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First Synthesis of Enantiopure 1,6-Difunctionalized Dodecahydrobenz[*f*]indenes

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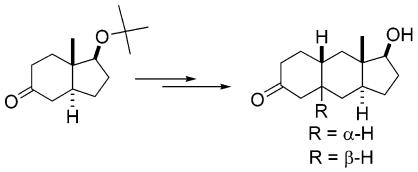

An enantiospecific route to the previously unreported 1,6-difunctionalized dodecahydrobenz[*f*]indene ring system is described. Optically pure Hajos−Parrish ketone is used as the building block for preparation of a 6-methyleneinden-5-ol. This allylic alcohol is then utilized in a Claisen rearrangement under Johnson's conditions to introduce a side chain that is further modified and cyclized to produce the benz[*f*]indene ring system.

During the course of our investigations of structure−activity studies of neurosteroid analogues acting at γ-aminobutyric acid type A receptors, a series of benz[*e*]indene analogues was synthesized and evaluated.[1,2] Because these benz[*e*]indene analogues were nearly as potent as their steroid counterparts, we then became interested in rearranging the rings to develop linear tricyclic neurosteroid analogues, the benz[*f*]indenes (Figure 1). However, there is currently no synthetic route reported for the total synthesis of the desired benz[*f*]-indenes. To date, the few existing examples of benz[*f*]-indenes are those that do not have functionality in the positions we require[3,4] or are aromatic.[5,6] In this paper, we describe a synthetic route for construction of the 1,6-difunctionalized dodecahydrobenz[*f*]indene ring system that could be easily modified to construct neurosteroid analogues.

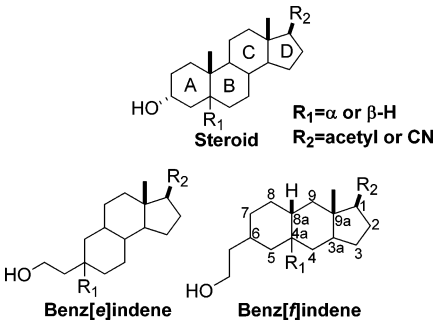

FIGURE 1. Structure of a steroid, benz[*e*]indene, and benz-[*f*]indene.

We utilized part of the reaction sequence reported by Collins et al. (Scheme 1) for the synthesis of racemic *abeo* estradiol.[7] In our instance, however, the unsaturated carboxylic acid **1** was prepared from the Hajos−Parrish ketone (7a*S*)-2,3,7,7a-tetrahydro-7a-methyl-1*H*-indene-1,(5,6*H*)-dione in optically pure form as previously described.[8,9] Hydrogenation over 10% Pd/$BaSO_4$ and decarboxylation of intermediate **2** yielded the enantiomerically pure indanone **3** (67%).[10] Because Collins et al.[7] were previously unsuccessful in their attempts to alkylate racemic indanone **3** at C-6 with several 2-(3′-methoxyphenyl)ethyl halides, but were able to carbomethoxylate **3** in high yield to the enolic β-keto ester **4**, we opted to follow this route. Using optically pure **3** we obtained the enolic β-keto ester **4** (83%). A LAH reduction of **4** yielded allylic alcohol **5** (61%). Although a precedent for the reduction of enolized β-keto esters to allylic alcohols exists,[11] the synthetic utility of this reaction has not been widely recognized.

