °C and the lithium enolate intermediate is reacted with excess iodomethane at −40 °C (1 h) and then ambient temperature (3−4 h) before quenching the reaction. This procedure gave compound (−)-**30** in 83% yield.[18] Refluxing compound (−)-**30** in methanolic HCl overnight afforded *ent*-cholestenone (−)-**31** in >95% yield. The *ent*-cholestenone had $[\alpha]_D$ = −91.0 (25 °C, *c* = 0.49, $CHCl_3$). Authentic cholestenone had $[\alpha]_D$ = +92.1 (25 °C, *c* = 0.59, $CHCl_3$). We consider the slightly unequal magnitude of the optical rotations of the cholestenone enantiomers to be experimental error since the precursor compound (+)-**10** contained no detectable amount of the stereoisomer, compound (−)-**9**.

The conversion of *ent*-cholestenone (−)-**31** to *ent*-cholesterol (+)-**1** was achieved via the dienol acetate **32**

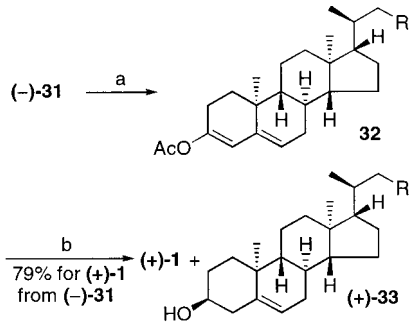
(18) As the scale of this reaction is increased, the reaction time needs to be increased so the reaction of the lithium enolate with iodomethane goes to completion.

SCHEME 7[a]



[a] Reagents and conditions: (a) (i) MeONa-MeOH, 25 °C, 12 h; (ii) 5 N aq NaOH, 25 °C, 1 h; (b) 1 mmHg, 80 °C, 3 h; (c) (i) Li, liq. NH_3, THF, −78 °C, 1 h; (ii) MeI, −40 °C to 25 °C, 4 h; (d) 6 N HCl, MeOH, reflux, 16 h. R = isopentyl; R_1 = 2-(2-methyl-1,3-dioxolan-2-yl)ethyl.

SCHEME 8[a]



[a] Reagents and conditions: (a) Me_3SiCl, NaI, Ac_2O, 25 °C, 1.5 h; (b) $NaBH_4$, EtOH, 25 °C, 16 h. R = isopentyl.

as shown in Scheme 8. The natural enantiomer of compound **32** has been prepared by several methods.[19−21] We chose the method cited in ref 20. Thus, *ent*-cholestenone (−)-**31** was reacted with Me_3SiCl/NaI in Ac_2O to give a quantitative yield of product **32**. Dienol acetate **32** was then reduced with $NaBH_4$ in EtOH overnight as described for the natural enantiomer of this compound.[21] We obtained *ent*-cholesterol (+)-**1** and its epimer (+)-**33** in yields of 79% and 10%, respectively. The *ent*-cholesterol obtained had $[\alpha]_D$ = +39.0 (25 °C, *c* = 0.29, $CHCl_3$) and natural cholesterol had $[\alpha]_D$ = −38.7 (25 °C, *c* = 0.60, $CHCl_3$).

(19) Ren, D.; Li, L.; Schwabacher, A. W.; Young, J. W.; Beitz, D. C. *Steroids* **1996**, *61*, 33.

(20) (a) Chowdhury, P. K.; Sharma, R. P.; Barua, J. N. *Tetrahedron Lett.* **1983**, *24*, 3383. (b) Wijnberg, J. B. P. A.; Groot, A. *Steroids* **1989**, *54*, 333.

(21) Kasal, A.; Trka, A. *Collect. Czech. Chem. Commun.* **1980**, *45*, 2985.

Conclusion

We synthesized *ent*-cholesterol from racemic compound (±)-**6** in 23 steps with an overall yield of 2.6%. The reported method should be particularly useful for preparing ^{13}C- and ^{2}H-labeled forms of *ent*-cholesterol in which the isotopic labels are located in the A- and/or B-ring of the steroid since the isotopic labels can be introduced near the end of the reaction sequence. We plan to use *ent*-cholesterol isotopically labeled in this manner for NMR studies of *ent*-cholesterol interactions with different types of membrane lipids.

We also improved upon a previous literature procedure[10] for the synthesis of either enantiomer of indenone **16**. Starting from methyl 3-oxo-6-octenoate, the only intermediate common to our synthetic route and that reported earlier, we obtained a 7.6% yield of each enantiomer of indenone **16**. The previously used method gives either enantiomer in a reported overall yield of 1.6%. More importantly, the procedure we report can be used to prepare the indenone **16** enantiomers on a scale of more than 10 g without difficulty, thereby facilitating the preparation of other vitamin D_3 and cholesterol analogues.

Finally, compound (−)-**13** and its enantiomer should be useful for the preparation of vitamin D_3 and cholesterol analogues in which the C-18 methyl group is either absent or modified. Such compounds are not readily available using other synthetic methods.

Experimental Section

General Methods. Melting points were determined on a micro hot stage and are uncorrected. NMR spectra were recorded in $CDCl_3$ at 300 MHz (^1H) or 75 MHz (^{13}C). IR spectra were recorded as films on a NaCl plate. Elemental analyses were carried out by M−H−W Laboratories, Phoenix, AZ. Solvents were used either as purchased or dried and purified by standard methodology. Flash chromatography was performed using silica gel (32−63 μm).

