Spiroannulation Approach to Pentalenene, an Angular Triquinane Sesquiterpene

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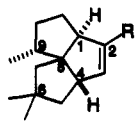
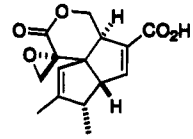
The route to the angular triquinane (±)-pentalenene (**1a**) followed from an efficient geminal acylation of the acetal of isophorone or its homolog **6b** by 1,2-bis((trimethylsilyl)oxy)cyclobutene (**3**) in the presence of boron trifluoride etherate. Ring cleavage and reclosure (**9** → **11**) secured the required spiro[4.4]nonane system with a pendant ketone function in place for the closure of the final, central ring. The relative stereochemistry at C-9 was established during hydrogenation over palladium of the C-3 double bond of **11**, but the facial selectivity was determined by the mode of reduction of the conjugated, orthogonal double bond at C-6 of **11**. After cyclization to the enone **17b**, the synthesis was completed by reductions of both the double bond and the ketone and simple dehydration. The 9-*epi* isomer (**26**) of (±)-pentalenene was synthesized also.

Introduction

Pentalenene (**1a**) and deoxypentalenic acid (**1b**) are biosynthetic precursors of pentalenolactone (**2**) and the other members of that family of sequiterpenoid antibiotics.[1] The angular triquinane structure of **1a** has been the target of a number of synthetic approaches.[2] The strategies involved in the previous approaches centered mainly on the formation of fused cyclopentane rings. In this paper[3] we present a novel spiro-annulation strategy that compares favorably with the published routes for the synthesis of (±)-pentalenene (**1a**). Our approach is based



1a R = Me
1b R = CO_2H



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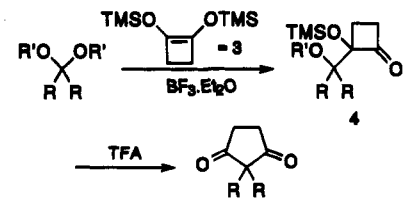
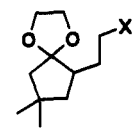
on a Lewis acid-catalyzed geminal acylation reaction of 1,2-bis((trimethylsilyl)oxy)cyclobutene (**3**) with an acetal of a ketone to give a 2,2-disubstituted 1,4-cyclopentanedione derivative (Scheme I). Kuwajima[4] introduced this transformation in a two-step procedure that involved isolation of a cyclobutanone intermediate (**4**). We modified this so that a one-pot process can now provide the spiro

Scheme I



diketone product directly.[5,6] However, the process is very sensitive to steric hindrance about the acetal carbon leading to much reduced yields.[6] Therefore, an efficient strategy demands an unencumbered ketal, so it is clear that the most obvious route, which would involve spiro-annulation onto a substrate like **5**, would not be viable.



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Results and Discussion

Scheme II summarizes our assembly of the triquinane skeleton. Acetalization of isophorone (**6a**) with ethane-1,2-diol under standard conditions was slow, but this generated mainly the desired double-bond-isomerized ketal **7a** along with unreacted **6a**. Treatment of the acetal with 3 equiv of **3** and 15 equiv of BF_3·Et_2O in CH_2Cl_2 at −78 °C provided the spiro-annulated diketone **8a** in a good yield. The position of the double bond in **8a** was established by NOE measurements. Addition of 5 equiv of methyllithium to **8a** led to the formation of the keto alcohol **9a** with almost complete diastereoselectivity. NOE measurements established that **9a** resulted by addition of the methyllithium to the face of the cyclopentanedione ring anti to the *gem*-dimethyl groups. Ozonolysis of **9a** provided the unstable intermediate **10a**, which, without purification, was cyclized with concomitant dehydration of the tertiary alcohol under acid catalysis to the [4.4] spiro system **11a** in 79% yield from **9a**. An attempt to

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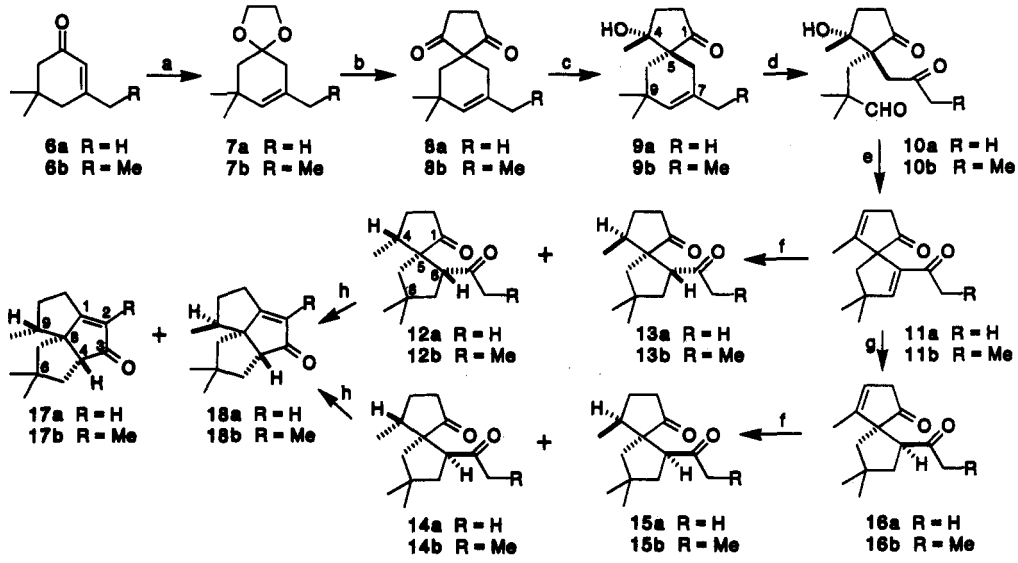
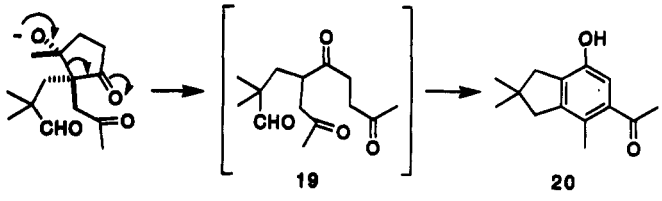
Scheme II[a]



[a] Reaction conditions: (a) $(CH_2OH)_2$, *p*-TsOH, C_6H_6; (b) 3, $BF_3{\cdot}Et_2O$, −78 °C to rt; (c) 5 equiv MeLi, THF, −78 °C; (d) (i) O_3, (ii) Me_2S; (e) *p*-TsOH, C_6H_6; (f) H_2, Pd–C; (g) 1. Li, NH_3; 2. PCC (h) KO-*t*-Bu.

Scheme III



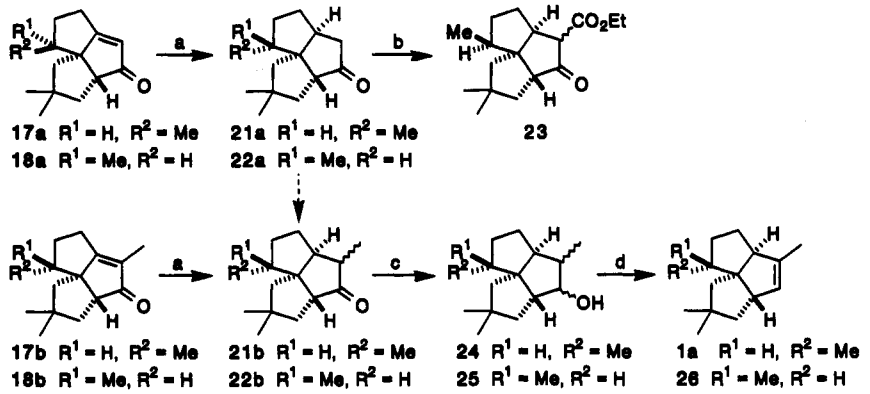
induce the aldol cyclization of **10a** with NaOMe led to an aromatic product (**20**) exclusively, presumably via retro-aldol condensation to **19** and alternative modes of recyclization (Scheme III). The C-3 double bond of **11a** would not move into conjugation, which removed the possibility at this stage of establishing an ultimately favorable relative stereochemistry at C-4 by equilibration.

