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Model Insect Antifeedants. Synthesis of Azadiradione Fragments through Acyl Radicals Cyclizations and Stannane Coupling Reactions

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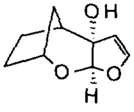
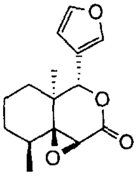
***Abstract*:** A diastereoselective and versatile synthesis of the model insect antifeedant **16** related to azadiradione has been achieved in nine steps starting from α-cyclocitral **1**. The key steps involve intramolecular alkene addition of an acyl radical and a Stille coupling reaction of a vinyl iodide with a stannylfuran.

Model compounds based on the C, D and associated furan rings of bioactive limonoids in some instances exhibit the same activity as archetypes. These are the cases of the insect antifeedant activity of the hydroxy furan acetal fragment of azadiradachtin[1] **I** and the bicyclic lactone related to limonin[2] **II**. We have found that model compounds related to azadiradione **III** and epoxyazadiradione **IV** are active insect antifeedants[3]. Surprisingly the epoxyketone **IV** is also a very active anti-HIV agent "in vitro" whose absence of cytotoxicity is very interesting[4].



I



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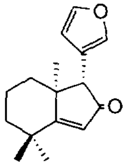

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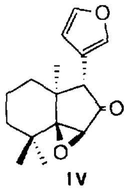
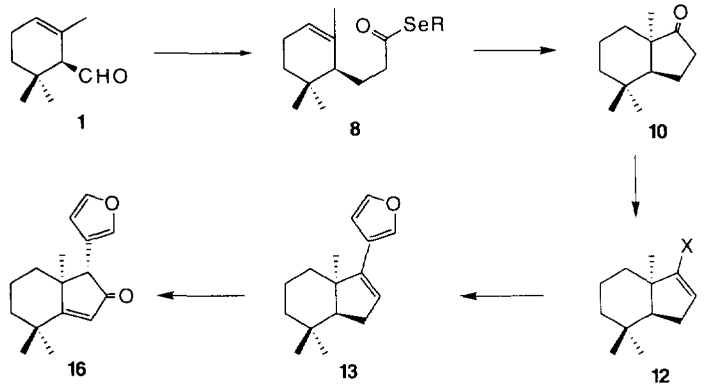


IV

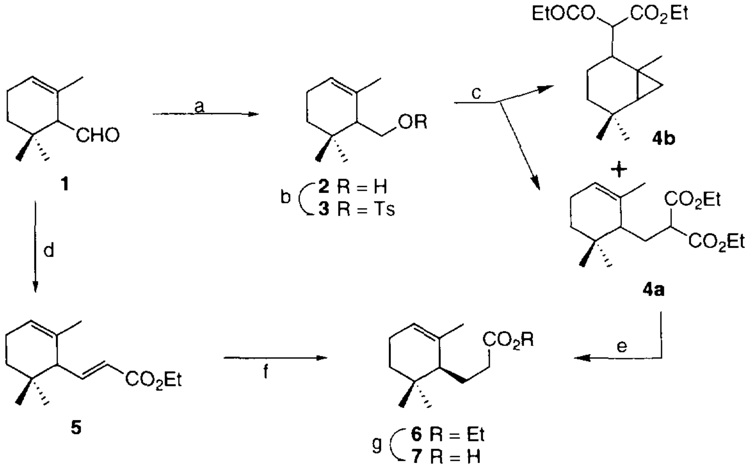
Recently, we started a program for the synthesis of model compounds of azadiradione and related limonoids, that contain only part of the skeleton and funcionality. We have been interested in developing short, efficient and versatile routes to compounds resembling the C, D, E portion of azadiradione[5] which can be used to probe structure-activity relationships.

The new strategy we have developed for the synthesis of model compounds is shown in scheme 1. The key steps of the stereoselective synthesis are intramolecular alkene addition of an acyl radical and a Stille type coupling of a vinyl iodide with a stannylfuran.



