studentship and Pfizer Central Research for financial support.

Registry No. 1, 1191-99-7; 2, 75213-94-4; 3, 43161-11-1; 3 (bromide), 2270-59-9; 4, 118495-28-6; 5, 459-88-1; 5 (X = OMs), 118495-32-2; 6, 22339-13-5; 7, 118495-29-7; 8, 459-89-2; 8 (X = OMs), 118495-33-3; 9, 113219-28-6; 10, 118495-30-0; 11, 118495-31-1; 1,1-bis(methylamino)propylamine, 118495-34-4.

Diels–Alder Reactions of Cycloalkenones. 15. Synthesis of *cis*- and *trans*-Δ^6-4a-Methyl-1-octalones[1]

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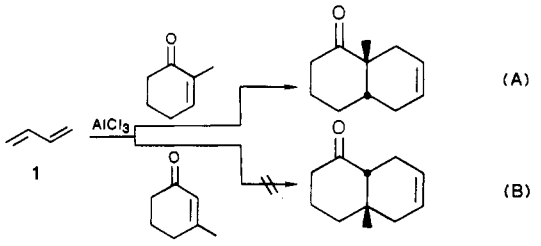
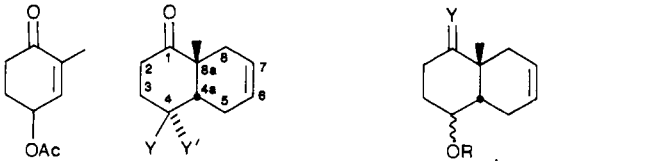
Angularly methylated octalones are useful intermediates for terpene or steroid synthesis. The high-yielding, Lewis acid catalyzed cycloaddition of 2-methyl-2-cyclohexenones and 1,3-butadienes, as illustrated for the simplest case in equation A,[3] yields nowadays easy access to such octalones in the cis isomer form. The lack of reactivity of 3-methyl-2-cyclohexenone toward 1,3-butadiene (**1**) in thermal or acid-induced Diels–Alder reactions (equation B)[4] precludes the ready preparation of *cis*-octalones (or *trans*-octalones, i.e., after equilibration) in which the angular methyl group is in a 1,3-positional relationship with the keto function. The following study was undertaken in order to overcome the obstacle and introduce full flexibility into the Diels–Alder reaction scheme.

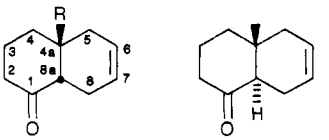


Cycloaddition of 1,3-butadiene (**1**) with 4-acetoxy-2-methyl-2-cyclohexenone (**2**) (prepared in 57% yield from 2-methyl-2-cyclohexenone on C(4)-bromination with *N*-bromosuccinimide and subsequent bromide displacement with potassium acetate) in degassed (i.e., oxygen-free) toluene solution under the influence of aluminum chloride at 40 °C led to a 1.3:1 mixture of ketoacetates **3a** and **3b** in 60% yield. It is noteworthy that the diastereofacial selectivity of the reaction was the same as that between 2,4-dimethyl-2-cyclohexenone and 1,3-butadiene (**1**),[5] in accord with the hypothesis of the cycloaddition being governed by stereoelectronic and conformational factors.[5]



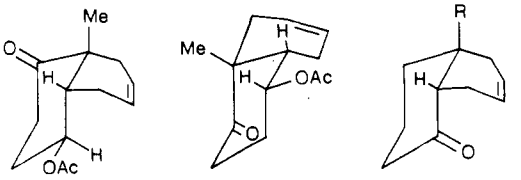
2 **3a**: Y = OAc, Y′ = H; **b**: Y = H, Y′ = OAc **4a**: Y = NNHSO$_2$C$_6$H$_4$Me-*p*, R = Ac; **b**: Y = H$_2$, R = Ac; **c**: Y = H$_2$, R = H

Conversion of the **3a–3b** ketoacetate mixture into its *p*-tosylhydrazone derivatives (**4a**), reduction of the latter with catecholborane,[6] base-induced hydrolysis of the resultant acetates **4b**, and Jones oxidation of alcohols **4c** furnished octalone **5a** in 36% overall yield. Base-catalyzed isomerization of the latter gave quantitatively a 4:1 trans–cis isomer mixture (ketones **6**[7] and **5a**).