Oxidation of allylic alcohol **5** to the corresponding α,β-unsaturated ketone for use in construction of the third ring of the required benz[*f*]indenes is not practical because of extremely rapid dimerization of this Michael acceptor at room temperature.[7] Alternatively, allylic alcohol **5** was subjected to Claisen rearrangement under Johnson's conditions[12] to give **6** with the correct number of methylene units for the required third ring (94%, Scheme 2). However, the end of the side chain on compound **6** contains an ethyl ester rather than the methyl ketone necessary for the ring closure. The ethyl ester **6** is easily converted to the methyl ketone **7** in one step utilizing the organotitanium Petasis reagent,[13] with hydrolysis of the resulting enol ether (77%).[14] Methyl

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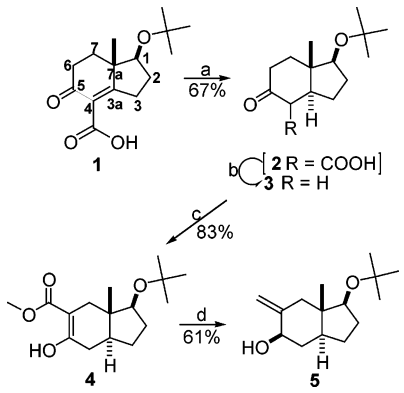
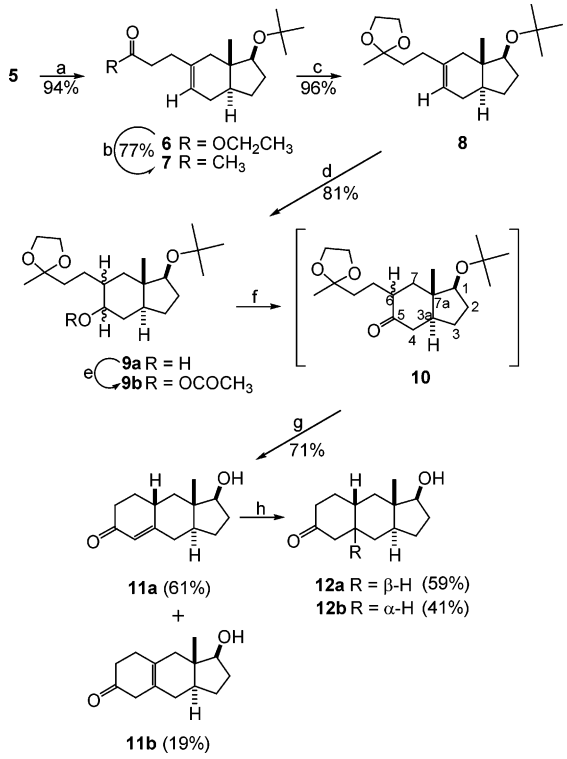
SCHEME 1[a]



[a] Key: (a) H_2, 5% Pd/$BaSO_4$; (b) 90 °C, high vacuum, 30 min; (c) NaH, dimethyl carbonate, THF; (d) $LiAlH_4$, THF, reflux.

SCHEME 2[a]



[a] Key: (a) triethyl orthoacetate, propionic acid, 138 °C; (b) Petasis reagent; $NaHCO_3$, H_2O/MeOH; Na_2SO_4, H_2SO_4; (c) ethylene glycol, PPTS, benzene, reflux; (d) BH_3−THF; NaOH, H_2O_2; (e) acetic anhydride, pyridine; (f) PCC, NaOAc, CH_2Cl_2; (g) 3 N HCl, MeOH, reflux; (h) H_2, 5% Pd/$BaSO_4$.

ketone **7** was then protected as the ketal **8** (96%), and the oxygen functionality at C-5 was introduced via hydroboration of the double bond. This hydroboration yielded a 5:1 mixture (based on the ^{1}H NMR intensity of the C-7a methyl group) of stereoisomers **9a** (81%). After acetylating **9a** to obtain **9b** it was determined, based on the NMR spectrum, that the major hydroboration product was that in which the hydroxyl group was on the face

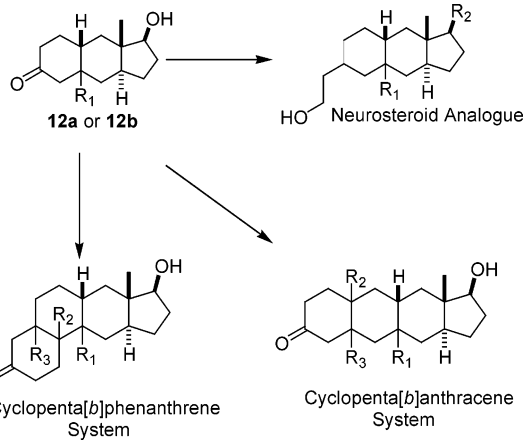


FIGURE 2. Precursor relationship of compounds **12a** and **12b** to neurosteroid analogues or additional ring systems.

