Synthesis of a CDE Fragment of the Insect Antifeedant 12-Hydroxyazadiradione

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A diastereoselective and versatile synthesis of the model insect antifeedant **23** related to 12-hydroxyazadiradione has been achieved in 11 steps starting from α-cyclocitral, **1**. The key steps involve intramolecular 1,3-dipolar cycloaddition of a nitrile oxide and a Stille coupling reaction of a vinyl iodide with a stannylfuran.

Introduction

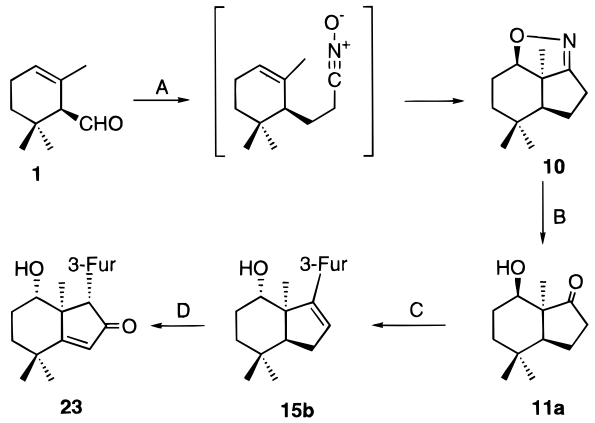
The 12-hydroxy derivatives of the havanensin limonoids are promising compounds of interest not only because of their bioactivity (anticancer, antifeedant)[1] but also because they are potential precursors[2] of the C-seco limonoids (salanin, azadirachtin), considered the most active of the limonoid family.[1b,3] However, despite these interesting properties, no synthetic approach has been made to this class of compounds and related CDE molecular fragments. Here, we have developed a plan for the synthesis of the CDE molecular fragments of 12-hydroxyazadiradione which is sufficiently versatile to access limonoids and pentacyclic analogs.

Results and Discussion

The plan has been divided into four phases (Scheme 1). The first (A) consists of the intramolecular cycloaddition of an unsaturated nitrile oxide, which builds up a tricyclic compound precursor of the hydroxy ketone, a key intermediate which will be obtained by heterocycle cleavage in the second phase (B). The third phase (C), insertion of a furan ring into the indane nucleus, is based on a novel Stille type coupling reaction. Finally the fourth phase (D) involves the elaboration of the cyclopentene inside the cyclopentenone.

The required isoxazoline **10** was obtained from the α-cyclocitral by two parallel procedures through the unsatured ester **3** (Scheme 2). Olefination of the α-cyclocitral (**1**)[4] followed by selective hydrogenation of the unsaturated ester **2** gave **3**, which was quantitatively reduced to the alcohol **4** with LAH. From this point onward we followed two paths to the isoxazoline **10**; one[5] through the oxime **6** and the other[6] through the nitroalkene **9**. The overall yield of the first route was 44% and the second was 46%.[7]

Scheme 1



The second phase of the synthetic plan involves the cleavage of the heterocycle to the hydroxy ketone (Scheme 3). This transformation was accomplished by treatment of **10** with Raney nickel in a mixture of methanol−water−acetic acid[8] to afford a mixture of the two epimeric hydroxy ketones **11a** and **11b** in a 6:4 ratio, respectively. Substitution of Raney nickel in acetic acid by Pd/C with boric acid increased selectivity and avoided the epimerization. The addition of sodium acetate to the reaction mixture changed the product ratio of hydroxy ketones **11a** and **11b** to 4:6, respectively (Scheme 3). A simple method to convert the hydroxy ketone **11a** with the axial hydroxyl group to the corresponding equatorial isomer **11b** is based on the Meerwein−Ponford−Verley[9] reaction which after 48 h afforded a 6(ax):4(eq) ratio mixture starting from pure axial isomer.

Insertion of the furan into the indan nucleus was first attempted by nucleophilic addition of 3-furyllithium.[10] The high acidity of cyclopentanones, the neopentylic character of the carbonyl group, and the presence of other oxygenated functions in the molecule are factors that hinder the nucleophilic reaction. These considerations led us to approach a more selective procedure compatible

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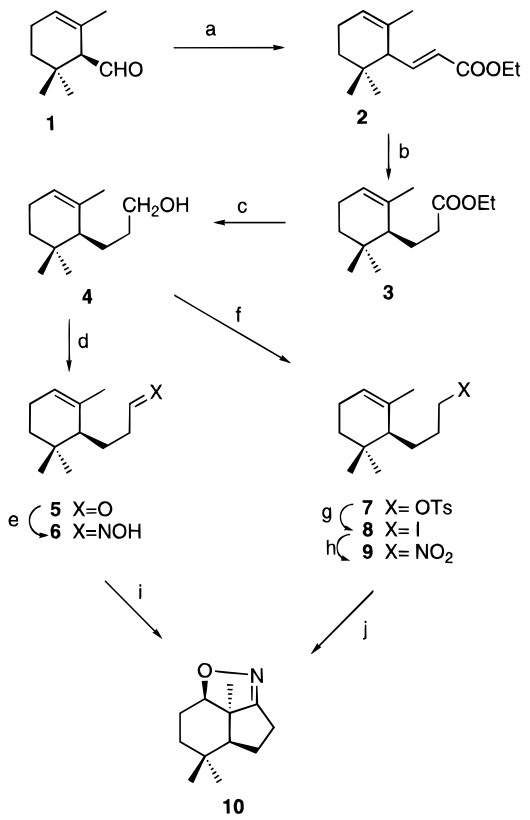
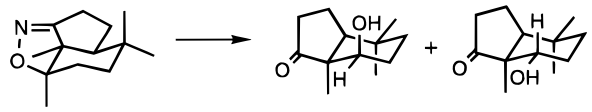
Scheme 2[a]



[a] (a) $(EtO)_2POCH_2CO_2Et$, NaH, benzene; (b) H_2, Pd/C, Et_2NH, AcOEt; (c) $LiAlH_4$, ether, 0 °C; (d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; (e) NaOAc, $NH_2OH{\cdot}HCl$, H_2O; (f) TsCl, py, CH_2Cl_2; (g) NaI, DMF; (h) $NaNO_2$, DMF; (i) NaClO, CH_2Cl_2; (j) PhNCO, Et_3N, benzene, 25 °C.