[1*R*-[1α(*R),2*β*(*R**)]]-2-(1,5-Dimethylhexyl)-5-oxocyclopentanecarboxylic Acid, Tetrahydro-4,4-dimethyl-2-oxo-3-furanyl Ester ((−)-9) and [1*S*-[1α(*S**),2*β*(*R**)]]-2-(1,5-Dimethylhexyl)-5-oxocyclopentanecarboxylic Acid, Tetrahydro-4,4-dimethyl-2-oxo-3-furanyl Ester ((+)-10).** The mixture of compound (±)-**8** (14.25 g, 56.0 mmol), (*R*)-pantolactone (8.47 g, 67.2 mmol), DMAP (1.37 g, 11.2 mmol), and toluene (500 mL) was refluxed with a Dean−Stark condenser for 6 h. The distilled toluene and methanol were removed periodically. The reaction mixture was cooled to room temperature, washed with 5% HCl (50 mL), 10% $NaHCO_3$ (30 mL), and water, and dried over Na_2SO_4. The solvent was removed, and the residue obtained was purified by chromatography (silica gel; hexanes/EtOAc, 20:1) to give compounds (−)-**9** (8.0 g, 40%) and (+)-**10** (8.2 g, 42%).

Compound (−)-**9** was obtained as white crystals: mp 49−51 °C (hexanes); $[\alpha]^{25}_D = -43.7$ ($c = 0.98$, $CHCl_3$); ^1H NMR δ 0.87 (d, $J = 6.6$ Hz, 6H), 0.97 (d, $J = 6.6$ Hz, 3H), 1.06 (s, 3H), 1.22 (s, 3H), 3.06 (d, $J = 11.4$ Hz, 1H), 4.03 (m, 2H), 5.39 (s, 1H); ^{13}C NMR δ 16.9, 19.6, 22.4, 22.6, 22.9, 24.5, 25.4, 27.8, 33.9, 37.3, 38.4, 39.0, 40.5, 47.5, 60.0, 75.3, 76.1, 169.4, 171.9, 211.7; IR ν_{max} 2958, 1793, 1762, 1735, 1467, 1155, 1089 cm^{-1}. Anal. Calcd for $C_{20}H_{32}O_5$: C, 68.15; H, 9.15. Found: C, 68.10; H, 9.01.

Compound (+)-**10** was obtained as white crystals: mp 69−71 °C (hexanes); $[\alpha]^{25}_D = +33.4$ ($c = 1.36$, $CHCl_3$); ^1H NMR δ 0.87 (d, $J = 6.6$ Hz, 6H), 0.96 (d, $J = 6.9$ Hz, 3H), 1.21 (s, 3H), 1.23 (s, 3H), 3.10 (d, $J = 11.4$, 1H), 4.05 (m, 2H), 5.43 (s, 1H); ^{13}C NMR δ 17.4, 19.7, 22.4, 22.6, 22.7, 24.2, 25.3, 27.8, 33.8, 37.6, 38.7, 39.1, 40.4, 46.7, 59.6, 75.6, 76.2, 169.6, 172.2, 211.8; IR ν_{max} 2959, 2931, 1792, 1760, 1732, 1116 cm^{-1}. Anal. Calcd for $C_{20}H_{32}O_5$: C, 68.15; H, 9.15. Found: C, 67.94; H, 9.23.

[1*R*-[1α(*R),2α(*S**)]]-2-(1,5-Dimethylhexyl)-5-oxo-1-(3-oxobutyl)cyclopentanecarboxylic Acid, Tetrahydro-4,4-dimethyl-2-oxo-3-furanyl Ester ((+)-11).** $NaOCH_3$ in CH_3OH (0.1 N, 24 mL) was cooled to 0 °C, and compound (+)-**10** (4.00 g, 11.4 mmol) in MeOH (15 mL) was added dropwise. After stirring at 0 °C for 20 min, methyl vinyl ketone (799 mg, 11.4 mmol) in MeOH (5 mL) was added dropwise. The reaction was stirred at 0 °C for another 1 h. Then AcOH (0.08 mL) was added to quench the reaction. The solvent was removed under reduced pressure, and the residue was taken up in EtOAc (50 mL), washed with water (2 ×10 mL), and dried over Na_2SO_4. After removal of the solvent, the residue was purified by chromatography (silica gel; hexanes/EtOAc, 6:1) to give compound (+)-**11** (2.83 g, 59%) as a colorless oil: $[\alpha]^{25}_D = +23.3$ ($c = 0.97$, $CHCl_3$); ^1H NMR δ 0.87 (d, $J = 6.6$ Hz, 6H), 0.99 (s, 3H), 1.00 (d, $J = 6.3$ Hz, 3H), 1.18 (s, 3H), 2.14 (s, 3H), 4.02 (s, 2H), 5.41 (s, 1H); ^{13}C NMR δ 18.2, 19.5, 22.4, 22.6, 22.7, 23.4, 25.2, 27.8, 28.3, 29.7, 34.3, 34.8, 38.4, 38.9, 39.1, 40.5, 52.4, 61.6, 75.3, 76.1, 170.0, 171.8, 207.9, 216.5; IR ν_{max} 2956, 1792, 1756, 1734, 1718, 1153 cm^{-1}. Anal. Calcd for $C_{24}H_{38}O_6$: C, 68.22; H, 9.06. Found: C, 68.35; H, 8.87.