Catalytic hydrogenation of **11a** over palladium yielded a mixture only two of the four possible diastereomeric products, **12a** and **13a**, which were inseparable by flash chromatography. The ^{13}C NMR shifts of C-1 were the same in both isomers, which suggested that these were of the same relative stereochemistry at C-6, but they were undoubtedly different at the nonepimerizable center (C-4) because aldol cyclization of this mixture with potassium *tert*-butoxide led to a mixture of tricyclic enones **17a** and **18a** (1:3.5). The major isomer was the latter, which had the incorrect stereochemistry at C-4. Nevertheless, the base-induced aldol cyclization of both had been smooth and rapid in spite of significant strain in the new carbon–carbon double bond as reflected in the unusually low-field ^{13}C NMR resonances for C-1 of the triquinane (δ 194.4 and 192.2 for **17a** and **18a**, respectively). The stereochemistry at C-9 of the triquinanes was determined by NOE measurements. For **17a** significant NOEs were observed for both the hydrogen on C-4 and one of the C-7 hydrogens on saturation of the doublet for the C-9 methyl because in this isomer the C-9 methyl was roughly equidistant to the aforementioned hydrogens. In contrast, in **18a** the C-9 methyl was close to the C-4 hydrogen but anti to C-7, which was too far for a significant NOE on saturation of the methyl doublet. Also, in the ^{13}C NMR spectra the C-7 signal of **17a** was more than 10 ppm upfield of the comparable signal for **18a**, which was consistent with a large γ_{gauche} effect in **17a**.

Although catalytic hyrogenation of **11a** produced mainly the undesired isomer **13a**, it was encouraging that the ratio was only 1:3.5, i.e., hydrogenation *did* take place to a significant extent on to the face of the C-3,4 double bond that was plainly hindered by the acetyl group ("syn"). It was possible that **12a** arose, at least partly, by isomerization of the double bond of **11a** into conjugation (C-2,3). In this process the C-4 stereogenic center might have been established with the methyl group assuming a thermodynamically-preferred stereochemistry. It this were indeed the case, then one might expect the proportion of the apparent syn-addition product to increase if the acetyl group could be made to hinder the C-3,4 double bond more effectively. Dissolving metal reduction of **11a** yielded a mixture of alcohols, but all of these converged to a single diketone product (**16a**) by PCC oxidation, but signal overlap in the ^1H NMR of **16a** gave the ambiguous results in NOE experiments to establish directly its relative stereochemistry. We were unable to find conditions under which **16a** would cyclize to a triquinane. Catalytic hydrogenation of **16a** over palladium provided a mixture of only the two isomeric products that had been absent in the direct hydrogenation of **11a**, i.e., **14a** and **15a**, in a ratio of 2:1, this time favoring the isomer with the desired stereochemistry at C-4. These were separated by flash chromatography. Aldol cyclization of each required epimerization at C-6, which was consistent with the somewhat more vigorous reaction conditions than were needed for **12a** and **13a**. In small-scale reactions, mixtures of **17a** and **18a** were hydrogenated over palladium quantitatively, but subsequent α-methylation of **21a** and **22a** was unexpectedly tricky, due to the coproduction of significant amounts of unmethylated and doubly methylated material, which was difficult to separate from the desired monomethylated product. Nevertheless, it was possible to α-acylate **22a** to produce compound **23** that is similar to deoxypentalenic acid (**1b**) (Scheme IV).

For pentalenene itself it was better to apply the reaction conditions already worked out to a sequence starting with **6b**. This proved to be less tidy in the earlier stages, but

Scheme IV[a]



[a] Reaction conditions: (a) H_2, Pd–C; (b) KH, $O(CO_2Et)_2$; (c) $NaBH_4$, MeOH; (d) *p*-TsOH, C_6H_6, reflux.

having just gained experience with the sequence starting from isophorone it was possible from **6b** to effect quickly sequences of reactions without isolation of the products. Ultimately, this proved superior in terms of overall yield. The major product of acetalization was **7b**, but it was accompanied by significant amounts of both isomers with exocyclic double bonds, which were chromatographically very similar to **7b**. Therefore, the sequence from **7b** was carried out with isomeric mixtures until separation became straightforward, i.e., after the production of **11b**. As before, catalytic hydrogenation of **11b** gave a mixture of diketones (**12b** and **13b**). Both cyclized easily with KO-*t*-Bu to give a 1:5 mixture of **17b** and **18b**, in which the product with the undesired stereochemistry at C-9 predominated. Also, in parallel with the initial sequence, dissolving metal reduction of **11b** yielded a single isomer (**16b**) after PCC oxidation. Just as with **16a**, **16b** would not cyclize to a triquinane, but after catalytic hydrogenation, presumably to **14b** and **15b**, the crude product mixture was immediately cyclized to give **17b** and **18b** in a ratio of 4:1 in favor of the former, desired isomer. (The ^{13}C NMR shifts for C-1 were δ 186.6 for **17b** and δ 184.3 for **18b**.) Indeed, greater stereoselectivity in the catalytic reduction of **16b** than in the case of **16a** was consistent with the larger 1-oxopropyl group of **16b** exerting a correspondingly greater influence on the development of the thermodynamically preferred stereochemistry at C-4 in the reduced product. The isomers **17b** and **18b** were separable by chromatography over $AgNO_3$-impregnated SiO_2.

Catalytic hydrogenation of **17b** and **18b** to **21b** and **22b** and $NaBH_4$ reduction gave epimeric mixtures of alcohols **24** and **25**.[7] It is curious that Crimmins and DeLoach[2d] experienced difficulty with the dehydration of **24**, as we found that dehydration of both **24** and **25** was straightforward using *p*-TsOH in benzene. From **24** the product was pentalenene (**1a**), and from **25** the product was 9-*epi*-pentalenene (**26**). The spectra (IR, ^1H and ^{13}C NMR) of these final products were in complete agreement with those of authentic materials.[8]

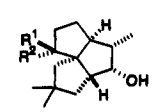
Experimental Section

General. All reactions were performed under nitrogen. Flash column chromatography ("chromatography") employed 230–400-mesh silica gel; the composition of the eluting solvent is given in parentheses. "Ether" refers to diethyl ether; "petroleum ether" refers to a hydrocarbon fraction boiling in the range 30–60 °C. IR spectra (cm^{-1}) were recorded as neat liquids. ^1H NMR spectra were obtained at 300 MHz in $CDCl_3$ solution unless otherwise noted; chemical shifts (δ) are relative to internal TMS, coupling constants (J) are in hertz. NOE measurements were made with difference spectra,[9] using previously described parameters.[10] NOE data take this form: saturated signal (enhanced signal, enhancement). ^{13}C NMR spectra are at 75 MHz in $CDCl_3$ unless otherwise noted; chemical shifts (δ) are relative to a solvent resonance, and following each shift the number of attached protons is provided, based on APT and heteronuclear correlation spectra. MS data are m/z (relative intensity compared to that of largest peak).

3-Ethyl-5,5-dimethylcyclohex-2-en-1-one (6b). A 3.0 M solution of EtMgBr (1.4 mL, 4.2 mmol) in ether was added cautiously to an ice-cooled solution of 3-ethoxy-5,5-dimethylcyclohex-2-en-1-one[11] (440 mg, 2.62 mmol) in anhyd THF (30 mL). The mixture was warmed to reflux and then maintained at that temperature for 1 h. The cooled solution was poured slowly into a cold aqueous 10% HCl solution, and the mixture was stirred overnight. Extraction with ether (×4) provided an organic solution that was washed with water (×3), 10% NaOH solution (×3), water again (×3), and brine (×2). The organic solution was dried ($MgSO_4$) and the solvent was removed under vacuum to give **6b** as a liquid (389 mg, 98%). IR: 1720, 1631. ^1H NMR δ: 5.88 (1H, br s), 2.22 (2H, s), 2.21 (2H, q, J = 7.4), 2.19 (2H, s), 1.10 (3H, t, J = 7.4), 1.04 (6H, s). ^{13}C NMR δ: 200.9 (0), 165.5 (0), 123.3 (1), 50.9 (2), 43.8 (2), 33.4 (0), 30.8 (2), 28.1 (2C, 3), 11.1 (3). MS: 152 (8, M^+), 96 (47), 81 (35), 77 (22), 68 (70), 67 (100).

