Articles

Limonoid Model Insect Antifeedants. A Stereoselective Synthesis of Azadiradione C, D, and E Fragments through Intramolecular Diazo Ketone Cyclization

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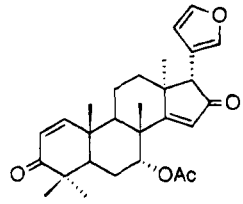
A stereoselective synthesis of model compound **18** of the insect antifeedant azadiradione has been accomplished starting from α-cyclocitral in 12 steps in 15% overall yield. The strategy for the synthesis is based on an intramolecular cyclopropanation of a diazo ketone and subsequent selective cleavage of a cyclopropyl ketone. Reactivity differences in the cleavage of the key cyclopropyl ketone **13** and its homolog **12** lacking the furyl ring are explored.

Introduction

The antifeedant activity of the limonoid azadiradione and related limonoids,[1] isolated from the Neem tree *Azadirachta indica* (A. Juss),[2] provides a promising opportunity for application to integrated pest management programs.[3]



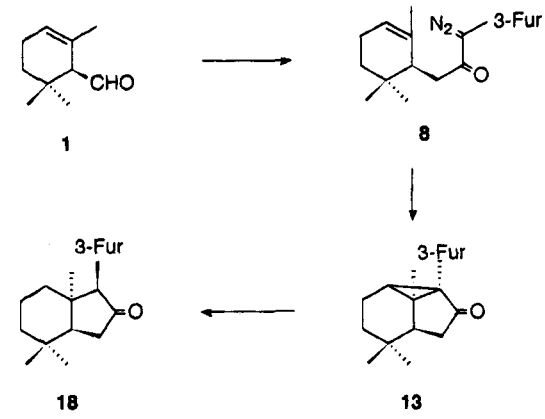
Azadiradione

The properties shown by these natural products have stimulated our interest in their synthesis and also in the preparation of simpler molecular fragments[4] which may display similar activity. A useful strategy for the synthesis of azadiradione and related limonoids would utilize a polycyclic cyclopropane derivative as a versatile synthetic intermediate. In this context, we explored a route that would allow for access to havanensin derivatives through the common cyclopropyl ketone **13** (Scheme 1). The strategy we have developed is based on the intramolecular cyclopropanation of a diazo ketone and selective cleavage of the resultant cyclopropyl ketone.

Results and Discussion

The first phase of the synthesis required the preparation of the diazo ketone **8**[5] (Scheme 2). Sequential coupling of sulfone **4a** with the aldehyde **3** afforded **5a** which was ultimately converted via oxidation, hydrogenation, and diazo transfer to **8**. In this case, the choice of the aldehyde was dictated by its superior nucleophilicity as compared to the corresponding methyl ester.

Scheme 1



The required aldehyde **3** was obtained by a four-step sequence from the readily available starting material cyclocitral **1**.[6] Reduction of **1** followed by mesylation and displacement by cyanide anion[7] furnished the nitrile **2**. This was then efficiently converted into the aldehyde **3** by reduction with DIBALH. The overall yield of this sequence was 69%.

Condensation[8] of the lithium derivative of sulfone **4a** with aldehyde **3** yielded a diastereomeric mixture of hydroxy sulfones **5a** in 58% yield along with a 2,3-disubstituted furyl compound (2%).[9] The sulfone **4a** was obtained from 3-furanmethanol, in a 66.5% overall yield,

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(1) (a) Kraus, W. Biologically active compounds from Meliaceae. In *Chemistry and Biotechnology of Biologically Active Natural Products*; Proceedings of the Second International Conference, Budapest, 15–19 August, 1983; Szántay, Cs., Ed.; Studies in Organic Chemistry. 17; Elsevier: Amsterdam, 1984; pp 331–345. (b) Champagne, D. E.; Koul, O.; Isman, M. B.; Scudder, G. E.; Towers, G. H. *Phytochemistry* **1992**, *31*, 377.

(2) (a) Taylor, D. A. H. *Prog. Chem. Org. Nat. Prod.* **1984**, *45*, 1. (b) Schmutterer, H. *Annu. Rev. Entomol.* **1990**, *35*, 271.

(3) (a) van Beek, T. A.; de Groot, A. *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 513. (b) Kulkarni, R. A. *Pure Appl. Chem.* **1986**, *58*, 917. (c) Jermy, T. *J. Chem. Ecol.* **1990**, *16*, 3151.

(4) (a) Mateos, A. F.; Blanco, J. A. *J. Org. Chem.* **1990**, *55*, 1349. (b) Mateos, A. F.; Blanco, J. A. *J. Org. Chem.* **1991**, *56*, 7084.

(5) The most obvious and simple access to diazo ketone would be the reaction of the acid chloride **10** with (3-furyl)diazomethane. Unfortunately, we were not able to achieve this reaction.

(6) (a) Gedye, R. N.; Aura, P. C.; Deck, K. *Can. J. Chem.* **1971**, *49*, 1764. (b) All compounds synthesized are racemic modifications, although only one enantiomer is depicted.

(7) Kaufman, T. S.; González Sierra, M.; Ruveda, E. A. *J. Chem. Soc., Perkin Trans 1* **1988**, 2323. The procedure reported by Cook et al. does not work: Cook, L. F.; Bowers, W.; Liotta, C. L. *J. Org. Chem.* **1974**, *39*, 3416.

(8) Kingsbury, C. A. *J. Org. Chem.* **1972**, *37*, 102.

(9) Paterson, I.; Gardner, M.; Bauks, B. J. *Tetrahedron* **1989**, 5283.

