Stereospecific Construction of Multiple Contiguous Quaternary Carbons. Total Synthesis of (±)-*cis, anti, cis*-1,8,12,12-Tetramethyl-4-oxatricyclo[6.4.0.0^{2,6}]dodecan-3-ol, a Thapsane Isolated from *Thapsia villosa* var *minor*†

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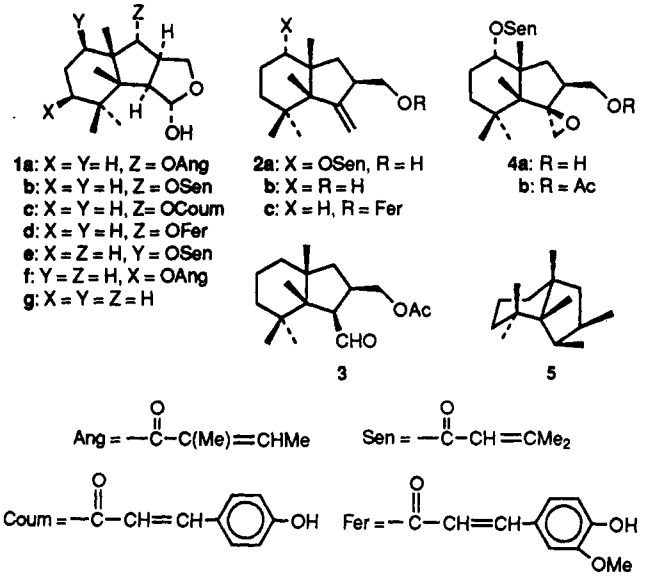
The details of the first total synthesis of a natural thapsane **1g** containing three contiguous quaternary carbon atoms, starting from cyclogeraniol (**9**) is described. The Claisen rearrangement of **9** with methoxypropene in the presence of a catalytic amount of propionic acid produced ketone **10**. Rhodium acetate-catalyzed intramolecular cyclopropanation of α-diazo-β-keto ester **12**, obtained from **10** via β-keto ester **8**, furnished cyclopropyl keto ester **7**. Lithium in liquid ammonia reductive cleavage of cyclopropyl compound **7** gave a 1:1 mixture of hydrindanone **6** and ketol **13**. Wittig methylenation of **6** furnished ester **21**. Epoxidation of **21**, followed by BF_3–OEt_2-catalyzed rearrangement of epoxide **23** afforded hemiacetal **25**. Treatment of hemiacetal **25** with triethylsilane in trifluoroacetic acid furnished lactone **22**, a degradation product of various thapsanes. Finally, DIBAH reduction of lactone **22** generated the thapsane **1g**.

In 1984, Rasmussen *et al.*[1] reported the isolation of a new sesquiterpene containing a new carbon skeleton, from the ethanolic extract of the roots of a Mediterranean umbelliferous plant, *Thapsia villosa L.* The structure as well as the absolute configuration of this new sesquiterpene was established as **1a**, by spectral and single crystal X-ray analysis. Shortly thereafter, Grande *et al.* reported the isolation of the corresponding senicioate ester **1b** from the benzene extract of the roots of *Thapsia villosa* var *minor*, along with four other hemiacetalic (**1c–f**), four nonacetalic (**2a–4a,4b**), and a dimeric thapsane as minor components having the same carbon framework.[2,3] The trivial name Thapsane was suggested for the bicyclic carbon skeleton, 2,3,3a,4,4,7a-hexamethylhydrindan (**5**), present in these compounds. Recently, Christensen *et al.* have reported the isolation of three additional thapsanes[4] (**2b,c, 1g**) from *Thapsia villosa* var *minor* collected near Capo Espichel (Chart I). The presence of an unique *cis,anti,cis*-3b,4,4,-7a-tetramethylperhydroindeno[1,2-*c*]furan framework,[1-4] containing three contiguous quaternary carbon atoms and five to six chiral centers makes thapsanes attractive synthetic targets. The generation of three contiguous quaternary carbons in the hydrindan framework to build the thapsane skeleton, poses a synthetic challenge. In continuation of our interest in the synthesis of sesquiterpenes containing multiple contiguous quaternary carbon atoms,[5,6] we report the first total synthesis of a natural thapsane (**1g**),[6] featuring a Claisen rearrangement and an intramolecular diazo ketone cyclopropanation reaction for the construction of vicinal quaternary carbon atoms.