Scheme 3

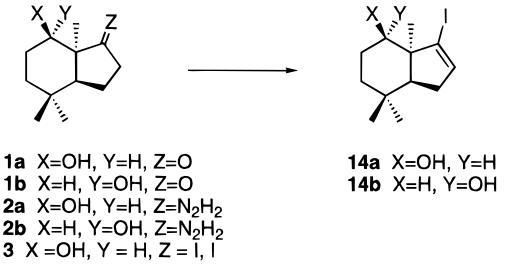


10 11a 11b

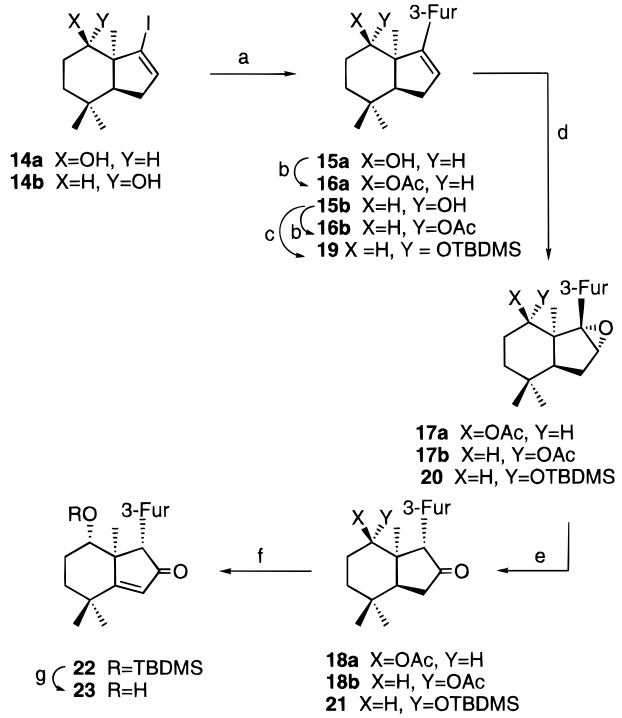
Raney Ni, H_2, AcOH	48%	32%
Pd/C, H_2, H_3BO_3	80%	0%
Pd/C, H_2, AcOH-NaOAc	30%	60%

with the structural characteristics and functional groups of the hydroxy ketone **11a**. One method which could fulfill our demands for the mild conditions, chemoselectivity, and low steric requirements would be a Stille type coupling reaction.[11] One partner for the coupling reaction would be tri-*n*-butyl(3-furyl)tin[12] and the other a enol triflate or, alternatively a vinyl iodide. Transformation of the carbonyl group to the enol triflate group was carried out by treatment with triflic anhydride and 2,6-di-*tert*-butyl-4-methylpyridine[13] in very low yield. The McMurry[14] procedure was unsuccessful. The discouraging results obtained in the preparation of the enol triflates prompted us to prepare the vinyl iodides **14a** and **14b** (Scheme 4).

Scheme 4



Scheme 5[a]



[a] (a) LiCl, $Pd(PPh_3)_4$, Bu_3(3-furyl)Sn, THF, reflux; (b) Ac_2O, py; (c) TBDMSCl, imidazole, DMF; (d) *m*-CPBA, CH_2Cl_2, −40 °C; (e) $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 °C; (f) (i) LDA, PhSeBr, THF; (ii) H_2O_2 30%, THF; (g) NBu_4F, THF.

The usual procedure to transform a ketone into a vinyl iodide is carried out through the corresponding hydrazone and subsequent treatment with iodine.[15] From both ketones **11a** and **11b**, the hydrazones **12a** and **12b** were obtained in nearly quantitative yield. The behavior of each hydrazone with iodine in the presence of triethylamine was very different: while the axial isomer **12a** gave the diiodo alcohol **13** exclusively in 80% yield, the equatorial isomer **12b** afforded the vinyl iodide **14b** only in 82% yield. Dehydrohalogenation of diiodo alcohol **13** to **14a** was achieved in 36% yield after 24 h treatment with DBU in xylene at 90 °C.

The coupling reaction of the vinyl iodides **14a** and **14b** separately and 3-furylstannane was carried out in THF under reflux using tetrakis(triphenylphosphine)palladium(0) as catalyst[11] to give the furan derivatives **15a** and **15b** in 60% and 81% yields, respectively (Scheme 5).

The last phase of the synthetic plan was attempted first with acetates **16a** and **16b**. Stereoselective epoxidation[16] of **16a** with *m*-CPBA in CH_2Cl_2 at −40 °C gave

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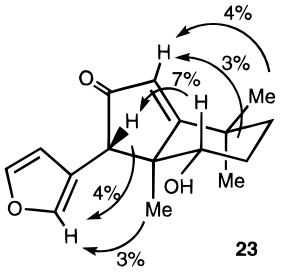

Figure 1.

the epoxide **17a** in quantitative yield. An α configuration was assigned to the oxiranic oxygen, assuming that the β face is more sterically hindered to the peracid approach (Scheme 5). This is consistent with the upfield shift in the ^{13}C NMR signal for the homoallylic carbon bearing an axial proton cis to the oxygenated function in the epoxide **17a** (47.67 ppm) as compared to the unsaturated precursor **16a** (55.86 ppm).[16]

Treatment of epoxide **17a** with boron trifluoride etherate[17] gave only the keto acetate **18a** in 87% yield. The assigned cis relationship to the angular methyl group and furan is based on the Coxon[18] mechanism for epoxide rearrangement and to the diamagnetic shielding effect caused in the methyl group by the furan which maintains the chemical shift of the methyl group under 1.07 ppm distant from 1.40 ppm for a trans methyl/furan relation.[16] By the same procedure, acetate **16b** was transformed into the ketone **18b**.

Attempts at dehydrogenation of **18b** to the corresponding enone (**23**, R = OAc) by the known sequence[19] of selenylation, oxidation, and selenoxide elimination were unsuccessful. Fortunately, the change in the hydroxyl protector group from acetyl to *tert*-butyldimethylsilyl permitted the transformation of the alkene **15b** into the enone **23**.

Silylation[20] of alcohol **15b** was achieved by treatment with *tert*-butyldimethylsilyl chloride and imidazole in DMF at 25 °C. The sequence described above for acetates, epoxidation and epoxide rearrangement, was applied to unsaturated silyl ether **19** to afford the ketone **21** in 42% yield. Dehydrogenation of the ketone **21** by the reported procedure[21] gave the enone **22**. Deprotection of the hydroxyl group with tetrabutylammonium fluoride yielded the CDE fragment of 12-hydroxyazadiradione **23**. Stereochemical assignements were based on NOE studies. Some representative data are shown in the Figure 1.

