Synthesis of *ent*-Cholesterol, the Unnatural Enantiomer

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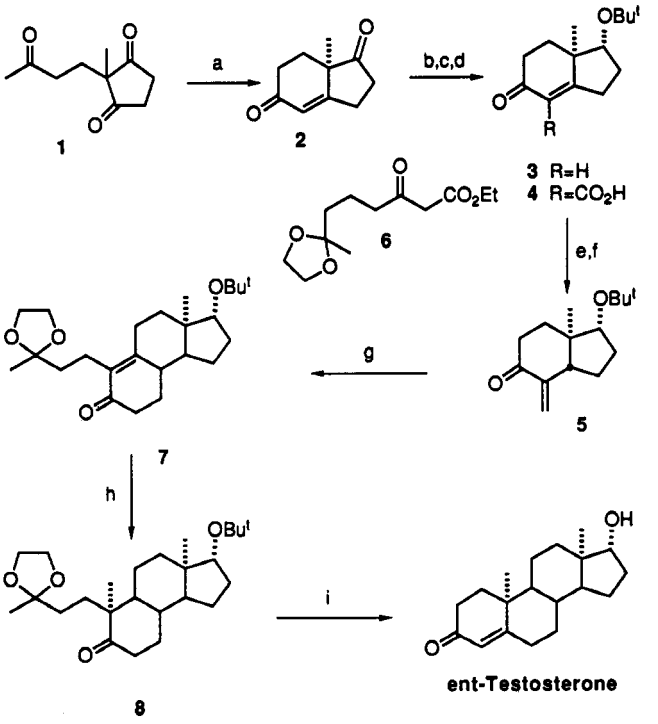
Cholesterol is ubiquitious in mammals and plays an important role in human health. The unique relationship between enantiomers makes *ent*-cholesterol, the unnatural enantiomer of cholesterol, a valuable new probe of cholesterol function in biochemical systems. We report the first enantioselective total synthesis of *ent*-cholesterol.

Cholesterol is a vital component of mammalian membranes. Its primary role is to stabilize membrane bilayers and mediate their fluidity.[1] It also interacts with membrane proteins and plays a role in proper membrane protein function.[2,3] Cholesterol can affect other membrane-bound biomolecules in two ways: by changing the structure and properties of the membrane or by directly binding with the biomolecule. *ent*-Cholesterol can be used as a probe to differentiate between these two modes of action. Two artificial membrane systems, one composed of natural cholesterol with a racemic phospholipid and the other composed of *ent*-cholesterol and the same racemic phospholipid, are exact mirror images and will have identical (achiral) physical properties. A chiral, nonracemic biomolecule that is sensitive to membrane properties will show the same behavior in both membrane systems, but a chiral, nonracemic biomolecule that binds with cholesterol[4] will form diastereomeric complexes and show different behavior in the two membrane systems.[5] We have used this simple test to demonstrate that ion channels formed from amphotericin B (Figure 1), a clinical antifungal agent, incorporate cholesterol.[6] Comparing the properties of biomolecules in the presence of enantiomeric cholesterols is a valuable new strategy that will help determine the function of cholesterol in biochemical systems.

All natural sterols have the same absolute configuration at the C-10 and C-13 quaternary centers, and so there is no simple way to convert readily available natural sterols into the enantiomeric series. Preparation of *ent*-cholesterol requires an enantioselective total synthesis. Cholesterol had been prepared twice by total synthesis. Woodward reported a formal total synthesis in 1952,[7] and Johnson reported a complete total synthesis of approximately 11 mg of racemic cholesterol in 1964.[8] In the 25 years since Johnson's work there have been significant advances in steroid synthesis, and we looked to the elegant stereoselective synthesis of 19-nor steroids by a group at Hoffmann-La Roche[9] for inspiration.

Scheme I[a]



[a] Key: (a) (i) D-proline, DMF, 7 days, rt (ii) H_2SO_4, DMF, 95 °C; (b) $NaBH_4$, EtOH; -5 °C; (c) isobutylene, H_3PO_4/BF_3–OEt_2; -78 °C; (d) $Mg(OMe)O_2COMe$, DMF, 125 °C; (e) H_2, $Pd/BaSO_4$, MeOH; (f) CH_2O, piperidine, $DMSO/H_2O$; (g) (i) **6**, NaOMe, MeOH; (ii) H_3O^+, 80 °C; (h) Li, NH_3, THF, -33 °C; MeI, -78 to -33 °C; (i) HCl, MeOH, reflux.

We used a modification of the Hoffmann-La Roche synthesis to prepare *ent*-testosterone (Scheme I). Achiral triketone **1** was prepared by Michael addition of 2-methyl-1,3-cyclopentandione to methyl vinyl ketone.[10] Enantioselective intramolecular aldol reaction catalyzed by commercially available D-proline followed by acid-catalyzed elimination gave the chiral ene dione **2** in 76% yield and 87% ee.[10,11] The single stereogenic center in dione **2** was employed to control the remaining stereocenters in *ent*-cholesterol. Selective reduction of the saturated ketone with 0.26 equiv of $NaBH_4$, followed by protection with isobutylene and acid, gave enone **3** in 90% yield. Treatment of enone **3** with Stiles' reagent[12] gave the

