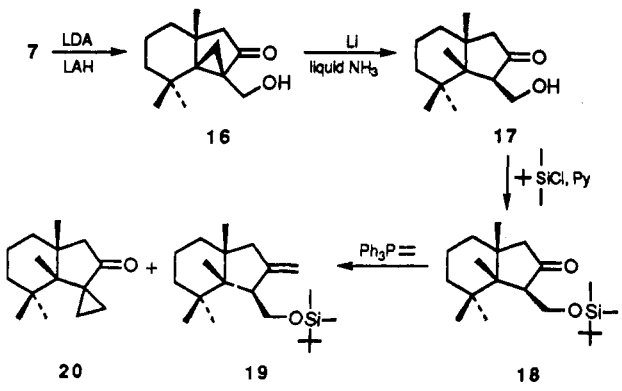
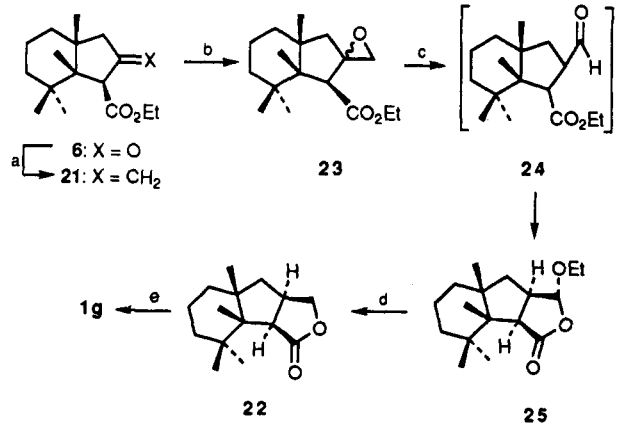
Scheme IV



Scheme V[a]



[a] Conditions: (a) $Ph_3P{=}CH_2$, C_6H_6, reflux; (b) MMPPA, EtOH, rt; (c) $BF_3{\cdot}OEt_2$, CH_2Cl_2, rt; (d) Et_3SiH, TFA, reflux; (e) DIBAH, PhMe, −78 °C.

Reaction of **18** with methylenetriphenylphosphorane in refluxing benzene furnished olefin **19** along with cyclopropyl ketone **20** in a 5:4 ratio in 80% yield. Cyclopropyl ketone **20** was apparently formed via β-silyloxy elimination, followed by cyclopropanation of the resultant enone with Wittig reagent, as observed in the case of sterically crowded enones.[19] The formation of a mixture of products in the olefination reaction discouraged us from further elaboration of **19** to thapsanes.

β-Keto ester **6** was successfully elaborated to the thapsane **1g** via the following route (Scheme V). Wittig olefination of β-keto ester **6** with methylenetriphenylphosphorane in refluxing benzene for 12 h furnished ester **21** in 78% yield (70% conversion). As the conversion of **21** to either a hydroxy ester or to lactone **22** via a hydroboration–oxidation sequence was unsuccessful, the ring C was constructed via epoxidation. Treatment of ester **21** with monoperoxyphthalic acid magnesium salt (MMPPA) in ethanol for 24 h furnished a 1:1 mixture of epimeric epoxides **23**. Treatment of epoxides **23** with a catalytic amount of BF_3–OEt_2 in CH_2Cl_2 gave not the expected rearrangement product **24**, but rather hemiacetal **25** in 49% yield. The formation of hemiacetal **25** can be rationalized by BF_3-mediated intramolecular trans acetalization of the epoxide rearrangement product **24**. The extra ethoxy group present in hemiacetal **25** was removed by ionic hydrogenation[20] with triethylsilane. Treatment of **25** with triethylsilane in refluxing trifluoroacetic acid furnished lactone **22** in 80% yield, which exhibited ^1H and ^{13}C NMR spectra identical with those of the lactone derived from the natural product. Finally, DIBAH reduction of **22** generated thapsane **1g** in 82% yield, which exhibited the ^1H NMR spectrum identical with that of natural thapsane.

In summary, the first total synthesis of a natural thapsane was achieved in 10 steps starting from cyclogeraniol (**9**).

Experimental Section

^1H and ^{13}C NMR chemical shifts (δ) and coupling constants (Hz) are reported in the standard fashion with reference to either internal tetramethylsilane (for ^1H) or the central line (77.1 ppm) of $CDCl_3$ (for ^{13}C). Off-resonance ^{13}C multiplicities, when recorded, are given in parentheses. Acme's silica gel (100-200 mesh) was used for column chromatography. All moisture-sensitive reactions were carried out using standard syringe-septum techniques under nitrogen atmosphere. Dry benzene and toluene were obtained by washing with H_2SO_4 followed by distillation over sodium and storage over pressed sodium wire. Dry THF was obtained by distillation over sodium benzophenone ketyl. CH_2Cl_2 and acetonitrile were distilled over P_2O_5. Pyridine, Et_3N, and diisopropylamine were dried by distilling over KOH. Dry ^{t}AmOH was obtained by distillation over sodium. Liquid ammonia was distilled over sodium. Tosyl azide,[21] ethyl diazoacetate,[22] and rhodium acetate[23] were prepared according to literature procedures. General workup and purification refers to the washing of the solvent extract with brine, drying over anhydrous Na_2SO_4, evaporation of solvent under reduced pressure, and purification of the residue over a silica gel (20 g/g of material) column using appropriate solvent.