opposite the C-7a methyl group. This was concluded because the hydrogen on C-5 appeared as a broad singlet ($\delta = 4.83$), indicating no transdiaxial coupling to the axial hydrogens on C-4 and C-6.

The mixture of isomers **9a** was carried forward in the synthesis, as the stereocenter at C-5 was eliminated in the next step via oxidation of **9a** by PCC to the ketone **10**. NMR analysis revealed that ketone **10** was a mixture of C-6 epimers. This crude product was used without characterization for the subsequent intramolecular aldol condensation. The aldol condensation yields two stereoisomers, enone **11a** (61%) and the tetrasubstituted olefin **11b** (19%). Enone **11a** was hydrogenated to yield a mixture of compounds **12a** (59%) and **12b** (41%) that were easily separable by column chromatography. A crystal structure of **12a** confirmed the assignment of all stereocenters. Compound **11b** was resistant to hydrogenation under these conditions.

In conclusion, a practical method for the construction of the dodecahydrobenz[*f*]indene ring system functionalized at positions 1 and 6 is described. The benz[*f*]indenes prepared are enantiopure and their enantiomers are accessible using the same reactions from the previously described enantiomer of compound **1**.[15] A ketone functionality at position 6 can be utilized either to introduce side chains at this position (e.g., to yield benz[*f*]indene analogues of neuroactive benz[*e*]indenes) or as an access point for the construction of the fourth six-membered ring of the cyclopenta[*b*]phenanthrene (*abeo* steroid ring system) or the linear cyclopenta[*b*]anthracene ring system (Figure 2).

Experimental Section

[3*S*-(3α,3aα,7a*β*)]-3-(1,1-Dimethylethoxy)-2,3,3a,4,7,7a-hexahydro-6-hydroxy-3a-methyl-1*H*-indene-5-carboxylic Acid, Methyl Ester (4). Sodium hydride (60% in paraffin) (1.10 g, 27.5 mmol) was suspended in dry THF (20 mL) with stirring under nitrogen. Dimethyl carbonate (3.7 mL, 44 mmol) was added, and the suspension was heated to reflux. Compound **3** (3.1 g, 14 mmol) was added in THF (40 mL), and the reaction was returned to reflux. After 36 h, the dark brown reaction was cooled, and acetic acid was added until the pH was ~5. The product was then extracted with chloroform (3 × 100 mL). The

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combined organic extracts were dried, filtered, and concentrated in vacuo to give a yellow oil. Chromatography (3% EtOAc in hexanes) gave the methyl ester **4** as a colorless oil (3.2 g, 83%): $[\alpha]^{25}_D = +100.9$ ($c = 1$, $CHCl_3$); ^{1}H NMR δ 12.31 (1H, s, enolic OH), 3.76 (3H, s), 3.53 (1H, t, $J = 8.3$ Hz), 2.41−2.22 (2H, m), 2.16−2.01 (1H, m), 2.00−1.82 (2H, m), 1.73−1.25 (4H, m), 1.17 (9H, s), 0.72 (3H, s); ^{13}C NMR δ 173.6, 172.1, 96.8, 80.0, 72.4, 51.3, 41.5, 39.8, 35.0, 32.0, 31.4, 28.7 (3 × C), 25.6, 10.5; IR ν_{max} 2972, 1654, 1362, 1269, 1210 cm^{-1}.