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(4) A difference observed between the two membrane systems can be attributed to a direct interaction between the chiral biomolecule and at least one of the two enantiomers of cholesterol. The most direct interpretation of this stereospecific recognition is binding.
(5) The same principle is involved in stereospecific recognition by olfactory receptors. The *R* and *S* enantiomers of carvone smell like spearmint and caraway, respectively, and this alone demonstrates that the sense of smell involves specific binding. (a) Russel, G. F.; Hill, J. I. *Science* **1971**, *172*, 1043-1044. (b) Friedman, L.; and Miller, J. G. *Science* **1971**, *172*, 1044-1046.
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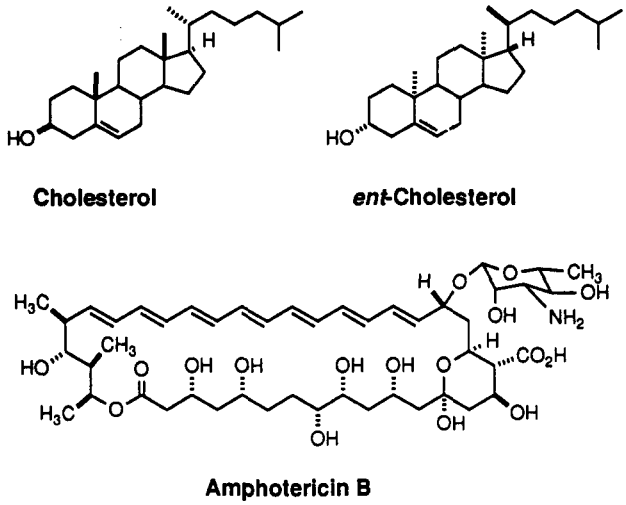
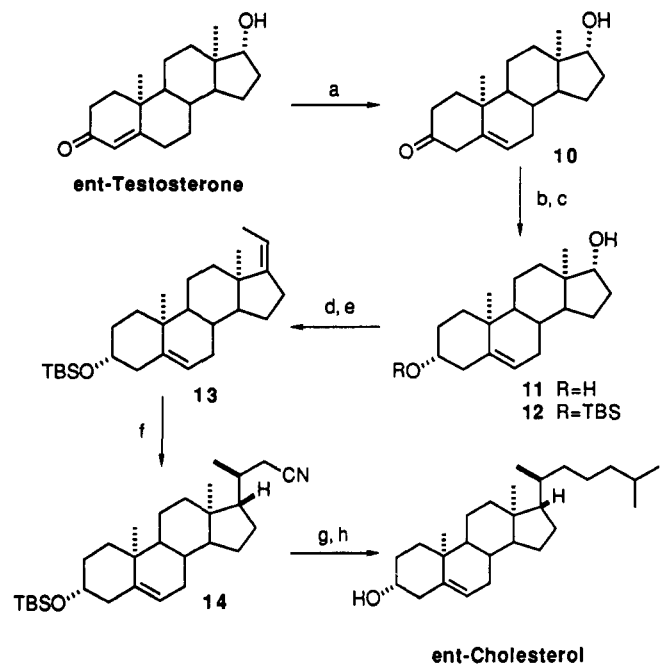


Figure 1. Amphotericin B and the enantiomers of cholesterol.

carboxylic acid **4** in 75% yield along with 18% recovered starting material. Hydrogenation set the trans ring junction, and reaction with aqueous formaldehyde gave the new enone **5** in 75% yield. A Robinson annulation between enone **5** and β-keto ester **6** gave *tricyclic* intermediate **7** in 69% yield. The Hoffmann-La Roche synthesis proceeded to cyclize the A-ring in *ent*-**7** en route to 19-nor steroids. We took this opportunity to introduce the C19 methyl group using a reductive alkylation procedure developed by Stork.[13] Enone **7** was reduced with 20 equiv of lithium in NH_3/THF at −33 °C, and the resulting lithium enolate was cooled to −78 °C and treated with excess iodomethane. After 1 h the mixture was warmed to −33 °C and worked up to give ketone **8** in 60% yield. This procedure was tricky, and deviations from these conditions lead to significant amounts of protonated or overalkylated byproducts at the expense of the desired product. The nicely crystalline ketone **8**, presumably formed in 87% ee, was recrystallized to constant rotation. Refluxing **8** in methanolic HCl overnight gave *ent*-testosterone[14] in quantitative yield.

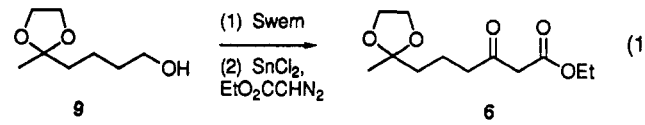
The β-keto ester **6** is a valuable annulating agent for rapidly appending sterol AB rings to CD ring intermediates by sequential Robinson annulations.[9b,15] It has been prepared by three general routes: from the acetal of ethyl 5-oxohexanoate,[9b,16] from the monoacetal of 2,6-heptanedione,[9a,17] or by alkylation of ethyl 3-oxobutyrate dianion.[15,18] However, none of these routes is well suited for a convenient, small-scale laboratory preparation. We have developed a new laboratory-scale preparation of **6** from ethyl 5-oxohexanoate that reliably gives pure material in four steps and 55% overall yield. The preparation is based on a new synthesis of β-keto esters from aldehydes and ethyl diazoacetate.[19] Acetal formation[20] and reduction of commercially available ethyl 5-oxohexanoate gave alcohol **9** in 94% overall yield (eq 1). Swern oxidation[21] followed

Scheme II[a]



[a] Key: (a) $KOBu^t$, $HOBu^t$, rt; HOAc; (b) $LiAl(OBu^t)_3H$, THF; (c) TBSCl, DMAP, Et_3N, CH_2Cl_2; (d) PCC, 4-Å sieves, CH_2Cl_2; (e) $EtPPh_3^+$ Br^-, $KOBu^t$, THF; (f) 9-BBN, THF; $ClCH_2CN$, KOAr, THF; (g) LDA, THF, −78 °C; $BrCH_2CH_2CH(CH_3)_2$; (h) (i) potassium, dicyclohexyl-18-crown-6, toluene; (ii) Bu_4NF, THF.

by tin(II) chloride catalyzed coupling with ethyl diazoacetate gve β-keto ester **6** in 59% yield without the need for further purification.