[*3S*α[3α(*R),3aα(*S**)]]-3-(1,5-Dimethylhexyl)-1,2,3,4,5,6-hexahydro-6-oxo-3a*H*-indene-3a-carboxylic Acid, Tetrahydro-4,4-dimethyl-2-oxo-3-furanyl Ester ((−)-13) and [1′*S*-[1′α(*R**),7′aα(*S**)]]-1-(1,5-Dimethylhexyl)-1′,2′,6′,7′-tetrahydrospiro[1,3-dioxolane-2,5′-[5*H*]indene]-7′a(3′*H*)-carboxylic Acid, Tetrahydro-4,4-dimethyl-2-oxo-3-furanyl Ester ((+)-14).** A mixture of compound (+)-**11** (4.22 g, 10 mmol), *p*-TsOH (1.26 g, 30% w/w), and toluene (100 mL) was refluxed using a Dean−Stark apparatus for 5−6 h, and the extent of reaction was monitored by TLC. The reaction was cooled to room temperature, and 1 mL of the solution was taken out and washed with aqueous $NaHCO_3$ and brine, followed by chromatography (silica gel; hexane/EtOAc, 6:1) to give compound (−)-**13** for product characterization. Ethylene glycol (6.20 g, 100 mmol) was added to the remainder of the solution. The reaction mixture was refluxed for another 2 h and cooled to room temperature. It was washed with 10% $NaHCO_3$ (2 × 30 mL) and water (2 × 30 mL) and dried over Na_2SO_4. The solvent was removed, and the residue obtained was purified by chromatography (silica gel; hexanes/EtOAc, 6:1) to give compound (+)-**14** (4.05 g, 90%).

Compound (−)-**13** was obtained as a colorless oil: $[\alpha]^{25}_D = -110.5$ ($c = 1.43$, $CHCl_3$); ^1H NMR δ 0.87 (d, $J = 6.6$ Hz, 6H), 1.02 (s, 3H), 1.07 (d, $J = 6.3$ Hz, 3H), 1.16 (s, 3H), 4.05 (s, 2H), 5.47 (s, 1H), 5.90 (m, 1H); ^{13}C NMR δ 18.1, 19.4, 22.3, 22.5, 22.6, 23.2, 27.3, 27.6, 30.5, 34.0, 34.3, 35.1, 35.3, 39.0, 40.2, 56.8, 57.1, 75.4, 75.9, 123.5, 170.2, 171.7, 172.1, 198.4; IR ν_{max} 2956, 1792, 1737, 1671, 1154 cm^{-1}. Anal. Calcd for $C_{24}H_{36}O_5$: C, 71.26. H, 8.97. Found: C, 71.32; H, 8.90.

Compound (+)-**14** was obtained as a colorless oil: $[\alpha]^{25}_D = +52.0$ ($c = 0.76$, $CHCl_3$); ^1H NMR δ 0.85 (d, $J = 6.6$ Hz, 6H), 0.95 (d, $J = 6.3$ Hz, 3H), 1.03 (s, 3H), 1.17 (s, 3H), 3.96 (m, 4H), 4.02 (s, 2H), 5.42 (s, 1H), 5.71(m, 1H); ^{13}C NMR δ 18.4, 19.6, 22.4, 22.6, 22.9, 23.2, 27.8, 32.3, 34.2, 34.3, 35.9, 37.6, 38.0, 39.2, 40.3, 59.1, 59.4, 64.4, 64.5, 74.8, 76.0, 108.6, 128.7, 141.5, 172.0, 173.3; IR ν_{max} 2956, 1795, 1734, 1087 cm^{-1}. Anal. Calcd for $C_{26}H_{40}O_6$: C, 69.61; H, 8.99. Found: C, 69.76; H, 9.07.

[1′*S*-[1′α(*R),7′aα]]-1′-(1,5-Dimethylhexyl)-1′,2′,6′,7′-tetrahydrospiro[1,3-dioxolane-2,5′-[5*H*]indene]-7′a(3′*H*)-methanol ((−)-15a).** $LiAlH_4$ (1.52 g, 40 mmol) was added to compound (+)-**14** (2.24 g, 5.0 mmol) dissolved in THF (100 mL). After the reaction mixture was refluxed for 2 h, it was cooled to 0 °C and water (4 mL) was added dropwise to quench the reaction. The reaction mixture was filtered through a pad of diatomaceous earth (Celite 545), washed thoroughly with ether. The combined filtrate was washed with water (20 mL), 5% HCl (20 mL), saturated aqueous $NaHCO_3$ (20 mL), and

brine (2 × 20 mL), and dried over Na_2SO_4. The solvent was removed, and the residue obtained was purified by chromatography (silica gel; hexanes/EtOAc, 6:1) to give compound (−)-**15a** (1.53 g, 95%) as a colorless oil: $[\alpha]^{25}_D = -31.0$ ($c = 1.12$, $CHCl_3$); ^{1}H NMR δ 0.86 (d, $J = 6.9$ Hz, 6H), 0.98 (d, $J = 6.3$ Hz, 3H), 3.73 (m, 2H), 3.96 (m, 4H), 5.71 (m, 1H); ^{13}C NMR δ 19.2, 22.4, 22.7, 23.4, 27.9, 31.7, 33.3, 34.2, 36.0, 36.6, 37.6, 39.5, 51.5, 57.3, 62.2, 64.4, 64.5, 109.0, 127.1, 142.5; IR ν_{max} 3487, 2931, 1468, 1364, 1086, 1046 cm^{-1}. Anal. Calcd for $C_{20}H_{34}O_3$: C, 74.49; H, 10.63. Found: C, 74.51; H, 10.50.