7,9,9-Trimethyl-1,4-dioxaspiro[4.5]dec-7-ene (7a). A solution of isophorone (2.19 g, 15.2 mmol), 1,2-ethanediol (4.2 mL, 76 mmol), and *p*-TsOH (300 mg) in benzene (100 mL) was heated at reflux overnight with a Barrett water separator. Solid $NaHCO_3$ was added and then H_2O. The aqueous layer was extracted with ether (×3), and the combined extracts were washed with brine. The organic solution was dried (anhyd K_2CO_3) and concentrated under vacuum. A quick distillation under vacuum of the residue removed the yellow color, and chromatography (1% acetone in

(7) Dissolving metal reduction of a mixture of **17b** and **18b** provided only two alcohols for which the ^1H NMR data of one were in agreement with **27**, which Crimmins and DeLoach[2d] produced by a different route. Thus, it was likely that the other isomer differed only at C-9, i.e., tentatively **28**. However, the yield in this reduction was relatively low (60% in the best of several small-scale trials).



27 R¹ = H, R² = Me
28 R¹ = Me, R² = H

(8) We are grateful to Professor E. Piers of the University of British Columbia for providing the spectra of **1a** and **26**.

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petroleum ether) provided **7a** (1.72 g, 62%) and 0.65 g (31%) of recovered isophorone.[12] For **7a**: ^{1}H NMR δ: 5.15 (1H, s), 3.93 (4H, s), 2.12 (2H, s), 1.66 (3H, s), 1.59 (2H, s), 1.04 (6H, s). ^{13}C NMR δ: 130.9 (1), 127.6 (0), 108.8 (0), 63.7 (2C, 2), 43.3 (2), 39.5 (2), 33.9 (0), 30.1 (2C, 3), 23.1 (3). MS: 182 (46, M$^+$), 167 (20), 96 (34), 87 (23), 86 (100).

7-Ethyl-9,9-dimethyl-1,4-dioxaspiro[4.5]dec-7-ene (7b). A solution of **6b** (3.40 g, 22.4 mmol), 1,2-ethanediol (6.2 mL, 112 mmol), and *p*-TsOH (400 mg) was treated as above. After the aqueous washes the organic solution was dried ($MgSO_4$). Quick distillation under vacuum of the residue removed the yellow color, and chromatography (1.5% acetone in petroleum ether) of the distillate provided 1.30 g (62%) a 4.5:1 mixture of **7b** and both exocyclic isomers as well as 1.40 g (28%) of recovered **6b**. NMR signals of **7b** from the mixture. ^{1}H NMR δ: 5.14 (1H, br s), 3.95 (4H, s), 2.15 (2H, s), 1.97 (2H, q, J = 7.3), 1.62 (2H, s), 1.05 (6H, s), 1.00 (3H, t, J = 7.3). ^{13}C NMR δ: 133.4 (0), 129.3 (1), 109.2 (0), 64.0 (2C, 2), 43.7 (2), 38.3 (2), 34.0 (0), 30.4 (2C, 3), 30.0 (2), 12.0 (3). MS (from GC-MS): 196 (11, M$^+$), 110 (34), 95 (49), 87 (34), 86 (100). For the exocyclic isomers, MS (from GC-MS): 196 (1, M$^+$), 140 (6), 127 (100), 86 (11), 83 (17).

7,9,9-Trimethylspiro[4.5]dec-7-ene-1,4-dione (8a). A solution of **7a** (722 mg, 3.42 mmol) in dry CH_2Cl_2 (60 mL) was stirred at −78 °C while freshly distilled BF_3·Et_2O (7.0 mL, 57 mmol) was added, followed, dropwise, by a solution of **3**[13] (3.0 mL, 11 mmol) in dry CH_2Cl_2 (10 mL). The solution was allowed to attain rt while being stirred overnight. The mixture was poured slowly to cold saturated $NaHCO_3$, and the aqueous layer was reextracted with CH_2Cl_2 (×3). The combined organic extracts were washed with saturated $NaHCO_3$ (×2) and brine (×2), then dried ($MgSO_4$), and concentrated under vacuum. Chromatography of the dark residue (10–16% EtOAc in hexane) gave **8a** as a colorless solid (601 mg, 85%): mp 85–86 °C. IR: 1721. ^{1}H NMR δ: 5.20 (1H, br s), 3.05 (2H, m), 2.63 (2H, m), 2.03 (2H, br s), 1.76 (3H, s), 1.66 (2H, s), 0.94 (6H, s); NOE data: 5.20 (1.76, 1%; 0.94, 1.5%), 0.94 (5.20, 17%; 1.66, 7%). ^{13}C NMR δ: 214.2 (2C, 0), 129.6 (1), 128.7 (0), 59.0 (0), 43.3 (2), 34.7 (2C, 2), 32.8 (0), 30.1 (2C, 3), 29.1 (2), 23.6 (3). MS: 206 (100, M$^+$), 191 (22), 178 (11), 163 (31), 149 (14), 145 (28), 131 (31), 107 (21), 91 (21). HRMS: calcd for $C_{13}H_{18}O_2$ 206.1306, found 206.1306.

7-Ethyl-9,9-dimethylspiro[4.5]dec-7-ene-1,4-dione (8b). A solution of the 4.5:1 mixture of **7b** and its exocyclic isomers (300 mg, 1.53 mmol) in dry CH_2Cl_2 (50 mL) was stirred at −78 °C while freshly distilled BF_3·Et_2O (1.88 mL, 15.3 mmol) was added, followed, over 10 min, by a solution of **3**[13] (1.22 mL, 4.59 mmol) in CH_2Cl_2 (20 mL). The solution was allowed to attain rt while being stirred overnight. The mixture was poured slowly into cold saturated $NaHCO_3$, and the aqueous layer was reextracted with CH_2Cl_2 (×3). The combined organic extracts were washed with saturated $NaHCO_3$ (×2) and brine (×2), then dried ($MgSO_4$), and concentrated under vacuum. Chromatography of the very dark residue (3% acetone in petroleum ether) provided 259 mg (77%) a 4.5:1 mixture of **8b** and both exocyclic isomers, and 26 mg (11%) of **6b** was recovered. NMR signals for **8b** from the mixture. ^{1}H NMR δ: 5.04 (1H, br s), 2.84 (4H, m), 2.05 (2H, q, J = 7.4), 1.82 (2H, s), 1.63 (2H, s), 1.004 (3H, t, J = 7.4), 0.998 (6H, s). ^{13}C NMR δ: 212.4 (2C, 0), 144.5 (0), 111.3 (1), 62.7 (0), 41.5 (2), 37.8 (2), 34.5 (2C, 2), 30.8 (2), 30.6 (0), 29.1 (2C, 3), 11.7 (3). MS (from GC-MS): 220 (88, M$^+$), 205 (41), 192 (24), 177 (84), 163 (62), 159 (57), 145 (81), 93 (57), 91 (100), 79 (57), 77 (82), 55 (94), 53 (50), 43 (65), 41 (99). MS (from GC-MS) for the two exocyclic isomers: 220 (82, M$^+$), 205 (76), 191 (14), 177 (46), 164 (24), 163 (31), 149 (44), 135 (27), 121 (74), 107 (66), 105 (43), 93 (61), 91 (93), 85 (46), 79 (71), 77 (86), 55 (84), 53 (49), 43 (48), 42 (49), 41 (100); 220 (33, M$^+$), 205 (12), 192 (32), 178 (30), 177 (89), 163 (34), 135 (24), 121 (31), 107 (30), 105 (23), 93 (34), 91 (49), 79 (50), 67 (36), 65 (27), 55 (76), 53 (47), 43 (50), 41 (100).