(1)

We had initially used ketone **8** of 87% ee to prepare *ent*-cholesterol with the intention of resolving the final material. Unfortunately, several diastereomeric derivatives of cholesterol were found to be inseparable by HPLC,[22] and we were forced to return to an earlier intermediate, ketone **8**, to separate out the minor enantiomer. The *ent*-testosterone prepared from recrystallized **8** was shown to be a single enantiomer by Mosher's ester analysis.[23] (*R*)-Mosher's ester derivatives from natural and *ent*-testosterone showed cleanly resolved C-18 methyl signals in the ^1H NMR spectra that could be assigned as >97% ee.[24]

It remained to adjust the A-ring functionality and attach the side chain. The procedures were originally tested using natural testosterone before applying them to the more precious *ent*-testosterone. Johnson had used a modification of Dauben's procedure[25] to complete the A-ring that involved a reduction of the kinetically formed β,γ-unsaturated ketone formed from a dienol acetate (eq 2). When applied to diacylated testosterone, this procedure invariably gave the desired homoallylic alcohol contaminated

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(22) The resolving agents tested with cholesterol were Mosher's acid chloride, (*S*)-1-(naphthyl)ethyl isocyanate, and (*S*)-α-methylbenzyl isocyanate.
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(24) Major diastereomer: 0.80 ppm (s, 0.994 H). Minor diastereomer: 0.74 ppm (s, 0.006 H).
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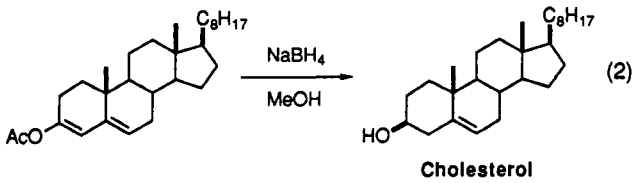

(2)

Cholesterol

with the inseparable allylic alcohol. This problem was avoided by deconjugating the enone by kinetic protonation[26] to give the readily separable β,γ-unsaturated ketone **10** in 73% yield accompanied by 25% of the starting *ent*-testosterone (Scheme II). Reduction of the β,γ-unsaturated ketone **10** with $Li(OBu^t)_3AlH$ gave the desired equatorial alcohol **11** in 95% yield with no detectable axial isomer.[27] In preparation for attaching the side chain the less hindered 3-hydroxyl was selectively protected by treatment with *tert*-butyldimethylsilyl chloride (TBSCl) and DMAP in CH_2Cl_2 to give the monosilyl diol **12** in 54% yield.[28] Starting diol **11** was isolated in 30% yield and recycled.

Attachment of the cholesterol side chain was accomplished by a modification of Midland's procedure.[29] PCC oxidation of the 17-alcohol **12** in the presence of 4-Å sieves gave the 17-ketone in a 77% yield. Wittig reaction with $EtPPh_3Br$ and $KOBu^t$ in refluxing THF gave the (*Z*)-alkene **13** as a single isomer in 83% yield. The stereochemistry at C-17 and C-20 was set by hydroboration with 9-BBN which enters from the top face of the alkene. Coupling the resulting hindered trialkylborane with chloroacetonitrile in the presence of a hindered base gave nitrile **14** as a single isomer in 47% yield. This relatively low yield may be due to our own inexperience with this complex reaction rather than any inherent shortcoming of the reaction. The side chain was completed by nitrile alkylation with 1-bromo-3-methylbutane and reductive decyanation.[30] Desilylation gave *ent*-cholesterol in 68% overall yield from nitrile **14**. The alkylation and reductive decyanation is an improvement over Midland's original nitrile reduction, Wittig reaction, and hydrogenation. Synthetic *ent*-cholesterol was spectroscopically identical to natural cholesterol in all respects except for the sign of the optical rotation.[31]

The unnatural enantiomer of cholesterol was prepared in 17 steps from triketone **1** and 2.7% overall yield. It will be a useful new tool for understanding the role of cholesterol in biological systems.

Experimental Section

Liquid chromatography was performed using forced flow (flash chromatography) of the indicated solvent system on EM Reagent silica gel 60 (230–400 mesh). THF and ether were distilled from potassium/benzophenone ketyl. CH_2Cl_2, diisopropylamine, and toluene were distilled from CaH_2. Air- and/or moisture-sensitive reactions were carried out under N_2 or Ar using flame-dried glassware and standard syringe/septa techniques. For each compound with a previously characterized enantiomer, the spectral data of the enantiomers were compared to confirm the new structure. NMR data for ^{13}C DEPT experiments are reported as quaternary (*C*), tertiary (*C*H), secondary (CH_2), and primary (CH_3) carbon atoms. For overlapping signals the number of carbon atoms are given in parentheses.

(−)-(7a*R*)-7,7a-Dihydro-7a-methyl-1,5(6*H*)-indandione (2).[10] Trione **1** was converted into the enantiomerically enriched dione **2** using the procedure described for the natural series except substituting D-proline for L-proline. A 31.7-g sample[10] of trione **1** (180 mmol, 1.0 equiv) gave 22.0 g (0.135 mol, 74% yield) of dione **2** as a yellow green solid: $[\alpha]^{24}_D = -302°$ (c = 1.00, C_6H_6). An analytical sample was recrystallized from ether and hexanes to give cream-colored crystals: mp 63–65 °C; $[\alpha]^{24}_D = -353°$ (c = 1.0, C_6H_6); IR (neat) 2963, 2870, 1746, 1681, 1687, 1651, 1644, 1448, 1148 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.96 (1 H, s), 3.10–2.67 (3 H, m), 2.53–2.36 (3 H, m), 2.13–2.07 (1 H, m), 1.91–1.74 (1 H, m), 1.31 (3 H, s); ^{13}C NMR (50 MHz, $CDCl_3$ DEPT) δ *C* 217.0, 198.1, 169, 48.7, *C*H 123.9, CH_2 35.9, 33.0, 29.3, 26.9, CH_3 20.6. Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 73.30; H, 7.56.