[1*S*-(1α,3a*β*,5α,7aα)]-1-(1,1-Dimethylethoxy)octahydro-7a-methyl-6-methyleninden-5-ol (5). LAH (1.2 g, 32 mmol) was suspended in dry THF (25 mL) with stirring under nitrogen. The suspension was cooled to 0 °C in an ice bath, and methyl ester **4** (2.8 g, 9.9 mmol) dissolved in THF (10 mL) was added via addition funnel. After addition, the reaction was heated to reflux. After 2 h, the reaction was cooled to 0 °C and water was added to quench the excess LAH. The reaction was filtered through Celite, washing with EtOAc. Chromatography (17% EtOAc in hexanes) gave compound **5** as a white solid (1.4 g, 61%): $[\alpha]^{25}_D = +5.4$ ($c = 1$, $CHCl_3$); mp 113−114 °C; ^{1}H NMR ($CDCl_3 + D_2O$) δ 5.07 (1H, m), 4.81 (1H, m), 4.05−3.97 (1H, dd, $J = 6.0$, 12.0 Hz), 3.46 (1H, t, $J = 8.1$), 2.33−2.29 (1H, m), 1.98−1.68 (3H, m), 1.57−1.40 (3H, m), 1.39−1.15 (3H, m), 1.13 (9H, s), 0.65 (3H, s); ^{13}C NMR δ 149.0, 107.2, 79.3, 72.9, 72.3, 45.2, 44.1, 43.3, 35.8, 31.8, 28.7 (3 × C), 25.0, 10.9; IR ν_{max} 3255, 2973, 1196, 1118, 1070 cm^{-1}. Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 10.99. Found: C, 75.77; H, 11.12.

[3*S*-(3α,3aα,7a*β*)]-3-(3-(1,1-Dimethylethoxy)-2,3,3a,4,7,7a-hexahydro-3a-methyl-1*H*-inden-5-yl)propionic Acid, Ethyl Ester (6). Compound **5** (14.5 g, 60.8 mmol) was dissolved in triethyl orthoacetate (79 mL, 0.43 mol), and to this was added a catalytic amount of propionic acid (0.3 mL, 4 mmol). The reaction was heated to 138 °C in a flask equipped with an evaporation condenser with stirring under nitrogen. After 12 h, the reaction was cooled to ambient temperature and the ethanol evaporated under reduced pressure to yield a colorless oil. Chromatography (5% EtOAc in hexanes) gave compound **6** as a colorless oil (17.7 g, 94%): $[\alpha]^{25}_D = +68.0$ ($c = 1$, $CHCl_3$); ^{1}H NMR δ 5.33 (1H, m), 4.11 (2H, q, $J = 7.2$ Hz), 3.47 (1H, t, $J = 8.3$ Hz), 2.37−2.17 (4H, m), 2.02−1.24 (10H, m), 1.23 (2H, t, $J = 7.5$ Hz), 1.11 (9H, s), 0.63 (3H, s); ^{13}C NMR δ 173.3, 135.5, 120.9, 80.5, 72.0, 60.0, 41.7, 41.6, 40.3, 33.1, 32.9, 31.2, 28.7 (3 × C), 28.1, 25.8, 14.1, 10.5; IR ν_{max} 2973, 1738, 1197, 1115, 1067 cm^{-1}. Anal. Calcd for $C_{19}H_{32}O_3$: C, 73.98; H, 10.46. Found: C, 73.60; H, 10.37.