***rel*-(4*R*,5*R*)-4-Hydroxy-4,7,9,9-tetramethylspiro[4.5]dec-7-en-1-one (9a).** A solution of **8a** (89 mg, 0.43 mmol) in dry ether (30 mL) was maintained at −78 °C while a 1.4 M solution of MeLi in ether (1.5 mL, 2.2. mmol) was slowly added. (The solution became cloudy during this addition.) The mixture was stirred for another 2 h at −78 °C and then it was poured onto ice-cold brine. More water was added and the aqueous layer was reextracted with ether (×3). The combined organic layers were washed with brine (×2), dried ($MgSO_4$), and concentrated under vacuum. Chromatography (2% acetone in petroleum ether) of the oily residue provided, in order of elution, 2.6 mg (3%) of **8a**, **9a** (83 mg, 86%) as a colorless oil, and 1.3 mg (1.4%) of the C-4 epimeric product. For **9a**. IR: 3426 (br), 1730. ^{1}H NMR: δ 5.18 (1H, br s), 2.56 (1H, m), 2.21 (2H, m), 1.88 (1 H, br m), 1.83 (1H, s, OH), 1.79 (2H, br s), 1.73 (3H, s), 1.73 (1H, d, J = 13.4) and 1.69 (1H, d, J = 13.4) as an AB quartet, 1.15 (3H, s), 1.00 (3H, s), 0.90 (3H, s). NOE data: 5.18 (1.73, 1%; 1.00, 1%, 0.90, 0.5%), 1.15 (1.79, 5%), 1.00 (5.18, 14%; AB quartet, 4%), 0.90 (5.18, 9%; AB quartet, 3%). ^{13}C NMR: δ 220.0 (0), 130.6 (1), 128.9 (0), 78.1 (0), 55.9 (0), 37.9 (2), 34.1 (2), 33.6 (2), 32.8 (3), 32.2 (0), 30.5 (2), 28.6 (3), 24.3 (3), 23.9 (3). MS: 222 (39, M$^+$), 189 (14), 164 (22), 149 (21), 147 (20), 131 (22), 123 (22), 107 (20), 99 (44), 43 (100). HRMS: calcd for $C_{14}H_{22}O_2$ 222.1618, found 222.1605. For the ***rel*-(4*R*,5*S*)** epimer of **9a**. ^{1}H NMR: δ 5.18 (1H, br s), 2.51–1.81 (7H, m), 1.78 (3H, s), 1.56 (1H, apparent dt), 1.36 (1H, d, J = 13.5), 1.29 (3H, s), 0.97 (3H, s), 0.86 (3H, s). MS: 222 (14, M$^+$), 189 (7), 149 (13), 147 (18), 107 (19), 105 (11), 99 (45), 91 (21), 83 (13), 43 (100).

6-Acetyl-4,8,8-trimethylspiro[4.4]nona-3,6-dien-1-one (11a). Ozone was passed through a solution of **9a** (100 mg, 0.45 mmol) in CH_2Cl_2 (15 mL) at −78 °C until the solution became blue. Excess ozone was displaced by a stream of O_2. Dimethyl sulfide (2 mL) was added, and the mixture was stirred overnight under N_2 during which time it was allowed to warm to rt. Concentration under vacuum provided crude **10a**. MS (from GC-MS): no M$^+$, 210 (1), 182 (9), 167 (9), 164 (9), 164 (9), 155 (17), 139 (14), 123 (21), 122 (14), 121 (18), 110 (14), 109 (18), 107 (35), 95 (33), 93 (20), 84 (16), 81 (31), 79 (29), 77 (18), 71 (20), 67 (32), 55 (31), 53 (19), 43 (100), 41 (50). This crude product was redissolved in benzene (20 mL) and *p*-TsOH (20 mg) was added. The solution was heated at reflux with a Barrett water separator for 2 h. After cooling, saturated $NaHCO_3$ was added, and the aqueous layer was reextracted with ether (×3). The combined organic solutions were washed with saturated $NaHCO_3$ (×3) and brine, dried ($MgSO_4$), and concentrated under vacuum to leave an oily black residue, from which chromatography (2% acetone in petroleum ether) provided **11a** (78 mg, 79%) as a colorless oil. IR: 1741, 1671, 1626. ^{1}H NMR: δ 6.69 (1H, s), 5.77 (1H, apparent narrow q), 3.18 (1H, d of apparent quintets, J = 22.7, 2.2), 2.85 (1H, d of apparent quintets, J = 22.7, 2.2), 2.26 (3H, s), 1.92 (1H, d, J = 13.9), 1.72 (1H, d, J = 13.9), 1.64 (3H, apparent q, J = 1.6), 1.31 (3H, s), 1.26 (3H, s); COSY confirmed an unusually large $^5J_{H-H}$ coupling between 3.18 and 2.85 (C-2H$_2$) and 1.64 (C-4Me). ^{13}C NMR: δ 219.3 (0), 195.3 (0), 157.1 (1), 142.7 (0), 141.7 (0), 121.5 (1), 68.3 (0), 46.5 (2), 45.5 (0), 41.9 (2), 29.7 (3), 29.1 (3), 26.5 (3), 14.6 (3). MS: 218 (37, M$^+$), 190 (12), 175 (82), 147 (38), 133 (32), 91 (20), 43 (100). HRMS: calcd for $C_{14}H_{18}O_2$ 218.1305, found 218.1293.

4,8,8-Trimethyl-6-(1-oxopropyl)spiro[4.4]nona-3,6-dien-1-one (11b) from the Mixture of 8b and Its Isomers. Following the procedure for **9a**, 200 mg (0.91 mmol) of the 4.5:1 mixture of **8b** and its isomers was treated with MeLi (3.3 mL of a 1.4 M solution) to give a mixture of keto alcohols. GC-MS analysis showed **9b** was the major product. MS: 236 (54, M$^+$), 203 (17), 178 (30), 163 (20), 161 (18), 145 (26), 137 (33), 99 (69), 91 (21), 55 (26), 43 (100). Without purification this mixture was dissolved in CH_2Cl_2 (50 mL) and ozonolysis was carried out as for **10a**. The crude product (presumably the unstable tetrafunctional compound **10b**) was redissolved in C_6H_6 (50 mL) to which *p*-TsOH (35 mg) was added, and this solution was heated at reflux with a Barrett water separator for 2 h. Workup (as for **11a**) provided a black residue, but chromatography (4% acetone in petroleum ether) yielded **11b** as a colorless oil (133 mg, 63% from the mixture of **8b** and its isomers). IR: 1748, 1672. ^{1}H NMR: δ 6.68 (1H, s), 5.76 (1H, narrow m), 3.20 (1H, d of apparent quintets, J = 22.7, 2.3), 2.85 (1H, d of apparent quintets, J = 22.7, 2.3), 2.64

(12) We are unable to optimize the reaction time when the reaction was run in toluene, *cf.* Constantino, M. G.; Nonate, P. M.; Petragnani, N. *J. Org. Chem.* **1986**, *51*, 253. GC-MS analysis showed that a buildup of oligomeric material of long retention time was competitive in rate with the consumption of the starting isophorone.

(13) (a) Bloomfield, J. J. *Tetrahedron Lett.* **1968**, 587. (b) Bloomfield, J. J.; Nelke, J. M. *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. VI, p 167. It is important in these double acylation reactions that **3** be very pure.[6]

(2H, symmetrical m), 1.90 (1H, d, J = 13.9), 1.71 (1H, d, J = 13.9), 1.62 (3H, br d, J = 1.7), 1.30 (3H, s), 1.25 (3H, s), 1.03 (3H, t, J = 7.3); COSY confirmed an unusually large $^5J_{H-H}$ coupling between 3.20 and 2.85 (C-2H_2) and 1.62 (C-4Me). ^{13}C NMR: δ 219.1 (0), 198.1 (0), 155.5 (1), 142.0 (0), 141.6 (0), 121.3 (1), 68.4 (0), 52.0 (0), 46.2 (2), 41.8 (2), 31.6 (2), 29.6 (3), 29.0 (3), 14.5 (3), 7.8 (3). MS: 232 (45, M$^+$), 217 (16), 189 (33), 176 (28), 175 (100), 161 (26), 147 (45), 133 (26), 91 (24), 57 (75), 41 (20). HRMS: calcd for $C_{15}H_{20}O_2$ 232.1463, found 232.1460.