Compounds 3–7 were prepared according to the procedures previously reported in the enantiomeric series.[9] Yields and spectral data are given below. (−)-(1*R*,7a*R*)-1-*tert*-Butoxy-7a-methyl-7,7a-dihydro-5(6*H*)-indanone (3): 90% yield from **2**; $[\alpha]^{25}_D = -52.3°$ (c = 1.00, $CHCl_3$); mp 62–64 °C; IR (neat) 2972, 1667, 1363, 1199, 1092 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.75 (1 H, s), 3.55 (1 H, dd, J = 7.6, 9.8 Hz), 2.8–2.6 (1 H, m), 2.58–2.28 (3 H, m), 2.08–1.64 (4 H, m), 1.16 (9 H, s), 1.09 (3 H, s); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ *C* 199.1, 175.0, 73.0, 44.8, *C*H 122.9, 79.7, CH_2 34.4, 33.4, 29.6, 26.9, CH_3 28.7 (3), 15.7. Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.98; H, 9.56. Found: C, 76.07; H, 9.78.

(−)-(1*R*,7a*R*)-5,6,7,7a-Tetrahydro-1-*tert*-butoxy-7a-methyl-5-oxo-4-indancarboxylic acid (4): 95% yield from **3**; $[\alpha]^{24}_D = -37°$ (c = 1.02, $CHCl_3$); mp 92.94 °C; IR (neat) 2974, 2776 (v br), 1745, 1667, 1622, 1445, 1195, 1101 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.65 (1 H, dd, J = 7.2, 10.3 Hz), 3.24–3.14 (2 H, m), 2.76–2.61 (2 H, m), 2.10–1.99 (2 H, m), 1.92–1.75 (2 H, m), 1.17 (9 H, s), 1.15 (3 H, s); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ *C* 202.9, 196.3, 164.4, 73.51, 48.4, *C*H 120.4, 78.8, CH_2 33.6, 31.9, 31.5, 30.0, CH_3 28.7 (3), 16.3.

(−)-(1*R*,3a*S*,7a*R*)-1-*tert*-Butoxy-7a-methyl-3a,6,7,7a-tetrahydro-4-methyleneindan-5(4*H*)-one (5): 75% yield from **4**; IR (neat) 2971, 2876, 1694, 1623, 1361, 1193, 1092 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.86 (1 H, t), 4.94 (1 H, t), 3.54 (1 H, dd, J = 6.85, 8.80 Hz), 3.45–3.22 (2 H, m), 3.11 (1 H, d, J = 9.53 Hz), 2.47–2.32 (2 H, m), 1.98–1.69 (2 H, m), 1.67–1.49 (2 H, m), 1.10 (9 H, s), 0.71 (3 H, s); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ *C* 201.8, 147.0, 72.3, 42.5, *C*H 79.8, 48.7, CH_2 117.8, 35.7, 33.6, 31.5, 22.4, CH_3 28.4 (3), 10.9.

(−)-3β-*tert*-Butoxy-3aβ-methyl-1,1,3,3a,4,5,8,9,9aβ,9bα-decahydro-6-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-7*H*-benz[*e*]inden-7-one (7): 78% yield from **5**; $[\alpha]_D = 3.59°$ (c = 1.09, $CHCl_3$); IR (neat) 2971, 2873, 1667, 1361, 1196, 1095, 906 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.87 (4 H, m), 3.34 (1 H, t, J = 8.20 Hz), 2.74 (1 H, dd, J = 3.0, 16.6 Hz), 2.40–2.18 (6 H, m), 1.90–1.80 (3 H, m), 1.54–1.49 (4 H, m), 1.29 (3 H, s), 1.08 (9 H, s), 0.82 (3 H, s); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ *C* 198.4, 159.4, 134.0, 109.8, 72.3, 42.0, *C*H 80.2, 50.8, 38.9, CH_2 64.6 (2), 38.1, 36.6, 31.2, 26.8, 26.6, 23.9, 20.1, CH_3 28.7 (3), 23.5, 10.9. Anal. Calcd for $C_{24}H_{34}O_4$: C, 73.81; H, 9.81. Found: C, 73.78; H, 10.13.

5-[(1,3-Dioxolan-2-yl)ethyl]hexanoate. A 100-mL flask equipped with a reflux condenser and a Dean-Stark trap filled with 4-Å sieves was charged with 13.5 g (85.1 mmol, 1.0 equiv) of ethyl 5-oxohexanoate, 8.4 g (135.0 mmol, 1.58 equiv) of ethylene glycol, and a catalytic amount of TsOH. Benzene (70 mL) was added, and the mixture was heated to reflux. After 12 h the reaction was cooled to rt and 0.5 mL of Et_3N was added. The mixture was concentrated under reduced pressure, and the resulting yellow oil was filtered through a silica gel plug using CH_2Cl_2 as the eluting solvent. The filtrate was concentrated under reduced pressure to give 18.4 g (91.0 mmol, 107% of theory) of a clear oil used directly in the next step. An analytical sample was prepared by further concentration on a high-vacuum pump (0.1 mm, 25 °C): IR (neat) 2982, 2881, 1732, 1259, 1180, 1064 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.11 (2 H, q, J = 7.14 Hz), 3.92 (4 H, m), 2.31 (2 H, t, J = 6.87 Hz), 1.78–1.67 (4 H, m), 1.31 (3 H, s), 1.24 (3 H, t, J = 7.13 Hz); ^{13}C NMR (50 MHz, $CDCl_3$ DEPT)

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(31) Natural cholesterol: mp = 146–147 °C; $[\alpha]^{25}_D = -40.0$ (c = 1.00, EtOH). *ent*-Cholesterol: mp = 146–147 °C; $[\alpha]^{25}_D = +40.6$ (c = 0.93, EtOH).

δ *C* 173.4, 109.7, CH_2 64.6 (2) 60.1, 38.3, 34.2, 19.6, CH_3 23.7, 14.2. Anal. Calcd for $C_{10}H_{18}O_4$: C, 59.39; H, 8.97. Found: C, 59.16; H, 9.11.