1-(1,3,3-Trimethyl-2-methylenecyclohexyl)-propan-2-one (10): A solution of cyclogeraniol (**9**, 1.08 g, 7 mmol), 2-methoxypropene (3 mL, 31 mmol), and propionic acid (catalytic) in toluene (3 mL) was placed in a sealed tube under nitrogen atmosphere and heated to 150–160 °C for 48 h. The reaction mixture was cooled, poured into water (15 mL), and extracted with benzene (30 mL × 3). The benzene extract was washed with aqueous $NaHCO_3$ solution. General workup and purification using 1:20 ethyl acetate–hexane as eluent furnished ketone **10** (885 mg, 65%) as a colorless oil: IR (neat) ν_{max} 1716, 1630, 905 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 4.97 (1 H, s), 4.84 (1 H, s), 2.62 (2 H, s), 2.08 (3 H, s), 0.8–1.7 (6 H, m), 1.2 (3 H, s), 1.14 (3 H, s), 1.12 (3 H, s); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 207.9 (s), 160.5 (s), 108.3 (t), 53.8 (t), 40.5 (t), 38.6 (t), 38.8 (s), 36.0 (s), 32. 3 (2 C, q), 30.9 (q), 29.5 (q), 18.3 (t); mass *m/e* 194 (M^+, 28%), 136 (95), 137 (100); HRMS *m/e* calcd for $C_{13}H_{22}O$ 194.1671, found 194.1680.

Ethyl 4-(1,3,3-Trimethyl-2-methylenecyclohexyl)-3-oxobutanoate (8). Procedure 1: To a solution of hexamethyldisilazane (6.33 mL, 30 mmol) in dry THF (20 mL) under nitrogen atmosphere at −78 °C was added a solution of *n*-BuLi (18.75 mL, 1.6 M in hexane, 30 mmol) dropwise over a 10-min period. The solution was brought to −50 °C, stirred for 20 min, and recooled to −78 °C. To LHMDS thus formed was added a solution of ketone **10** (1.943 g, 10 mmol) in dry THF (5 mL) dropwise, and the mixture was stirred at the same temperature for 1 h. Ethyl chloroformate (1.43 mL, 15 mmol) was then added in one portion and the reaction mixture was slowly warmed to rt and stirred for 5 h. The reaction was quenched with aqueous NH_4Cl (15 mL)

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and extracted with ether (40 mL × 3). General workup and purification using 1:20 ethyl acetate–hexane as eluent furnished β-keto ester 8 (2.13 g, 80%) as a yellow oil: IR (neat) ν_{max} 1750, 1725, 1635, 910 cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) δ 4.87 (2 H, m), 4.12 (2 H, q, J = 7 Hz), 3.2 (2 H, s), 2.67 (2 H, s), 1.2–1.8 (6 H, m), 1.27 (3 H, t, J = 7 Hz), 1.22 (3 H, s), 1.17 (6 H, s); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 201.6 (s), 167.1 (s), 160.5 (s), 108.6 (t), 61.1 (t), 53 .4 (t), 51.2 (t), 40.5 (t), 38.6 (t), 39.1 (s), 36.2 (s), 32.5 (q), 31.2 (q), 29.5 (q), 18.4 (t), 14.0 (q); mass m/e 266 (M$^+$, 16%), 137 (100); HRMS m/e calcd for $C_{16}H_{26}O_3$ 266.1882, found 266.1894.

Procedure 2: To a stirred suspension of $SnCl_2 \cdot 2H_2O$ (113 mg, 0.5 mmol) in CH_2Cl_2 (10 mL), was added a solution of ethyl diazoacetate (576 mg, 5 mmol, CH_2Cl_2, 4 mL) followed by a few drops of a solution of aldehyde[11] 11 (900 mg, 5 mmol) in CH_2Cl_2 (3 mL). When nitrogen evolution began, the remaining solution of aldehyde was added dropwise over a 10-min period. After nitrogen evolution stopped (1 h), evaporation of CH_2Cl_2 and purification furnished β-keto ester 8 (930 mg, 70%).

Ethyl 4-(1,3,3-Trimethyl-2-methylenecyclohexyl)-2-diazo-3-oxobutanoate (12): To a stirred solution of β-keto ester 8 (1.86 g, 7 mmol) in dry acetonitrile (6 mL) was added tosyl azide (1.38 g, 7 mmol) followed by triethylamine (0.98 mL, 7 mmol), and the mixture was stirred at rt for 12 h. Evaporation of solvent and triethylamine under reduced pressure and purification using 1:20 ethyl acetate–hexane furnished diazo compound 12 (1.7 g, 83%) as a yellow oil: IR (neat) ν_{max} 2135, 1725, 1660, 905 cm^{-1}; ^{1}H NMR (60 MHz, CCl_4) δ 4.91 (1 H, s), 4.84 (1 H, s), 4.2 (2 H, q, J = 7 Hz), 3.01 (2 H, s), 1.1–1.9 (6 H, m), 1.31 (3 H, t, J = 7 Hz), 1.21 (3 H, s), 1.13 (6 H, s); mass m/e 292 (M$^+$, 8%), 95 (100); HRMS m/e calcd for $C_{16}H_{24}N_2O_3$ 292.1787, found 292.1772.