Scheme 1

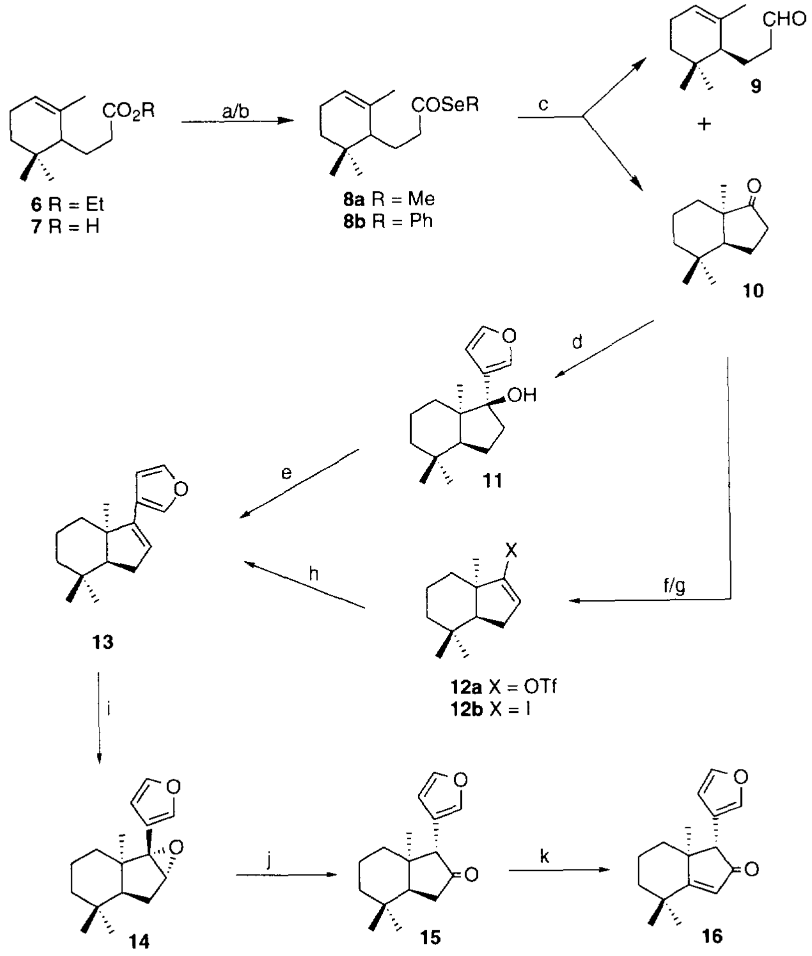
The ester **6**, the precursor of the selenoester **8**, which is the substrate of the intramolecular cyclization, was obtained from α-cyclocitral **1**[6] by two different methods (Scheme 2). Method A: Reduction of α-cyclocitral **1** with $LiAlH_4$ in ether followed by tosylation and nucleophilic displacement with malonate anion in refluxing toluene afforded a 6:4 mixture of diesters **4a** and **4b** in 72% yield[7]. Desethoxycarbonylation of diester **4a** by the Krapcho method[8] afforded the monoester **6** in 81% yield. The abnormal results obtained in the displacement of α-cyclogeranyl tosylate **3**, lowering the expected yield of **6**, prompted us to follow another method to obtain the selenoester **8**. Method B: Wadsworth-Emmons olefination[9] of aldehyde **1** in benzene at room temperature afforded the unsaturated ester **5** in 90% yield. Selective hydrogenation of the conjugated double bond to yield **6** quantitatively was accomplished with Pd/C (5%) in ethyl acetate and added diethylamine[10]. In the absence of the amine, a mixture of mono and dihydrogenated products was obtained.



(a) $LiAlH_4$, ether, 0ºC; (b) TsCl, Pyr., CH_2Cl_2; (c) $CH_2(CO_2Et)_2$, Na, toluene,reflux; (d) $(EtO)_2POCH_2CO_2Et$, NaH, benzene; (e) NaCl, H_2O, DMSO, reflux; (f) H_2, Pd/C, Et_2NH, AcOEt; (g) KOH, EtOH, H_2O, 50ºC.

Scheme 2

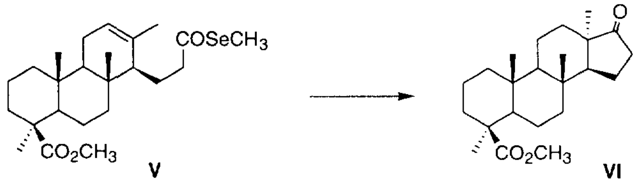
From ester **6** we obtained the methyl selenoester **8a** and the phenyl selenoester **8b** following the methods of Sviridov[11] and Crich[12], respectively. Treatment of the ester **6** with $Me_2Al(SeMe)$ in dichloromethane at room temperature afforded the methyl selenoester **8a** in almost quantitative yield (Scheme 3). The hydrolysis of ethyl ester **6** to afford the carboxylic acid **7**, followed by treatment first with triehylamine and then by PhSeCl and tributyl phosphine, produced the expected selenoester **8b** in 73% yield from ester **6**.