Chart I



The retrosynthetic analysis of thapsane, based on the Claisen rearrangement[7] and intramolecular diazo ketone cyclopropanation[8] reactions, readily identified the hydrindanone **6**, cyclopropyl β-keto ester **7**, and β-keto ester **8** as key intermediates with cyclogeraniol (**9**) as the starting material (Scheme I). Cyclogeraniol (**9**) which contains a single quaternary carbon atom was obtained from β-ionone by controlled ozonation[9] followed by direct reduction of the ozonide with sodium borohydride.[5g] The second quaternary carbon atom was introduced using a Claisen rearrangement (Scheme II). Thus, Claisen rear-

† Dedicated to Professor Gilbert Stork.

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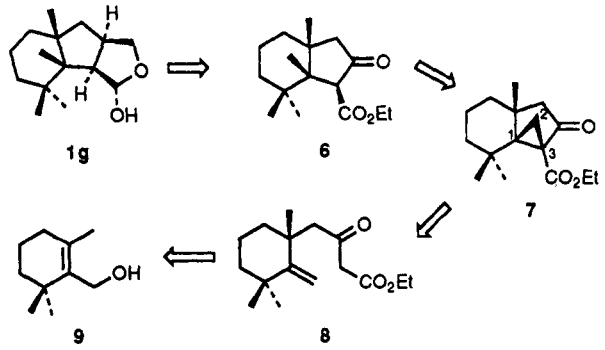
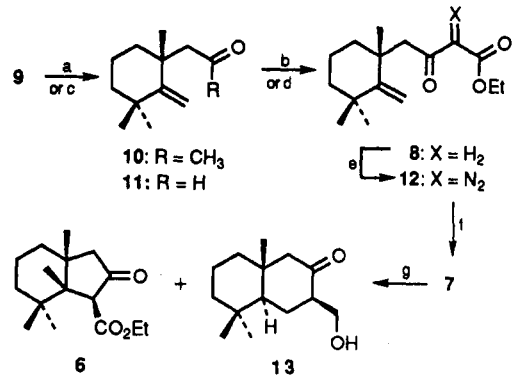
Scheme I



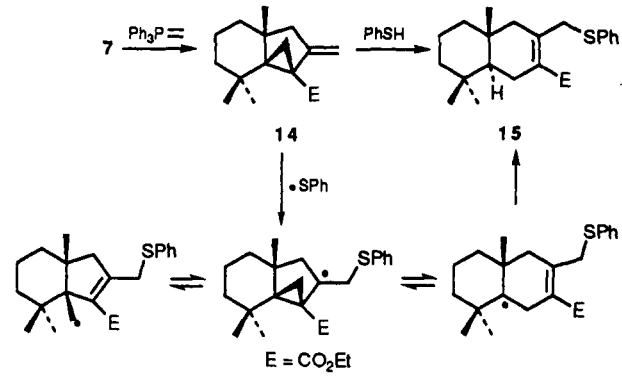
Scheme II[a]



[a] Conditions: (a) CH_2=C(OMe)CH_3, EtCOOH, PhMe, 160 °C (for **10**); (b) LHMDS, THF, ClCOOEt, −78 °C → rt (from **10**); (c) CH_2=CHOEt, $Hg(OAc)_2$, PhMe, 180 °C (for **11**); (d) $N_2CHCOOEt$, $SnCl_2$, CH_2Cl_2 (from **11**); (e) TsN_3, Et_3N, MeCN; (f) $Rh_2(OAc)_4$, C_6H_6, rt; (g) Li, liquid NH_3, THF.

rangement[5c,7b] of cyclogeraniol (**9**) with methoxypropene and a catalytic amount of propionic acid in toluene in a sealed tube (150–160 °C) furnished ketone **10** in 65% yield. Generation of the kinetic enolate of ketone **10** with lithium hexamethyldisilazide in dry THF at −78 °C, followed by quenching with ethyl chloroformate, furnished β-keto ester **8** in 80% yield. Alternatively, **8** was also obtained via the Lewis acid[10] catalyzed intermolecular insertion of ethyl diazoacetate to aldehyde **11**. Treatment of aldehyde **11** (obtained from **9** via the Claisen rearrangement with ethyl vinyl ether and mercuric acetate)[11] with ethyl diazoacetate in the presence of $SnCl_2$ furnished β-keto ester **8** in 70% yield. The third quaternary carbon was introduced in a stereospecific manner using an intramolecular diazo ketone cyclopropanation reaction. Diazo transfer reaction of β-keto ester **8** with tosyl azide in the presence of triethylamine in acetonitrile, afforded diazo compound **12** in 83% yield. Rhodium acetate-catalyzed decomposition of **12** in benzene at room temperature[12] furnished stereospecifically cyclopropyl compound **7**, in 65% yield. The reductive cleavage of the cyclopropane ring in keto ester **7** with lithium in liquid ammonia at −33 °C furnished a 1:1 mixture of hydrindanone **6** and ketol **13** in 64% yield. Products **6** and **13** were formed by the selective cleavage