Ethyl 6,10,10-Trimethyl-4-oxo-tricyclo[4.4.0.0^{1,3}]decane-3-carboxylate (7): To a stirred solution of diazo compound 12 (1.6 g, 5.5 mmol) in dry benzene (200 mL) was added a catalytic amount of $Rh_2(OAc)_4$, and the reaction mixture was stirred at rt for 24 h. The catalyst was filtered off. Evaporation of benzene and purification of residue using 1:20 ethyl acetate–hexane as eluent furnished cyclopropane 7 (0.95 g, 65%) which was recrystallized from petroleum ether: mp 68 °C; IR (neat) ν_{max} 1745, 1722 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.2 (2 H, q, J = 7.1 Hz), 1.96 (2 H, AB q, J_{AB} = 17.8 Hz, $\Delta\nu_{AB}$ = 65 Hz), 1.87 (1 H, d, J = 6 Hz), 1.39 (1 H, d, J = 6 Hz), 1.4–1.7 (6 H, m), 1.29 (3 H, t, J = 7.2 Hz), 1.22 (3 H, s), 1.17 (3 H, s), 0.65 (3 H, s); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 207.0 (s), 167.7 (s), 60.6 (t), 54.1 (s), 49.3 (t), 49.0 (s), 38.9 (t), 38.6 (t), 38.1 (s), 33.0 (s), 27.6 (q), 26.8 (q), 22.5 (q), 18.1 (t), 17.7 (t), 13.6 (q); mass m/e 264 (M$^+$, 7%), 122 (100); HRMS m/e calcd for $C_{16}H_{24}O_3$ 264.1725, found 264.1733. Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.90; H, 9.34.

(1β,6β,7β)-Ethyl 1,5,5,6-Tetramethyl-8-oxobicyclo[4.3.0]-nonane-7-carboxylate (6) and (1β,4β,6α)-4-(Hydroxymethyl)-1,7,7-trimethylbicyclo[4.4.0]decan-3-one (13): To stirred, freshly distilled liquid ammonia (80 mL) placed in a three-necked flask equipped with a Dewar condenser was added compound 7 (920 mg, 3.5 mmol) in dry THF (4 mL), followed by small pieces of freshly cut lithium (120 mg, 17.5 mmol). The resulting blue solution was stirred at −33 °C for 10 min, the reaction was quenched with solid NH_4Cl, and the ammonia was evaporated. The residue was taken up in water (20 mL) and extracted with ether (35 mL × 3). General workup and purification using 1:20 ethyl acetate–hexane as eluent furnished β-keto ester 6 (300 mg, 32%) as a colorless viscous oil: IR (neat) ν_{max} 1758, 1731 cm^{-1}; ^{1}H NMR (60 MHz, CCl_4) δ 4.09 (2 H, q, J = 7.1 Hz), 3.59 (1 H, s), 2.12 (2 H, AB q, J_{AB} = 18.6 Hz, $\Delta\nu_{AB}$ = 26 Hz), 1–1.9 (6 H, m), 1.26 (3 H, t, J = 7.1 Hz), 1.23 (3 H, s), 1.18 (3 H, s), 1.07 (3 H, s), 0.84 (3 H, s); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 211.3 (s), 169.6 (s), 61.4 (d), 60.3 (t), 53.3 (t), 50.9 (s), 40.1 (s), 36.9 (2 C, t), 35.9 (s), 28.3 (q), 25.0 (q), 23.3 (q), 14.0 (q), 18.2 (t), 13.8 (q); mass m/e 266 (M$^+$, 12%); HRMS m/e calcd for $C_{16}H_{26}O_3$ 266.1882, found 266.1863.

Further elution of the column using 3:20 ethyl acetate–hexane as eluent furnished ketol 13 (250 mg, 32%) as a colorless oil: IR (neat) ν_{max} 3450, 1704 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.7 (2 H, d, J = 5.1 Hz), 2.46 (1 H, m), 2.11 (2 H, AB q, J_{AB} = 12.8 Hz, $\Delta\nu_{AB}$ = 47 Hz), 1.93 (1 H, m), 1.15–1.7 (9 H, m), 0.99 (3 H, s), 0.87 (3 H, s), 0.86 (3 H, s); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 214.0 (s), 62.4 (t), 59.7 (t), 52.3 (d), 51.9 (d), 42.3 (t), 41.7 (t), 39.3 (s), 33.3 (2 C, q & s), 26.5 (t), 21.4 (q), 19.4 (q), 18.8 (t); mass m/e 224 (M$^+$, 27%), 123 (100); HRMS m/e calcd for $C_{14}H_{24}O_2$ 224.1776, found 224.1762.

(3α,6β)-Ethyl 4-Methylene-6,10,10-trimethyltricyclo-[4.4.0.0^{1,3}]decane-3-carboxylate (14): To a stirred suspension of methyltriphenylphosphonium bromide (1.82 g, 5.1 mmol) in dry benzene (6 mL) was added a 1 M solution of potassium *tert*-amylate in *tert*-amyl alcohol (5 mL, 5 mmol), and the resulting yellow solution was stirred at rt for 20 min. To this solution was added β-keto ester 7 (396 mg, 1.5 mmol) and the mixture was stirred at rt for 12 h. The reaction was quenched with saturated aqueous NH_4Cl solution (10 mL) and extracted with ether (30 mL × 3). General workup and purification using ethyl acetate–hexane (1:30) as eluent furnished ester 14 (295 mg, 75%) as a colorless oil: IR (neat) ν_{max} 1731, 1659, 865 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.79 (1 H, br s), 4.74 (1 H, d, J = 2.3 Hz), 4.18 (2 H, q, J = 7.2 Hz), 1.98 (1 H, t of d, J = 15.6, 2.3 Hz), 1.78 (1 H, d, J = 15.6 Hz), 1.4–1.7 (6 H, m), 1.48 (1 H, d, J = 5.8 Hz, 1.03 (1 H, d, J = 5.8 Hz), 1.3 (3 H, t, J = 7.2 Hz), 1. 09 (3 H, s), 1.08 (3 H, s), 0.61 (3 H, s); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 171.7 (s), 149.5 (s), 104.8 (t), 60.6 (t), 52.3 (s), 46.4 (t), 44.5 (s), 41.1 (s), 39.2 (t), 37.3 (t), 33.3 (s), 27.6 (q), 27.4 (q), 23.4 (q), 18.9 (t), 15.6 (t), 14.0 (q); mass m/e 262 (M$^+$, 18%), 123 (100); HRMS m/e calcd for $C_{17}H_{26}O_2$ 262.1933, found 262.1941.