5-(1,3-Dioxolan-2-yl)hexanol (9). A dry 1-L three-neck flask equipped with an addition funnel and a mechanical stirrer was charged with 6.91 g (0.182 mol, 2.13 equiv) of $LiAlH_4$. Ether (200 mL) was added, and the slurry was cooled to 0 °C in an ice bath. The crude ester (18.4 g) in 200 mL of ether was added dropwise over 0.5 h. The ice bath was removed, and the slurry was allowed to stir at rt overnight. Water (7 mL) was added carefully, followed by 7 mL of 15% NaOH. The white slurry was stirred for 0.5 h, a final portion of 21 mL of water was added, and the mixture was stirred for an additional 0.5 h. The white aluminum salts were removed by filtration and washed with two 100-mL portions of ether. The combined ether portions were concentrated under reduced pressure to give 12.9 g (80.6 mmol, 94% yield) of a clear oil: IR (neat) 3416 (br), 2944, 1377, 1222, 1140, 1070 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.83–3.70 (4 H, m), 3.40 (2 H, t, *J* = 6.25 Hz), 3.30 (1 H, s), 1.50–1.23 (6 H, m), 1.13 (3 H, s); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ *C* 109.7, CH_2 64.1 (2), 61.7, 38.4, 32.3, 19.8, CH_3 23.2. Anal. Calcd for $C_8H_{16}O_3$: C, 58.98; H, 10.07. Found: C, 59.71; H, 10.07.

5-(1,3-Dioxolan-2-yl)hexanal. To 8.42 mL (96.8 mmol, 1.2 equiv) of oxalyl chloride in 260 mL CH_2Cl_2 at −78 °C was added 9.68 mL (0.137 mol, 1.7 equiv) of DMSO with rapid stirring. After 15 min, 12.9 g (80.0 mmol, 1 equiv) of 5-(1,3-dioxolan-2-yl)hexanol in 20 mL of CH_2Cl_2 was added. After 20 min, 56.2 mL (0.403 mole, 5 equiv) of Et_3N was added, and the mixture was allowed to warm to rt over 30 min before the reaction was quenched with 80 mL of 1 N $NaHSO_4$. The layers were separated, and the aqueous layer was extracted with ethyl acetate (2 × 50 mL). The combined organic layers were washed with saturated $NaHCO_3$ and brine and dried (Na_2SO_4). The solution was filtered and concentrated under reduced pressure to give 13.0 g of a slightly yellow oil used directly in the next step. An analytical sample was purified by flash chromatography: IR (neat), 2983, 1715, 1377, 1235, 1059 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.69 (1 H, s), 3.91–3.81 (4 H, m), 2.40 (2 H, t), 1.71–1.58 (4 H, m), 1.24 (3 H, s); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ *C* 202.1, 109.4, CH_2 64.4 (2), 43.6, 38.1, 16.4, CH_3 23.5. Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.54; H, 8.96.

Ethyl 7-(1,3-Dioxolan-2-yl)-3-oxooctanoate (6). To 1.5 g (8.06 mmol, 0.1 equiv) of $SnCl_2$ in a 500-mL flask equipped with a gas bubbler was added 180 mL of CH_2Cl_2 and 9.33 mL (88.7 mmol, 1.2 equiv) of ethyl diazoacetate. 5-(1,3-Dioxolan-2-yl)-hexanal (13.0 g, 80.6 mmol, 1.0 equiv) in 20 mL of CH_2Cl_2 was added, and the mixture was stirred until gas evolution ceased. The solution was filtered through Celite to remove the $SnCl_2$ and concentrated under reduced pressure. The crude yellow green oil was purified by bulb-to-bulb distillation (125–155 °C (0.1 Torr)) to yield 11.51 g (47.2 mmol, 59% yield from **9**) of a yellow green oil: IR (neat) 2983, 2882, 1746, 1714, 1644, 1312, 1252, 1159, 1059 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.18 (2 H, q, *J* = 7.12 Hz), 3.92 (4 H, m), 3.42 (2 H, s), 2.57 (2 H, t, *J* = 6.83 Hz), 1.70–1.61 (4 H, m), 1.30 (3 H, s), 1.27 (3 H, t, *J* = 7.12 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ *C* 202.4, 167.0, 109.4, CH_2 64.4 (2), 60.9, 49.0, 42.5, 37.8, 17.8, CH_3 23.5, 13.9.

(−)-3β-*tert*-Butoxy-3aβ,5aβ-dimethyl-1,2,3,3a,4,5,5a,6,8,9,-9aβ,9bα-dodecahydro-6-[2-(2-methyl-1,3-dioxolan-2-yl)-ethyl]-7*H*-benz[*e*]inden-7-one (8). To 87 mg of lithium wire (12.4 mmol, 19.4 equiv) in 90 mL of anhydrous NH_3 (distilled from sodium metal) at −33 °C was added 250 mg of enone (0.64 mmol, 1.0 equiv) in 16 mL of THF. After 30 min the blue solution was cooled to −78 °C, and 2.44 mL (39 mmol, 61 equiv) of MeI in 10 mL of THF was added. The solution was stirred for 1 h at −78 °C, warmed to −33 °C for 30 min, and quenched with excess solid NH_4Cl. The flask was placed in a warm water bath to allow the NH_3 to evaporate, after which enough water was added to dissolve the NH_4Cl. The layers were separated, and the aqueous layer was extracted three times with 10-mL portions of ether. The combined organic layers were washed with 20 mL of brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting crude yellow oil was chromatographed (MPLC, 15% ethyl acetate/hexanes, 2-cm column, 9 mL/min) to give 0.155 g (0.384 mmol, 60% yield) of a white crystalline solid: $[\alpha]^{24}_D$ = −26.9° (*c* = 1.02, $CHCl_3$). This material was combined with that from an earlier reaction and recrystallized to a constant rotation from petroleum ether: $[\alpha]^{24}_D$ = −35.0° (*c* = 1.11, $CHCl_3$); mp 100–101 °C; IR (neat) 2971, 1706, 1361, 1195, 1074, 949 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.94 (4 H, m), 3.31 (1 H, t, *J* = 8.02 Hz), 2.53 (1 H, m), 2.25 (1 H, m), 1.96–1.92 (11 H, m), 1.30 (3 H, s), 1.27–1.10 (3 H, m), 1.08 (9 H, s), 1.04 (3 H, s), 1.00–0.80 (3 H, m), 0.72 (3 H, s); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ *C* 215, 109.8, 72.1, 50.1, 42.2, *C*H 80.4, 50.3, 47.4, 34.5, CH_2 64.2 (2), 37.9, 36.5, 32.8, 30.8, 30.5, 28.8, 23.5, 20.9, CH_3 23.6 (3), 20.6, 23.5, 11.4. Anal. Calcd for $C_{25}H_{42}O_4$: C, 73.85; H, 10.41. Found: C, 73.76; H, 10.34.