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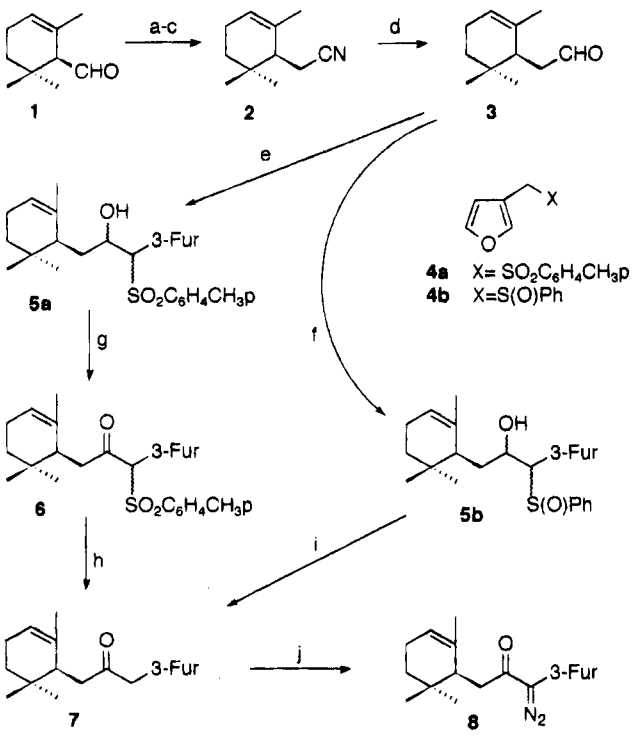
Scheme 2

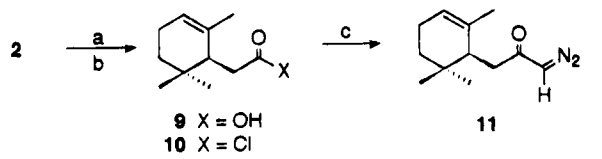


[a] (a) $LiAlH_4$, ether, 0 °C; (b) MsCl, pyridine, CH_2Cl_2, 0 °C; (c) NaCN, DMSO, 60 °C; (d) DIBALH, hexane, −30 °C; (e) (3-furyl)(*p*-toluenesulfonyl)methane (**4a**), *n*-BuLi, DME, −30 °C; (f) (3-furyl)(benzenesulfinyl)methane (**4b**), *n*-BuLi, THF, −30 °C; (g) Jones reagent, acetone, 0 °C; (h) Na(Hg) 6%, Na_2HPO_4, MeOH; (i) toluene, Na_2CO_3, 110 °C; (j) *p*-acetamidobenzenesulfonyl azide, DBU, CH_3CN, 0 °C.

by chlorination[10] and subsequent chloride displacement from the intermediate by *p*-toluenesulfinate.[11] Oxidation of hydroxy sulfones **5a** with Jones reagent at 0 °C afforded only the keto sulfone **6** in 90% yield; neither manganese dioxide nor Swern reagent worked. Reductive desulfurization of keto sulfone **6** was achieved by treatment with sodium amalgam in methanol[12] to provide the ketone **7** in 71% yield.

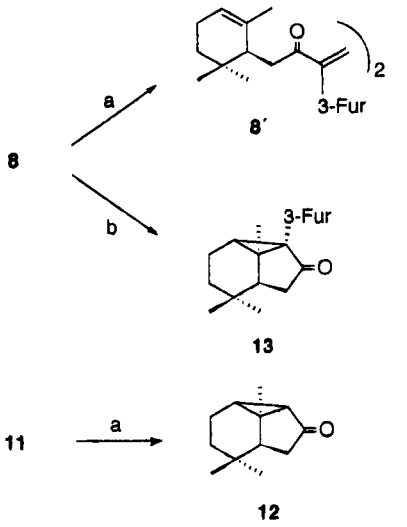
An alternative synthesis of ketone **7** from the aldehyde **3** involved coupling the sulfoxide **4b** with the aldehyde **3**, followed by dehydrosulfonylation of the diastereomeric hydroxy sulfoxide mixture **5b**. The required sulfoxide **4b** was obtained from 3-furanmethanol in three steps, bromination, displacement with thiophenoxide,[13] and selective oxidation with sodium metaperiodate,[14] in 54% overall yield. Deprotonation of **4b** with butyllithium at −30 °C in ether afforded the sulfinyl anion. Condensation[15] of this anion with aldehyde **3** was more effective (85%) than condensation with the anion of **4a** (58%), perhaps due to reduced steric hindrance. Dehydrosulfonylation[16] of the hydroxy sulfoxide mixture **5b** took place smoothly in refluxing toluene with added sodium carbonate to afford the ketone **7** in 62% overall yield from **3**.

Scheme 3



[a] (a) KOH, $(CH_2OH)_2$, reflux; H^+; (b) $(COCl)_2$, 0 °C; (c) CH_2N_2, ether, 0 °C.

Scheme 4



[a] (a) $Rh_2(OAc)_4$, CH_2Cl_2, 25 °C; (b) bis(*N-tert*-butylsalicylaldiminato)copper(II), toluene, 110 °C.

The diazo transfer reaction to ketone **7** failed with either tosyl azide or methanesulfonyl azide. However, using *p*-acetamidobenzenesulfonyl azide[17] and DBU in acetonitrile gave the diazo ketone **8** in 86% yield. The stability of furyl diazo ketone **8** was reasonably good in an ether solution at 0 °C, but significant decomposition occurred in the presence of weak acids such as SiO_2. Thus, column chromatography only afforded partial purification of diazo ketone **8**.

The cyclopropanation and subsequent cleavage of the cyclopropane ring, the second and third phases of the proposed synthesis (Scheme 1), were studied in a parallel way with the furyl diazo ketone **8** and its analog **11** lacking the furyl ring.

The diazo ketone **11** was prepared from the nitrile **2** in three steps (Scheme 3). Base hydrolysis of nitrile **2** gave the carboxylic acid **9** after acidification. The ^1H NMR spectrum of **9** suggests that the position of the trisubstituted double bond was not altered under the hydrolytic conditions used. Carboxylic acid **9** was treated with oxalyl chloride to produce the acid chloride **10** which, on exposure to diazomethane, afforded diazo ketone **11** in 78% overall yield.