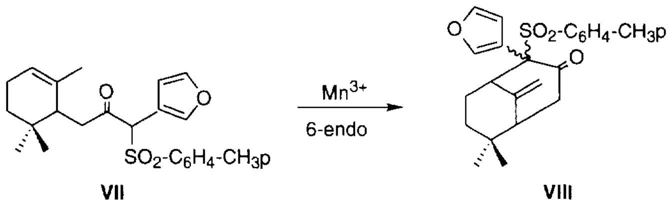


(a) $(CH_3)_2Al(SeCH_3)$, CH_2Cl_2, 0ºC; (b) (i)Et_3N, CH_2Cl_2; (ii) Bu_3P, PhSeCl, THF, 20ºC; (c)Bu_3SnH AIBN, benzene, reflux; (d) 3-Furyl-Li, $CeCl_3$, THF, -78ºC; (e) $SOCl_2$, pyridine, CH_2Cl_2, 0ºC; (f) 2,6-di-tert-butyl-4-methyl-pyridine,Tf_2O, CH_2Cl_2, 20ºC; (g) (i) $N_2H_4.H_2O$, Et_3N, EtOH, reflux; (ii) I_2, Et_3N, THF, 20ºC; (h) LiCl, Pd-$(PPh_3)_4$, Bu_3(3-furyl)-Sn, THF, reflux; (i) m-CPBA, CH_2Cl_2, -40ºC; (j) $BF_3.Et_2O$, CH_2Cl_2, 0ºC; (k) (i) LDA, PhSeCl, THF; (ii) H_2O_2 30%, THF.

Scheme 3

Treatment of phenyl selenoester **8b** with tri-n-butyltinhydride afforded (54% yield) the aldehyde **9** and the ketone **10** in 1:4 yield, respectively. This result contrasts with the finding reported by Boger[13], who observed that intramolecular alkene addition reactions of 5-hexenyl radicals bearing alkyl substitution at the 5-position result in preferential 6-endo cyclization. This regioselectivity has been attributed to the kinetic deceleration of 5-exo-trig due to steric effects and by acceleration of 6-endo-trig cyclization due to radical stability. Our case is clearly an exception to Boger's experience. Formation of the aldehyde **9**, the product from selenoester reduction which has not been found in previous work[13], is in this case a competitive reaction. We confirmed the 5-exo-trig regioselectivity found in the cyclization of selenoester **8b** by repeating, with the same results, the reaction with the rigid tricyclic selenoester **V**, to yield the ketone **VI**[14]. The 5-exo-trig cyclization preference found for the acyl radicals derived from selenoester **8b** and **V** is the same as that reported by Stork[15] with allyl and vinyl radicals. However, the alkyl radical generated from **VII** by Mn (III) afforded only one product **VIII** resulting from 6-endo-trig cyclization[16]. Few differences in the reactivity (yield 54%, ketone **10**: aldehyde **9** ratio 7:3) with respect to phenyl selenoester **8b** were found in the treatment of the methyl selenoester **8a** with tri-n-butyltin hydride.





The preparation of ketone **10** (Scheme 3) defines a simple synthetic procedure which may eventually be employed in the synthesis of many indanones[17].

Insertion of a furyl ring in the indanone nucleus was attempted by nucleophilic addition of 3-furyllithium[18] to ketone **10** with negative results; unchanged starting material was recovered. The substitution of the organolithium reagent for a dichlorocerate[19] gave the alcohol **11** in 75% yield. Unfortunately, this procedure fails when applied to sterically hindered ketones such as **VI**. The stereochemistry of the furylalcohol **11** was assigned on the basis of the preferential attack of the organometallic reagent from the less sterically hindered α face of the ketone **10**. Dehydration of alcohol **11** with thionyl chloride afforded the alkene **13**[19b] in 90% yield (Scheme 3).

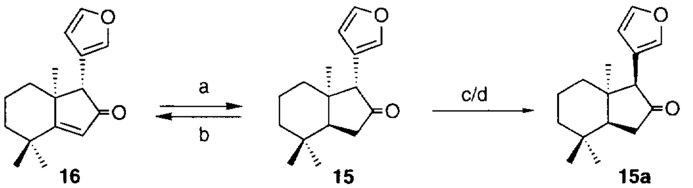
The lack of general applicability of the insertion procedure due to the low reactivity of the organocerium reagent and other reasons, such as incompatibility with other functions (esters, alcohols, etc) in polyfunctional molecules, handling difficulties, etc., led us to approach a more selective method, like a Stille coupling reaction.

A partner for the coupling reaction would be the enol triflate **12a** or the vinyl iodide **12b** (Scheme 3), and the other partner the tributyl-(3-furyl)tin[20]. Preparation of enol triflate **12a** was accomplised from the ketone **10** by the established procedures[21] in 77% yield. The vinyl iodide **12b** was obtained from the ketone 10 following the Barton's procedure[22] in 95% yield.

The coupling reaction of enol triflate **12a** or vinyl iodide **12b** and tributyl-(3-furyl)-tin was carried out in THF under reflux using tetrakis(triphenylphosphine) palladium (0) as a catalyst to give the indene **13** in 86% and 84% yield respectively.

The cyclopentene **13** was next epoxidized stereoselectively with *m*-CPBA in dichloromethane at -30 °C to give the epoxide **14** almost quantitatively. An α configuration was assigned to oxyranic oxygen assuming that the β face is more sterically hindered to the peracid approach. Another argument in favour of the α-orientation of the epoxide is the upfield shift of the ^{13}C NMR signal for the homoallylic carbon bearing an axial proton cis to the oxygenated function of the epoxide **14** (47.78 ppm) when compared to unsaturated precursor **13** (56.79 ppm)[3].