***ent*-Testosterone.**[14] Ketone **8** (0.264 g, 0.65 mmol) was heated to reflux in 7 mL of methanol with 1.5 mL of 3 N HCl for 24 h. The mixture was cooled to rt, and the methanol was removed under reduced pressure. Water (10 mL) was added, and the aqueous layer was extracted three times with 10-mL portions of CH_2Cl_2. The combined organic layers were washed with 5 mL of aqueous $NaHCO_3$ and 5 mL of brine and dried (Na_2SO_4). The solution was filtered, and the solvent was removed under reduced pressure to give 0.187 g (0.64 mmol, 99% yield) of *ent*-testosterone: mp 152–154 °C; IR (neat) 2943, 1667, 1614, 1230, 1055, 731 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.69 (1 H, s), 3.61 (1 H, t, *J* = 8.09 Hz), 2.38–2.25 (4 H, m), 2.05–1.94 (4 H, m) 1.86–1.63 (2 H, m), 1.60–1.18 (6 H, m), 1.16 (3 H, s), 1.09–0.83 (4 H, m), 0.76 (3 H, s); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ *C* 199.5, 171.3, 42.8, 38.6, *C*H 123.8, 81.4, 53.8, 50.4, 35.7, CH_2 36.5, 35.8, 34.0, 32.8, 31.6, 30.5, 23.4, 20.7, CH_3 17.4, 11.0. Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.87. Found: C, 79.22; H, 9.54.

***ent*-17β-Hydroxy-5-androsten-3-one (10).** Potassium *tert*-butoxide, 0.700 g (6.23 mmol, 10 equiv), was added to 0.180 g of *ent*-testosterone in 4.6 mL of 2-methyl-2-propanol and stirred at rt. After 2 h the reaction was quenched by adding 19 mL of 10% acetic acid. Saturated $NaHCO_3$ was added to neutralize the solution, and the aqueous layer was extracted with three 10-mL portions of ether. The combined organic layers were washed with 10 mL of $NaHCO_3$ and 10 mL of brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The product was purified by chromatography (SiO_2, 50% ethyl acetate/hexanes) to give 40 mg of recovered *ent*-testosterone (0.14 mmols, 22% yield) and 130.6 mg (0.456 mmol, 73% yield) of the product as a crystalline solid: mp 137–140 °C; $[\alpha]^{25}_D$ = +4.9° (*c* = 0.99, EtOH); IR (KBr) 2937, 1718, 1458, 1375, 1070 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.29 (1 H, s), 3.60 (1 H, t, *J* = 8.36 Hz), 3.25 (1 H, d, *J* = 16.4 Hz), 2.76 (1 H, dd, *J* = 2.0, 16.4 Hz), 2.38 (1 H, ddd, *J* = 5.6, 14.0, 14.0), 2.23 (1 H, d, *J* = 15.3 Hz), 2.00–1.92 (3 H, m), 1.81 (1 H, d, *J* = 12.3 Hz), 1.55–1.20 (9 H, m), 1.17 (3 H, s), 1.10–0.93 (3 H, m), 0.73 (3 H, s); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ *C* 210.0, 138.4, 42.5, 36.7, *C*H 122.4, 81.4, 50.9, 49.0, 31.7, CH_2 48.8, 37.4, 36.6, 36.2, 31.1, 30.1, 23.2, 20.7, CH_3 10.8, 19.0. Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.87. Found: C, 79.16; H, 9.67.

***ent*-5-Androstene-3β,17β-diol (11).** Enone **10** (130 mg, 0.451 mmol, 1 equiv), in 1 mL of THF was added to 1.14 mL of 1 M $LiAl(OtBu)_3H$ (1.14 mmol, 2.5 equiv) precooled to 0 °C. After 1 h the solution was warmed to rt, stirred for an additional 30 min, and then poured into 20 mL of 1 N HCl precooled to 0 °C. The layers were separated, and the aqueous layer was extracted with three 15-mL portions of 1:1 THF–ether. The combined organic layers were washed with $NaHCO_3$ and brine and dried ($MgSO_4$). The solution was filtered, and the solvent was removed under reduced pressure to give 142 mg of the product as a slightly yellow solid which was used without further purification in the next step. A small sample was purified for characterization by chromatography: mp 174–178 °C; IR (KBr) 3469, 2941, 2883, 1436, 1081, 1053 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.29 (1 H, d, *J* = 5.10 Hz), 3.62 (1 H, t, *J* = 8.4 Hz), 3.46 (1 H, m), 2.18 (1 H, m), 2.00 (1 H, m), 1.80 (4 H, m), 1.50 (8 H, m), 1.40 (1 H, m), 0.99 (3 H, s), 0.89 (3 H, s), 0.87 (9 H, s), 0.73 (3 H, s), 0.03 (6 H, s); ^{13}C NMR (75 MHz, DMSO-d_6, DEPT) δ *C* 141.1, 42.9, 32.1, *C*H 12.4, 81.8, 71.6, 51.3, 50.3, 32.0, CH_2 42.3, 37.3, 36.6, 31.6, 30.5, 25.6, 23.5, 20.7, CH_3 11.1, 19.5.