[3*S*-(3α,3aα,7a*β*)]-4-(3-(1,1-Dimethylethoxy)-2,3,3a,4,7,7a-hexahydro-3a-methyl-1*H*-inden-5-yl)butan-2-one (7). Compound **6** (15.6 g, 50.6 mmol) was dissolved in a 12% w/v solution of dimethyltitanocene in toluene (200 mL), prepared according to the method of Payack et al.[13] The reaction was heated to 90 °C for 15.5 h. At this time, the orange/red solution was cooled to 40 °C, and $NaHCO_3$ (9.3 g), MeOH (150 mL), and water (8 mL) were added. The reaction was heated at 40 °C for 14 h. The resulting green suspension was cooled and filtered through Celite, washing with Et_2O. The solvent was removed under reduced pressure to yield a yellow oil. This oil was resuspended in THF (200 mL) and a 1:1 mixture of saturated Na_2SO_4 and 10% H_2SO_4 (200 mL). This biphasic reaction was stirred at ambient temperature. After 1 h, the reaction was partitioned between Et_2O and water. The aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic extracts were dried, filtered, and concentrated in vacuo to give a yellow oil. Chromatography (7% EtOAc in hexanes) gave compound **7** as a colorless oil (10.9 g, 77%): $[\alpha]^{25}_D = +75.6$ ($c = 1$, $CHCl_3$); ^{1}H NMR δ 5.33 (1H, m), 3.48 (1H, t, $J = 9$ Hz), 2.51 (2H, t, $J = 7.5$ Hz), 2.25−2.15 (2H, m), 2.14 (3H, s), 2.12−1.61 (4H, m), 1.59−1.16 (5H, m), 1.15 (9H, s), 0.67 (3H, s); ^{13}C NMR δ 208.7, 135.7, 120.6, 80.5, 72.1, 42.3, 41.9, 41.6, 40.3, 31.8, 31.2, 29.7, 28.7 (3 × C), 28.1, 25.8, 10.5; IR ν_{max} 2972, 1719, 1361, 1197, 1115, 1067 cm^{-1}. Anal. Calcd for $C_{18}H_{30}O_2$: C, 77.65; H, 10.86. Found: C, 77.80; H, 10.66.

[3*S*-(3α,3aα,7a*β*)]-2-[2-(3-(1,1-Dimethylethoxy)-2,3,3a,4,7,7a-hexahydro-3a-methyl-1*H*-inden-5-yl)ethyl]-2-methyl-[1,3]dioxolane (8). In a round-bottom flask equipped with a Dean−Stark trap and reflux condenser was dissolved compound **7** (10.9 g, 0.0391 mol) in benzene (200 mL). To this were added ethylene glycol (22 mL, 0.39 mol) and a catalytic amount of PPTS (3.26 g, 13.0 mmol). The reaction was heated to reflux for 14 h. At this time the pale yellow reaction was cooled to ambient temperature. The organic layer was washed with H_2O (2 × 50 mL) and brine (2 × 50 mL), dried, filtered, and concentrated in vacuo to give a yellow oil. Chromatography (7% EtOAc in hexanes) gave compound **8** as a colorless oil (12.1 g, 96%): $[\alpha]^{25}_D = +79.3$ ($c = 1$, $CHCl_3$); ^{1}H NMR δ 5.34 (1H, m), 3.96−3.92 (4H, m), 3.47 (1H, t, $J = 8.3$ Hz) 2.05−2.00 (3H, m), 1.90−1.64 (6H, m), 1.63−1.35 (4H, m), 1.32 (3H, s), 1.14 (9H, s), 0.67 (3H, s); ^{13}C NMR δ 136.9, 119.8, 110.0, 80.6, 72.2, 64.6 (2 × C), 42.1, 41.7, 40.5, 37.7, 32.3, 31.3, 28.8 (3 × C), 28.2, 25.9, 23.8, 10.6; IR ν_{max} 2974, 2881, 1362, 1197, 1115, 1059 cm^{-1}. Anal. Calcd for $C_{20}H_{34}O_3$: C, 74.49; H, 10.63. Found: C, 74.60; H, 10.44.