Ethyl *trans*-4-[(Phenylthio)methyl]-6,10,10-trimethylbicyclo[4.4.0]dec-3-ene-3-carboxylate (15): A solution of olefin 14 (262 mg, 1 mmol) and thiophenol (0.11 mL, 1.1 mmol) in benzene (2 mL) was placed in a sealed tube and heated to 80 °C for 12 h. The reaction mixture was cooled, poured into water (10 mL), and extracted with ether (15 mL × 3). The organic layer was washed with 5% aqueous NaOH. General workup and purification using ethyl acetate–hexane (1:20) as eluent furnished ester 15 (268 mg, 72%) as a yellow oil: IR (neat) ν_{max} 1713, 1653 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.32 (2 H, d, J = 7.1 Hz), 7.1–7.3 (3 H, m), 4.18 (1 H, d, J = 11 Hz), 4.04 (2 H, q, J = 7.5 Hz), 3.61 (2 H, d, J = 11 Hz), 1.91–2.4 (5 H, m), 1.0–1.7 (6 H, m), 1.2 (3 H, t, J = 7.3 Hz), 0.83 (6 H, s), 0.8 (3 H, s); ^{13}C NMR (67.5 MHz, $CHCl_3$ + $CDCl_3$) δ 168.2 (s), 141.9 (s), 136.7 (s), 130.9 (2 C, d), 128.7 (2 C, d), 127.1 (s), 126.4 (d), 60.2 (t), 50.8 (t), 48.1 (d), 42.7 (t), 41.3 (t), 38.2 (t), 32.7 (q), 32.5 (2 C, s), 25.4 (t), 21.2 (q), 19.1 (q), 18.7 (t), 14.2 (q); mass m/e 372 (M$^+$, 67%), 326 (100); HRMS m/e calcd for $C_{23}H_{32}O_2S$ 372.2123, found 372.2129.

(1β,6β,7β)-7-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-1,5,5,6-tetramethylbicyclo[4.3.0]nonan-8-one (18): To a stirred solution of ketol 17[13d] (280 mg, 1.25 mmol) in dry pyridine (2 mL) was added *tert*-butyldimethylchlorosilane (265 mg, 1.5 mmol) and DMAP (catalytic), and the reaction mixture was stirred at rt for 36 h. Water (8 mL) was added and the mixture was extracted with CH_2Cl_2 (10 mL × 3). The organic layer was washed with 2% aqueous HCl (10 mL). General workup and purification using ethyl acetate–hexane (1:20) as eluent furnished TBDMS ether 18 (385 mg, 91%) as a colorless solid: mp 62–64 °C; IR ($CHCl_3$) ν_{max} 1734 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 4.0 (1 H, dd, J = 9.7), 3.73 (1 H, dd, J = 9.7, 2.2 Hz), 2.5 (1 H, m), 2.05 (2 H, AB q, J_{AB} = 16.6 Hz, $\Delta\nu_{AB}$ = 38 Hz), 1.0–1.8 (6 H, m), 1.18 (3 H, s), 1.06 (6 H, s), 0.88 (3 H, s), 0.85 (9 H, s), 0.0 (6 H, s); mass m/e 281 (M$^+$ − ^{t}Bu, 100%); HRMS m/e calcd for $C_{16}H_{29}O_2Si$ (M$^+$ − ^{t}Bu) 281.1937, found 281.1936. Anal. Calcd for $C_{20}H_{38}O_2Si$: C, 70.94; H, 11.31. Found: C, 70.59; H, 11.31.

(1β,6β,7β)-8-Methylene-7-[[(*tert*-butyldimethylsilyl)oxy]-methyl]-1,5,5,6-tetramethylbicyclo[4.3.0]nonane (19) and 1,5,5,6-Tetramethylbicyclo[4.3.0]nonan-8-one-7-spirocyclopropane (20): To a stirred suspension of methyltriphenylphosphonium bromide (1.8 g, 5.1 mmol) in dry benzene (6 mL) was added a 1 M solution of potassium *tert*-amylate in *tert*-amyl alcohol (5 mL, 5 mmol), and the resulting yellow solution was stirred at rt for 20 min. To this solution was added a benzene (3 mL) solution of ketone 18 (340 mg, 1 mmol), and the mixture was stirred at reflux for 8 h. The reaction mixture was cooled, saturated aqueous NH_4Cl solution (8 mL) was added, and the mixture was extracted with ether (30 mL × 3). General workup and purification using hexane as eluent furnished olefin 19 (150 mg, 45%) as a colorless oil: IR (neat) ν_{max} 1083, 936 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.23 (1 H, br s), 4.85 (1 H, br s), 3.89 (1 H, dd, J = 9.4, 2.6 Hz), 3.46 (1 H, dd, J = 9.3, 8.2 Hz), 2.7 (1