***ent*-3-*O*-[(1,1-Dimethylethyl)dimethylsilyl]-5-androstene-3β,17β-diol (12).** To 107 mg (0.369 mmol, 1.0 equiv) of crude **11** in 5 mL of CH_2Cl_2 and 1 mL of THF was added 64 mg of *tert*-butyldimethylsilyl chloride (0.443 mmol, 1.2 equiv), 54 mg of 4-(dimethylamino)pyridine (0.44 mmol, 1.2 equiv), and 77 μL of Et_3N (0.55 mmol, 1.5 equiv). After 1 day the reaction was quenched with NH_4Cl. The layers were separated and ex-

tracted with three 5-mL portions of CH_2Cl_2, and the organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting crude solution was purified by flash chromatography (30% ethyl acetate/hexanes) to give 80 mg (0.198 mmols, 54% yield) of **12**. In addition, 32 mg of the unreacted starting material (0.109 mmol, 30% yield) was eluted using THF. The product was a crystalline solid: mp 166–168 °C; IR (neat) 3284, 2929, 2901, 2854, 1654, 1249, 1098, 834, 772 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.29 (1 H, d, J = 5.10 Hz), 3.62 (1 H, t, J = 8.4 Hz), 3.46 (1 H, m), 2.18 (2 H, m), 2.00 (2 H, m), 1.80 (4 H, m), 1.50 (8 H, m), 1.40 (1 H, m), 0.99 (3 H, s), 0.89 (3 H, s), 0.87 (9 H, s), 0.73 (3 H, s), 0.03 (6 H, s); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ *C* 141.5, 42.5, 36.5, 18.1, CH 120.7, 89.7, 72.4, 51.2, 50.2, 32.0, CH_2 42.8, 37.4, 36.6, 32.1, 31.5, 30.5, 23.5, 20.7, CH_3 25.9 (3), 19.3, 11.0, –4.6 (2). Anal. Calcd for $C_{25}H_{44}O_2Si$: C, 74.20; H, 10.97. Found: C, 74.17; H, 11.08.

***ent*-3-*O*-[(1,1-Dimethylethyl)dimethylsilyl]-3β-hydroxy-5-androsten-17-one.** To 114 mg (0.290 mmol, 1.0 equiv) of **12** in 5 mL of CH_2Cl_2 was added 0.377 g of PCC and 0.50 g of 4-Å sieves. The reaction was stirred overnight, and then 20 mL of ether was added and the solution was filtered through Celite. The solution was concentrated under reduced pressure and chromatographed (SiO_2, 5% ethyl acetate/hexanes) to give 86.7 mg (0.216 mmol, 77% yield) of a white solid: mp 138–140 °C; IR (KBr) 2929, 1748, 1458, 1254, 1091, 837 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.31 (1 H, d, J = 4.86 Hz), 3.46 (1 H, m), 2.43 (1 H, dd, J = 6,14 Hz), 2.17–1.05 (18 H, m), 0.99 (3 H, s), 0.87 (3 H, s), 0.85 (9 H, s), 0.23 (6 H, s); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ *C* 220.8, 141.8, 47.6, 36.8, 18.3, *C*H 120.4, 72.5, 51.9, 50.4, 31.6, CH_2 42.9, 37.4, 35.9, 32.1, 31.5, 30.9, 21.9, 20.4 CH_3 26.0 (3), 19.5, 13.5, –4.5 (2); HRMS (EI) m/e calcd for $C_{25}H_{42}O_2Si$ (M^+) 402.2953, found (M^+) 402.229 22.

***ent*-3-*O*-[(1,1-Dimethylethyl)dimethylsilyl]-(3β,17*Z*)-pregna-5,17(20)-dien-3-ol (13).** Potassium *tert*-butoxide, 0.193 g (1.73 mmol, 8.0 equiv), and 0.480 g of ethyltriphenylphosphonium bromide (1.29 mmol, 6.0 equiv) were mixed in 2 mL of THF. After 15 min 86.7 mg of androstenone (0.216 mmol, 1.0 equiv) in 2 mL of THF was added and the solution was stirred for 1 day. Water was added, the layers were separated, and the aqueous layer was extracted with three 10-mL portions of ether. The combined organic layers were washed with three 10-mL portions of 10% H_2O and dried ($MgSO_4$). The solution was filtered and concentrated under reduced pressure. The crude product was purified by chromatography (SiO_2, 6% ethyl acetate/hexanes) to give 74.7 mg (0.179 mmol, 83% yield) of the olefin: $[\alpha]^{24}_D$ = +41.6° (*c* = 0.20, $CHCl_3$); mp 130–132 °C; IR (KBr) 2936, 1465, 1252, 1084, 837 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.31 (1 H, d, J = 5.14 Hz), 5.13 (1 H, q, J = 7.11 Hz), 3.16 (1 H, m), 2.29–1.08 (19 H, m), 1.65 (3 H, d, J = 7.11 Hz), 1.00 (3 H, s), 0.88 (12 H, s), 0.5 (6 H, s); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ *C* 150.2, 141.5, 44.0, 36.7, 18.2, *C*H 121.0, 113.4, 72.5, 56.5, 50.2, 31.4, CH_2 42.9, 37.3, 37.0, 32.0, 31.7, 31.5, 24.4, 21.2, CH_3 25.9 (3), 19.3, 16.6, 13.1, –4.6 (2); HRMS (EI) m/e calcd for $C_{27}H_{46}OSi$ (M^+) 414.331 77, found (M^+) 414.3283.