[1′*S*-[1′α(*R),7′aα]]-1′-(1,5-Dimethylhexyl)-1′,2′,6′,7′-tetrahydrospiro[1,3-dioxolane-2,5′-[5*H*]indene]-7′a(3′*H*)-methanol, Methane Sulfonate (15b).** To the solution of compound (−)-**15a** (1.55 g, 4.81 mmol) and Et_3N (4.27 g, 5.88 mL, 42.3 mmol) in CH_2Cl_2 (180 mL) was added MsCl (1.21 g, 0.82 mL, 10.6 mmol) at 0 °C. The resultant reaction mixture was stirred at room temperature for 2 h. It was then washed with water and dried over Na_2SO_4. The solvent was removed to give compound **15b** (2.07 g) quantitively. It was used without further purification. An analytical sample of compound **15b** was purified by chromatography (silica gel; hexanes/EtOAc, 15:1) and was obtained as a colorless oil: ^{1}H NMR δ 0.86 (d, $J = 6.6$ Hz, 6H), 0.98 (d, $J = 5.7$ Hz, 3H), 2.97 (s, 3H), 3.96 (m, 4H), 4.21 (d, $J = 10.2$ Hz, 1H), 4.33 (d, $J = 10.2$ Hz, 1H), 5.61 (m, 1H); ^{13}C NMR δ 19.1, 22.4, 22.6, 23.2, 27.9, 31.4, 33.1, 33.5, 35.9, 36.6, 36.7, 37.3, 39.4, 49.4, 57.6, 64.4, 64.5, 68.7, 108.6, 127.2, 141.6; IR ν_{max} 2952, 1468, 1357, 1175, 1085 cm^{-1}. Anal. Calcd for $C_{21}H_{36}O_5S$: C, 62.97; H, 9.06; S, 8.01. Found: C, 62.84; H, 8.95; S, 8.23.

[1′*S*-[1′α(*R),7′aα]]-1′-(1,5-Dimethylhexyl)-1′,2′,3′,6′,7′,7′a-hexahydro-7′a-(iodomethyl)spiro[1,3-dioxolane-2,5′-[5*H*]-indene] ((+)-15c).** To the solution of compound 15b (2.07 g, 5.18 mmol) in 1,4-dioxane (200 mL) were added LiI (2.57 g, 19.2 mmol) and $NaHCO_3$ (1.61 g, 19.2 mmol), and the reaction mixture was refluxed under N_2 for 2 h. After removal of the 1,4-dioxane under reduced pressure, the residue was dissolved in EtOAc (100 mL), washed with water, and dried over Na_2SO_4. The solvent was removed, and the residue obtained was purified by chromatography (silica gel; hexanes/EtOAc, 20:1) to give compound (+)-**15c** (1.64 g, 79% from compound (−)-**15a**) as a colorless oil. $[\alpha]^{25}_D = +34.2$ ($c = 0.85$, $CHCl_3$); ^{1}H NMR δ 0.86 (d, $J = 6.6$ Hz, 6H), 0.99 (d, $J = 6.0$ Hz, 3H), 3.32 (d, $J = 10.5$ Hz, 1H), 3.49 (d, $J = 10.5$ Hz, 1H), 3.96 (m, 4H), 5.60 (m, 1H); ^{13}C NMR δ 9.0, 19.9, 22.4, 22.7, 23.4, 27.9, 31.4, 32.5, 35.8, 36.5, 36.6, 37.8, 39.3, 48.9, 57.7, 64.4, 64.5, 108.6, 125.8, 143.9; IR ν_{max} 2952, 1466, 1364, 1225, 1103 cm^{-1}. Anal. Calcd for $C_{20}H_{33}IO_2$: C, 55.56; H, 7.69. Found: C, 55.67; H, 7.79.

[1′*S*-[1′α(*R),7′aα]]-1′-(1,5-Dimethylhexyl)-1′,2′,3′,6′,7′,7′a-hexahydro-7′a-methylspiro[1,3-dioxolane-2,5′-[5*H*]indene] ((−)-15d).** To compound (+)-**15c** (1.60 g, 3.70 mmol) in THF (50 mL) was added Superhydride (1.0 M in THF, 37.0 mL, 37.0 mmol). The resultant solution was refluxed for 3 h. The reaction was cooled to 0 °C, and water (5 mL) was added dropwise to quench the reaction. It was then washed with brine and dried over Na_2SO_4. Removal of the solvent gave compound (−)-**15d** (1.12 g, 99%). It was used without further purification. An analytical sample of compound (−)-**15d** was purified by chromatography (silica gel; hexanes/EtOAc, 20:1) and was obtained as a colorless oil: $[\alpha]^{25}_D = -16.5$ ($c = 1.12$, $CHCl_3$); ^{1}H NMR δ 0.86 (d, $J = 6.6$ Hz, 6H), 0.92 (d, $J = 6.0$ Hz, 3H), 0.96 (s, 3H), 3.96 (m, 4H), 5.31 (m, 1H); ^{13}C NMR δ 15.5, 18.8, 22.5, 22.7, 23.4, 27.9, 31.2, 33.7, 35.9 (2 × C), 36.3, 38.2, 39.5, 45.9, 57.8, 64.3, 64.5, 109.3, 121.8, 147.8; IR ν_{max} 2953, 1467, 1357, 1261, 1093, 1013 cm^{-1}. Anal. Calcd for $C_{20}H_{34}O_2$: C, 78.38; H, 11.18. Found: C, 78.17; H, 11.28.