5a, R = Me; **b**, R = H **6**

The gross structure and relative configuration of ketones **3** were determined by ^{13}C NMR spectroscopy and carbon shift comparison with models **3** (Y = Me, Y′ = H)[5] and **3** (Y = H, Y′ = Me).[5] The latter shift correlation revealed ketoacetates **3a** and **3b** to possess predominantly the solution conformations **7** and **8**, respectively. Gross structure and conformational analysis of ketone **5a** depended on the interpretation of its ^{13}C NMR data and carbon shift analysis of octalone **5b**.[6b] Conformational analysis of the latter ketone, in turn, required correlation of its carbon shifts with those of the conformationally biased ketones 2α,6-dimethyl- and 2β,6-dimethyl-**5b**.[5] These analyses showed compounds **5** to prefer conformation **9** in solution. Finally, the ^{1}H chemical shifts of the angular methyl groups of ketones **5a** (1.11 ppm) and **6** (0.79 ppm) are consistent with the assigned configurations.[8]



7 **8** **9**

The above, short preparation makes methyloctalones **5a** and **6** readily available for natural product synthesis. In this connection it is of interest that the ethylene ketal of methyloctalone **6**, acquired by a multistep preparation,[9,10] has been utilized recently for the synthesis of the sesquiterpenes (±)-β-costol,[11] (±)-β-costal,[11] (±)-β-arctiol,[11]

(1) For the previous paper, see: Angell, E. C.; Fringuelli, F.; Guo, M.; Minuti, L.; Taticchi, A.; Wenkert, E. *J. Org. Chem.* **1988**, *53*, 4325.
(2) (a) University of California. (b) Università di Perugia.
(3) Fringuelli, F.; Pizzo, F.; Taticchi, A.; Halls, T. D. J.; Wenkert, E. *J. Org. Chem.* **1982**, *47*, 5056.
(4) Fringuelli, F.; Pizzo, F.; Taticchi, A.; Wenkert, E. *J. Org. Chem.* **1983**, *48*, 2802.
(5) Angell, E. C.; Fringuelli, F.; Pizzo, F.; Porter, B.; Taticchi, A.; Wenkert, E. *J. Org. Chem.* **1986**, *51*, 2642.
(6) (a) Kabalka, G. W.; Hutchins, R.; Natale, N. R.; Yang, D. T. C.; Broach, V. *Org. Synth.* **1979**, *59*, 42. (b) Angell, E. C.; Fringuelli, F.; Pizzo, F.; Taticchi, A.; Wenkert, E. *J. Org. Chem.* **1988**, *53*, 1424.
(7) Whereas ketone **6** has not been described previously in pure form, it has been reported as a minor constituent in a four-component mixture of products of the acid-catalyzed cyclization of 2-(3-butenyl)-3-methyl-2-cyclohexenone (Cooper, J. L.; Harding, K. E. *Tetrahedron Lett.* **1977**, 3321).
(8) van der Gen, A.; Wiedhaup, K.; Swoboda, J. J.; Dunathan, H. C.; Johnson, W. S. *J. Am. Chem. Soc.* **1973**, *95*, 2656 and references therein.
(9) Torii, S.; Inokuchi, T.; Yamafuji, T. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 2640.
(10) Garratt, P. J.; Porter, J. R. *J. Org. Chem.* **1986**, *51*, 5450.
(11) Torii, S.; Inokuchi, T. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 2642.