***ent*-3-[(1,1-Dimethylethyl)dimethylsiloxy]-(3β)-24-norchol-5-ene-23-nitrile (14).**[29] To 72.0 mg of **13** (0.17 mmol, 1.0 equiv) in 0.5 mL THF was added 0.35 mL of 0.5 M 9-BBN (0.17 mmol, 1.0 equiv). The reaction was stirred overnight and then cooled to 0 °C. To this mixture was added 0.50 mL of 0.5 M potassium 2,6-di-*tert*-butyl-4-methylphenoxide (prepared from potassium metal and the phenol in THF) and 13 μL of chloroacetonitrile (0.204 mmol, 1.2 equiv). After 1 h, 100 μL of ethanol was added and the reaction was allowed to warm to rt for 15 min before adding 5 mL of hexanes. The mixture was washed with three 15-mL portions of 1 N NaOH and two 5-mL portions of brine. The solution was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by chromatography (SiO_2, 5% ethyl acetate/hexanes) to give 63.2 mg (0.079 mmol, 47% yield) of a white solid: $[\alpha]^{23}_D$ = +42.9° (*c* = 0.48, $CHCl_3$); mp 170–171 °C; IR (KBr) 2936, 1254, 1089, 840 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.30 (1 H, d, J = 5.1 Hz), 3.46 (1 H, m), 2.29 (1 H, dd, J = 3.8, 16.7 Hz), 2.25 (2 H, m), 1.88 (2 H, m), 1.81–1.45 (13 H, m), 1.34–1.20 (3 H, m), 1.15 (3 H, d, J = 6.6 Hz), 1.11–1.03 (2 H, m), 0.99 (3 H, s), 0.83 (9 H, s), 0.69 (3 H, s), 0.05 (6 H, s); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ *C* 141.3, 118.7, 42.6, 36.3, 18.0, *C*H 121.0, 72.6, 56.6, 54.8, 50.0, 33.6, 31.9, CH_2 42.2, 39.4, 37.4, 32.1, 31.8, 28.1, 24.8, 24.2, 21.0, CH_3 25.7 (3), 19.2, 19.1, 11.7, –4.8 (2). HRMS (CI, CH_4) m/e calcd for $C_{29}H_{49}OSi$ ($M + H^+$) 456.3661, found ($M + H^+$) 456.3369.

***ent*-22-Cyanocholesterol.** To 0.280 mL of diisopropylamine in 10 mL of THF at 0 °C was added 0.80 mL of 2.5 M *n*-BuLi. A separate solution of 31 mg of **14** (0.068 mmol, 1.0 equiv) and 2,2'-dipyridyl in 1 mL of THF was cooled to –78 °C, 0.80 mL of the 0.18 M lithium diisopropylamide solution (0.14 mmol, 2.1 equiv) was added, and the combined solution was stirred for 15 min. 1-Bromo-3-methylbutane (81 μL, 0.68 mmol, 10 equiv) was added, and stirring was continued for another 2 h. The reaction was quenched with aqueous NH_4Cl. The layers were separated, and the aqueous layer was extracted with ether (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The product was purified by chromatography (SiO_2, 4% ethyl acetate/hexanes) to give 29.4 mg (0.056 mmol, 82% yield) of a white solid: mp 221–224 °C; IR (neat) 2934, 2245, 1253, 1085, 839 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.13 (1 H, d), 3.47 (1 H, m), 2.58 (1 H, m), 2.21 (2 H, m), 2.00 (3 H, m), 1.96–1.04 (24 H, m), 0.98 (3 H, s), 0.89 (6 H, d, J = 7.43 Hz), 0.88 (9 H, s), 0.68 (3 H, s), 0.05 (6 H, s); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) *C* 141.4, 120.9, 42.3, 36.4, 18.2, *C*H 121.0, 72.5, 56.5, 54.2, 50.0, 38.3, 36.8, 31.9, 27.8, CH_2 42.8, 39.6, 39.1, 37.4, 36.9, 31.8, 28.8, 28.1, 24.2, 21.0, CH_3 26.0 (3), 22.5 (2), 19.4, 14.6, 12.0, –4.8 (2); HRMS (EI) m/e calcd for $C_{34}H_{58}NOSi$ ($M - H^+$) 524.4287, found ($M - H^+$) 524.4288.

***ent*-Cholesterol.** To 29.4 mg of *ent*-22-cyanocholesterol (0.056 mmol, 1.0 equiv) in 2 mL of toluene was added 0.217 g of potassium metal and 42.4 mg (0.11 mmol, 2.0 equiv) of dicyclohexyl-18-crown-6. After 5.5 h 3 mL of 2-propanol was added to quench the excess potassium. The solvent was removed under reduced pressure, and 5 mL of water was added. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The organic layer was dried (Na_2SO_4) and filtered, and the solvent was removed at reduced pressure. The crude product was treated with 0.30 mL of 1 M Bu_4NF for 15 h. Ammonium chloride was added, the layers were separated, and the aqueous layer was extracted twice with 5-mL portions of CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated at reduced pressure to give 18 mg (0.047 mmol, 83% yield) of (+)-cholesterol: $[\alpha]^{25}_D$ = +40.6° (*c* = 0.93, EtOH); mp 146–147 °C; IR (KBr) 3655, 2933, 1462, 1069 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.33 (1 H, d, J = 5.22 Hz), 3.51 (1 H, m), 2.26 (2 H, m), 1.99 (2 H, m), 1.83 (4 H, m), 1.54–1.02 (22 H, m), 0.99 (3 H, s), 0.90 (6 H, d, J = 6.5 Hz), 0.67 (3 H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.9, 121.7, 71.8, 56.7, 56.1, 50.1, 42.3, 39.7, 39.5, 37.2, 36.5, 36.1, 35.8, 31.9, 31.9, 31.7, 29.7, 28.2, 28.0, 24.3, 23.8, 22.8, 22.6, 21.1, 19.4, 18.7, 11.8. HRMS (EI) m/e calcd for $C_{27}H_{46}O$ (M^+) 386.3548, found (M^+) 386.3539.

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