Experimental Section

General Methods. Commercial reagents were used as received. Dichloromethane, pyridine, diethylamine, diisopropylamine, and dimethylformamide were distilled under nitrogen from calcium hydride or BaO. Ether and tetrahydrofuran were distilled from sodium. Hexane and ethyl acetate were distilled before use. Melting points were determined on a hot-stage apparatus and are not corrected. The ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution at 200 and 50 MHz, respectively. IR spectra were obtained as thin films. Mass spectra were obtained on a VG-TS 250 instrument. All reactions were carried out under an atmosphere of nitrogen in glassware dried overnight and cooled under nitrogen. Reactions were monitored by TLC. Flash column chromatographies were carried out using silica gel 60 (0.040−0.063 mm Merck). Organic extracts were washed with saturated NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure with the aid of a rotary evaporator.

Ethyl 3-(2,6,6-Trimethyl-2-cyclohexenyl)-2-propenoate (2). A dry three-necked flask equipped with stirrer, condenser, and dropping funnel was purged with dry nitrogen and charged with a 68.6% dispersion of sodium hydride in mineral oil (2.4 g, 69 mmol) and dry benzene (21 mL). To this stirred mixture was added dropwise triethyl phosphonoacetate (14.2 mL, 72 mmol). During the addition period, the temperature was maintained at 30−35 °C. A vigorous evolution of hydrogen was noted during this part of the reaction. After the addition of triethyl phosphonoacetate had been completed, the mixture was stirred for 1 h at room temperature to ensure complete reaction. To this nearly clear solution was added dropwise α-cyclocitral (**1**) (10 g, 65.8 mmol). The mixture was stirred for an additional 1 h at room temperature and diluted with ether, and water was then added dropwise. The organic layer was separated, and the aqueous phase was extracted with ether. The combined extracts were washed with brine and dried (Na_2SO_4). Evaporation of the solvent left the unsaturated ester **2** as a colorless oil (13.2 g, 90%): IR 1715 cm^{-1}; ^1H NMR δ 0.82 (3H, s), 0.89 (3H, s), 1.27 (3H, t, J = 7 Hz), 1.53 (3H, s), 4.15 (2H, q, J = 7 Hz), 5.45 (1H, br s), 5.76 (1H, d, J = 15.5 Hz), 6.76 (1H, dd, J = 15.5 Hz and J' = 9.7 Hz); ^{13}C NMR δ 166.10, 149.44, 131.56, 122.11, 122.01, 59.75, 53.65, 32.04, 30.79, 27.29, 26.41, 22.62, 22.37, 13.87; MS *m*/*z* (relative intensity) 222 (11, M^+), 177 (8), 166 (36), 93 (100), 77 (31). Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.68; H, 10.10.

Ethyl 3-(2,6,6-Trimethyl-2-cyclohexenyl)propanoate (3). To a solution of **2** (5 g, 22.3 mmol) in ethyl acetate (45 mL) and diethylamine (5 mL) was added 1.25 g of 10% Pd/C. This stirred mixture was blanketed with hydrogen (1 atm). After 3 h the catalyst was removed by filtration, and the filtrate was evaporated to give the ester **3** as a colorless oil (5 g, 100%): IR 1738 cm^{-1}; ^1H NMR δ 0.86 (3H, s), 0.91 (3H, s), 1.24 (3H, t, J = 7 Hz), 1.67 (3H, s), 2.33 (2H, t, J = 10 Hz), 4.11 (2H, q, J = 7 Hz), 5.32 (1H, br s); ^{13}C NMR δ 173.68, 135.49, 120.88, 59.99, 48.45, 34.31, 32.44, 31.40, 27.45 (2), 25.73, 23.31, 22.88, 14.14; MS *m*/*z* (relative intensity) 224 (7, M^+), 195 (25), 177 (29), 123 (88.6), 95 (52), 55 (100). Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.91; H, 10.73.

3-(2,6,6-Trimethyl-2-cyclohexenyl)propanol (4). To a slurry of LAH (3.4 g, 88.8 mmol) in dry ether (100 mL) at 0 °C was added dropwise a solution of the ester **3** (10 g, 44.6 mmol) in dry ether (150 mL). The mixture was vigorously stirred for 10 min, after which it was quenched with $Na_2SO_4 \cdot 10H_2O$. The resulting mixture was filtered, and the filtrate was concentrated in vacuo to give the alcohol **4** as a colorless oil (7.8 g, 96%): IR 3374 cm^{-1}; ^1H NMR δ 0.86 (3H, s), 0.91 (3H, s), 1.67 (3H, s), 3.58 (2H, m), 5.27 (1H, br s); MS *m*/*z* (relative intensity) 178 (2, M^+), 123 (7), 109 (23), 95 (26), 83 (21), 69 (78), 55 (100). Anal. Calcd for $C_{12}H_{22}O$: C, 79.06; H, 12.16. Found: C, 79.10; H, 12.18.

3-(2,6,6-Trimethyl-2-cyclohexenyl)propanal (5). A solution of dimethyl sulfoxide (6.7 mL, 94.4 mmol) in CH_2Cl_2 (25 mL) was added dropwise to a stirred solution of oxalyl chloride (4 mL, 47.2 mmol) in CH_2Cl_2 (155 mL) under N_2 at −60 °C. After 5 min, a solution of the alcohol **4** (7.8 g, 42.8 mmol) in CH_2Cl_2−DMSO (3:1, 62 mL) was added dropwise. The reaction mixture was stirred for a further 20 min, triethylamine (31 mL, 224 mmol) was added at −60 °C, and stirring was continued for a further 10 min. Then, it was allowed to warm to room temperature, and water was added. The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2. The combined extracts were washed with water, dried (Na_2SO_4), and filtered. The solvent was

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removed to afford the aldehyde **5** as a colorless oil (7.7 g, 100%): IR 1726 cm^{-1}; ^1H NMR δ 0.88 (3H, s), 0.95 (3H, s), 1.66 (3H, s), 2.47 (2H, m), 5.35 (1H, br s), 9.74 (1H, m). Anal. Calcd for $C_{12}H_{20}O$: C, 75.74; H, 11.18. Found: C, 75.80; H, 11.20.