[1*S*-[1α(*R),7aα]]-1-(1,5-Dimethylhexyl)-1,2,3,6,7,7a-hexahydro-7a-methyl-5*H*-inden-5-one ((−)-16).** To compound (−)-**15d** (1.12 g, 3.65 mmol) in THF (50 mL) was added 2 N HCl (20 mL). The solution was stirred at room-temperature overnight (16 h). Ether (50 mL) was added, and the mixture was washed with saturated aqueous $NaHCO_3$ and brine and dried over Na_2SO_4. The solvent was removed, and the residue obtained was purified by chromatography (silica gel; hexanes/EtOAc, 20:1) to give compound (−)-**16** (0.88 g, 91% from compound (+)-**15c**) as a colorless oil: $[\alpha]^{25}_D = -69.5$ ($c = 0.91$, $CHCl_3$); ^{1}H NMR δ 0.88 (d, $J = 6.3$ Hz, 6H), 0.97 (d, $J = 6.3$ Hz, 3H), 1.09 (s, 3H), 5.74 (m, 1H); ^{13}C NMR δ 16.0, 18.6, 22.4, 22.7, 23.6, 26.7, 27.9, 28.8, 33.4, 34.3, 35.7, 37.0, 39.3, 44.9, 55.7, 121.5, 180.3, 199.5; UV λ_{max} 239.9 nm; IR ν_{max} 2954, 1672, 1467, 1197 cm^{-1}. Anal. Calcd for $C_{18}H_{30}O$: C, 82.38; H, 11.52. Found: C, 82.19; H,11.39. The NMR data were consistent with literature data.[10]

[1*S*-[1α(*R),7aα]]-1-(1,5-Dimethylhexyl)-2,3,5,6,7,7a-hexahydro-7a-methyl-5-oxo-1*H*-indene-4-carboxylic Acid, Methyl Ester (20).** Compound (−)-**16** (524 mg, 2 mmol) and magnesium methyl carbonate (2.0 M solution in DMF, 5 mL, 10 mmol) were heated at 125 °C under Ar for 2 h. The reaction was cooled to room temperature, poured into a mixture of 12 N HCl (10 mL) and ice (30 g), and extracted with diethyl ether (4 × 50 mL). The combined organic extracts were washed with cold brine until neutral pH was obtained and then dried over Na_2SO_4 to give an ethereal solution of crude compound **17**.

The solution of crude compound **17** in diethyl ether was cooled to 0 °C, and a diethyl ether solution of diazomethane was added. When the reaction was completed (monitored by TLC), it was quenched immediately with acetic acid. The solution was then washed with aqueous $NaHCO_3$ and brine and dried over Na_2SO_4. The solvent was removed, and the residue obtained was purified by chromatography (silica gel; hexanes/EtOAc, 20:1) to give compound **20** (440 mg, 69% from compound (−)-**16**) as a colorless oil: ^{1}H NMR δ 0.88 (d, $J = 6.6$ Hz, 6H), 0.98 (d, $J = 6.6$ Hz, 3H), 1.13 (s, 3H), 3.80 (s, 3H); ^{13}C NMR δ 16.1, 18.7, 22.4, 22.6, 23.6, 26.9, 27.9, 28.6, 33.3, 33.9, 35.6 (2 × C), 39.3, 45.9, 51.9, 55.4, 127.2, 166.7, 181.2, 194.7; IR ν_{max} 2953, 1740, 1676, 1643, 1232 cm^{-1}.

[1*S*-[1α(*R),3a*β*,4*β*,7aα]]-1-(1,5-Dimethylhexyl)octahydro-7a-methyl-5-oxo-1*H*-indene-4-carboxylic Acid, Methyl Ester ((−)-21).** Compound **20** (235 mg, 0.733 mmol) was dissolved in MeOH (100 mL) and hydrogenated (50 psi, H_2; 5% Pd/$BaSO_4$, 94 mg) for 1.5 h. The reaction mixture was then filtered through a pad of Celite 545 to remove catalyst, and the solvent was distilled under reduced pressure. The product was purified by chromatography (silica gel; hexanes/EtOAc, 20:1) to give compound (−)-**21** (225 mg, 95%) as a colorless oil; $[\alpha]^{25}_D = -19.5$ ($c = 1.11$, $CHCl_3$); ^{1}H NMR δ 0.87 (d, $J = 6.3$ Hz, 6H), 0.94 (d, $J = 6.3$ Hz, 3H), 0.96 (s, 3H), 3.33 (d, $J = 12.9$ Hz, 1H), 3.74 (s, 3H); ^{13}C NMR δ 11.2, 18.5, 22.4, 22.7, 23.6, 24.8, 27.9, 28.7, 35.5, 35.7, 37.3, 37.4, 39.3, 41.9, 51.9 (2 × C), 54.5, 58.9, 170.2, 206.4; IR ν_{max} 2953, 1749, 1713, 1467, 1255 cm^{-1}. Anal. Calcd for $C_{20}H_{34}O_3$: C, 74.49; H, 10.63. Found: C, 74.25; H, 10.53.