The epoxide **14** in dichloromethane with boron trifluoride etherate afforded only the ketone **15**[23] in almost quantitative yield. Treatment of **15** with either pTsOH in benzene or $NaOCH_3$ in CH_3OH afforded the isomer **15a**[19b] quantitatively. Dehydrogenation of the ketone **15** was carried out by sequential reaction with LDA followed by phenylselenyl chloride, oxidation with hydrogen peroxide and selenoxide elimination[24] to afford the CDE azadiradione fragment **16** in 45% yield. The enone **16** was chemically correlated with epoxy ketone **IV** whose structure has been determined by X ray diffraction analysis[4].



(a) H_2, Pd (C) 10%, EtOH; (b) (i) LDA, PhSeCl, THF; (ii) H_2O_2 30%, THF; (c) NaMeOH, MeOH, 0ºC;(d) pTsOH, benzene, reflux.

The short and versatile synthesis developed in this work is currently being applied to tetracyclic analogs.

Experimental

General Methods. Commercial reagents were used as received. Dichloromethane, pyridine, diethylamine, diisopropylamine and dimethyl sulphoxide were distilled under nitrogen from calcium hydride or BaO. Ether, tetrahydrofuran, toluene and benzene 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. 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 presure with the aid of a rotary evaporator.

α-Cyclogeraniol 2. $LiAlH_4$ (1.37 g, 36 mmol) was added to a solution of α-cyclocitral **1** (10 g, 65.8 mmol) in dry ether (100 ml) at 0°C. The mixture was allowed to stir at room temperature. The reaction was stirred under N_2 at this temperature for 30 min. and quenched by the addition of $Na_2SO_4 \cdot 10\ H_2O$ (1.16 g, 3.6 mmol). The mixture was then stirred for 20 min. at 25°C and filtered. Removal of solvent afforded a crude oily product which was identified as the α-cyclogeraniol **2** (9.8 g, 97% yield): IR 3000 and 2975 cm^{-1}; ^1H NMR δ 0.87 (3H, s), 1.01 (3H, s), 1.74 (3H, s), 3.71 (2H, d, J=6 Hz) and 5.58 (1H, s); ^{13}C NMR δ 22.72, 22.83, 27.56 (2), 31.62, 32.38, 52.09, 61.42, 123.98 and 132.07; MS m/z (relative intensity) 154 (32, M^+), 139 (42), 121 (100), 93 (98), 79 (80), 69 (76) and 55 (92).

Cyclogeranyl *p*-toluenesulfonate 3. To a stirred solution of the α-cyclogeraniol **2** (9.8 g, 63.7 mmol) in pyridine (32 ml) at 0°C, *p*-toluensulphonyl chloride (18.6 g, 95.4 mmol) was gradually added. After 48 h at 0 °C, the mixture was poured into ice-water and stirred for an additional 30 minutes at room temperature. The two phase system was extracted with ether. The combined ethereal extracts were washed with aqueous HCl (2N), $NaHCO_3$ (5%) and brine, dried, filtered and evaporated to yield the cyclogeranyl *p*-toluenesulfonate **3** as a viscous oil (19.6 g, 100% yield): ^1H NMR δ 0.85 (3H, s), 0.88 (3H, s), 1.57 (3H, s), 2.44 (3H, s), 4.01 (2H, m), 5.43 (1H, br s), 7.32 (2H, d, J 8.2 Hz), 7.77 (2H, d, J 8.2 Hz).

Ethyl 2-ethoxycarbonyl-3-(2,6,6-trimethyl-2-cyclohexenyl)-propanoate 3.- To a solution of sodium diethyl malonate, prepared from sodium (1.2 g, 52.2 mmol) and diethyl malonate (9 g, 56.5 mmol) in toluene (126 ml), was added a solution of the tosyl compound **3** (11.6 g, 37.7 mmol) in toluene (103 ml). After 24 h reflux the mixture was cooled, the solid was filtered off, and the filtrate was evaporated. The residue was chromatographed on silica gel using hexane-ether (95-5) as the eluting solvent.

The first fraction (4.79 g, 43%) was a colorless oil identified as the unsaturated diester **4a**: ^1H NMR δ 0.81 (3H, s), 0.88 (3H, s), 1.18 (6H, t, J 7 Hz), 1.62 (3H, s), 3.42 (1H, t, J 6 Hz), 4.12 (4H, q, J 7 Hz), 5.24 (1H, broad s); ^{13}C NMR δ 168.73, 168.73, 135.36, 120.54, 60.59, 60.59, 52.07, 46.37, 32.28, 30.47, 29.77, 26.88, 26.87, 22.80, 22.54, 13.61, 13.61.