Oxime of 3-(2,6,6-Trimethyl-2-cyclohexenyl)propanal (6). A solution of hydroxylamine hydrochloride (30 g) in water (110 mL) was added to a solution of the aldehyde **5** (7.7 g, 43 mmol) in ether (454 mL). The mixture was vigorously stirred at room temperature, and a solution of sodium carbonate (46 g) in water (110 mL) was added dropwise. After the mixture was stirred for an additional 10 min, the layers were separated. The aqueous phase was extracted with ether. The combined extracts were washed with brine, dried (Na_2SO_4), filtered, and evaporated to give an oily product identified as a mixture of the oximes **6** (7.68 g, 92%): IR 3268, 1709 cm^{-1}; ^1H NMR δ 0.87 (6H, s), 0.92 (3H, s), 0.93 (3H, s), 1.67 (6H, s), 5.32 (2H, br s), 6.72 (1H, t, J = 5.9 Hz), 7.41 (1H, t, J = 5.9 Hz); MS *m/z* (relative intensity) 195 (1, M^+), 110 (7), 96 (21), 83 (27), 74 (44), 59 (41), 55 (100).

***p*-Toluenesulfonate of 3-(2,6,6-Trimethyl-2-cyclohexenyl)propanol (7).** To a stirred solution of the alcohol **4** (5 g, 27.5 mmol) in pyridine (13.3 mL) at 0 °C was gradually added *p*-toluenesulfonyl chloride (7.86 g, 41.5 mmol). After 12 h at 0 °C, the mixture was poured into ice−water and stirred for an additional 30 min at room temperature. The two-phase system was extracted with ether. The combined ethereal extracts were washed with aqueous HCl (2 N), $NaHCO_3$ (5%), and brine, dried (Na_2SO_4), filtered, and evaporated to yield the tosylate **7** as a viscous oil (8.1 g, 88%): IR 1362, 1177 cm^{-1}; ^1H NMR δ 0.81 (3H, s), 0.82 (3H, s), 1.58 (3H, s), 2.43 (3H, s), 3.98 (2H, t, J = 6.4 Hz), 5.26 (1H, br s), 7.32 (2H, d, J = 8.2 Hz), 7.77 (2H, d, J = 8.2 Hz).

3-(2,6,6-Trimethyl-2-cyclohexenyl)propyl Iodide 8. A mixture of the tosylate **7** (8.1 g, 24.1 mmol) and sodium iodide (7.23 g, 48.2 mmol) in acetone (80 mL) was stirred under N_2 at room temperature for 20 h. Then, the solvent was removed in vacuo, and water was added to the residue which was extracted with ether. The combined extracts were washed with aqueous Na_2SO_3 (10%) and brine, dried (Na_2SO_4), and filtered. Removal of the solvent afforded a yellow oily residue identified as the iodide **8** (6.54 g, 93%): IR 2926, 2868, 1451, 1366, 1188, 1179 cm^{-1}; ^1H NMR δ 0.85 (3H, s), 0.92 (3H, s), 1.68 (3H, s), 3.16 (2H, t, J = 7 Hz), 5.30 (1H, br s); MS *m/z* (relative intensity) 292 (4, M^+), 236 (83), 109 (33), 91 (24), 81 (100), 67 (65), 55 (36).

3-(2,6,6-Trimethyl-2-cyclohexenyl)nitropropane (9). A mixture of the iodide **8** (6.54 g, 22.4 mmol) and sodium nitrite (3.09 g, 44.8 mmol) in DMF (46 mL) was stirred under N_2 at room temperature for 6 h. The mixture was poured into ice and allowed to warm to room temperature. It was extracted with ether, and the combined extracts were washed with water and brine, dried (Na_2SO_4), and filtered. Removal of the solvent afforded a residue which was flash chromatographed using hexane−ether (95:5) as eluent.

The first fraction (0.90 g, 19%) was a yellow oil identified as the nitrite compound **9a**: IR 1647 cm^{-1}; ^1H NMR δ 0.87 (3H, s), 0.91 (3H, s), 1.67 (3H, s), 4.66 (2H, m), 5.31 (1H, br s).

The second fraction (3.1 g, 67%) was a viscous yellow oil identified as the nitro alkene **9**: IR 1553 cm^{-1}; ^1H NMR δ 0.86 (3H, s), 0.90 (3H, s), 1.66 (3H, s), 4.35 (2H, t, J = 6.9 Hz), 5.33 (1H, br s); MS *m/z* (relative intensity) 211 (9, M^+), 163 (7), 123 (18), 107 (24), 93 (47), 91 (53), 81 (80), 79 (93), 67 (51), 55 (100).

(4a*SR*,7*RS*,7a*SR*)-4,4,7a-Trimethylperhydroindene[1,7-*cd*]isoxazoline (10). Procedure A. To a solution of the oximes **6** (5 g, 25.6 mmol) and triethylamine (0.2 mL) in CH_2Cl_2 (50 mL) at 0 °C was added dropwise a solution of aqueous sodium hypochlorite (10%, 46 mL) over a period of 15 min. After the mixture was stirred for half an hour, it was added water, and the organic layer was separated. The aqueous phase was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4), and filtered. The solvent was removed, and the residue was purified by flash chromatography using hexane−ether (1:1) as eluent to yield the isoxazoline **10** as colorless oil (2.5 g, 50%): IR 1450, 1390, 1370 cm^{-1}; ^1H NMR δ 0.78 (3H, s), 0.86 (3H, s), 1.21 (3H, s), 2.39 (2H, m), 4.23 (1H, dd, J = 7.3 Hz and J' = 8.7 Hz); ^{13}C NMR δ 20.26, 22.15, 25.46, 29.67 (2), 31.27, 31.57, 33.48, 50.14, 60.67, 84.10, 174.48; MS *m/z* (relative intensity) 193 (58, M^+), 176 (33), 163 (68), 107 (71), 81 (56), 69 (89), 55 (100). Anal. Calcd for $C_{12}H_{19}NO$: C, 74.57; H, 9.91; N, 7.24. Found: C, 74.51; H, 9.88; N, 7.23.

Procedure B. To a solution of the nitroalkene **9** (2.88 g, 13.6 mmol) in benzene (88 mL) was added phenyl isocyanate (6 mL, 55.2 mmol) and a catalytic amount of triethylamine (0.35 mL). The reaction mixture was stirred at room temperature for 2 days. Aqueous ammonium hydroxide (10%) was added to precipitate the urea which was filtered off. The filtrate was concentrated in vacuo, and the residue was purified by flash chromatography (eluent: hexane−ether, 1:1) to afford the isoxazoline **10** (1.92 g, 73%).