H, t of d, J = 8.2, 2.3 Hz), 2.47 (1 H, q of d, J = 15.4, 2.8 Hz), 1.8 (1 H, d, J = 15.4 Hz), 1.05–1.7 (6 H, m), 1.03 (3 H, s), 0.94 (3 H, s), 0.91 (3 H, s), 0.78 (3 H, s), 0.89 (9 H, s), 0.03 (6 H, s); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 154.6 (s), 107.6 (t), 67.0 (t), 50.4 (2 C, t & d), 49.5 (s), 42.8 (s), 38.3 (t), 36.3 (t), 29.4 (q), 26.2 (q), 25.2 (q), 22.7 (q), 18.8 (t), 18.4 (s), 13.0 (q), −5.2 (2 C, q); mass *m/e* 336 (M^+, 1%), 279 (100); HRMS *m/e* calcd for $C_{21}H_{40}OSi$ 336.2848, found 336.2850.

Further elution of the column with ethyl acetate–hexane (1:20) as eluent furnished cyclopropyl ketone **20** (77 mg, 35%) which was recrystallized from ether: mp 127–128 °C; IR (neat) ν_{max} 1731 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 2.3 (2 H, AB q, J_{AB} = 18 Hz, $\Delta\nu_{AB}$ = 56 Hz), 0.6–1.7 (10 H, m), 1.11 (3 H, s), 0.96 (3 H, s), 0.90 (3 H, s), 0.88 (3 H, s); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 219.1 (s), 50.3 (t), 45.9 (s), 41.7 (s), 38.4 (2 C, s & t), 37.6 (s), 34.9 (t), 29.7 (q), 28.8 (q), 26.0 (q), 15.3 (q), 18.3 (t), 17.4 (t), 12.4 (t); mass *m/e* 220 (M^+, 11%), 137 (100); HRMS *m/e* calcd for $C_{15}H_{24}O$ 220.1827, found 220.1818.

Ethyl (1β,6β,7β)-8-Methylene-1,5,5,6-tetramethylbicyclo[4.3.0]nonane-7-carboxylate (21): To a stirred suspension of methyltriphenylphosphonium bromide (1.8 g, 5.1 mmol) in dry benzene (6 mL) was added 1 M solution of potassium *tert*-amylate in *tert*-amyl alcohol (5 mL, 5 mmol), and the resulting yellow solution was stirred at rt for 20 min. To this solution was added a benzene (4 mL) solution of β-keto ester **6** (265 mg, 1 mmol) and the mixture stirred at reflux for 12 h. The reaction mixture was cooled, diluted with saturated NH_4Cl solution (8 mL), and extracted with ether (25 mL × 3). General workup and purification using benzene–hexane (1:5) as eluent furnished ene ester **21** (145 mg, 55%) as a viscous oil: IR (neat) ν_{max} 1746, 880 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.9 (1 H, q, J = 2.5 Hz), 4.81 (2 H, q, J = 2.5 Hz), 4.13 (2 H, m), 3.7 (1 H, q, J = 2.7 Hz), 2.53 (1 H, q of d, J = 16.3, 2.9 Hz), 1.97 (1 H, d, J = 16.3 Hz), 1.15–1.7 (6 H, m), 1.28 (3 H, t, J = 7.2 Hz), 1.1 (6 H, s), 0.98 (3 H, s), 0.83 (3 H, s); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 174.2 (s), 149.3 (s), 107.9 (t), 59.9 (t), 54.7 (d), 52.5 (s), 48.7 (t), 43.0 (s), 37.6 (t), 36.3 (t), 36.1 (s), 28.6 (q), 25.0 (q), 22.6 (q), 14.3 (q), 18.8 (t), 13.9 (q); mass *m/e* 264 (M^+, 76%), 107 (100); HRMS *m/e* calcd for $C_{17}H_{28}O_2$ 264.2089, found 264.2078.

Further elution of the column using 3:1 benzene–hexane as eluent furnished unreacted ketone **6** (79 mg, 30%).

Ethyl (1β,6β,7β,8α)- and (1β,6β,7β,8β)-1,5,5,6-Tetramethylbicyclo[4.3.0]nonane-8-spirooxirane-7-carboxylates (23): To a stirred solution of magnesium monoperoxyphthalate hexahydrate (247 mg, 0.5 mmol) in absolute ethanol (2 mL) was added a solution of ester **21** (132 mg, 0.5 mmol) in ethanol (1 mL) and the mixture stirred at rt for 24 h. The solvent was evaporated under reduced pressure and the residue was taken in water (5 mL) and extracted with CH_2Cl_2 (8 mL × 3). General workup and purification using 1:20 ethyl acetate–hexane as eluent furnished a 1:1 mixture of epoxides **23** (97 mg, 69%) as a colorless oil: IR (neat) ν_{max} 1737 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$, for two isomers) δ 3.96–4.2 (2 H, m), 3.59 and 3.46 (1 H, s), 2.76 (AB q, J_{AB} = 5.3 Hz, $\Delta\nu_{AB}$ = 15 Hz) and 2.63 (AB q, J_{AB} = 4.3 Hz, $\Delta\nu_{AB}$ = 13 Hz) (2 H), 2.34 (d, J = 14.3 Hz) and 2.14 (d, J = 14 Hz, 1 H), 1.33–2.0 (7 H, m), 1.33 (s), 1.15 (s), 1.14 (s), 1.11 (s), 1.0 (s), 0.82 (s) and 0.79 (s) (12 H), 1.23 and 1.22 (3 H, t, J = 7.2 Hz); mass *m/e* 265 (M^+ − Me, 18%), 142 (100); HRMS *m/e* calcd for $C_{17}H_{28}O_3$ 280.2039, found 280.2016.