Decomposition of diazo ketone **11** with rhodium acetate[18] led to the cyclopropyl ketone **12** (58%) (Scheme 4). Under the same reaction conditions, the furyl diazo ketone **8** afforded the "dimer" **8'** [19] instead of the desired cyclopropane derivative **13**. Treatment of **8** with bis(*N*-

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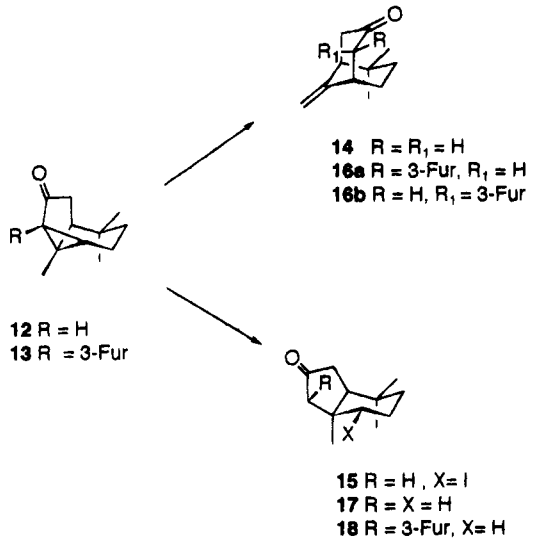
(11) Wildeman, J.; van Lensen, A. M. *Synthesis* **1979**, 733.
(12) Trost, B.; Arndt. H. C.; Strege, P. *Tetrahedron Lett.* **1976**, 3477.
(13) Herriot, A. W.; Picker, D. *Synthesis* **1975**, 447.
(14) (a) Leonard, N. J.; Johnson, C. R. *J. Org. Chem.* **1962**, *27*, 282. (b) Madesclaire, M. *Tetrahedron* **1986**, 5459.
(15) Kocienski, P. J.; Lithgoe, B.; Ruston, S. *J. Chem. Soc., Perkin Trans. 1* **1978**, 829.
(16) (a) Trost, B. M.; Salzman, T. N.; Kunio, H. *J. Am. Chem. Soc.* **1976**, *98*, 4887. (b) The base was necessary to neutralize the liberated sulfenic acid, which would cause damage to the furan ring.
(17) (a) Davies, H. M. L.; Clark, T. J.; Smith, H. D. *J. Org. Chem.* **1991**, *56*, 3817. (b) Regitz, M.; Hocker, J.; Liedhegener, A. *Organic Syntheses;* Wiley: New York, 1973; Collect. Vol. V, p 179.
(18) Paulissen, R.; Reimlinger, H.; Hayez, E.; Hubert, A. J.; Teyssie, Ph. *Tetrahedron Lett.* **1973**, 2233.
(19) Cane, D.; Pulikkottil, J. T. *J. Am. Chem. Soc.* **1984**, *106*, 5295.

Scheme 5



tert-butylsalicylaldiminato)copper(II)[20] as a decomposition catalyst provided the furyl cyclopropane **13** in 57% yield.

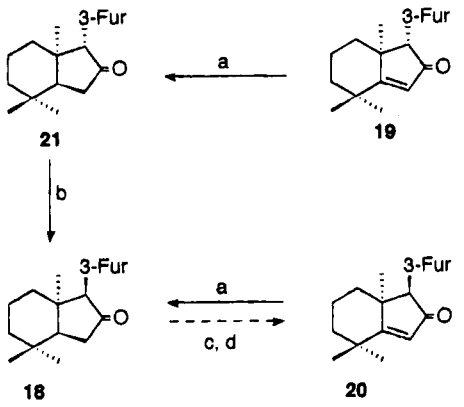
Ring cleavage of the cyclopropyl moiety in ketone **13** is the last phase of our proposed synthesis (Scheme 1). After the failure of the powerful nucleophiles PhSeNa and PhSNa,[21] we attempted to promote cleavage in both cyclopropyl ketones using Me_3SiI which has been very effective in the ring cleavage reaction of analogous substrates.[22] While the ketone **12** afforded a mixture of unsaturated ketone **14** and iodo ketone **15** in a ratio of 45:55 (63% yield), the furyl ketone **13** furnished a mixture of the unsaturated ketones **16a** and **16b** in 66% yield (Scheme 5). The observed selectivity in the latter cleavage may be attributed to the larger steric requirements of the furyl ring compared to the hydrogen atom.

Reductive opening of cyclopropyl ketones **12** and **13** with lithium in liquid ammonia at −40 °C was chemo- and stereospecific,[23] providing the ketones **17** and **18**, respectively (Scheme 5). This reduction is presumably governed by stereoelectronic effects. Because of geometric constraints, the overlap between the C_1-C_2 bond and the π system of the carbonyl group is minimal, whereas the C_2-C_9 bond is favorably aligned with the π system, resulting in the exclusive cleavage of the C_2-C_9 bond in both ketones.

The trans orientation of the methyl group with respect to the furyl substituent in the ketone **18** was determined by comparison with the hydrogenation products from the ketones **19** and **20**.[4] Hydrogenation of the enone **19** afforded the ketone **21** which was correlated with **18** by treatment with methanolic sodium methoxide at 0 °C (Scheme 6). Ketone **18** could be converted to enone **20** by sequential reaction with LDA followed by phenylselenyl chloride, oxidation with hydrogen peroxide, and elimination of selenoxide.[24]

The synthesis developed in this work with "molecular fragments" of limonoids is sufficiently versatile to access limonoids and analogs.

Scheme 6



[a] (a) Pd/C, 10%, AcOEt, H_2, rt; (b) NaMeO, MeOH, 0 °C; (c) LDA, PhSeCl, THF, −78 °C; (d) H_2O_2, THF, 0 °C.

Experimental Section

General Methods. Commercial reagents were used as received. Acetonitrile, dichloromethane, pyridine, diglyme, and dimethylformamide were distilled under nitrogen from calcium hydride. Ether, tetrahydrofuran, toluene, benzene, and 1,2-dimethoxyethane were distilled from sodium. Hexane was 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. $LiAlH_4$ (2.06 g, 54.2 mmol) was added to a solution of α-cyclocitral **1** (15 g, 98.7 mmol) in dry ether (75 mL) at 0 °C. The mixture was allowed to stir at room temperature. The reaction mixture was stirred under N_2 at this temperature for 30 min, and the reaction was quenched by the addition of $Na_2SO_4 \cdot 1\ H_2O$ (1.75 g, 5.4 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[25] (15 g, 98% yield): IR 3000, 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), 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, 132.07; MS *m/z* (relative intensity) 154 (32, M^+), 121 (100), 55 (92).

Cyclogeranyl Methanesulfonate. To a stirred solution of the α-cyclogeraniol (13.6 g, 88.3 mmol) in dichloromethane (50 mL) and pyridine (50 ml) at 0 °C was gradually added a solution of methanesulfonyl chloride (20.3 g, 177 mmol). After 13 h at room temperature, 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, filtered, and evaporated to yield the cyclogeranyl methanesulfonate as a light colorless oil (18.4 g, 90% yield): IR 1375, 1185 cm^{-1}; ^1H NMR δ 1.00 (3H, s), 1.10 (3H, s), 1.80 (3H, s), 2.90 (3H, s), 4.30 (2H, m), 5.50 (1H, m).