The second fraction (3.24 g, 29%) was a colorless oil identified as the saturated diester **4b**: ^1H NMR δ 0.12 (1H, dd, J 5 Hz and J' 9.3 Hz), 0.25 (1H, dd, J 5 Hz and J' 5.7 Hz), 0.42 (1H, dd, J 5.7 Hz and J' 9.3 Hz), 0.86 (3H, s), 1.06 (6H, s), 1.26 (3H, t, J 7 Hz), 1.27 (3H, t, J 7 Hz), 3.47 (1H, d, J 8 Hz), 4.17 (2H, q, J 7 Hz), 4.18 (2H, q, J 7 Hz); ^{13}C NMR δ 169.23, 169.23, 60.88, 60.88, 55.27, 38.92, 34.57, 32.94, 31.97, 29.06, 28.20, 27.24, 21.43, 19.34, 13.98, 13.98, 13.19.

Ethyl 3-(2,6,6-trimethyl-2-cyclohexenyl)-propanoate 6.- To a solution of the diester **4a** (1.99 g, 6.70 mmol) in DMSO (6.7 ml) were added water (0.24 ml, 13 mmol) and sodium chloride (0.76 g, 13 mmol). The suspension was refluxed for 22 h under N_2, after which it was diluted with ethyl acetate (65 ml). The solution was washed with brine, dried (Na_2SO_4), and evaporated to afford the unsaturated ester **6** as a colorless oil (1.22 g, 81%): 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, broad 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.

Ethyl 3-(2,6,6-trimethyl-2-cyclohexenyl)-2-propenoate 5.- 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 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 1h 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, 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 **5** as a colorless oil (13.2g, 90%): IR 1715 cm^{-1}; ^{1}H 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 6.- To a solution of **5** (1g, 4.46 mmol) in ethyl acetate (9 ml), and diethylamine (1 ml) was added 250 mg of 10% Pd on carbon. This stirred mixture was blanketed with hydrogen (1 atm). After 165 min the catalyst was removed by filtration and the filtrate was evaporated to give the ester **6** (1 g, 100%).

3-(2,6,6-Trimethyl-2-cyclohexenyl)-propanoic acid 7.- The ester **6** (2g, 8.93 ml) was heated at 50 °C for 1 h in a mixture of ethanol (25 ml) and water (3.6 ml) containing potassium hydroxide (1.04 g, 18.61 ml). After cooling and solvent removal, the residual solid was dissolved in water, acidified with 2N-hydrochloric acid, and the solution was extracted with ether. The extract was washed with brine, dried (Na_2SO_4), filtered, and evaporated to afford the acid **7** as a viscous colorless oil (1.68 g, 96%): IR 3400-3200, 1703 cm^{-1}; ^{1}H NMR δ 0.89 (3H, s), 0.93 (3H, s) 1.67 (3H, s), 5.35 (1H, br s). Anal. Calcd. for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.47; H, 10.25.

4,4,7a-Trimethyl-perhydroindan-1-one 10.-

Procedure A.- (1) Methyl selenoester 8a. Nitrogen was bubbled for 25 min through a stirred solution of ethyl ester **6** (700 mg, 3.12 mmol) in CH_2Cl_2 (17 ml). The solution was cooled to 0 °C, and an aliquot of $(CH_3)_2Al(SeCH_3)$ solution (3.5 ml, ca. 2M in toluene) was added by syringe. After 30 min, the cold bath was removed, and after an additional 30 min the reaction was quenched with moist $Na_2S_2O_3$. After the generation of gas had ceased, the mixture was diluted with ether (100 ml) and washed with water and brine, and the organic layer was dried (Na_2SO_4). Filtration and solvent removal gave the methyl selenoester **8a** as a greenish viscous oil (853 mg, 100%).

(2) Cyclization the 8a.- A solution of methyl seleno ester **8a** (825 mg, 3.12 mmol), Bu_3SnH (1.65 ml, 6.24 mmol), and AIBN in benzene (156 ml) was heated at 85 °C for 90 min. The mixture was cooled, the solvent was removed, and the residue was purified by flash chromatography (hexane-ether, 90-10) to afford the aldehyde **9** as a colorless oil (91 mg, 16%): ^{1}H NMR δ 0.88 (3H, s), 0.95 (3H, s), 1.66

(3H, s), 5.35 (1H, br s), 9.74 (1H, m). Anal. Calcd. for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.91; H, 10.97; and the indanone **10** as a colorless oil (213 mg, 38%): IR 1741 cm^{-1}; ^{1}H NMR δ 0.84 (3H, s), 1.02 (3H, s), 1.14 (3H, s), 2.22 (2H, m); ^{13}C NMR δ 221.68, 52.97, 47.91, 35.42, 34.83, 31.15, 28.69, 28.47, 27.90, 22.47, 20.97, 17.89; MS m/z (relative intensity): 180 (10, M$^+$), 136 (9.6), 95 (25), 55 (52), 41 (100).