(1β,2α,5α,6α,8β)-5-Ethoxy-1,8,12,12-tetramethyl-4-oxatricyclo[6.4.0.0^{2,6}]undecan-3-one (25): To a stirred solution of epoxide **23** (92 mg, 0.33 mmol) in dry CH_2Cl_2 (2 mL) was added a drop of BF_3–Et_2O, and the mixture was stirred for 2 h at rt. The reaction was quenched with saturated aqueous $NaHCO_3$ (3 mL) and extracted with CH_2Cl_2 (5 mL × 3). General workup and purification using 1:20 ethyl acetate–hexane as eluent furnished hemiacetal **25** (45 mg, 49%) which was recrystallized from petroleum ether to furnish a white solid: mp 98–100 °C; IR ($CHCl_3$) ν_{max} 1764 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.13 (1 H, d, J = 2.1 Hz), 3.9 (1 H, q of d, J = 9, 7 Hz), 3.5 (1 H, q of d, J = 9, 7 Hz), 3.38 (1 H, d, J = 11 Hz), 2.85 (1 H, d of q, J = 11, 2 Hz), 1.7 (2 H, dd, J = 10, 1.7 H z), 1.1–1.6 (6 H, m), 1.22 (3 H, t, J = 7.1 Hz), 1.08 (6 H, s), 0.96 (3 H, s), 0.92 (3 H, s); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 177.0 (s), 107.9 (d), 64.9 (t), 52.1 (s), 51.4 (d), 47.0 (s), 45.5 (t), 44.4 (d), 38.6 (t), 36.4 (t), 35.9 (s), 30.4 (q), 24.6 (q), 22.8 (q), 15.1 (2 C, q), 18.6 (t); mass *m/e* 280 (M^+, 100%); HRMS *m/e* calcd for $C_{17}H_{20}O_3$ 280.2039, found 280.2025. Anal. Calcd for $C_{17}H_{28}O_3$: C, 72.82; H, 10.06. Found: C, 73.38; H, 10.34.

(1β,2α,6α,8β)-1,8,12,12-Tetramethyl-4-oxatricyclo[6.4.0.0^{2,6}]undecan-3-one (22): To a stirred solution of hemiacetal **25** (42 mg, 0.15 mmol) in trifluoroacetic acid (1 mL) was added triethylsilane (0.25 mL, 0.16 mmol) and the mixture was refluxed for 5 h. Trifluoroacetic acid was removed under reduced pressure and the residue was taken in water (5 mL) and extracted with CH_2Cl_2 (5 mL × 3). The organic phase was washed with saturated aqueous $NaHCO_3$. General workup and purification using 1:20 ethyl acetate–hexane as eluent furnished lactone **22** (28 mg, 80%), which was recrystallized from petroleum ether to afford a white crystalline solid: mp 120–123 °C (lit.[4] 123–125 °C); IR ($CHCl_3$) ν_{max} 1761 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.41 (1 H, t, J = 9.2 Hz), 3.92 (1 H, dd, J = 9.1, 5 Hz, H-5β), 3.28 (1 H, d, J = 11.7 Hz), 3.13 (1 H, m), 1.7 (2 H, d, J = 8.5 Hz), 1.2–1.7 (6 H, m), 1.093 (3 H, s), 1.095 (3 H, s), 0.98 (3 H, s), 0.97 (3 H, s); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 178.3, 73.3, 52.4, 51.1, 49.3, 47.9, 38.7, 36.8, 36.2, 18.7, 30.7, 24.6, 22.8, 15.1; mass *m/e* 236 (M^+, 61%), 152 (100); HRMS *m/e* calcd for $C_{15}H_{24}O_2$ 236.1776, found 236.1803.

(1β,2α,3α,6α,8β)-1,8,12,12-Tetramethyl-4-oxatricyclo[6.4.0.0^{2,6}]undecan-3-ol (thapsane 1g): To a solution of lactone **22** (28 mg, 0.12 mmol) in toluene (1 mL), under a nitrogen atmosphere at −78 °C, was added a solution of DIBAH (0.1 mL, 1.2 M in toluene, 0.12 mmol), and the mixture was stirred for 1 h at −78 °C. The reaction mixture was warmed to rt, quenched with saturated aqueous NH_4Cl (5 mL), and extracted with ether (5 mL × 3). General workup and purification using 1:10 ethyl acetate–hexane as eluent furnished thapsane **1g** (23 mg, 80%), which was recrystallized from petroleum ether: mp 82–84 °C (lit.[4] 85–87.5 °C); IR ($CHCl_3$) ν_{max} 3580, 3375 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.35 (1 H, s), 4.15 (1 H, t, J = 8 Hz), 3.62 (1 H, dd, J = 8.2, 2 Hz), 2.8–3.0 (2 H, m), 2.5 (1 H, br s), 1.2–1.7 (8 H, m), 1.02 (3 H, s), 0.96 (3 H, s), 0.91 (3 H, s), 0.83 (3 H, s).

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Supplementary Material Available: ^{1}H and ^{13}C NMR spectra of **6**, **8**, **10**, **13**, **14**, **19**, **20**, **21**, **23**, and **25** (19 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.