***rel*-(4*R*,5*R*,6*R*)- and *rel*-(4*R*,5*S*,6*S*)-6-Acetyl-4,8,8-trimethylspiro[4.4]-nonan-1-one (12a and 13a).** A suspension of **11a** (89 mg, 0.41 mmol) in dry MeOh (30 mL) and 100 mg of 5% Pd/C was shaken under 3 atm of H_2 for 1 h. This was filtered through a pad of Celite, and the filtrate was concentrated under vacuum. Chromatography (4% acetone in petroleum ether) of the residue provided an oil (91 mg, 100%), which was composed of an inseparable mixture of **12a** and **13a** (1:3.5, respectively). Spectral data are for the mixture. IR: 1733, 1712. For **12a**: ^{1}H NMR: δ 2.91 (1H, dd, J = 6.9, 13.4), 2.60-1.46 (multiplets), 2.12 (3H, s), 1.13 (3H, s), 1.06 (3H, s), 1.00 (3H, d, J = 6.8). ^{13}C NMR: δ 224.3 (0), 209.5 (0), 60.6 (0), 58.2 (1), 44.1 (2), 41.7 (2), 38.7 (1), 37.8 (0), 37.3 (2), 30.2 (3), 29.9 (3), 29.2 (3), 29.0 (2), 14.4 (3). MS (from GC-MS): 222 (10, M$^+$), 179 (23), 166 (21), 152 (29), 138 (24), 123 (32), 121 (23), 95 (34), 81 (27), 55 (31), 43 (100), 41 (38). For **13a**. ^{1}H NMR: δ 3.23 (1H, dd, J = 6.4, 13.4), 2.12 (3H, s), 2.60–1.46 (multiplets), 1.86 (1H, d, J = 13.5), 1.31 (1H, d, J = 13.5), 1.18 (3H, s), 1.08 (3H, s), 1.05 (3H, d, J = 6.9). ^{13}C NMR: δ 224.3 (0), 209.1 (0), 59.5 (0), 58.7 (1), 52.1 (2), 45.6 (2), 41.4 (1), 38.3 (2), 37.3 (0), 30.6 (3), 29.3 (2C, 3), 28.7 (2), 15.5 (3). MS (from GC-MS): 222 (15, M$^+$), 194 (8), 180 (20), 179 (27), 161 (18), 147 (25), 138 (34), 123 (29), 121 (25), 119 (19), 107 (19), 95 (36), 91 (19), 81 (24), 55 (29), 43 (100), and 41 (36). HRMS (epimeric mixture): calcd for $C_{14}H_{22}O_2$ 222.1618, found 222.1612.

***rel*-(4*R*,5*R*,6*R*)- and *rel*-(4*R*,5*S*,6*S*)-4,8,8-Trimethyl-6-(1-oxopropyl)spiro[4.4]nonan-1-one (12b and 13b).** Hydrogenation of **11b** (279 mg, 1.20 mmol) and chromatography of the residue after workup provided an oil (284 mg, 100%), which was composed of **12b** and **13b** (1:5, respectively). Spectral data for the mixture. IR: 1731, 1711. For **24b**. ^{1}H NMR (clearly discernable signals only): δ 2.93 (1H, dd, J = 6.5, 6.9), 2.43 (2H, q, J = 7.3), 1.85 (1H, d, J = 13.7), 1.30 (1H, d, J = 13.7), 1.12 (3H, s), 1.05 (3H, s), 1.00 (3H, d, J = 7.2), 0.99 (3H, t, J = 7.4). ^{13}C NMR: δ 223.4 (0), 211.9 (0), 60.4 (0), 57.7 (1), 43.7 (2), 41.6 (2), 38.7 (1), 37.9 (0), 37.3 (2), 34.6 (2), 30.1 (3), 29.9 (3), 28.8 (2), 14.3 (3), 7.2 (3). MS (from GC-MS): 236 (22, M$^+$), 180 (57), 179 (60), 161 (51), 152 (58), 147 (49), 138 (48), 137 (30), 123 (32), 121 (30), 119 (43), 109 (29), 95 (38), 57 (100), 55 (50), 41 (49). For **13b**. ^{1}H NMR (clearly discernable signals only): δ 3.24 (1H, dd, J = 6.4, 7.0), 2.44 (2H, q, J = 7.2), 1.85 (1H, d, J = 13.7), 1.30 (1H, d, J = 13.7), 1.18 (3H, s), 1.08 (3H, s), 1.04 (3H, d, J = 7.0), 1.00 (3H, t, J = 7.2). ^{13}C NMR: δ 224.2 (0), 221.6 (0), 59.5 (0), 57.8 (1), 51.8 (2), 45.6 (2), 41.2 (1), 38.2 (2), 37.1 (0), 34.7 (2), 30.6 (3), 29.0 (3), 28.7 (2), 15.4 (3), 7.6 (3). MS (from GC-MS): 236 (28, M$^+$), 180 (66), 179 (49), 161 (31), 152 (42), 147 (48), 138 (58), 123 (27), 121 (28), 109 (27), 95 (35), 57 (100), 55 (47), 41 (50). HRMS (epimeric mixture): calcd for $C_{15}H_{24}O_2$ 236.1776, found 236.1773.

***rel*-(5*R*,6*S*)-6-Acetyl-4,8,8-trimethylspiro[4.4]non-3-en-1-one (16a).** Lithium (30 mg, 4.3 mmol) was added to liquid NH_3 (30 mL) at −78 °C followed by a solution of **11a** (206 mg, 0.95 mmol) in THF (10 mL). The temperature was raised to −33 °C, and the mixture was stirred for 30 min. Solid NH_4Cl was added, the cooling bath was removed, and the NH_3 was allowed to evaporate overnight. The residue was extracted into ether, and the organic solution was washed with brine (×2), dried ($MgSO_4$), and concentrated under vacuum. The residue was redissolved in CH_2Cl_2 (50 mL), PCC (614 mg, 2.85 mmol) was added, and this was stirred for 15 h. Filtration through a pad of Florisil removed the black precipitate, and ether was passed through the pad. The combined filtrates were concentrated under vacuum, and chromatography (2% acetone in petroleum ether) of the residue gave **16a** (167 mg, 81%) as a colorless oil. IR: 1745, 1710, 1643. ^{1}H NMR: δ: 5.70 (1H, br s), 3.51 (1H, dd, J = 6.3, 13.5), 2.98 (1H, dm, J = 23.4), 2.85 (1H, dm, J = 23.4), 2.04 (1H, t, J = 13.1), 1.93 (3H, s), 1.71–1.50 (6H, m), 1.15 (3H, s), 1.14 (3H, s). ^{13}C NMR δ: 220.9 (0), 207.7 (0), 144.2 (0), 121.0 (1), 64.0 (0), 60.1 (1), 49.4 (2), 43.5 (2), 41.5 (2), 37.8 (0), 29.7 (3), 29.2 (3), 28.7 (3), 15.4 (3). MS: 220 (14, M$^+$), 177 (45), 149 (20), 107 (43), 93 (48), 91 (21), 77 (20), 43 (100), 41 (35). HRMS: calcd for $C_{14}H_{20}O_2$ 220.1462, found 220.1457.

***rel*-(5*R*,6*S*)-4,8,8-Trimethyl-6-(1-oxopropyl)spiro[4.4]non-3-en-1-one (16b).** Following the procedure for **16a**, 89 mg (0.39 mmol) of **11b** in NH_3 (30 mL) and Li metal (13.5 mg) yielded, after PCC oxidation and chromatography (3% acetone in petroleum ether), **16b** (78 mg, 86%) as a colorless oil.[14] IR: 1745, 1709. ^{1}H NMR: δ 5.68 (1H, nar m), 3.49 (1H, dd, J = 6.1, 7.2), 2.98 (1H, d of apparent quintets, J = 25.6, 2.3), 2.83 (1H, d of apparent quintets, J = 25.6, 2.3), 2.28–1.95 (3H, m), 1.73–1.50 (6H, m, including 3H nar m at 1.69), 1.15 (3H, s), 1.14 (3H, s), 0.95 (3H, t, J = 7.2). ^{13}C NMR: δ 220.9 (0), 210.1 (0), 144.3 (0), 120.9 (1), 64.1 (1), 59.1 (1), 49.4 (2), 43.5 (2), 41.5 (2), 37.8 (0), 34.9 (2), 29.7 (3), 28.7 (3), 15.4 (3), 7.4 (3). MS: 234 (24, M$^+$), 177 (78), 149 (34), 107 (64), 93 (67), 91 (29), 57 (100), 41 (47). HRMS: calcd for $C_{15}H_{22}O_2$ 234.1619, found 234.1614.