Scheme III



of either C_3–C_2 or C_3–C_1 bonds of cyclopropane. It is well established[13] that in the lithium–liquid ammonia reductive cleavage of cyclopropyl ketones, the cyclopropane bond which overlaps best with the p-orbital of the carbonyl carbon will be cleaved. Accordingly, transfer of an electron to the ketone carbonyl results in the cleavage of the C_3–C_2 bond leading to β-keto ester **6**. On the other hand, transfer of an electron to the ester carbonyl results in the cleavage of the C_3–C_1 bond, because in the sterically less-hindered conformation the C_3–C_1 bond has better overlap with the π-system of the carbonyl of ester, followed by further reduction leading to ketol **13**. This is further supported by the fact that a primary alcohol was obtained from the ester, analogous to the lithium–ammonia reduction of α,β-unsaturated esters to the corresponding primary alcohols.[14] The trans ring junction was assigned based on analogy with known octalone reductions[15] and the stereochemistry at C_4 was assigned based on thermodynamic considerations.[13d]

It was anticipated that the generation of a radical at C-4 of the tricyclo[4.4.0.$0^{1,3}$]decane system would lead to opening of the cyclopropane in the desired fashion, generating a hydrindane with a methyl group at the ring junction. Addition of •SPh to the vinyl cyclopropane moiety of ester **14** was explored for the generation of the radical at C-4 (Scheme III). Ester **14** was prepared from **7** via Wittig olefination, with methylenetriphenylphosphorane[17] at room temperature in 75% yield. Treatment of vinyl cyclopropane **14** with 1 equiv of thiophenol in refluxing benzene for 12 h afforded ester **15** in 72% yield. The formation of product **15** can be explained by a homoallyl–cyclopropylmethyl–homoallyl radical rearrangement.[18] The cyclopropylmethyl radical generated by the addition of thiophenol leads to the formation of a homoallyl radical which is in equilibrium with the thermodynamically more stable homoallyl radical leading to the formation of ester **15**.

Alternatively, treatment of ketol **16**[13d] with lithium–ammonia furnished hydrindanone **17**. The hydroxy group in ketol **17** was protected as its TBDMS ether **18** and the final carbon atom required for the thapsane framework was introduced using a Wittig methylenation (Scheme IV).

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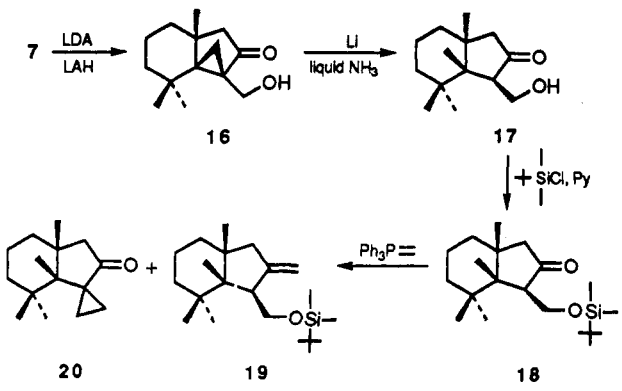
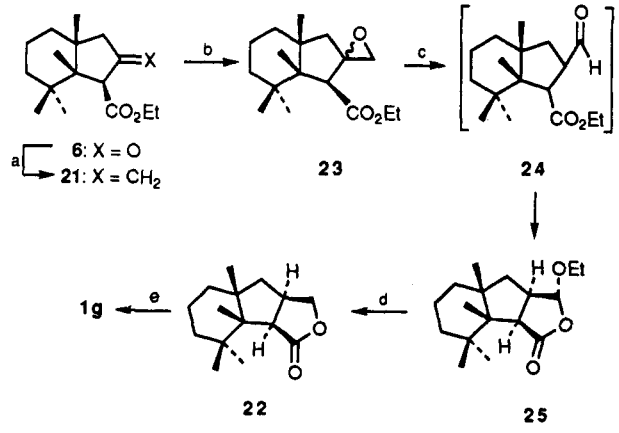
Scheme IV



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.