Procedure B.- (1) Phenyl selenoester 8b. To a stirred solution of acid **7** (1.68 g, 8.67 mmol) in dry CH_2Cl_2 (17.3 ml) under a nitrogen atmosphere at room temperature was added a solution of triethylamine (1.2 ml, 8.57 mmol) in CH_2Cl_2 (8.57 ml). The mixture was stirred for 10 min and then evaporated under reduced pressure to give the crude triethylammonium salt as a colourless oil. Tributylphosphine (2.13 ml, 8.57 mmol) was added with stirring at room temperature to a solution of PhSeCl (1.66 g, 8.57 mmol) in dry THF (13 ml) under a nitrogen atmosphere followed after 10 min by the triethylammonium salt in THF (21.6 ml). After complete consumption of the acid (12 h) the reaction mixture was poured onto diethyl ether. The organic layer was further washed with NaOH (5%), water, and brine. The ethereal solution was dried (Na_2SO_4), filtered and evaporated to give the phenyl selenoester **8b** as a greenish viscous oil (2.07 g, 73%): ^{1}H NMR δ 0.89 (3H, s), 0.95 (3H, s), 1.70 (3H, s), 5.40 (1H, br s), 7.2-7.7 (5H, m).

(2) Cyclization the 8b.- A solution of phenyl selenoester **8b** (1.73 g, 5.15 mmol) and AIBN in refluxing benzene (89 ml) was treated dropwise (syringe pump, 1h) with a solution of Bu_3SnH (1.5 ml, 5.66 mmol) in benzene (35 ml). The mixture was cooled, the solvent was removed, and the residue was purified by flash chromatography (hexane-ether, 90-10) to afford the aldehyde **9** (102 mg, 11%), and the indanone **10** (399 mg, 43%).

1-(3-Furyl)-4,4,7a-trimethyl-perhydroindan-1-ol 11.- A cold (-78 °C), magnetically stirred solution of n-butyllithium in hexane (1.29 ml of 1.6 M, 2.07 mmol) was treated dropwise under nitrogen with 3-bromofuran (247 mg, 1.68 mmol) dissolved in dry THF (4.2 ml). After 10 min, the mixture was added to a cold (-78 °C), magnetically stirred suspension of anhydrous $CeCl_3$ [from 0.83 g, 2.23 mmol, of the heptahydrate dried at 130 °C and 0.1 Torr for 3 h and stirred for 3 h in THF (6.9 ml)]. After this mixture had been stirred for 2 h at -78 °C, ketone **10** (100 mg, 0.56 mmol) in THF (0.5 ml) was introduced; stirring was maintained at -78 °C for 1h, and warming to 25 °C was allowed to proceed slowly. After cooling to 0°C, quenching was accomplished through addition of a saturated NH_4Cl solution. The product was extracted with ether and the combined organic layers were dried (Na_2SO_4) and evaporated. Chromatograpy of the residue on silica gel (hexane-ether, 90-10) gave the alcohol **11**[19b] as a pale yellow oil (104 mg, 75%): IR 3450 cm^{-1}; ^{1}H NMR δ 0.82 (6H, s), 0.93 (3H, s), 6.37 (1H, m), 7.30 (1H, m), 7.34 (1H, m); ^{13}C NMR δ 142.05, 138.92, 132.16, 110.24, 83.68, 51.07, 46.00, 37.35, 33.74, 32.19, 30.67, 28.88, 28.36, 23.16, 22.05, 19.10; MS m/z (relative intensity) 248 (6, M$^+$), 163 (3), 123 (25), 110 (100), 95 (37).

1-(3-Furyl)-4,4,7a-trimethyl-4,4a,5,6,7,7a-hexahydro-3H-indene 13 .- $SOCl_2$ (0.06 ml, 0.8 mmol) was added at 0 °C with stirring under N_2 to a solution of the corresponding hydroxy compound **11** (100 mg, 0.4 mmol) in dry CH_2Cl_2 (5 ml) and dry pyridine (0.13 ml, 1.6 mmol). The mixture was stirred at 0°C for 5 min and then poured into ice. The heterogeneous mixture was gradually warmed to room temperature. It was then extracted three times with CH_2Cl_2. The combined extracts were washed with aqueous HCl (2N), $NaHCO_3$ (5%), and brine and then dried (Na_2SO_4). The solvent was evaporated to give compound **13**^{19b} as a colorless oil (83 mg, 90%)): ^{1}H NMR δ 0.91 (3H, s), 1.08 (3H, s), 1.29 (3H, s), 2.23 (2H, m), 5.69 (1H, t, J 2.6 Hz), 6.41 (1H, m), 7.35 (1H, m), 7.38 (1H, m); ^{13}C NMR δ 146.10, 142.33, 138.12, 124.49 (2), 110.36, 56.79, 47.67, 35.49, 35.28, 33.44, 32.06, 30.96, 29.00, 25.35, 18.51.