Studies on the Synthesis of Mavacurine-Type Indole Alkaloids. First Total Synthesis of (±)-2,7-Dihydropleiocarpamine

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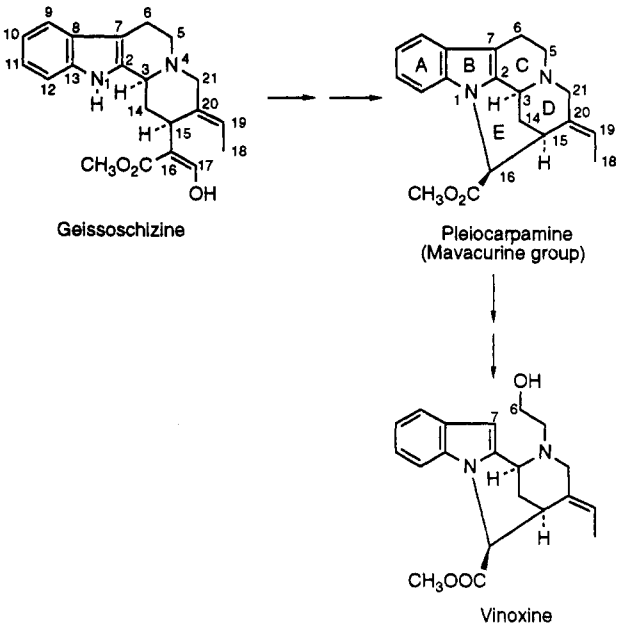
Closure of the six-membered C ring of pentacyclic mavacurine-type alkaloids from suitably substituted tetracyclic substructures embodying rings ABDE of these alkaloids, either by electrophilic cyclization upon the indole 3-position or by intramolecular alkylation of the piperidine nitrogen, failed. In contrast, 6a-homopleiocarpamine (**45**) has been synthesized from dithioacetal **42** by an electrophilic cyclization involving the closure of the seven-membered C ring. The first total synthesis of the alkaloid 2,7-dihydropleiocarpamine (**58**) has been achieved by photocyclization of the tetracyclic chloroacetamide **54** as the key step. The required tetracyclic ABDE ring systems were prepared by a straightforward sequence consisting of nucleophilic addition of a 1-indoleacetatic ester enolate to the γ position of a pyridinium salt, acid cyclization of the resulting 1,4-dihydropyridine, and final elaboration of the (*E*)-ethylidene substituent. An alternative synthesis of the tetracyclic alkaloid vinoxine (**10a**) is also reported.

The mavacurine-type alkaloids[1] (C-mavacurine, pleiocarpamine) constitute a small subgroup of Corynanthean indole alkaloids (C_{4f} skeletal variation, according to the Hesse's classification)[2] and are structurally characterized by the presence of a bond between N-1 and C-16[3] giving an additional ring E. Consequently, they incorporate a bridged pentacyclic 2*H*-2,12-methanoindolo[2,3-*a*]quinolizine system, corresponding to the 1,16-cyclocorynan stereoparent. Other characteristic structural features are the presence of an oxidized one-carbon substituent (CH_2-OH or CO_2CH_3) at C-16 and a two-carbon chain, usually an *E*-configurated ethylidene, at C-20.

Biogenetically the mavacurine alkaloids are formally derived from geissoschizine (Scheme I), a key intermediate along the biosynthetic pathway of monoterpenoid indole alkaloids, although the details of the formation of the key bond N-1/C-16 (closure of the E ring) still remain unknown.[4] The tetracyclic alkaloid vinoxine[5] would be formed by further hydrolytic cleavage of the tryptamine C-6/C-7 bond. Pleiocarpamine also constitutes one half of several bisindole alkaloids.[6]

The additional N-1/C-16 bond causes these molecules to adopt a hemispherical shape. Consequently, the groups inside the sphere (β-face) exhibit strong transannular interactions whereas the α-face is easily accessible to chemical reagents.[1]

Scheme I. Biosynthesis and Biogenetic Numbering



These alkaloids have received little attention from a synthetic standpoint: only the total synthesis of (±)-C-mavacurine, via (±)-16-epipleiocarpamine and (±)-nor-mavacurine, has been reported so far.[7] Additionally, the partial synthesis of (+)-16-epipleiocarpamine from (+)-geissoschizine[8] and several syntheses of pentacyclic model structures[9-11] and 19,20-dihydro analogs[9,12] have been reported. All these synthetic approaches (Scheme II) involve, as the key reaction, the formation of N-1/C-16

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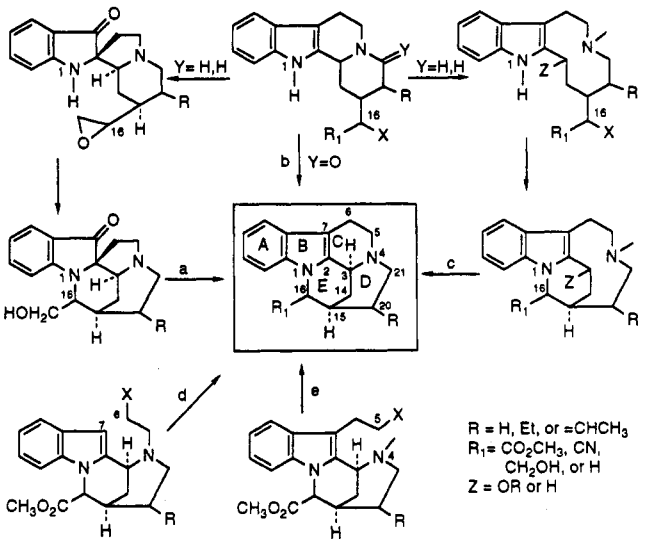
Scheme II. Synthetic Strategies



bond, either from a tetracyclic pseudoindoxyl derivative followed by a skeletal rearrangement of the resulting pentacyclic norfluorocurine system (via a)[9,13] or from an indolo[2,3-*a*]quinolizidine derivative. In the latter case, closure of the E ring can occur either directly (via b)[10] or, in most cases, after C/D ring cleavage (solvolytic[8,10,12] or reductive[7,11]) with final reclosing of the C-3/N-4 bond by transannular cyclization (solvolytic[8,12] or oxidative[7,11]; via c). These syntheses lead to products with a H-15/H-16 trans-relationship, i.e., the same relative stereochemistry as in C-mavacurine but the opposite of pleiocarpamine.