Reduction of Isoxazoline 10. Procedure A. A solution of the isozaxoline **10** (1.5 g, 7.77 mmol) in methanol (21 mL) containing acetic acid (3 mL) was hydrogenated in presence of Raney nickel W-2 for 12 h at room temperature and atmospheric pressure. After filtration of the catalyst through Celite, the solvent was removed in vacuo and the residue was extracted with ether and washed with satured aqueous $NaHCO_3$. The dried organic phase was concentrated at reduce pressure to give a residue which was chromatographed using hexane−ether (7:3) as eluent.

The first fraction (731 mg, 48%) which was a crystalline product was identified as the hydroxy ketone **11a**: mp 68 °C; IR 3479, 1738 cm^{-1}; ^1H NMR δ 0.86 (3H, s), 0.98 (3H, s), 1.19 (3H, s), 2.21 (2H, m), 3.62 (1H, dd, J = 2.2 Hz and J' = 3.0 Hz); ^{13}C NMR δ 22.03, 23.56, 26.63, 27.25, 29.71, 31.66 (2), 37.30, 51.49, 53.27, 73.75, 225.15; MS *m/z* 196 (2, M^+), 181 (14), 140 (53), 123 (15), 97 (100), 81 (22), 69 (15), 55 (24). Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.49; H, 10.31.

The second fraction (487 mg, 32%) was identified as the hydroxy ketone **11b**: IR 3455, 1728 cm^{-1}; ^1H NMR δ 0.91 (3H, s), 1.10 (3H, s), 1.20 (3H, s), 2.39 (2H, m), 3.51 (1H, dd, J = 7.2 Hz and J' = 10.6 Hz); ^{13}C NMR δ 16.84, 22.23, 25.30, 28.92, 29.25, 31.56, 33.93, 36.56, 52.47, 55.01, 67.89, 222.92; MS *m/z* (relative intensity) 196 (1, M^+), 181 (10), 140 (7), 97 (100), 79 (8), 67 (11), 55 (22). Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.40; H, 10.30.

Procedure B. To a solution of the isoxazoline **10** (734 mg, 3.80 mmol) in a mixture of methanol−water (5:1, 21.8 mL) was added boric acid (470 mg, 7.60 mmol) and Pd/C of 10% (220 mg). The resulting mixture was hydrogenated for 12 h at 50 °C and atmospheric pressure. After filtration of the catalyst through Celite, the solvent was removed in vacuo. Water was added to the residue which was extracted with ether. The combined extracts were washed with brine, dried (Na_2SO_4), and filtered. The solvent was evaporated to afforded a product identified as the hydroxy ketone **11a** (596 mg, 80%).

Procedure C. To a solution of the isoxazoline **10** (1 g, 5.2 mmol) in methanol (10 mL) was added aqueous sodium acetate−acetic acid (2 M, 1:1, 0.75 mL) and Pd/C of 10% (300 mg). The resulting mixture was hydrogenated for 1 h 15 min at 50 °C and atmospheric pressure. After filtration of the catalyst through Celite, the solvent was removed in vacuo and the residue was extracted with ether and washed with satured aqueous $NaHCO_3$. The dried organic phase was concentrated at reduce pressure to give a residue which was chromatographed using hexane−ether (7:3) as eluent to afford the hydroxy ketone **11a** (300 mg, 30%) and the hydroxy ketone **11b** (600 mg, 60%).

Epimerization of Hydroxy Ketone 11b. A mixture of the hydroxy ketone **11a** (1 g, 5.10 mmol), aluminum isopropoxide (1 g), acetone (1.5 mL), and 2-propanol (15 mL) was refluxed under N_2 with magnetic stirring for 2 days. Then, it was cooled to room temperature, poured into aqueous HCl (6%), and extracted with ether. The combined extracts were washed with brine, dried (Na_2SO_4), and filtered. Removal of solvent afforded a residue which was flash chromatographed using hexane−ether (7:3) as eluent to give the hydroxy ketone **11a** (540 mg, 54%) and the hydroxy ketone **11b** (360 mg, 36%).

Synthesis of (4a*SR*,7*RS*,7a*SR*)-7-Hydroxy-1-iodo-4,4,7a-trimethyl-4,4a,5,6,7,7a-hexahydro-3*H*-indene (14a). (A) Hydrazone Preparation. A solution of the hydroxy ketone **11a** (750 mg, 3.82 mmol) in ethanol (13.3 mL) was treated with triethylamine (2.6 mL) and hydrazine hydrate (6.6 mL), and the solution was heated under reflux for 24 h. The solvent was evaporated, the residue was dissolved in dichloromethane, and the solution was washed with water to neutrality. Then the organic phase was dried (Na_2SO_4) and evaporated to give the corresponding hydrazone **12a** (765 mg, 95%): IR 3430, 1469, 1110 cm^{-1}; ^1H NMR δ 0.69 (3H, s), 0.86 (3H, s), 1.26 (3H, s), 3.47 (1H, m) ppm.

(B) Vinyl Iodide 14a. A solution of the above hydrazone **12a** (765 mg, 3.64 mmol) in THF (24.4 mL) and triethylamine (5.1 mL) was treated with iodine until a slight excess was present (cessation of nitrogen evolution, brown color not discharged) and then was added diethyl ether. The ethereal solution was washed successively with aqueous 2 N HCl, water to neutrality, aqueous $NaHSO_3$ (10%), water, saturated aqueous $NaHCO_3$, and brine. The organic phase was then dried (Na_2SO_4) and evaporated to give the diiodide **13** (1.26 g, 80%): ^1H NMR δ 0.91 (3H, s), 0.93 (3H, s), 1.29 (3H, s), 4.75 (1H, m) ppm.

To a solution of diiodide **13** (1.26 g, 2.98 mmol) in xylene (6.8 mL) was added DBN (1.1 mL). The mixture was heated at reflux for 24 h. Then, it was cooled and diluted with ether. The resulting mixture was washed sucesively with aqueous Na_2CO_3 (10%) and brine, dried (Na_2SO_4), and evaporated. Chromatography of the residue on silica gel with pentane as eluent gave the vinyl iodide **14a** as a yellow oil (320 mg, 36%): IR 3488, 1670, 1384, 1015 cm^{-1}; ^1H NMR δ 0.94 (3H, s), 1.06 (3H, s), 1.19 (3H, s), 3.46 (1H, m), 6.50 (1H, m) ppm.