[1′*S*-[1′α(*R),3′a*β*,4′*β*,7′aα]-1′-(1,5-Dimethylhexyl)octahydro-7′a-methylspiro[1,3-dioxolane-2,5′-[5*H*]indene]-4′-carboxylic Acid, Methyl Ester ((−)-22).** A mixture of compound (−)-**21** (380 mg, 1.18 mmol), ethylene glycol (730 mg, 11.8 mmol), and *p*-TsOH (114 mg, 30% w/w) in benzene (200 mL) was refluxed using a Dean−Stark apparatus overnight (14 h). The reaction mixture was cooled to room temperature, washed with aqueous $NaHCO_3$ and brine, and dried over Na_2SO_4. The solvent was removed, and the residue was purified by chromatography (silica gel; hexanes/EtOAc, 20:1) to give compound (−)-**22** (420 mg, 97%) as a colorless oil: $[\alpha]^{25}_D = -7.63$ ($c = 1.66$, $CHCl_3$); ^{1}H NMR δ 0.76 (s, 3H), 0.88 (d, $J = 6.6$ Hz, 6H), 0.90 (d, $J = 6.6$ Hz, 3H), 2.74 (d, $J = 12.9$ Hz, 1H), 3.68 (s, 3H), 3.93 (m, 4H); ^{13}C NMR δ 10.9, 18.4, 22.4, 22.6, 23.6, 23.8, 27.8, 28.2, 32.4, 35.6, 35.7, 35.8, 39.3, 41.9, 49.1, 51.0, 51.5, 54.7, 64.7, 64.8, 109.8, 172.0; IR ν_{max} 2952, 1740, 1434, 1165 cm^{-1}. Anal. Calcd for $C_{22}H_{38}O_4$: C, 72.09; H, 10.45. Found: C, 72.24; H, 10.53.

[1′*S*-(1′α(*R),3′a*β*,4′*β*,7′aα]-1′-(1,5-Dimethylhexyl)octahydro-7′a-methylspiro[1,3-dioxolane-2,5′-[5*H*]indene]-4′-methanol ((−)-23).** $LiAlH_4$ (218 mg, 4.60 mmol) was added to a solution of compound (−)-**22** (420 mg, 1.15 mmol) in

diethyl ether (50 mL) and refluxed for 1.5 h. The reaction mixture was cooled to 0 °C and water (2 mL) was added dropwise to quench the reaction. The precipitate that formed was filtered through a pad of Celite 545. The solvent was removed from the filtrate and the residue was purified by chromatography (silica gel; hexanes/EtOAc, 8:1) to give compound (−)-**23** (372 mg, 96%) as a colorless oil; $[\alpha]^{25}_D = -13.8$ ($c = 1.38$, $CHCl_3$); ^{1}H NMR δ 0.77 (s, 3H), 0.86 (d, $J = 6.6$ Hz, 6H), 0.90 (d, $J = 6.6$ Hz, 3H), 3.00 (t, $J = 5.4$ Hz, 1H), 3.60 (m, 1H), 3.79 (m, 1H), 4.02 (m, 4H); ^{13}C NMR δ 11.0, 18.5, 22.4, 22.7, 23.6, 23.8, 27.9, 28.5, 30.7, 35.6, 35.9, 36.1, 39.4, 42.3, 44.7, 48.3, 55.2, 61.0, 64.0, 64.4, 113.0; IR ν_{max} 3545, 2952, 1468, 1151, 1055 cm^{-1}. Anal. Calcd for $C_{21}H_{38}O_3$: C, 74.51; H, 11.31. Found: C, 74.69; H, 11.16.

[1*S*-(1α(*R),3a*β*,4*β*,7aα]-1-(1,5-Dimethylhexyl)octahydro-4-hydroxymethyl-7a-methyl-5*H*-inden-5-one ((−)-24).** Dilute HCl (2 N, 5 mL) was added to compound (−)-**23** (390 mg, 1.15 mmol) dissolved in acetone (50 mL). The solution was stirred at room temperature for 1−2 h, and saturated aqueous $NaHCO_3$ was added to the solution to neutralize the acid. Most of the acetone was removed under reduced pressure, and the oily product residue was dissolved in EtOAc (50 mL). The EtOAc was washed with water and dried over Na_2SO_4. The solvent was removed, and the residue obtained was purified by chromatography (silica gel; hexanes/EtOAc, 8:1) to give compound (−)-**24** (325 mg, 96%) as a colorless oil: $[\alpha]^{25}_D = -33.3$ ($c = 2.19$, $CHCl_3$); ^{1}H NMR δ 0.87 (d, $J = 6.6$ Hz, 6H), 0.93 (d, $J = 6.6$ Hz, 3H), 0.99 (s, 3H), 3.67 (m, 3H); ^{13}C NMR δ 11.3, 18.4, 22.4, 22.7, 23.7, 24.3, 27.9, 29.1, 29.6, 35.5, 35.8, 38.1, 39.3, 42.5, 51.8, 52.5, 54.8, 61.1, 215.8; IR ν_{max} 3435, 2953, 1700, 1467, 1050 cm^{-1}. Anal. Calcd for $C_{19}H_{34}O_2$: C, 77.50; H, 11.64. Found: C, 77.31; H, 11.46.