***rel*-(4*R*,5*R*,6*R*)- and *rel*-(4*R*,5*S*,6*R*)-6-Acetyl-4,8,8-trimethylspiro[4.4]nonan-1-one (14a and 15a).** A suspension of **16a** (98 mg, 0,45 mmol) in dry MeOH (30 mL) and 250 mg of 5% Pd/C was shaken under 3 atm of H_2 for 1.5 h. This was filtered through a pad of silica gel, and the filtrate was concentrated under vacuum. Chromatography (4% acetone in hexane) of the residue provided, as colorless oils, **14a** (63 mg, 64%) and **15a** (36 mg, 36%). For **14a**. IR: 1735, 1708. ^{1}H NMR: δ 3.75 (1H, dd, J = 6.2, 13.6), 2.34 (1H, ddd, J = 1.0, 9.0, 19.4), 2.15 (1H, m), 2.00 (3H, s), 1.98 (1H, dd, J = 12.5, 13.6), 1.93–1.82 (2H, m), 1.75 (1H, d, J = 13.8), 1.55 (1H, ddd, J = 1.0, 6.2, 12.5), 1.34 (1H, m), 1.20 (1H, dd, J = 1.0, 13.8), 1.10 (3H, s), 1.04 (3H, d, J = 6.5), 1.03 (3H, s). ^{13}C NMR: δ 220.3 (0), 208.6 (0), 61.8 (0), 55.5 (1), 43.0 (2), 42.6 (2), 38.1 (1), 37.3 (0), 35.8 (2), 31.0 (3), 29.4 (3), 29.1 (3), 27.1 (2), 14.7 (3). MS: 222 (3, M$^+$), 207 (5), 179 (4), 161 (13), 152 (99), 137 (56), 123 (21), 110 (64), 109 (25), 95 (22), 81 (24), 55 (29), 43 (100). For **15a**. IR: 1733, 1707. ^{1}H NMR: δ 3.15 (1H, dd, J = 4.5, 9.1), 2.56 (1H, apparent br quintet, J ≈ 7.0), 2.38 (1H, dddd, J = 1.0, 2.8, 10.2, 18.9), 2.28 (1H, dd, J = 9.1, 13.4), 2.20 (1H, d, of apparent t, J ≈ 18.3, 9.0), 2.16 (3H, s), 2.06 (1H, m), 1.91 (1H, d, J = 13.5), 1.73 (1H, d, J = 13.5), 1.71 (1H, dd, J = 4.5, 13.4), 1.60 (1H, dddd, J = 2.1, 2.8, 8.8, 12.6), 1.02 (3H, s), 0.98 (3H, s), 0.76 (3H, d, J = 7.1). NOE data: 3.15 (2.16, 1%; 1.71, 6%), 2.56 (1.91, 8%; 0.76, 1%), 0.76 (3.15, 1.4%; 2.56, 0.8%). ^{13}C NMR: δ 221.2 (0), 210.7 (0), 64.9 (0), 55.1 (1), 51.1 (2), 43.9 (2), 39.2 (1), 37.9 (0), 32.9 (2), 31.8 (2C, 3), 30.1 (3), 26.3 (2), 17.4 (3). MS: 222 (8, M$^+$), 207 (7), 179 (19), 161 (33), 152 (60), 137 (30), 123 (35), 110 (17), 109 (23), 95 (36), 81 (27), 55 (31), 43 (100).

***rel*-(4*R*,8*R*,9*R*)- and *rel*-(4*R*,8*R*,9*S*)-6,6,9-Trimethyltricyclo[6.3.0.0^{4,8}]undec-1-en-3-one (17a and 18a) from 12a and 13a.** KO-*t*-Bu (184 mg, 1.64 mmol) was added to a solution of **12a** and **13a** (1:3.5 mixture, 182 mg, 0.82 mmol) in C_6H_6 (40 mL). After 20 min at rt TLC indicated that all the starting materials were consumed. H_2O (50 mL) was added, and the aqueous layer was extracted with ether (×3). The combined organic extracts were washed with brine (×2), dried ($MgSO_4$), and concentrated under vacuum to give a very pale yellow oil. Chromatography (2% acetone in petroleum ether) of this oil failed to separate the C-9 epimers **17a** and **18a**, which were recovered in a 1:3.5 ratio (141 mg, 84%). UV (MeOH): 240 (ε = 1150). For other spectral data see below.

***rel*-(4*R*,8*R*,9*R*)-6,6,9-Trimethyltricyclo[6.3.0.0^{4,8}]undec-1-en-3-one (17a) from 14a.** KO-*t*-Bu (76 mg, 0.68 mmol) was added to a solution of **14a** (70 mg, 0.32 mmol) in C_6H_6 (10 mL). The highly colored solution was heated at reflux for 20 min. After the solution was cooled to rt, aqueous 10% HCl was added. The aqueous layer was extracted with EtOAc (×3), and the combined organic layers were washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated under vacuum. Chromatography of the residue (2% acetone in hexane) provided **17a** (45 mg, 70%) as a colorless oil. IR: 1705, 1631. ^{1}H NMR ($CDCl_3$): δ 5.76 (1H, br s), 2.63–2.48 (2H, m), 2.40 (1H, br d, J = 9.8), 2.05–1.91 (2H, m), 1.81–1.43 (3H, m), 1.63 (1H, d, J =

(14) Contamination of the product in some experiments in which the dissolving metal reduction product was not worked up in a timely fashion appeared to be due to epimerization at C-6. An extra dd appeared in the ^{1}H NMR spectrum at δ 3.74 (C-6H).

13.2), 1.25 (1H, dd, J = 0.9, 13.2), 1.06 (3H, d, J = 6.6), 1.03 (3H, s), 0.89 (3H, s). ^{1}H NMR (C_6D_6): δ 5.65 (1H, br s), 2.21 (1H, br d, J = 9.8, C-4H), 2.15 (1H, br d, J = 13.2), 2.15–1.90 (2H, m), 1.56–1.43 (2H, m), 1.30 (1H, br d, J = 13.5, C-7H), 1.26–1.02 (2H, m), 0.92 (3H, s), 0.88 (3H, s), 0.87 (1H, m), 0.71 (3H, d, J = 6.5, C-9Me). NOE data (C_6D_6): 1.30 (0.71, 1.4%), 0.71 (2.21, 5%; 1.30, 7%). ^{13}C NMR: δ 214.7 (0), 194.4 (0), 123.9 (1), 64.9 (0), 57.8 (1), 42.9 (2), 41.3 (1), 41.0 (0), 39.4 (2), 32.6 (2), 31.5 (3), 29.2 (3), 25.5 (2), 14.6 (3). MS: 204 (83, M$^+$), 189 (22), 176 (1), 162 (48), 161 (39), 148 (100), 147 (80), 134 (49), 133 (56), 120 (65), 119 (62), 107 (90), 105 (62), 91 (86), 79 (37), 77 (54), 41 (56).

***rel*-(4*R*,8*R*,9*S*)-6,6,9-Trimethyltricyclo[6.3.0.0^{4,8}]undec-1-en-3-one (18a) from 15a.** KO-*t*-Bu (121 mg, 1.08 mmol) was added to a solution of **15a** (110 mg, 0.50 mg) in C_6H_6 (10 mL). The highly colored solution was heated at reflux for 15 min. After the solution was cooled to rt, aqueous 10% HCl was added. The aqueous layer was extracted with EtOAc (×3), and the combined organic layers were washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated under vacuum. Chromatography of the residue (2% acetone in hexane) provided **18a** (64 mg, 63%) as a colorless oil. IR: 1703, 1631. ^{1}H NMR: δ 5.77 (1H, br s), 2.69 (1H, dd, J = 5.8, 8.1, C-4H), 2.60–2.49 (2H, m), 2.27 (1H, m), 2.11 (1H, m, C-9H), 1.81–1.73 (2H, m), 1.61 (1H, d, J = 13.0), 1.58 (1H, m), 1.46 (1H, d, J = 13.0, C-7H), 1.02 (3H, s), 0.93 (3H, s), 0.74 (3H, d, J = 7.1). NOE data: 2.69 (0.74, 1%), 2.11 (1.46, 4%; 0.74, 1.2%), 1.46 (2.11, 2.5%), 0.74 (2.69, 10%; 2.11, 5%). ^{13}C NMR: δ 215.2 (0), 192.2 (0), 123.8 (1), 66.7 (0), 53.9 (1), 51.0 (2), 42.6 (2), 42.5 (0), 40.1 (1), 32.3 (2), 30.1 (3), 28.9 (3), 23.7 (2), 16.6 (3). MS: 204 (84, M$^+$), 189 (18), 176 (6), 162 (47), 161 (28), 148 (100), 147 (64), 134 (37), 133 (53), 120 (53), 119 (46), 107 (70), 105 (46), 91 (60), 77 (39), 41 (44). HRMS: calcd for $C_{14}H_{18}O$ 204.1503, found 204.1496.