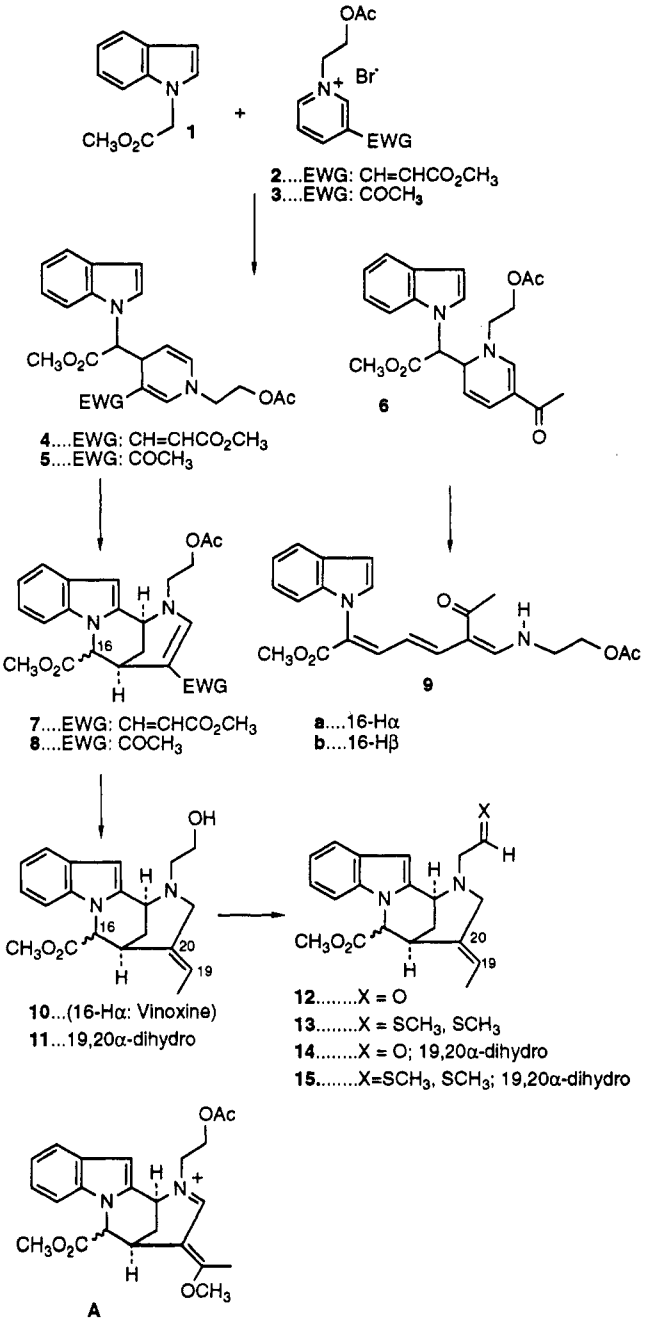
In this paper, we report a new synthetic entry to the alkaloids of the mavacurine group, based on the closure of the C ring in the last synthetic steps from an appropriately N-4-substituted tetracyclic system embodying rings ABDE of the mavacurine alkaloids (bond formed C-6/C-7; via d). We also report the results obtained when developing an alternative strategy consisting in the closure of the C ring in the key step by formation of N-4/C-5 bond (via e).

Results and Discussion

In a previous work we have reported[14] the first total synthesis of the alkaloid vinoxine (**10a**), a tetracyclic analog of pleiocarpamine having a 2-hydroxyethyl chain at the piperidine nitrogen, by reaction of the enolate derived from methyl 1-indoleacetate (**1**) with pyridinium salt **2** followed by acid cyclization of the intermediate 1,4-dihydropyridine **4** and further elaboration of the (*E*)-ethylidene substituent from the resulting tetracyclic compound **7** (Scheme III).[15] This methodology, based on the nucleophilic addition of an indole-containing enolate to the γ-position of a pyridinium salt followed by cyclization of the resulting 1,4-dihydropyridine, has successfully been used for the synthesis of bridged indole alkaloids belonging to several structural types.[14,16,17]

Vinoxine (**10a**) itself or some derivative of this alkaloid with the appropriate functionality at C-6 were envisaged

Scheme III



as immediate precursors of pentacyclic mavacurine alkaloids by formation of the C-6/C-7 bond by means of electrophilic cyclization upon the indole 3-position. For this reason, we initially explored an alternative synthesis of vinoxine based on the above synthetic strategy but using a pyridinium salt bearing an acetyl group, instead of acrylate, as the electron-withdrawing substituent at the β-position.[18] As expected, interaction of ester **1** with pyridinium bromide **3** in the presence of an excess of LDA

(13) For the rearrangement of the norfluorocurine to the normavacurine skeleton, see refs 1 and 10. This rearrangement implies the formation of the C-6/C-7 bond, the β-position of the indole ring (C-7) acting as an electrophilic center.

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