[3*S*-(3α,3aα,7a*β*)]-2-[2-(3-(1,1-Dimethylethoxy)octahydro-6-hydroxy-3a-methylinden-5-yl)ethyl]-2-methyl[1,3]-dioxolane (9a). Compound **8** (6.4 g, 20 mmol) was dissolved in dry THF (80 mL). To this was added a 1.0 M solution of borane−tetrahydrofuran complex in THF (60 mL). The reaction was stirred at room temperature. After 2 h, the reaction was cooled to 0 °C, and 10% NaOH (75 mL) was carefully added dropwise. Following this, 30% H_2O_2 (75 mL) was added, and the reaction was stirred at room temperature. After 1 h, the reaction was complete and the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine (2 × 100 mL), dried, filtered, and concentrated in vacuo to give a colorless oil. Chromatography (50% EtOAc in hexanes) gave a 5:1 mixture of 2 stereoisomers of compound **9a** as a white powder (5.5 g, 81%). The major isomer was that in which reduction occurred from the face opposite the methyl group. The mixture was partially separated on a silica gel column (20% EtOAc in hexanes) to obtain the major isomer for characterization. The bulk of the mixture was carried forward without further purification. Major isomer: $[\alpha]^{25}_D = +35.6$ ($c = 1$, $CHCl_3$); mp 64−65 °C; ^{1}H NMR δ 3.99−3.92 (4H, m), 3.87 (1H, s), 3.44−3.39 (1H, m), 1.92−1.78 (1H, m), 1.75−1.60 (6H, m), 1.56−1.34 (8H, m), 1.32 (3H, s), 1.13 (9H, s), 0.76 (3H, s); ^{13}C NMR δ 110.0, 81.7, 72.1, 71.1, 64.6 (2 × C), 42.1, 41.8, 38.4, 37.4, 37.3, 30.8, 30.6, 28.8, 28.7 (3 × C), 25.7, 23.7, 13.3; IR ν_{max} 3427, 2973, 1462, 1361, 1195, 1059 cm^{-1}. Anal. Calcd for $C_{20}H_{36}O_4$: C, 70.55; H, 10.66. Found: C, 70.41; H, 10.55.

[1*S*-(1α,3a*β*,7aα)]-1-(1,1-Dimethylethoxy)-octahydro-3a-methyl-6-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-5*H*-inden-5-one (10). Compound **9a** (5.3 g, 16 mmol) was dissolved in CH_2Cl_2. To this was added NaOAc (4.1 g, 49 mmol) followed by PCC (7.0 g, 32 mmol). The reaction was stirred under N_2 at room temperature for 3 h. Then Et_2O was added to precipitate the PCC and the reaction was filtered through a short column of silica gel. The solvent was removed in vacuo to yield a pale yellow oil. This uncharacterized mixture (4.7 g) was carried forward without further purification.

[1*S*-(1α,3a*β*,8aα,9aα)]-1,2,3,3a,4,7,8,8a,9,9a-Decahydro-1-hydroxy-9a-methyl-6*H*-benz[*f*]inden-6-one (11a) and [1*S*-(1α,3a*β*,9aα)]-1,2,3,3a,4,5,7,8,9,9a-Decahydro-1-hydroxy-9a-methyl-6*H*-benz[*f*]inden-6-one (11b). Mixture **10** (5.5 g, 16 mmol) was dissolved in MeOH (150 mL), and 3 N HCl (45 mL) was added. The reaction was heated to 81 °C and allowed to reflux for 12 h. At this time, the reaction was cooled to room temperature, and the methanol was removed under reduced pressure. EtOAc (100 mL) and H_2O (50 mL) were added to the dark yellow oil. The aqueous layer was extracted with EtOAc (3 × 25 mL). The organic layer was washed with 15% $NaHCO_3$ (3 × 40 mL) and brine (3 × 40 mL), dried, and concentrated in vacuo to give a yellow oil. Chromatography (33% EtOAc in hexanes) gave 2.2 g (61%) of **11a** as a white solid and 0.67 g (19%) of **11b** as a colorless oil.