[1*S*-(1α(*R),3a*β*,4*β*,7aα]-1-(1,5-Dimethylhexyl)octahydro-7a-methyl-4-[[(methylsufonyl)oxyl]methyl]-5*H*-inden-5-one (25).** MsCl (624 mg, 5.45 mmol) was added dropwise to compound (−)-**24** (320 mg, 1.09 mmol) and Et_3N (1.10 g, 1.52 mL, 10.9 mmol) dissolved in CH_2Cl_2 (50 mL). The solution was stirred at room temperature for 2 h. The reaction solution was then washed with water and dried over Na_2SO_4. After removal of the solvent, the residue was filtered through silica gel using hexanes/EtOAc (4:1) as the eluent. The solvent was removed to give compound **25** as colorless oil which was used without further purification: ^{1}H NMR δ 0.84 (d, $J = 6.6$ Hz, 6H), 0.91 (d, $J = 6.3$ Hz, 3H), 0.96 (s, 3H), 3.04 (s, 3H), 4.43 (dd, $J = 3.0$ Hz, $J = 9.9$ Hz, 1H), 4.22 (dd, $J = 4.8$ Hz, $J = 9.9$ Hz, 1H); ^{13}C NMR δ 11.0, 18.4, 22.4, 22.6, 23.5, 24.3, 27.8, 28.9, 35.4, 35.7, 36.7, 37.4, 37.6, 39.2, 42.6, 49.8, 51.1, 54.6, 66.9, 209.2.

[3*S*-(3α,3aα,9aα,9b*β*)]-3-(1,5-Dimethylhexyl)-1,2,3,3a,4,5,8,9,9a,9b-decahydro-3a-methyl-6-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-7*H*-benz[*e*]inden-7-one ((+)-29). Ethyl 2-methyl-*β*-oxo-1,3-dioxolane-2-hexanoate **26**[1] (660 mg, 2.69 mmol) dissolved in MeOH (40 mL) and benzene (40 mL) was added to a NaOMe−MeOH solution (0.14 M, 43 mL). After the mixture was stirred for 5 min, compound **25** (404 mg, 1.08 mmol) dissolved in MeOH (40 mL) and benzene (40 mL) was added dropwise. The solution was stirred overnight (12 h), and 5 N aqueous NaOH (34 mL) was added. The mixture was stirred for another 1 h at room temperature, and the solvent was removed under reduced pressure. Ice−water (50 mL) was added to the stirred mixture, the mixture was extracted with hexanes (2 × 20 mL), and the extracts were discarded. Diethyl ether (100 mL) was added to the aqueous phase, and the pH of the aqueous phase in the heterogeneous mixture was adjusted to pH 3 using 6 N HCl at 0 °C. The solvent phases were separated, and the aqueous layer was extracted again with diethyl ether (4 × 50 mL). The diethyl ether extracts were combined, and after solvent removal, the residue obtained was heated at 80 °C under high vacuum (1 mm) for 3 h to convert unisolated compound **28** to product (+)-**29**. The residue obtained was purified by chromatography (silica gel; hexanes/EtOAc, 10:1) to give compound (+)-**29** (323 mg, 69% form compound (−)-**24**) as a colorless oil: $[\alpha]^{25}_D = +18.6$ ($c = 3.65$, $CHCl_3$,); ^{1}H NMR δ 0.83 (s, 3H), 0.87 (d, $J = 6.3$ Hz, 6H), 0.93 (d, $J = 6.3$ Hz, 3H), 3.95 (m, 4H); ^{13}C NMR δ 11.11, 18.4, 19.8, 22.4, 22.7, 23.4, 23.6, 24.3, 26.8, 27.1, 27.9, 28.1, 35.6, 35.9, 37.1, 38.0, 38.8, 39.2, 39.4, 41.9, 55.7, 56.3, 64.5 (2 × C), 98.8, 109.9, 133.5, 159.8; IR ν_{max} 2951, 1668, 1608, 1374, 1060 cm^{-1}. Anal. Calcd for $C_{28}H_{46}O_3$: C, 78.09; H, 10.77. Found: C, 78.10; H, 10.84.

[3*S*-(3α,3aα,5a*β*,6*β*,9aα,9b*β*)]-3-(1,5-Dimethylhexyl)-dodecahydro-3a-methyl-6-[2-(2-methyl-1,3-dioxolan-2-yl-)ethyl]-7*H*-benz[*e*]inden-7-one ((−)-30). Li metal (45.5 mg, 6.5 mmol) was dissolved in stirred anhydrous liquid NH_3 (45 mL) at −78 °C to yield a blue solution to which was added compound (+)-**29** (140 mg, 0.325 mmol) dissolved in THF (15 mL). After 1 h, MeI (2.77 g, 19.5 mmol) in THF (10 mL) was added. The resultant slurry was stirred at −78 °C for 1 h and then at ambient temperature until monitoring by TLC indicated that the reaction was complete (3−4 h). Then NH_4Cl (0.5 g) was added, and the liquid NH_3 was allowed to evaporate. Water (20 mL) was added, the resultant mixture was extracted with diethyl ether (3 × 50 mL), and the combined extracts were dried with Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by chromatography (silica gel; hexanes/EtOAc, 10:1) to give compound (−)-**30** (120 mg, 83%) as a colorless oil: $[\alpha]^{25}_D = -34.6$ ($c = 1.29$, $CHCl_3$); ^{1}H NMR δ 0.73 (s, 3H), 0.87 (d, $J = 6.6$ Hz, 6H), 0.91 (d, $J = 6.6$ Hz, 3H), 1.09 (s, 3H), 1.36 (s, 3H), 3.96 (m, 4H); ^{13}C NMR δ 11.8, 18.5, 21.0, 21.2, 22.4, 22.7, 23.3, 23.7, 24.1, 27.9, 28.0, 28.9, 31.2, 32.9, 34.7, 35.6, 36.0, 38.2, 39.4 (2 × C), 42.4, 47.2, 50.4, 55.8, 56.0, 64.4, 64.5, 110.4, 215.2; IR ν_{max} 2936, 1707, 1466, 1376, 1067 cm^{-1}. Anal. Calcd for $C_{29}H_{50}O_3$: C, 77.97; H, 11.28. Found: C, 78.02; H, 11.36.