***rel*-(4*R*,8*R*,9*R*)- and *rel*-(4*R*,8*R*,9*S*)-2,6,6,9-Tetramethyltricyclo[6.3.0.0^{4,8}]undec-1-en-3-one (17b and 18b) from 12b and 13b.** KO-*t*-Bu (132 mg, 1.18 mmol) was added to a solution of **12b** and **13b** (1:5 mixture, 140 mg, 0.59 mmol) in C_6H_6 (40 mL). The mixture was stirred at rt for 0.5 h. After addition of H_2O the aqueous layer was extracted into ether (×3). The combined organic solutions were washed with brine (×2) then dried ($MgSO_4$) and concentrated under vacuum. Chromatography (2% acetone in petroleum ether) of the residue provided 109 mg (84%) of a mixture of **17b** and **18b** in a 1:5 ratio, respectively.

***rel*-(4*R*,8*R*,9*R*)- and *rel*-(4*R*,8*R*,9*S*)-2,6,6,9-Tetramethyltricyclo[6.3.0.0^{4,8}]undec-1-en-3-one (17b and 18b) from 16b.** A suspension of **16b** (114 mg, 0.49 mmol) in dry MeOH (30 mL) and 250 mg of 5% Pd/C was shaken under 3 atm of H_2 for 1 h. This was chromatographed rapidly through a very short column of silica gel to provide 111 mg of an oil. KO-*t*-Bu (58 mg, 0.52 mmol) was added to a solution of a portion of this oil (60 mg) in dry C_6H_6 (35 mL). The mixture was heated at reflux for 0.5 h. Workup was as above. Chromatography (3% acetone in petroleum ether) of the residue provided 46 mg (81% from **16b**) of a mixture of **17b** and **18b** in a 4:1 ratio, respectively. Rechromatography (2% diethyl ether in petroleum ether) using 20% silver nitrate on silica gel separated these isomers. For **17b**. IR: 1706, 1666. ^{1}H NMR ($CDCl_3$): δ 2.50 (2H, m), 2.36 (1H, d, J = 9.7), 2.04–1.16 (7H, m), 1.66 (3H, br s), 1.05 (3H, d, J = 6.4 Hz), 1.02 (3H, s), 0.81 (3H, s). ^{1}H NMR (C_6D_6, prominent signals): δ 1.65 (3H, br s), 0.90 (3H, s), 0.87 (3H, s), 0.76 (3H, d, J = 6.2). ^{13}C NMR: δ 214.3 (0), 186.6 (0), 130.6 (0), 62.6 (0), 57.0 (1), 43.1 (2), 41.4 (1), 40.8 (0), 39.3 (2), 32.7 (2), 31.5 (3), 29.1 (3), 24.2 (2), 14.7 (3), 8.5 (3). MS: 218 (43, M$^+$), 203 (14), 176 (15), 162 (72), 147 (27), 121 (100). HRMS: calcd for $C_{15}H_{22}O$ 218.1669, found 218.1665. For **18b**. IR: 1705, 1667. ^{1}H NMR ($CDCl_3$): δ 2.66 (1H, dd, J = 4.0, 4.9), 2.44 (2H, m), 2.32–1.51 (5H, m), 1.67 (3H, br s), 1.55 (1H, d, J = 12.9), 1.44 (1H, d, J = 12.9), 1.01 (3H, s), 0.87 (3H, s), 0.67 (3H, d, J = 7.1). ^{1}H NMR (C_6D_6, prominent signals): δ 2.58 (1H, dd, J = 3.7, 6.1, C-4H), 1.67 (3H, br s), 1.30 (1H, d, J = 12.7), 1.11 (1H, d, J = 12.7), 0.85 (3H, s), 0.84 (3H, s), 0.42 (3H, d, J = 7.0, C-9Me). NOE data (C_6D_6): 2.58 (0.42, 1.2%), 0.42 (2.58, 14%). ^{13}C NMR: δ 214.7 (0), 184.3 (1), 130.6 (0), 64.3 (0), 53.1 (1), 50.8 (2), 42.6 (2), 42.2 (2), 40.2 (1), 32.2 (2), 30.0 (3), 28.8 (3), 22.2 (2), 16.5 (3), 8.5 (3). MS: not significantly different from that of **17b**. HRMS: calcd for $C_{15}H_{22}O$ 218.1669, found 218.1669.

5-Acetyl-7-hydroxy-2,2,4-trimethylindan (20). Crude **10a** was produced by ozonolysis of **9a** (64 mg, 0.29 mmol) as described for **11a**. This crude **10a** was dissolved in a solution of NaOMe (27 mg of Na in 10 mL of MeOH). The mixture was stirred at rt for 1 h before H_2O was added and much of the MeOH was evaporated under vacuum. The product was extracted into ether (×3), and the combined extracts were washed with brine (×2), dried ($MgSO_4$), and concentrated under vacuum. Chromatography (7% acetone in petroleum ether) provided **20** (39 mg, 62%) as colorless crystals: mp 138–139 °C. IR: 3197, 1650, 1595, 1461. ^{1}H NMR: δ 7.00 (1H, s), 5.14 (1H, br s, OH), 2.71 (4H, s), 2.53 (3H, s), 2.30 (3H, s), 1.18 (6H, s). ^{13}C NMR: δ 202.4 (0), 149.5 (0), 146.4 (0), 137.7 (0), 132.5 (0), 126.4 (0), 114.4 (1), 47.2 (2), 43.9 (2), 39.7 (0), 29.8 (3), 29.2 (2C, 3), 16.8 (3). MS: 218 (33, M$^+$), 203 (100), 175 (9), 43 (52). HRMS: calcd for $C_{14}H_{18}O_2$ 218.1305, found 218.1317.

***rel*-(1*R*,4*S*,8*R*,9*S*)-6,6,9-Trimethyltricyclo[6.3.0.0^{4,8}]-undecan-3-one (21a).** A suspension of **17a** (43 mg, 0.21 mmol) in dry MeOH (25 mL) and 200 mg of 5% Pd/C was shaken under 3 atm of H_2 for 1 h. This was filtered through a pad of silica gel. The filtrate was concentrated, and chromatography (4% acetone in hexane) of the residue provided **21a** (43 mg, 98%) as a colorless oil. IR: 1736. ^{1}H NMR: δ 2.78 (1H, dd, J = 9.2, 18.5), 2.46–2.41 (2H, m), 2.14–2.05 (2H, m), 1.92–1.59 (5H, m), 1.37–1.32 (3H, m), 1.01 (3H, s), 0.98 (3H, s), 0.97 (3H, d, J = 6.7). ^{13}C NMR: δ 223.0 (0), 62.7 (0), 59.4 (1), 47.9 (2), 46.8 (2), 45.7 (1), 44.6 (2), 42.9 (1), 41.3 (0), 34.5 (2), 31.3 (2), 29.5 (3), 29.2 (3), 15.5 (3). MS: 206 (44, M$^+$), 191 (37), 163 (44), 135 (30), 107 (62), 95 (71), 79 (49), 55 (52), 41 (100).

***rel*-(1*R*,4*S*,8*R*,9*R*)-6,6,9-Trimethyltricyclo[6.3.0.0^{4,8}]-undecan-3-one (22a).** A suspension of **18a** (40 mg, 0.19 mmol) was hydrogenated as for **21a** to provide **22a** (39 mg, 98%) as a colorless oil. IR: 1736. ^{1}H NMR: δ 2.74 (1H, dd, J = 11.6, 19.1), 2.50–2.43 (2H, m), 2.05 (1H, ddd, J = 1.9, 7.3, 19.1), 1.94–1.70 (4H, m), 1.65–1.43 (4H, m), 1.17 (1H, dd, J = 6.1, 12.1), 1.03 (3H, s), 0.98 (3H, d, J = 6.6), 0.79 (3H, s). ^{13}C NMR: δ 224.1 (0), 60.9 (0), 56.3 (2), 53.6 (1), 47.0 (2), 46.0 (1), 45.8 (2), 45.4 (1), 39.6 (0), 33.2 (2), 32.7 (2), 29.7 (3), 28.1 (3), 14.0 (3). MS (from GC-MS): 206 (24, M$^+$), 191 (16), 163 (39), 150 (51), 124 (23), 107 (62), 95 (53), 81 (48), 41 (100).