4,4,7a-Trimethyl-4,4a,5,6,7,7a-hexahydro-3H-inden-1-yl triflate 12a .-

Method A.- A solution of ketone **10** (73 mg, 0.41 mmol) in THF (0.81 ml) was added to a solution of LDA (0.49 mmol) in THF (1.3 ml) at -78 °C and the resulting solution was stirred for 30 min. A solution of N-phenyltrifluoromethanesulfonimide (155 mg, 0.43 mmol) in THF (0.81 ml) was added, and the reaction was stirred at 0 °C for 30 min and 12 h at room temperature. After solvent removal at the rotary evaporator, the resulting residue was purified by chromatography on silica gel (pentane elution) to yield the enol triflate **12a** as a colorless oil (20 mg, 16%): ^{1}H NMR δ 0.88 (3H, s), 1.04 (3H, s), 1.21 (3H, s), 2.18 (3H, s), 5.52 (1H, m).

Method B.- A solution of the ketone **10** (50 mg, 0.28 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (98 mg, 0.48 mmol) in dry dichloromethane (2.1 ml) was treated with triflic anhydride (0.07 ml, 0.42 mmol) at 0 °C and stirred at room temperature for 24 h. The solvent was removed in vacuo and the residue combined with pentane. The solid was filtered off and washed with additional pentane. The organic solution was washed with 2N HCl, and then water until neutral, dried (Na_2SO_4), and evaporated. Chromatography of the residue on silica gel with pentane as eluent gave the enol triflate **12a** (40 mg, 77%), and the ketone **10** (20 mg).

1-(3-Furyl)-4,4,7a-trimethyl-4,4a,5,6,7,7a-hexahydro-3H-indene 13 .- To a slurry of LiCl (17 mg, 0.40 mmol) and Pd-(PPh_3)$_4$ (3 mg, 2.0 mol%) in THF (0.3 ml) was added a solution of enol triflate **12a** (40 mg, 0.13 mmol) and tri-nbutyl-(3-furyl)-tin (46.5 mg, 0.13 mmol) in THF (1 ml). This was heated under reflux for 10 h, cooled to room temperature, and diluted with pentane. The resulting solution was washed sequentially with water, 10% ammonium hydroxide, water, and brine. This solution was dried (Na_2SO_4), filtered through a small pad of silica gel and concentrated to yield the indene **13** (28 mg, 86%).

Synthesis of 1-iodo-4,4,7a-trimethyl-4,4a,5,6,7,7a-hexahydro-3H-indene 12b.-

(A) Hydrazone preparation.-A solution of the indanone **10** (105 mg, 0.58 mmol) in ethanol (2 ml) was treated with triethylamine (0.4 ml) and hydrazine hydrate (1 ml) and the solution was heated under reflux for 5 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 (90 mg, 80%): IR 3374, 2959, 2928, 2864, 1655, 1468, 1454, 1371 cm^{-1};^{1}H NMR δ 0.81 (3H, s), 1.03 (3H, s), 1.28 (3H, s).

(B) Vinyl iodide 12b.- A solution of the above hydrazone (90 mg, 0.46 mmol) in THF (3.1 ml) and triethylamine (0.65 ml) was treated with iodine until a slight excess was present (cessation of nitrogen evolution, brown colour not discharged) and then was added diethyl ether. The ethereal solution was washed successively with aqueous 2N 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 **12b** as a yellow oil (127 mg, 95%): ^{1}H NMR δ 0.82 (3H, s), 1.04 (3H, s), 1.29 (3H, s), 6.05 (1H, m).

1-(3-Furyl)-4,4,7a-trimethyl-4,4a,5,6,7,7a-hexahydro-3H-indene 13 .- To a slurry of LiCl (41 mg, 0.95 mmol) and Pd-$(PPh_3)_4$ (7.2 mg, 2.0 mol%) in THF (1 ml) was added a solution of vinyl iodide **12b** (89 mg, 0.31 mmol) and tri-nbutyl-(3-furyl)-tin (111 mg, 0.31 mmol) in THF (2.1 ml). This was heated under reflux for 10 h, cooled to room temperature, and diluted with pentane. The resulting solution was washed sequentially with water, 10% ammonium hydroxide, water and brine. This solution was dried (Na_2SO_4), filtered through a small pad of silica gel and concentrated to yield the indene **13** (60 mg, 84%).

1-(3-Furyl)-4,4,7a-trimethyl-1,2-epoxy-perhydroindene 14.- A solution of *m*-chloroperoxybenzoic acid (202 mg, 1.17 mmol) in dry CH_2Cl_2 (2 ml) was added dropwise at -40°C to a solution of the indene **13** (90 mg, 0.39 mmol) in dry CH_2Cl_2 (4 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 ether. 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 **14** as a colorless oil (90 mg, 94%): ^{1}H NMR δ 0.84 (3H, s), 1.03 (3H, s), 1.22 (3H, s), 3.42 (1H, s), 6.37 (1H, m), 7.35 (1H, m), 7.42 (1H, m); ^{13}C NMR δ 142.39, 141.00, 112.80, 110.60, 77.00, 62.10, 47.78, 46.00, 34.90, 34.00, 31.89, 30.97, 29.57, 28.97, 20.87, 18.37. Anal. Calcd. for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 78.61; H, 9.33.