(2,6,6-Trimethyl-2-cyclohexenyl)acetonitrile (2). Sodium cyanide (6.3 g, 128.5 mmol) was added to a solution of cyclogeranyl methanesulfonate (10 g, 43.1 mmol) in dimethyl sulfoxide (60 mL). The mixture was heated for 5 h at 60 °C. After the mixture was cooled, water (200 mL) was added. Extraction with ether followed by washing, drying, and evaporation of the solvent with a Vigreux column left a viscous oil identified as the nitrile **2** (7.0 g, 99.7% yield): IR 2980, 2200 cm^{-1}; ^1H NMR δ 0.92 (3H, s), 1.00 (3H, s), 1.74 (3H, s), 2.40

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(21) Scarborough, R. M.; Toder, B. H.; Smith, A. B. *J. Am. Chem. Soc.* **1980**, *102*, 3904.
(22) (a) Miller, D. R.; Mc Kean, D. R. *J. Org. Chem.* **1981**, *46*, 2412. (b) Demuth, M.; Mikhail, G. *Tetrahedron* **1983**, 991.
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(24) Corey, E. J.; Hahl, R. W. *Tetrahedron Lett.* **1989**, *30*, 3023.
(25) Bouveault, M. L. *Bull. Soc. Chim. Fr.* **1910**, *7*, 354.

(2H, m), 5.51 (1H, m); ^{13}C NMR δ 17.35, 22.41, 26.53, 27.04 (2), 30.81, 32.01, 45.99, 119.83, 123.49, 132.12; MS *m/z* (relative intensity) 163 (8, M$^+$) 121 (100), 93 (68), 81 (62), 69 (60).

(2,6,6-Trimethyl-2-cyclohexenyl)acetaldehyde (3). To a solution of nitrile **2** (5 g, 30.7 mmol) in hexane (250 mL) at −30 °C was added a solution of diisobutylaluminum hydride (1 M) in hexane (35.3 mL) with stirring. After 3 h at room temperature, the solution was treated with saturated ammonium chloride (100 mL), and after an additional 20 min, 5% aqueous sulfuric acid (50 mL) was added. The two-phase system was extracted with ether. The extract was washed with brine, dried, filtered, and evaporated. Chromatography of the residue and elution with hexane−ether (8:2) produced the aldehyde **3** as a colorless oil (4 g, 78.5% yield): IR 2980, 1710 cm^{-1}; ^{1}H NMR δ 0.81 (3H, s), 0.93 (3H, s), 1.64 (3H, s), 5.40 (1H, m), 9.80 (1H, t, *J* = 2.4 Hz); ^{13}C NMR δ 22.46, 26.06 (2), 26.76, 31.39, 38.14, 43.51, 45.14, 121.61, 134.28, 202.83; MS *m/z* (relative intensity) 166 (2, M$^+$), 153 (4), 107 (60), 81 (100), 55 (32). Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.40; H, 10.73.

(3-Furyl)(*p*-toluenesulfonyl)methane (4a). To a suspension of sodium *p*-toluenesulfinate (6.4 g, 36.0 mmol) in 1,2-dimethoxyethane (40 mL) were added (3-furyl)chloromethane (4 g, 34.0 mmol)[10] and tetrabutylammonium bromide (0.55 g, 1.70 mmol). The mixture was heated under reflux for 8 h. After the mixture was cooled, ice−water (170 mL) was added and the near white precipitate was collected, washed with water and then with petroleum ether, and dried to give **4a** as a crystalline solid (7.64 g, 95% yield): mp 106−107 °C; IR 2980, 1450 cm^{-1}; ^{1}H NMR δ 2.42 (3H, s), 4.15 (2H, s), 6.30 (1H, m, H-β′), 7.21 (1H, m, H-α), 7.30 (2H, d, *J* = 8 Hz), 7.36 (1H, m, H-α′), 7.59 (2H, d, *J* = 8 Hz); ^{13}C NMR δ 21.58, 53.34, 111.58, 112.97, 128.53 (2), 129.61 (2), 135.09, 142.80, 143.33, 144.81; MS *m/z* (relative intensity) 236 (8, M$^+$), 81 (100), 53 (58). Anal. Calcd for $C_{12}H_{12}O_3S$: C, 60.99; H, 5.08; S, 13.57. Found: C, 60.92; H, 5.01; S, 13.48.