11a: $[\alpha]^{25}_D = +95.6$ ($c = 1$, $CHCl_3$); mp 114−115 °C; ^{1}H NMR δ 5.84 (1H, s), 3.73−3.68 (1H, m), 2.61−2.43 (1H, m), 2.42−2.25 (4H, m), 2.19−2.02 (4H, m), 1.70−1.37 (5H, m), 1.03−0.94 (1H, m), 0.91 (3H, s); ^{13}C NMR δ 200.2, 166.3, 125.7, 80.7, 44.3, 44.1, 43.2, 37.3, 35.7, 34.2, 30.4, 30.2, 25.1, 10.4; IR ν_{max} 3419, 2949,

1667, 1044, 732 cm^{-1}. Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.18; H, 9.02.

11b: $[\alpha]^{25}_D = +157.9$ ($c = 1.3$, $CHCl_3$); ^1H NMR δ 3.82−3.77 (1H, t, $J = 8.2$ Hz), 2.76 (2H, s), 2.50−2.45 (2H, m), 2.38−2.29 (2H, m), 2.16−2.04 (1H, m), 1.97−1.74 (4H, m), 1.73−1.23 (5H, m), 0.71 (3H, s); ^{13}C NMR δ 211.4, 127.7, 124.7, 81.1, 44.1, 42.7, 42.1, 40.2, 38.5, 32.5, 30.5, 30.3, 25.0, 10.0; IR ν_{max} 3417, 2956, 2880, 1714, 1042 cm^{-1}. Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.20, H, 9.00.

[1*S*-(1α,3a*β*,4a*β*,8aα,9aα)]-Dodecahydro-1-hydroxy-9a-methyl-6*H*-benz[*f*]inden-6-one (12a) and [1*S*-(1α,3a*β*,4aα,8aα,9aα)]-Dodecahydro-1-hydroxy-9a-methyl-6*H*-benz[*f*]-inden-6-one (12b). Compound **11a** (3.5 g, 15 mmol) was dissolved in EtOAc (150 mL). To this was added 5% $Pd/BaSO_4$ (696 mg). The reaction was hydrogenated (60 psi, H_2) for 3 h. At this time, the reaction was filtered through a short column of Celite to remove the catalyst, washing with EtOAc. The solvent was removed in vacuo, and the crude NMR showed the product to be a 60:40 mixture of **12a** to **12b**. Chromatography (50% EtOAc in hexanes) yielded the two stereoisomers **12a** (2.06 g, 59%) as a white solid and **12b** (1.42 g, 41%) as a colorless oil.

12a: $[\alpha]^{25}_D = +68.0$ ($c = 1.6$, $CHCl_3$); mp 100−101 °C; ^1H NMR δ 3.69−3.64 (1H, t, $J = 9.0$ Hz), 2.39−2.28 (3H, m), 2.18−2.04 (2H, m), 1.94−1.81 (3H, m), 1.70−1.15 (10H, m), 0.80 (3H, s); ^{13}C NMR δ 211.6, 81.3, 48.4, 44.4, 44.1, 43.6, 43.2, 41.5, 37.1, 33.3, 33.0, 30.5, 25.0, 11.2; IR ν_{max} 3423, 2912, 1712, 1044 cm^{-1}. Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.64; H, 9.77.

12b: $[\alpha]^{25}_D = +70.7$ ($c = 0.75$, $CHCl_3$); ^1H NMR δ 3.79−3.73 (1H, t, $J = 9.0$ Hz), 2.60−2.51 (1H, m), 2.41−2.22 (3H, m), 2.17−1.91 (4H, m), 1.90−1.64 (2H, m), 1.60−1.25 (8H, m), 0.84 (3H, s); ^{13}C NMR δ 211.4, 127.7, 124.7, 81.1, 44.1, 42.7, 42.1, 40.2, 38.5, 32.5, 30.5, 30.2, 25.0, 10.0; IR ν_{max} 3427, 2918, 1712, 1046, 753 cm^{-1}. Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.80; H, 9.78.

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Supporting Information Available: Experimental data for compounds **1**−**3**, X-ray crystallographic data, and a projection view of compound **12a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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