1-(3-Furyl)-4,4,7a-trimethyl-perhydroinden-2-one 15.- To a solution of the epoxide **14** (90 mg, 0.36 mmol) in dry CH_2Cl_2 (25 ml) was added boron trifluoride-diethyl ether (0.05 ml) at 0°C and the reaction mixture was stirred for 5 min. Water was added and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 and the combined extract were washed with $NaHCO_3$ (5%) and brine and then dried (Na_2SO_4). Evaporation of the solvent afforded the ketone **15**[23a] as a colorless oil (81 mg, 90%): IR 2980, 1720 cm^{-1}; ^{1}H NMR δ 0.88 (6H, s), 0.99 (3H, s), 2.45 (2H, m), 3.28 (1H, s), 6.17 (1H, m), 7.23 (1H, m), 7.32 (1H, m); ^{13}C NMR δ 218.19, 142.81, 140.71, 119.22, 111.02, 55.71, 49.76, 42.39, 39.85, 37.17, 34.42, 32.37, 31.19, 26.56, 25.98, 18.35; MS m/z (relative intensity) 246 (52, M$^+$), 165 (55), 123 (100), 108 (92).

1-(3-Furyl)-4,4,7a-trimethyl-perhydroinden-2-one 15a.- A solution of the ketone **15** (32 mg, 0.13 mmol) in benzene (1 ml) was refluxed in presence of monohydrate p-toluensulfonic acid (3 mg, 0.016 mmol) for 3h. The cooled solution was diluted with ether and washed with a saturated aqueous solution of $NaHCO_3$ and brine, dried and evaporated to give the ketone **15a** as a colorless solid (32 mg, 100%): mp 78-79 °C; IR 2980, 1740 cm^{-1}; ^{1}H NMR δ 0.88 (3H, s), 1.17 (3H, s), 1.24 (3H, s), 2.32 (2H, m), 3.17 (1H, s), 6.20 (1H, m), 7.27 (1H, m), 7.39 (1H, m); ^{13}C NMR δ 18.33, 25.52, 28.83, 29.33, 31.35, 32.29, 33.51, 39.47, 42.30, 50.96, 62.08, 111.64, 119.20, 141.64, 142.44, 218.67; MS m/z (relative intensity) 246 (50, M$^+$), 123 (100), 108 (90), 81 (56). Anal. Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 78.06; H, 8.92.

1-(3-Furyl)-4,4,7a-trimethyl-2,4,5,6,7,7a-hexahydro-1H-inden-2-one 16.-To a cooled (-78 °C) solution of indanone 15 (68 mg, 0.27 mmol) in THF (0.8 ml) was added a solution of diisopropylamide (prepared from diisopropylamine (0.085 ml, 0.61 mmol) in THF (1.2 ml) and n-BuLi (0.35 ml, 0.55 mmol, 1.6 M). The reaction mixture was stirred for 30 min, and then a solution of phenylselenyl chloride (79.3 mg, 0.41 mmol) in THF (1.2 ml) was added dropwise. The resulting heterogeneous mixture was stirred and gradually warmed to room temperature. Quenching with aqueous satured NH_4Cl, the aqueous layer was extracted with ether, followed by successive washing of the combined organic layers with water and brine. Evaporation of the solvent afforded a residue which was dissolved in THF (1.5 ml). To this ice-cooled solution was then added 30% hydrogen peroxide (1 ml). The reaction mixture was stirred and gradually warmed to room temperature before addition of water. The heterogeneous mixture was extracted with ether, and the combined organic layers were washed with brine and dried (Na_2SO_4). Evaporation of the solvent give an oily yellow residue which was chromatographed on silica gel using hexane-ether (90-10) to yield the indenone **16**[3] as a colorless solid (30 mg, 45%): mp 86-87 °C; IR 3000-2900, 1700, 1605, 1460, 1380, 1160, 1020 and 870 cm^{-1}; ^1H NMR δ 1.00 (3H, s), 1.23 (3H, s), 1.26 (3H, s), 3.42 (1H, s), 5.96 (1H, s), 6.22 (1H, m), 7.39 (1H, m), 7.40 (1H, m); ^{13}C NMR δ 18.60, 24.82, 27.35, 31.07, 35.87, 39.36, 40.72, 48.11, 59.87, 111.25, 118.89, 125.13, 141.42, 142.55, 191.45, 205.74. Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.69; H, 8.20. Found: C, 78.68; H, 8.21.

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