***ent*-Cholest-4-en-3-one ((−)-31).** A solution of compound (−)-**30** (192 mg, 0.43 mmol) in MeOH (10 mL) and 6 N HCl (2 mL) was refluxed under N_2 overnight (16 h). Most of the MeOH was removed under reduced pressure. Water (20 mL) was added, and it was extracted with EtOAc (4 × 50 mL). The combined EtOAc extracts were washed with aqueous $NaHCO_3$ and brine and dried over Na_2SO_4. The solvent was removed, and the residue was purified by chromatography (silica gel; hexanes/EtOAc, 15:1) to give compound (−)-**31** (156 mg, 95%) as white crystals: mp 80−81 °C (MeOH); $[\alpha]^{25}_D = -91.0$ ($c = 0.49$, $CHCl_3$); ^{1}H NMR δ 0.71 (s, 3H), 0.87 (d, $J = 6.6$ Hz, 6H), 0.91 (d, $J = 6.3$ Hz, 3H), 1.18 (s, 3H), 5.72 (m, 1H); ^{13}C NMR δ 11.8, 17.3, 18.5, 20.9, 22.5, 22.7, 23.7, 24.1, 27.9, 28.1, 32.0, 32.9, 33.9, 35.5, 35.6, 35.7, 36.0, 38.5, 39.4, 39.6, 42.3, 53.8, 55.8, 56.1, 123.8, 171.9, 199.9; IR ν_{max} 2933, 1676, 1618, 1467 cm^{-1}. Anal. Calcd for $C_{27}H_{44}O$: C, 84.31; H, 11.53. Found: C, 84.47; H, 11.46.

***ent*-Cholesterol ((+)-1).** N_2 was bubbled for 5 min through stirred Ac_2O (1 mL) containing compound (−)-**31** (50 mg, 0.13 mmol) and NaI (78 mg, 0.52 mmol). The mixture was cooled to 0 °C, and after Me_3SiCl (56.4 mg, 66 μL, 0.52 mmol) was added dropwise, the reaction was allowed to warm to room temperature and stirring was continued for 1.5 h. The reaction mixture was then poured into saturated aqueous $NaHCO_3$ (20 mL). After the mixture was stirred for 10 min, the product was extracted using hexanes (4 × 50 mL). The combined extracts were washed with aqueous $NaHCO_3$ (5 mL), 10% aqueous $Na_2S_2O_3$ (2 × 10 mL), and water and dried over Na_2SO_4. The solvent was removed to yield compound **32** which was used without further purification or characterization. Compound **32** was dissolved in EtOH (5 mL), and $NaBH_4$ (50 mg) was added. The solution was stirred under N_2 overnight (14 h). Most of the EtOH was removed under reduced pressure, and the residue was dissolved in EtOAc (50 mL) and washed with 5% HCl (10 mL), aqueous $NaHCO_3$ (10 mL), brine (10 mL) and dried over Na_2SO_4. The solvent was removed, and the residue obtained was purified by chromatography (silica gel; hexanes/EtOAc, 20:1) to give *ent*-cholesterol (+)-**1** (39.8 mg, 79% from (−)-**31**) and its epimer (+)-**33** (5.6 mg, 10% from (−)-**31**).

Compound (+)-**33** was characterized only by its ^{1}H NMR spectrum which was identical to that of an authentic sample of the (−)-**33** enantiomer.

ent-Cholesterol (+)-**1** was obtained as colorless crystals: mp. 147−148 °C (EtOH−H_2O); $[\alpha]^{25}_D = +39.0$ ($c = 0.29$, $CHCl_3$); ^{1}H NMR δ 0.68 (s, 3H), 0.86 (d, $J = 6.6$ Hz, 6H), 0.91 (d, $J = 6.6$ Hz, 3H), 1.01 (s, 3H), 3.53 (m, 1H), 5.35 (m, 1H); ^{13}C NMR δ 11.7, 18.6, 19.3, 21.0, 22.5, 22.7, 23.7, 24.2, 27.9, 28.1, 31.5, 31.8 (2 × C), 35.7, 36.1, 36.4, 37.2, 39.4, 39.7, 42.2 (2 × C), 50.0, 56.1, 56.7, 71.8, 121.8, 140.9; IR ν_{max} 3431, 2934, 1466, 1376, 1058 cm^{-1}.

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Supporting Information Available: Spectral data and/or experimental procedures for compounds (±)-**6**, (±)-**8**, (+)-**16**, and **19**. This material is available free of charge via Internet at http://pubs.acs.org.

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