1-(3-Furyl)-1-(*p*-toluenesulfonyl)-3-(2,6,6-trimethyl-2-cyclohexenyl)propan-2-ol (5a). To a solution of **4a** (1.65 g, 7 mmol) in DME (21 mL) under nitrogen cooled to −30 °C was added *n*-butyllithium (1.6 M, 5.25 mL, 8.4 mmol) in hexane with stirring. After 25 min, aldehyde **3** (1.16 g, 7 mmol) was added. The mixture was stirred at −30 °C for 20 min. Then, saturated aqueous NH_4Cl (25 mL) was added, and the resulting mixture was gradually warmed to room temperature. Extraction with ether followed by washing, drying, and evaporation of the solvent left a crude oil which was separated by flash chromatography using hexane−ether (7:3) as the eluent. The first fraction eluted was an oily mixture of threo isomers **5aT** (1.04 g, 37%): IR 3250, 2980 cm^{-1}; ^{1}H NMR δ 0.77 (3H-3H′, s), 0.83 (3H-3H′, s), 1.58 (3H-3H′, s), 2.40 (3H-3H′, s), 3.96 (1H, d, *J* = 1.6 Hz), 3.99 (1H′, d, *J* = 1.6 Hz), 4.69 (1H, m), 4.79 (1H′, m), 5.20 (1H, m), 5.24 (1H′, m), 6.40 (1H′, m, H-β′), 6.43 (1H, m, H-β′), 7.23 (2H-2H′, d, *J* = 8 Hz), 7.33 (1H-1H′, m, H-α), 7.42 (1H-1H′, m, H-α′), 7.56 (2H-2H′, d, *J* = 8 Hz); ^{13}C NMR δ 21.50 (2), 22.93 (2), 23.69, 26.80′, 26.83, 27.00′, 27.38 (2), 30.61, 31.20′, 32.46 (2), 35.50′, 36.77, 45.10′, 45.35, 67.18, 67.20′, 68.40′, 68.60, 113.21 (2), 119.90 (2), 120.01, 121.00′, 128.77 (4), 129.48 (4), 134.50′, 134.57, 136.69 (2), 142.56 (2), 143.79 (2), 144.86 (2); MS *m/z* (relative intensity) 402 (4, M$^+$), 123 (100), 81 (100), 69 (35). The second fraction was a mixture of erythro isomers **5aE** (590 mg, 21%): IR 3250, 2980 cm^{-1}; ^{1}H NMR δ 0.80 (3H, s), 0.86 (6H′, s), 0.87 (3H, s), 1.66 (3H′, s), 1.72 (3H, s), 2.40 (3H-3H′, s), 3.99 (1H′, d, *J* = 8 Hz), 4.02 (1H, d, *J* = 8 Hz), 4.64 (1H-1H′, m), 5.20 (1H′, m), 5.26 (1H, m), 6.25 (1H, m, H-β′), 6.31 (1H′, m, H-β′), 7.04 (1H-1H, m, H-α), 7.20 (2H-2H′, d, *J* = 8 Hz), 7.32 (1H-1H′, m, H-α′), 7.64 (2H-2H′, d, *J* = 8 Hz); ^{13}C NMR δ 21.51, 22.94, 22.63, 26.54, 28.13, 29.61, 32.83, 37.48, 44.22, 69.25, 69.78, 110.60, 115.93, 119.48, 128.77 (2), 129.34 (2), 134.50, 137.28, 142.71, 143.38, 144.00; MS *m/z* (relative intensity) 402 (2, M$^+$), 139, 123 (100), 81 (100), 69 (35). The third compound was an oily product identified as 1-[2-[3-[(*p*-toluenesulfonyl)methyl]furyl]]-2-(2,6,6-trimethylcyclohexenyl)ethan-1-ol (**5c**) (56 mg, 2%): IR 3300, 2980, 1700 cm^{-1}; ^{1}H NMR δ 0.86 (3H, s), 0.93 (3H, s), 1.61 (3H, s), 2.43 (3H, s), 4.27 (2H, s), 4.80 (2H, t, *J* = 3 Hz), 5.28 (1H, m), 5.99 (1H, d, *J* = 1.9 Hz, H-β′), 7.26 (1H, d, *J* = 1.9 Hz, H-α′), 7.28 (2H, d, *J* = 8 Hz), 7.81 (2H, d, *J* = 8 Hz); ^{13}C NMR δ 21.62, 23.10, 23.46, 27.11, 27.38, 31.20, 32.51, 36.89, 45.20, 53.51, 66.90, 108.40, 112.62, 120.53, 128.65 (2), 129.78 (2), 135.24, 136.5, 136.76, 141.32, 145.00; MS *m/z* (relative intensity) 402 (4, M$^+$), 81 (94), 61 (100).

1-(3-Furyl)-1-(*p*-toluenesulfonyl)-3-(2,6,6-trimethyl-2-cyclohexenyl)propan-2-one (6). Jones reagent (1.57 mL) was added dropwise with stirring to a solution of **5a** (1.70 g, 4.2 mmol) in acetone (190 mL) at 0 °C. After the mixture was stirred for 15 min, 2-propanol was added in small portions to discharge a brown color in the upper layer. The mixture was concentrated in vacuo to afford a residue which was dissolved with water and extracted with ether. The organic layers were washed with brine, dried over Na_2SO_4, and filtered. Evaporation of the solvent left a crude oil which was purified by flash chromatography using hexane−ether (7:3) as the eluent to yield a viscous colorless oil identified as the ketone **6** (1.51 g, 90%): IR 2980, 1720 cm^{-1}; ^{1}H NMR δ 0.60 (3H, s), 0.84 (3H, s), 1.61 (3H, s), 2.39 (3H, s), 2.75 (2H, m), 5.20 (1H, s), 5.29 (1H, m), 6.40 (1H, m, H-β′), 7.19 (2H, d, *J* = 8 Hz), 7.30 (1H, m, H-α), 7.32 (1H, m, H-α′), 7.41 (2H, d, *J* = 8 Hz); ^{13}C NMR δ 21.57, 22.65, 22.99, 26.55, 26.78, 29.84, 37.50, 43.31, 46.90, 72.25, 111.20, 113.85, 114.00, 121.37, 128.80 (2), 129.20 (2), 135.17, 143.00, 143.30, 145.00, 200.20; MS *m/z* (relative intensity) 400 (10, M$^+$), 236 (68), 123 (98), 91 (100), 41 (50). Anal. Calcd for $C_{23}H_{28}O_4S$: C, 68.97; H, 7.04; S, 8.00. Found: C, 68.82; H, 7.02; S, 7.93.

1-(3-Furyl)-3-(2,6,6-trimethyl-2-cyclohexenyl)propan-2-one (7). Procedure A. To a stirred solution of **6** (1.0 g, 2.5 mmol) and anhydrous disodium hydrogen phosphate (1.42 g, 10 mmol) in dry methanol (250 mL) was added pulverized 6% sodium amalgam (3.75 g). The solution was then stirred for 7 h at room temperature. The solvent was evaporated, and the residue was poured over water (200 mL). The aqueous layer was extracted with ether, and the combined extracts were washed and dried. The solvent was evaporated, and the residue was purified by flash chromatography using hexane−ether (9:1) as the eluent. The yield of purified oily ketone **7** was 437 mg (71%): IR 2980, 1720 cm^{-1}; ^{1}H NMR δ 0.72 (3H, s), 0.88 (3H, s), 1.54 (3H, s), 2.25 (2H, m), 3.54 (2H, s), 5.3 (1H, m), 6.30 (1H, m, H-β′), 7.36 (1H, m, H-α), 7.37 (1H, m, H-α′); ^{13}C NMR δ 22.67, 22.85, 26.50, 26.64, 31.40, 31.98, 39.22, 43.38, 43.62, 111.36, 117.55, 121.00, 135.56, 140.43, 142.98, 193.30; MS *m/z* (relative intensity) 246 (18, M$^+$), 122 (85), 81 (100), 53 (34). Anal. Calcd for $C_{16}H_{22}O_2$: C, 78.00; H, 9.00. Found: C, 77.94; H, 8.92.