Synthesis of (4a*SR*,7*SR*,7a*SR*)-7-Hydroxy-1-iodo-4,4,7a-trimethyl-4,4a,5,6,7,7a-hexahydro-3*H*-indene (14b). (A) Hydrazone Preparation. Hydroxy ketone **11b** (750 mg) was treated in essentially the same manner as described above except the reaction was completed after 5 h to give the corresponding hydrazone **12b** (765 mg, 95%): IR 3374, 1460, 1074 cm^{-1}; ^1H NMR δ 0.87 (3H, s), 1.09 (3H, s), 1.21 (3H, s), 3.40 (1H, m) ppm; MS *m*/*z* (relative intensity) 210 (2, M^+), 207 (6), 180 (3), 135 (6), 110 (7), 96 (20), 83 (30), 74 (54), 69 (42), 59 (55), 55 (100).

(B) Vinyl Iodide 14b. A solution of the above hydrazone **12b** (765 mg, 3.64 mmol) in THF (24.4 mL) and triethylamine (5.1 mL) was treated with iodine until a slight excess was present (cessation of nitrogen evolution, brown color not discharged) and then was added diethyl ether. The ethereal solution was washed successively with aqueous 2 N HCl, water to neutrality, aqueous $NaHSO_3$ (10%), water, saturated aqueous $NaHCO_3$, and brine. The organic phase was then dried (Na_2SO_4) and evaporated to give the vinyl iodide **14b** as a yellow oil (913 mg, 82%): IR 3381, 1651, 1458, 1053 cm^{-1}; ^1H NMR δ 0.89 (3H, s), 1.07 (3H, s), 1.24 (3H, s), 3.65 (1H, m), 6.30 (1H, m) ppm; MS *m*/*z* (relative intensity) 306 (11, M^+), 206 (24), 161 (30), 99 (37), 91 (33), 81 (100), 77 (71), 69 (15), 55 (48).

(4a*SR*,7*RS*,7a*SR*)-1-(3-Furyl)-4,4,7a-trimethyl-4,4a,5,6,7,7a-hexahydro-3*H*-inden-7-ol (15a). To a slurry of LiCl (80 mg, 1.87 mmol) and $Pd(PPh_3)_4$ (14 mg, 2.0 mol %) in THF (1.7 mL) was added a solution of vinyl iodide **14a** (187 mg, 0.61 mmol) and 3-(tributylstannyl)furan (217 mg, 0.61 mmol) in THF (4.5 mL). This mixture was heated under reflux for 2 days, cooled to room temperature, and diluted with pentane. The resulting solution was washed sequentially with water, 10% ammonium hydroxyde, water, and brine. This solution was dried (Na_2SO_4) and filtered. Removal of the solvent afforded a residue which was flash chromatographed using hexane−ether (9:1) as eluent to yield the alcohol **15a** as a colorless oil (90 mg, 60%): IR 3560, 1460, 1159, 1045 cm^{-1}; ^1H NMR δ 0.95 (3H, s), 1.11 (3H, s), 1.30 (3H, s), 3.76 (1H, m), 6.13 (1H, m), 6.44 (1H, m), 7.39 (1H, m), 7.43 (1H, m); ^{13}C NMR δ 24.49, 24.82, 27.94, 29.74, 31.03, 31.45, 35.06, 52.20, 55.86, 71.11, 109.80, 122.00, 130.43, 138.07, 139.91, 142.82 ppm; MS *m*/*z* (relative intensity) 246 (24, M^+), 213 (21), 158 (100), 147 (39), 129 (12), 115 (22), 91 (27), 77 (23), 55 (40). Anal. Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 78.08; H, 8.89.

(4a*SR*,7*SR*,7a*SR*)-1-(3-Furyl)-4,4,7a-trimethyl-4,4a,5,6,7,7a-hexahydro-3*H*-inden-7-ol (15b). Vinyl iodide **14b** (780 mg) was treated the same manner as described above. Flash chromatography (hexane−ether, 8:2) gave the alcohol **15b** as a white solid (508 mg, 81%): mp 58−59 °C; IR 3416, 1456, 1161, 1047 cm^{-1}; ^1H NMR δ 0.92 (3H, s), 1.12 (3H, s), 1.33 (3H, s), 3.60 (1H, m), 5.90 (1H, m), 6.52 (1H, m), 7.38 (1H, m), 7.62 (1H, m); ^{13}C NMR δ 18.19, 27.94, 29.46, 30.75, 32.15, 33.44, 34.57, 52.00, 59.59, 77.60, 110.69, 126.17 (2), 139.48, 142.34, 145.00; MS *m*/*z* (relative intensity) 246 (47, M^+), 231 (21), 147 (100), 131 (27), 115 (54), 91 (78), 77 (57), 55 (98). Anal. Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 78.05; H, 9.07.

1-(3-Furyl)-4,4,7a-trimethyl-4,4a,5,6,7,7a-hexahydro-3*H*-inden-7-yl Acetate (16a). A solution of **15a** (75 mg, 0.31 mmol), pyridine (1 mL), DMAP (1 mg), and acetic anhydride (1 mL) was stirred at room temperature for 7 days and poured into water. The mixture was extracted with diethyl ether, and the organic phase was washed successively with 2 N HCl and aqueous $NaHCO_3$. The organic layer was dried (Na_2SO_4) and concentrated to afford 87 mg (100%) of the title compound **16a** as an oil: IR 1740 cm^{-1}; ^1H NMR δ 0.97 (3H, s), 1.11 (3H, s), 1.30 (3H, s), 1.86 (3H, s), 5.03 (1H, m), 5.89 (1H, m), 6.34 (1H, m), 7.31 (2H, m). Anal. Calcd for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39. Found: C, 74.88; H, 8.42.

1-(3-Furyl)-4,4,7a-trimethyl-4,4a,5,6,7,7a-hexahydro-3*H*-inden-7-yl Acetate 16b. A solution of **15b** (438 mg, 1.78 mmol), pyridine (1 mL), DMAP (1 mg), and acetic anhydride (1 mL) was stirred at room temperature for 4 h and poured into water. The mixture was extracted with diethyl ether, and the organic phase was washed successively with 2 N HCl and aqueous $NaHCO_3$. The organic layer was dried (Na_2SO_4) and concentrated to afford 514 mg (100%) of the title compound **16b** as an oil: IR 1750 cm^{-1}; ^1H NMR δ 0.92 (3H, s), 1.13 (3H, s), 1.41 (3H, s), 1.85 (3H, s), 4.37 (1H, m), 5.85 (1H, t, J = 2.6 Hz), 6.41 (1H, m), 7.29 (1H, m), 7.41 (1H, m). Anal. Calcd for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39. Found: C, 74.89; H, 8.37.