Acylation of 22a. A solution of **21a** and **22a** (70% **22a**, 56 mg, 0.27 mmol) in C_6H_6 (5.0 mL) was added to KH (77 mg of 35% oil dispersion, washed ×3 with hexane) in C_6H_6 (7.0 mL), followed by $O(CO_2Et)_2$[15] (60 μL, 0.4 mmol). The mixture was heated at reflux for 4 h. The solution was cooled to below rt in an ice bath before 10% aqueous HCl was added. The aqueous layer was reextracted with ether (×3). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated under vacuum to leave a residue that GC-MS suggested contained **23** and isomers. Chromatography (1.5% acetone in petroleum ether) afforded **23** (21 mg, 41%) as a mixture, epimeric at C-2. ^{1}H NMR (distinct signals only): δ 4.23 (q, J = 7.1), 3.48 (q, J = 7.0), 3.03 (dm, $J \approx$ 9.6), 2.86 (dm, $J \approx$ 8.8), 1.34 (t, J = 7.1), 1.21 (t, J = 7.0), 1.06 (3H, s), 1.00 (3H, s), 0.94 (3H, d, J = 6.6). MS (of the *single component* by GC-MS): 278 (3, M$^+$), 219 (2), 206 (10), 191 (15), 178 (15), 177 (20), 163 (20), 150 (58), 149 (46), 148 (32), 121 (84), 108 (30), 107 (42), 105 (27), 94 (48), 91 (58), 81 (36), 79 (50), 77 (48), 55 (80), 41 (100).

(±)-Pentalenene (1a) from 17b. A suspension of **17b** (25 mg, 0.12 mmol) was hydrogenated as for **21a** to provide **21b** (26 mg) as a colorless oil composed of two diastereomers. IR: 1736, 1462. MS of both isomers were very similar (from GC-MS): 220 (77, M$^+$), 205 (24), 177 (31), 164 (75), 163 (87), 149 (41), 137 (20), 136 (28), 135 (30), 124 (81), 123 (25), 122 (22), 121 (64), 109 (72), 108 (31), 107 (67), 105 (24), 96 (21), 95 (66), 93 (54), 91 (50), 82 (36), 81 (52), 77 (42), 69 (27), 67 (34), 55 (64), 41 (100). This was dissolved in MeOH, and, while stirring at 0 °C, $NaBH_4$ (9.0 mg, 0.24 mmol) was added in small portions over 1 h. After addition of H_2O, most of the MeOH was removed under vacuum. This was extracted with ether (×3), and the combined organic solutions were washed with brine (×2), dried ($MgSO_4$), and concentrated under vacuum to provide 27 mg of a mixture of alcohols **24**. IR: 3338 (br), 1463. MS of all isomers very similar (from GC-MS):

(15) Hellou, J.; Kingston, J. F.; Fallis, A. G. *Synthesis* **1984**, 1014.

222 (3, M^+), 207 (4), 204 (12), 189 (15), 165 (21), 123 (18), 121 (14), 110 (17), 109 (67), 107 (39), 95 (45), 93 (31), 91 (30), 81 (35), 79 (33), 77 (24), 69 (23), 67 (28), 67 (28), 57 (24), 55 (59), 43 (56), 41 (100). A solution of the alcohol mixture **24** (27 mg, 0.12 mmol) and *p*-TsOH (ca. 5 mg) in dry C_6H_6 (20 mL) was heated at reflux for 2 h as some of the solvent was allowed to distill off. The cooled solution was poured into a saturated $NaHCO_3$ solution, and this was extracted with ether (×3). The combined organic solutions were washed with saturated $NaHCO_3$ solution and then brine and dried ($MgSO_4$), and the solvent was removed under carefully controlled vacuum to provide **1a** (22 mg, 88%) as a rather volatile liquid. IR: 3044, 1450, 1365. ^1H NMR: δ 5.15 (1H, br s), 2.66 (1H, m), 2.54 (1H, br d, J = 8.9), 1.86–1.14 (9H, m), 1.61 (3H, br s), 0.982 (3H, s), 0.977 (3H, s), 0.89 (3H, d, J = 6.8). ^{13}C NMR: δ 140.4 (0), 129.5 (1), 64.8 (0), 62.0 (1), 59.3 (1), 48.9 (2), 46.8 (2), 44.6 (1), 40.5 (0), 33.5 (2), 29.9 (3), 29.1 (3), 27.6 (2), 17.0 (3), 15.5 (3). MS: 204 (50, M^+), 189 (43), 162 (27), 161 (22), 148 (57), 147 (91), 133 (41), 119 (62), 107 (33), 106 (74), 105 (99), 93 (25), 92 (25), 91 (100), 77 (38), 55 (31), 41 (69). HRMS: calcd for $C_{15}H_{24}$ 204.1877, found 204.1879.

(±)-9-*epi*-Pentalenene (26) from 18b. Following the same sequence as above for **17b** → **1a**, 42 mg of **18b** was (i) hydrogenated to **22b** as a diastereomeric mixture (IR: 1736, 1462. MS as for **21b**), (ii) reduced with $NaBH_4$ to **25** (IR: 3320 (br), 1461. MS as for **24**), and (iii) dehydrated to provide **26** (34 mg, 88%) as a liquid. IR: 3027, 1445, 1377, 1363. ^1H NMR: δ 5.17 (1H, br s), 2.88 (1H, m), 2.62 (1H, br d, J = 8.1), 1.70–1.25 (9H, m), 1.60 (3H, br s), 0.97 (6H, s), 0.93 (3H, d, J = 6.7). ^{13}C NMR: δ 140.5 (0), 131.5 (1), 63.2 (1), 54.5 (2), 50.3 (1), 46.0 (2), 44.9 (1), 39.7 (0), 32.8 (2), 31.5 (2C, 3), 29.1 (2), 28.4 (1), 15.3 (3), 13.4 (3). MS: very similar to **1a**. HRMS: calcd for $C_{15}H_{24}$ 204.1877, found 204.1879.

***rel*-(1*R*,2*R*,3*R*,4*S*,8*R*,9*S*)- and *rel*-(1*R*,2*R*,3*R*,4*S*,8*R*,9*R*)-2,6,6,9-Tetramethyltricyclo[6.3.0.0^{4,8}]undecan-3-ol (27 and 28).** A 1:5 mixture of **17b** and **18b** (57 mg, 0.26 mmol) in THF (5.0 mL) was added to Li (9.0 mg, 1.3 mmol) in NH_3 (20 mL) at −78 °C, the temperature was allowed to rise to −33 °C, and the mixture was stirred for another 35 min. Solid NH_4Cl was added and the NH_3 was allowed to evaporate overnight. Ether and H_2O were added, and the aqueous layer was reextracted with ether (×3). The combined organic solutions were washed with brine, dried ($MgSO_4$), and concentrated under vacuum. Chromatography (4% acetone in petroleum ether) provided a 1:5 mixture, respectively, of **27** and **28** (35 mg, 60%). IR: 3333 (br). For **27** (from spectra of the mixture). ^1H NMR (unoverlapped signals): δ 3.52 (1H, dd, J = 7.0, 9.0), 1.09 (3H, s), 1.02 (3H, d), 1.00 (3H, s), 0.88 (3H, d, J = 6.7). MS (from GC-MS): very similar to **24**. For **28** (from spectra of the mixture): ^1H NMR (unoverlapped signals): δ 3.56 (1H, dd, J = 1.2, 8.5), 1.08 (3H, s), 1.02 (3H, s), 1.01 (3H, d, J = 6.3), 0.95 (3H, d, J = 6.6). MS (from GC-MS): very similar to **24**.

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Supplementary Material Available: ^1H NMR spectra for compounds **1a**, **8a**, **9a**, **11a**, **11b**, **12a** and **13a**, **12b** and **13b**, **14a**, **15a**, **16a**, **16b**, **17a**, **17b**, **18a**, **18b**, **20**, **21a**, **22a**, and **26** (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.