Procedure B. A solution of **5b** (810 mg, 2.18 mmol) in toluene (20 mL) and Na_2CO_3 (150 mg) was heated at 110 °C for 20 h. The mixture was then cooled, and the solvent was evaporated, yielding a crude product which was separated by flash chromatography using hexane−ether (9:1) as the eluent. The yield of purified **7** was 72.2% (387 mg).

(3-Furyl)bromomethane. A solution of PBr_3 (5 g, 18.5 mmol) in anhydrous ether (10 mL) was added dropwise to a solution of 3-furanmethanol (5 g, 51 mmol) in ether (50 mL) being stirred at 0 °C. After 30 min at 0 °C, the mixture was decanted. The organic layer was gradually cooled to −18 °C, and then an aqueous 35% potassium hydroxide solution (12.6 mL) was added. The ether layer was decanted and treated with solid potassium hydroxide. The solvent was removed in vacuo to yield (3-furyl)bromomethane (7.2 g, 87%) which was kept in ether at 0 °C under N_2 for use: IR 1500, 1100 cm^{-1}; ^{1}H NMR δ 4.34 (2H, s), 6.41 (1H, m, H-β′), 7.37 (1H, m, H-α), 7.44 (1H, m, H-α′).

(3-Furyl)(phenylthio)methane. Thiophenol (5 g), sodium hydroxide (3 g), water (50 mL), (3-furyl)bromomethane (5 g, 31 mmol), benzene (40 mL), and tetrabutylammonium bromide (100 mg) were combined and stirred vigorously with a mechanical stirrer for 12 h at room temperature. The organic layer was separated, washed with water, dried over sodium sulfate, and evaporated on a rotatory evaporator to give an oil. Distillation at reduced pressure afforded (3-furyl)(phenylthio)methane (4.9 g, 83%): ^{1}H NMR δ 3.95 (2H, s), 6.37 (1H,

m, H-β′), 7.22 (5H, m), 7.34 (1H, m, H-α), 7.35 (1H, m, H-α′); MS *m/z* (relative intensity) 190 (100, M^+), 109 (100), 81 (100), 65 (82).

(3-Furyl)(benzenesulfinyl)methane (4b). To sodium metaperiodate (5.6 g, 26 mmol) in water (100 mL) was added (3-furyl)(phenylthio)methane (4.9 g, 25.8 mmol). The mixture was stirred for 16 h at room temperature. The precipitated sodium iodate was removed by filtration, and the filtrate was extracted with methylene chloride. The combined extracts were washed with brine, dried, and evaporated, yielding a crude product which was separated by flash chromatography using hexane–ether (1:1) as the eluent. The first one eluted was a product identified as **4b** (4 g, 75%): ^{1}H NMR δ 3.87 (2H, s), 6.10 (1H, m, H-β′), 7.16 (1H, m, H-α), 7.20 (5H, m), 7.30 (1H, m, H-α′). Anal. Calcd for $C_{11}H_{10}O_2S$: C, 64.05; H, 4.89; S, 15.54. Found: C, 63.98; H, 4.82; S, 15.49. The second compound was a product identified as (3-furyl)(benzenesulfonyl)methane (740 mg, 12.9%).

1-(3-Furyl)-1-(benzenesulfinyl)-3-(2,6,6-trimethyl-2-cyclohexenyl)propan-2-ol (5b). A solution of sulfoxide **4b** (2 g, 9.7 mmol) in tetrahydrofuran (30 mL) was stirred and kept at −30 °C under N_2 during dropwise addition of *n*-butyllithium (1.6 M in hexane, 8.3 mL, 13.2 mmol). After a further 30 min, aldehyde **3** (1.2 g, 7.2 mmol) in THF (10 mL) was added dropwise. Stirring was continued at −30 °C for 30 min. Then, saturated aqueous NH_4Cl (6 mL) was added, and the resulting mixture was gradually warmed to room temperature. Extraction with ether followed by washing, drying, and evaporation of the solvent left a crude oil that was purified by flash chromatography using hexane–ether (1:1) as the eluent to yield a mixture of diastereoisomers **5b** (2.3 g, 86%): IR 3400, 2980 cm^{-1}; ^{1}H NMR (of threo isomer) δ 0.87 (3H, s), 0.91 (3H, s), 1.65 (3H, s), 3.50 (1H, d, J = 2 Hz), 4.65 (1H, m), 5.30 (1H, m), 6.03 (1H, m, H-β′), 7.21 (5H, m), 7.29 (1H, m, H-α), 7.38 (1H, m, H-α′); MS *m/z* (relative intensity) 372 (2, M^+), 123 (98), 81 (100).

1-Diazo-1-(3-furyl)-3-(2,6,6-trimethyl-2-cyclohexenyl)-propan-2-one (8). 1,8-Diazabicyclo[5.4.0]undec-7-enone (167 mg, 1.1 mmol) was added to a stirred solution of the ketone **7** (246 mg, 1.0 mmol) and *p*-acetamidobenzenesulfonyl azide (240 mg, 1.00 mmol) in acetonitrile (5 mL) at 0 °C. After being stirred for 2 h at 0 °C, the solution was treated with 2% sodium hydroxide solution (5 mL). The two-phase system was extracted with hexane–ether. The extract was washed with brine, dried, and evaporated, yielding a red oil identified as the α-diazo ketone **8** (234 mg, 86%). The crude oil in hexane may be kept at 0 °C under nitrogen for use: IR 2980, 2040, 1650 cm^{-1}; ^{1}H NMR δ 0.81 (3H, s), 0.92 (3H, s), 1.63 (3H, s), 5.40 (1H, m), 6.29 (1H, m, H-β′), 7.49 (2H, m, H-α, H-α′).

(2,6,6-Trimethyl-2-cyclohexenyl)acetic Acid (9). A solution of potassium hydroxide (4.8 g, 86 mmol) and the nitrile **2** (1.4 g, 8.6 mmol) in diethyleneglycol (50 mL), was heated for 40 h at 190 °C. After the mixture was cooled, water (100 mL) was added and the mixture was extracted with ether. The aqueous phase was acidified by dropwise addition of 2 N hydrochloric acid and extracted again with ether. The combined extracts were washed with brine, dried, filtered, and evaporated to yield the acid **9** as a viscous oil (1.35 g, 87%): IR 3350, 1700 cm^{-1}; ^{1}H NMR δ 0.91 (3H, s), 0.93 (3H, s), 1.67 (3H, s), 2.20 (2H, m), 5.29 (1H, m). Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.40; H, 9.84.