Synthesis of the Silyl Ether 19. A mixture of the alcohol **15b** (270 mg, 1.10 mmol), *tert*-butylchlorodimethylsilane (662 mg, 4.39 mmol), and imidazole (621 mg, 9.13 mmol) in dry DMF (1 mL) was stirred overnight under N_2 at room temperature. This mixture was extracted with hexane. The combined extracts were concentrated in vacuo, filtered through a small pad of silica gel, and concentrated to yield the silyl ether **19** as a colorless oil (335 mg, 85%): IR 2934, 2864, 1562, 1351, 1209, 987 cm^{-1}; ^1H NMR δ −0.30 (3H, s), −0.03 (3H, s), 0.83 (9H, s), 0.87 (3H, s), 1.13 (3H, s), 1.37 (3H, s), 3.60 (1H, dd, J = 3.7 Hz and J' = 10.7 Hz), 5.86 (1H, t, J = 6.7 Hz), 6.47 (1H, m), 7.28 (1H, m), 7.52 (1H, m) ppm. Anal. Calcd for $C_{22}H_{36}O_2Si$: C, 73.27; H, 10.06. Found: C, 73.33; H,9.89.

(1*SR*,2*RS*,4a*SR*,7*RS*,7a*SR*)-1-(3-Furyl)-4,4,7a-trimethyl-1,2-epoxyperhydroind-7-yl Acetate (17a). A solution of *m*-chloroperoxybenzoic acid (157 mg, 0.91 mmol) in dry CH_2Cl_2 (8.7 mL) was added dropwise under N_2 at −30 °C to a solution of acetate **16a** (87 mg, 0.31 mmol) in dry CH_2Cl_2 (2.6 mL), and the resulting mixture was stirred at this temperature for an additional 30 min. A solution of Na_2SO_3 (10%) was added, and the resulting heterogeneous mixture was stirred and gradually warmed to room temperature. The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2. The combined extracts were washed with $NaHCO_3$ (5%), water, and brine, dried (Na_2SO_4), and filtered. Removal of the solvent afforded the epoxy compound **17a** as a viscous oil (87 mg, 94%): IR 1730, 1255, 1027 cm^{-1}; ^1H NMR δ 0.90 (3H, s), 1.04 (3H, s), 1.28 (3H, s), 1.93 (3H, s), 3.58 (1H, s), 4.83 (1H, m), 6.26 (1H, m), 7.34 (1H, m), 7.41 (1H, m) ppm; ^{13}C NMR δ 20.50, 21.32, 22.57, 28.59, 29.40, 30.67, 30.80, 31.07, 44.87, 47.67, 64.12, 65.79, 75.06, 109.73, 120.33, 140.94, 142.79, 169.90 ppm.

(1*SR*,2*RS*,4a*SR*,7*SR*,7a*SR*)-1-(3-Furyl)-4,4,7a-trimethyl-1,2-epoxyperhydroind-7-yl Acetate (17b). Acetate **16b** (514 mg) was treated in essentially the same manner as described above except the reaction was completed after 90 min to give the epoxy acetate **17b** as a colorless solid (542 mg) in 100% yield: mp 84−86 °C; IR 1738, 1373, 1248, 1032 cm^{-1}; ^1H NMR δ 0.86 (3H, s), 1.08 (3H, s), 1.42 (3H, s), 1.54 (3H, s),

3.52 (1H, s), 4.62 (1H, m), 6.48 (1H, m), 7.32 (1H, m), 7.38 (1H, m) ppm; ^{13}C NMR δ 16.03, 20.39, 24.34, 28.88, 29.67, 30.32, 31.24, 33.56, 45.58, 50.57, 60.02, 66.44, 74.35, 111.18, 120.98, 141.20, 142.33, 170.38 ppm. Anal. Calcd for $C_{18}H_{24}O_4$: C, 71.03; H, 7.95. Found: C, 71.09; H, 7.88.

(1*SR*,2*RS*,4a*SR*,7*SR*,7a*SR*)-7-(*tert*-Butyldimethylsilyl)-1-(3-furyl)-4,4,7a-trimethyl-1,2-epoxyperhydroindene (20). Compound **19** (320 mg) was treated in essentially the same manner as described above to give the epoxy compound **20** as a colorless oil (217 mg, 65%): IR 2953, 2870, 1120, 898 cm^{-1}; ^{1}H NMR δ −0.34 (3H, s), −0.07 (3H, s), 0.72 (9H, s), 0.84 (3H, s), 1.07 (3H, s), 1.37 (3H, s), 3.58 (1H, s), 3.62 (1H, m), 6.45 (1H, m), 7.29 (1H, m), 7.40 (1H, m).

(1*RS*,4a*SR*,7*RS*,7a*RS*)-1-(3-Furyl)-4,4,7a-trimethyl-2-oxoperhydroind-7-yl Acetate (18a). To a solution of the epoxide **17a** (87 mg, 0.28 mmol) in dry CH_2Cl_2 (10 mL) was added boron trifluoride−diethyl ether (0.05 mL) at 0 °C, and the reaction mixture was stirred for 5 min. Then, it was diluted with ether, and water was added. The layers were separated, and the organic phase was washed with $NaHCO_3$ (5%) and brine and then dried (Na_2SO_4). Evaporation of the solvent afforded a residue which was flash chromatographed using hexane−ether (8:2) as eluent to give a white solid identified as the ketone **18a** (76 mg, 87%): mp 82−84 °C; IR 1738, 1238, 1021 cm^{-1}; ^{1}H NMR δ 0.95 (3H, s), 1.00 (3H, s), 1.07 (3H, s), 1.95 (3H, s), 3.23 (1H, s), 4.90 (1H, m), 6.18 (1H, m), 7.23 (1H, m), 7.37 (1H, m) ppm; ^{13}C NMR δ 20.83, 23.80, 24.22, 29.34, 29.89, 30.21, 32.15, 40.88, 45.25, 49.96, 55.11, 77.00, 111.23, 120.06, 140.99, 142.93, 170.12, 218.19 ppm; MS *m*/*z* (relative intensity) 304 (14, M$^+$), 244 (49), 229 (30), 203 (31), 160 (21), 139 (26), 121 (43), 108 (62), 91 (52), 79 (52), 69 (44), 55 (100). Anal. Calcd for $C_{18}H_{24}O_4$: C, 71.03; H, 7.95. Found: C, 71.06; H, 7.92.

(1*RS*,4a*SR*,7*SR*,7a*RS*)-1-(3-Furyl)-4,4,7a-trimethyl-2-oxoperhydroind-7-yl Acetate (18b). Acetate **17b** (542 mg) was treated in essentially the same manner as described above. Flash chromatography (hexane−ether, 8:2) gave the ketone **18b** as an oily product (471 mg, 87%): IR 1742, 1246, 1013 cm^{-1}; ^{1}H NMR δ 0.91 (3H, s), 0.97 (3H, s), 1.10 (3H, s), 2.06 (3H, s), 3.30 (1H, s), 4.72 (1H, m), 6.15 (1H, m), 7.23 (1H, m), 7.37 (1H, m) ppm; ^{13}C NMR δ 20.05, 20.89, 23.58, 28.48, 29.94, 32.04, 32.80, 39.91, 45.83, 50.58, 54.91, 74.62, 110.74, 119.15, 140.77, 142.87, 170.38, 215.76 ppm; MS *m*/*z* (relative intensity) 304 (20, M$^+$), 244 (42), 203 (100), 162 (32), 139 (66), 121 (27), 107 (70), 91 (58), 79 (56), 67 (28), 55 (73). Anal. Calcd for $C_{18}H_{24}O_4$: C, 71.03; H, 7.95. Found: C, 71.10; H, 8.07.

(1*RS*,4a*SR*,7*SR*,7a*RS*)-7-(*tert*-Butyldimethylsilyl)-1-(3-furyl)-4,4,7a-trimethylperhydroinden-2-one (21). Compound **20** (217 mg) was treated in essentially the same manner as described above. Flash chromatography (hexane−ether, 9:1) gave an oily compound identified as the ketone **21** (139 mg, 64%): IR 1739, 1243, 1124 cm^{-1}; ^{1}H NMR δ 0.04 (3H, s), 0.05 (3H, s), 0.86 (3H, s), 0.89 (9H, s), 0.92 (3H, s), 1.10 (3H, s), 3.42 (1H, s), 3.45 (1H, dd, J = 4.8 Hz and J' = 9.8 Hz), 6.15 (1H, m), 7.19 (1H, m), 7.36 (1H, m); MS *m*/*z* (relative intensity) 376 (2, M$^+$), 319 (24), 225 (39), 197 (10), 171 (19), 105 (11), 91 (17), 77 (17), 75 (100), 69 (15), 59 (19), 55 (23).

(1*RS*,7*SR*,7a*RS*)-7-(*tert*-Butyldimethylsilyl)-1-(3-furyl)-4,4,7a-trimethyl-2,4,5,6,7,7a-hexahydro-1*H*-inden-2-one (22). To a solution of lithium diisopropylamide, prepared from diisopropylamine (0.09 ml, 0.66 mmol) and 1.6 M butyllithium in hexane (0.38 mL, 0.61 mmol) under N_2 at −78 °C, was added dropwise a solution of the ketone **21** (75 mg, 0.20 mmol) in THF (1.3 mL). After enolate formation was complete (30 min), a solution of phenylselenyl bromide (198 mg, 0.84 mmol) in THF (1 mL) was added dropwise at −78 °C. After an additional 30 min, the reaction mixture was allowed to warm to room temperature, quenched by addition of aqueous saturated NH_4Cl, and extracted with ether. The combined extracts were dried (Na_2SO_4) and filtered. The solvent was removed to afforded the phenylseleno ketone.

To a solution of above selenylated ketone in THF (2 mL) at 0 °C was added 30% hydrogen peroxide (0.2 mL). The reaction mixture was stirred at room temperature for 5 min and diluted with ether, and then water was added. The organic layer was separated, and the aqueous phase was extracted with ether. The combined extracts were washed with brine, dried (Na_2SO_4), and filtered. The solvent was removed to give a residue which was flash chromatographed using hexane−ether (8:2) as eluant to yield the indenone **22** (55 mg, 75%); IR 1699 1103 cm^{-1}; ^{1}H NMR δ 0.09 (3H, s), 0.10 (3H, s), 0.87 (9H, s), 1.04 (3H, s), 1.22 (3H, s), 1.25 (3H, s), 3.47 (1H, s), 3.59 (1H, dd, J = 4.3 Hz and J' = 10.7 Hz), 6.00 (1H, s), 6.19 (1H, m), 7.31 (1H, m), 7.34 (1H, m); ^{13}C NMR δ 8.96 (2), 18.19, 25.97 (3), 26.71, 28.49, 31.03, 35.92, 38.51, 54.52, 57.20, 81.11, 112.09, 120.06, 126.98, 142.16 (2), 191.39, 207.13; MS *m*/*z* (relative intensity) 374 (10, M$^+$), 220 (36), 205 (100), 177 (11), 145 (14), 105 (11), 91 (28), 78 (39), 67 (21), 57 (69), 55 (47).

(1*RS*,7*SR*,7a*RS*)-1-(3-Furyl)-7-hydroxy-4,4,7a-trimethyl-2,4,5,6,7,7a-hexahydro-1*H*-inden-2-one (23). A solution of ketone **22** (30 mg, 0.08 mmol) and Bu_4NF (76 mg, 0.24 mmol) in THF (0.5 mL) was stirred at room temperature for 8 h. Aqueous saturated solution NH_4Cl was then added, and the resulting mixture was extracted with ether. The combined extracts were washed with brine, dried (Na_2SO_4), and filtered. The solvent was removed to give a residue which was flash chromatographed using hexane−ether (1:1) as eluant to yield the indenone **23** as a crystalline solid (19 mg, 90%): mp 125 °C; IR 3453, 1687, 1602, 1033 cm^{-1}; ^{1}H NMR δ 1.13 (3H, s), 1.27 (3H, s), 1.28 (3H, s), 3.16 (1H, s), 3.90 (1H, dd, J = 4.4 Hz and J' = 10.4 Hz), 6.13 (1H, s), 6.25 (1H, m), 7.35 (2H, m) ppm; ^{13}C NMR δ 18.04, 26.22, 26.87, 30.88, 37.77, 39.78, 53.83, 57.09, 77.42, 109.95, 124.80, 126.99, 140.71, 143.49, 191.78, 205.89 ppm; MS *m*/*z* (relative intensity) 260 (54, M$^+$), 227 (76), 203 (44), 186 (70), 175 (39), 161 (61), 147 (24), 128 (34), 115 (50), 91 (82), 77 (100), 55 (51), 55 (94). Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.89; H, 7.77.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of compounds **10**, **13**, **14a**, **14b**, **15a**, **15b**, **25a**, **25b**, **26a**, **26b**, **27a**, **27b**, **31**, and **32** and the NOE experiment of the compound **32** (32 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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