(2,6,6-Trimethyl-2-cyclohexenyl)acetyl Chloride (10). Carboxylic acid **9** (357 mg, 1.96 mmol) was dissolved in dry benzene (2 mL). Oxalyl chloride (0.56 mL) was added to the magnetically stirred solution under nitrogen dropwise at 0 °C. After 15 min at 0 °C, the mixture was allowed to stir at room temperature for 2 h. Benzene and oxalyl chloride (excess) were removed in vacuo to yield the acid chloride **10** as a colorless oil (393 mg, 100%): IR 2910, 1800 cm^{-1}.

1-Diazo-3-(2,6,6-trimethyl-2-cyclohexenyl)propan-2-one (11). A solution of the acid chloride **10** (392 mg, 1.95 mmol) in anhydrous benzene (3 mL) was added dropwise to a stirred solution of diazomethane (0.30 M in anhydrous ether, 16 mL) at 0 °C. After 15 min at 0 °C, the mixture was allowed to stir at room temperature for 2 h. Removal of the solvent left a red oil identified as the α-diazo ketone **11** (362 mg, 90%) which was used in the next reaction without further purification: IR 2980, 2040, 1650 cm^{-1}; ^{1}H NMR δ 0.82 (3H, s), 0.90 (3H, s), 1.64 (3H, s), 5.24 (1H, s), 5.35 (1H, m); ^{13}C NMR δ 22.54, 22.60 (2), 26.42 (2), 31.17, 31.90, 44.54, 53.59, 120.94, 135.22, 194.74.

1,6,6-Trimethyltricyclo[3.4.0.0^{2,9}]nonan-3-one (12). A solution of the α-diazo ketone **11** (362 mg, 1.75 mmol) in dry methylene chloride (3 mL) was added dropwise to a magnetically stirred suspension of dirhodium tetraacetate in methylene chloride (10 mL) under nitrogen at 25 °C. The solution was stirred for 20 min at room temperature. The solvent was evaporated, and the residue was purified by flash chromatography using hexane–ether 7:3 as the eluent to yield cyclopropane ketone **12** as a colorless oil (181 mg, 58%): IR 2980, 1710 cm^{-1}; ^{1}H NMR δ 0.81 (3H, s), 1.02 (3H, s), 1.38 (3H, s), 2.41 (2H, m); ^{13}C NMR δ 18.64, 23.88, 24.80, 27.71, 29.17, 30.43, 31.21, 34.85, 39.98, 44.35, 45.41, 185.82; MS *m/z* (relative intensity) 178 (80, M^+), 121 (100), 109 (79), 79 (82), 69 (80), 55 (48). Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.78; H, 10.07.

1,6,6-Trimethyl-2-(3-furyl)tricyclo[3.4.0.0^{2,9}]nonan-3-one (13). A solution of diazo ketone **8** (50 mg, 0.18 mmol) in toluene (7 mL) was added dropwise from a constant rate addition funnel to a stirred refluxing solution of bis(*N-tert*-butylsalicyladiminato)copper(II) catalyst (4.2 mg, 0.01 mmol) in toluene (7 mL) (total addition time, 2.5 h). The solution was cooled, concentrated, and purified by flash chromatography using hexane–ether (7:3) as the eluent. The yield of purified cyclopropane–ketone **13** was 57% (25 mg): IR 2980, 1720, 1610 cm^{-1}; ^{1}H NMR δ 0.86 (3H, s), 1.07 (3H, s), 1.24 (3H, s), 2.49 (2H, m), 6.19 (1H, m, H-β′), 7.28 (1H, m, H-α), 7.34 (1H, m, H-α′); ^{13}C NMR δ 18.19, 20.73, 24.82, 27.60, 29.31, 31.34, 34.67, 40.50, 43.22, 43.99, 45.27, 110.82, 121.31, 140.96, 142.85, 214.90; MS *m/z* (relative intensity) 244 (5, M^+), 112 (66), 69 (100), 57 (98). Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.70; H, 8.19.

6,6-Dimethyl-9-methylenebicyclo[3.3.1]nonan-3-one (14) and 4,4,7a-Trimethyl-7α-iodoperhydroindan-2-one (15). To a solution of **12** (54.0 mg, 0.3 mmol) in methylene chloride (4 mL) at −78 °C was added iodotrimethylsilane (0.1 mL, 140 mg, 0.7 mmoles). The solution was then stirred for 5 min at −78 °C. The solution was diluted with ether and washed with saturated Na_2SO_3 solution and brine. The organic phase was removed and dried. Solvent removal yielded a crude product which was separated by flash chromatography using hexane-ether (9:1) as the eluent. The first compound eluted was an oily product identified as **14** (15 mg, 28%): ^{1}H NMR δ 0.90 (3H, s), 0.94 (3H, s), 2.42 (4H, m), 4.78 (1H, d, J = 2 Hz), 4.89 (1H, d, J = 2 Hz); ^{13}C NMR δ 27.03, 28.52, 30.19, 31.20, 35.55, 39.34, 45.35, 48.61, 50.84, 108.02, 150.17, 211.16; MS *m/z* (relative intensity) 178 (8, M^+), 149 (92), 71 (65), 57 (100). Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.89; H, 10.09. The second oily compound was identified as **15** (33 mg, 35%): ^{1}H NMR δ 0.82 (3H, s), 1.17 (3H, s), 1.43 (3H, s), 2.05 (1H, d, J = 18.6 Hz), 2.49 (1H, d, J = 18.6 Hz), 4.14 (1H, dd, J = 12.6 Hz and J = 4.2 Hz); ^{13}C NMR δ 28.09, 28.67, 30.91, 32.25, 33.40, 36.46, 40.82, 42.66, 44.43, 52.42, 56.56, 216.32; MS *m/z* (relative intensity) 307 (8, M^+), 167 (60), 149 (100), 112 (38), 83 (45), 71 (78).

2-(3-Furyl)-6,6-dimethyl-9-methylenebicyclo[3.3.1]-nonan-3-one (16). To a solution of **13** (40 mg, 0.16 mmol) in methylene chloride (2 mL) at −78 °C was added iodotrimethylsilane (0.05 mL). The solution was then stirred for 5 min at −78 °C. The solution was diluted with ether, washed with saturated Na_2SO_3 solution and brine, dried, and evaporated, yielding a crude product which was separated by flash chromatography using hexane–ether (8:2) as the eluent. The yield of purified mixture of epimers **16a** and **16b** was 66% (26 mg): IR 2980, 1720 cm^{-1}; ^{1}H NMR δ 0.95 (3H, s), 0.96 (3H′, s), 0.98 (3H-3H′, s), 2.50 (2H-2H′, m), 3.50 (1H, d, J = 2 Hz), 3.70 (1H′, d, J = 4 Hz), 5.00 (2H-2H′, m), 6.32 (1H, m, H-β′), 6.37 (1H′, m, H-β′), 7.31 (1H, m, H-α), 7.38 (1H′, m, H-α), 7.40 (1H, m, H-α′), 7.60 (1H′, m, H-α′); ^{13}C NMR δ 24.72, 27.10, 28.40, 29.87′, 31.15, 31.36′, 35.71, 42.23, 44.74, 45.00′, 46.44′, 51.48, 51.59′, 52.70, 54.19′, 108.25, 110.50′, 110.04, 110.73′, 119.93, 128.82′, 139.39, 141.29′, 142.24, 142.68′, 1150.64, 206.69,

210.71'; MS *m/z* (relative intensity) 244 (50, M^+), 149 (100), 121 (70), 95 (80), 84 (45), 69 (72), 57 (82). Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.62; H, 8.18.

3a,7,7-Trimethylperhydroindan-2-one (17). Following the procedure described by Dauben et al.,[23] a solution of the cyclopropane ketone **12** (89 mg, 0.5 mmol) in ether (10 mL) was added to a solution of lithium (6 mg) in dry liquid ammonia. The solution was then stirred for 15 min at −40 °C. At the end of the reaction, a 100% excess of solid ammonium chloride was added. The ammonia was distilled, and 50 mL of distilled water was added. The ethereal layer was separated, the water layer was extracted with ether, and the extracts were combined. The ethereal solution was washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. Evaporation of the solvent left a crude oil which was purified by flash chromatography using hexane−ether (85:15) as the eluent. The yield of purified ketone **17** was 90% (81 mg): IR 2928, 2870, 1740 cm^{-1}; ^1H NMR δ 0.78 (3H, s), 1.05 (3H, s), 1.20 (3H, s), 2.06 (2H, s), 2.18 (2H, d, J = 9.4 Hz); ^{13}C NMR δ 18.54, 27.58, 29.05, 30.34, 32.02, 33.28, 33.89, 38.42, 41.12, 51.28, 55.96, 218.50. Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.91; H, 11.14.

1β-(3-Furyl)-4,4,7a-trimethylperhydroindan-2-one (21). To a stirred suspension of 10% palladium on carbon catalyst (11 mg) in ethyl acetate (0.4 mL) under H_2 was added at room temperature a solution of **19** (50 mg, 0.20 mmol) in ethyl acetate (0.20 mL) and NH_4OH (0.04 mL). Stirring was continued for 1 h. The catalyst was removed by filtration and washed with ethyl acetate. The filtrate was concentrated, and the residue was purified by chromatography on silica gel (elution with hexane−ether, 85:15) to give an oily product identified as the ketone **21** (47 mg, 95.5%): IR 2980, 1720 cm^{-1}; ^1H NMR δ 0.88 (6H, s), 0.99 (3H, s), 2.45 (2H, m), 3.28 (1H, s), 6.17 (1H, m, H-β'), 7.23 (1H, m, H-α), 7.32 (1H, m, H-α'); ^{13}C NMR δ 18.35, 25.98, 26.56, 31.19, 32.37, 34.42, 37.17, 39.85, 42.39, 49.76, 55.71, 111.02, 119.22, 140.71, 142.81, 218.19; MS *m/z* (relative intensity) 246 (52, M^+), 165 (55), 123 (100), 108 (92). Anal. Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 78.00; H, 8.87.

1α-(3-Furyl)-4,4,7a-trimethylperhydroindan-2-one (18). Procedure A. By the same procedure described above, a solution of the cyclopropane ketone **13** (100 mg, 0.41 mmol) in ether (10 mL) was added to a solution of lithium (6 mg) in dry liquid ammonia. The solution was then stirred for 15 min at −40 °C. At the end of the reaction, a 100% excess of solid ammonium chloride was added. The ammonia was distilled, and 50 mL of distilled water was added. The ethereal layer was separated, the water layer was extracted with ether, and the extracts were combined. The ethereal solution was washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. Evaporation of the solvent left a crude solid which was purified by flash chromatography using hexane−ether (85:15) as the eluent. The yield of purified ketone **18** was 70 mg (70%): mp 78−79 °C; IR 2980, 1740 cm^{-1}; ^1H NMR δ 0.88 (3H, s), 1.17 (3H, s), 1.24 (3H, s), 2.32 (2H, s), 3.17 (1H, s), 6.20 (1H, m, H-β'), 7.27 (1H, m, H-α), 7.39 (1H, m, H-α'); ^{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, 141.62, 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.

Procedure B. To a stirred solution of the ketone **21** (47 mg, 0.19 mmol) in methanol (3.8 mL) was added a solution of sodium methoxide in methanol (0.30 mL). After 1 h at room temperature, the mixture was concentrated in vacuo to afford a residue, which was dissolved with water and extracted with ether. The organic layers were washed with brine, dried over Na_2SO_4, and filtered. Evaporation of the solvent left a crude solid identified as the ketone **18** (43 mg, 91%).

Procedure C. To a stirred suspension of 10% palladium on carbon catalyst (11 mg) in ethyl acetate (0.4 mL) under H_2 was added at room temperature a solution of **20** (50 mg, 0.20 mmol) in ethyl acetate (0.20 mL) and NH_4OH (0.04 mL). After 1 h, the catalyst was removed by filtration and washed with ethyl acetate. The filtrate was concentrated, and the residue was purified by chromatography on silica gel (elution with hexane−ether, 85:15) to give ketone **18** as a white solid (47 mg, 94%).

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Supplementary Material Available: ^1H and ^{13}C NMR spectra of compounds **7**, **12**−**15**, **17**, **18**, and **21** and ^1H NMR spectrum of mixture **16** (17 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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