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(±)-eudesma-4(14),7(11)-dien-8-one,[11] and (±)-vetiselinene.[10]

Experimental Section

Melting points were determined on a Büchi 550 melting point apparatus and are uncorrected. Infrared spectra of carbon tetrachloride solutions were recorded on a Perkin-Elmer 257 spectrophotometer and ^{1}H NMR spectra of deuteriochloroform solutions (internal standard Me_4Si) on a Varian EM-390 spectrometer. ^{13}C NMR spectra of deuteriochloroform solutions were taken on a Nicolet NT-200, wide-bore, broad-band spectrometer, operating with an Oxford magnet at 50.31 MHz in the Fourier transform mode. The carbon shifts are in ppm downfield from Me_4Si; $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm. GC analyses were performed on a Hewlett-Packard 5880A chromatograph with 30-m (0.2-mm diameter) SP-2340 fused silica capillary columns, an "on column" injection system, and hydrogen as the carrier gas. Absorption chromatography was carried out on Merck silica (0.040–0.063 mm, 230–400-mesh ASTM). The Diels–Alder adducts were crystallized from pentane.

4-Acetoxy-2-methyl-2-cyclohexenone (2). A mixture of 4.00 g (36 mmol) of 2-methyl-2-cyclohexenone, 8.30 g (47 mmol) of *N*-bromosuccinimide, and 300 mg (0.83 mmol) of dibenzoyl peroxide in 46 mL of dry carbon tetrachloride was refluxed for 7 h and then cooled to room temperature. The resultant precipitate was filtered and discarded and the filtrate concentrated to a 20-mL volume. A mixture of 9.2 g (93 mmol) of potassium acetate and 1.0 g (2.2 mmol) of methyltrioctylammonium chloride in 5 mL of water was added and stirred at 25 °C for 14 h. Ether (70 mL) and 35 mL of water were added and the aqueous layer was extracted with ether. The combined organic layer and extract were dried (Na_2SO_4) and evaporated. Chromatography on 100 g of silica gel and elution with 4:1 pentane–ether yielded 3.48 g (57%) of colorless, liquid keto ester **2**: IR C=O 1745 (s), 1685 (s), C—O 1230 (s) cm^{-1}; ^{1}H NMR δ 1.75 (s, 3, 2-Me), 2.05 (s, 3, acetyl Me), 5.40 (br s, 1, H-4), 6.50 (br s, 1, H-3); ^{13}C NMR δ 15.0 (Me), 20.3 (ester Me), 28.5 (C-5), 34.3 (C-6), 67.6 (C-4), 136.9 (C-2), 141.8 (C-3), 169.6 (ester C=O), 197.3 (C=O).

Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.33; H, 7.17.

4β-Acetoxy-8aβ-methyl-3,4α,4aβ,5,8,8a-hexahydro-1(2*H*)-naphthalenone (3a) and 4α-Acetoxy-8aβ-methyl-3,4β,4aβ,5,8,8a-hexahydro-1(2*H*)-naphthalenone (3b). Keto ester **2** (840 mg, 5 mmol) was added to a suspension of 600 mg (4.5 mmol) of anhydrous aluminum trichloride in 25 mL of dry toluene under nitrogen and the mixture stirred at room temperature for 80 min. A 3 M toluene solution of 1,3-butadiene (**1**) (15 mL) was added and the mixture degassed (2 min at −78 °C/14 Torr and the flask then closed) and kept at 40 °C for 7 h. It was cooled, poured into ice water, and extracted with ether. The extract was washed with 10% sodium bicarbonate solution, dried, and evaporated. Chromatography of the residue (a 1.3:1 **3a–3b** mixture by GC analysis) on 30 g of 20% silver nitrate impregnated silica gel and gradient elution with 200:1 to 50:1 pentane–ether mixtures gave 150 mg (13.5%) of colorless, crystalline keto ester **3a**, 100 mg (9%) of colorless, crystalline keto ester **3b**, and 416 mg (37.5%) of a colorless, solid **3a–3b** mixture.

Octalone **3a**: mp 63–64 °C; IR C=CH 3025 (w), C=O 1745 (s), 1718 (s), C=C 1660 (w), C—O 1240 (s) cm^{-1}; ^{1}H NMR δ 1.13 (s, 3, Me), 2.02 (s, 3, acetyl Me), 4.8–5.0 (m, 1, H-4), 5.60 (br s, 2, H-6, H-7); ^{13}C NMR δ 20.1 (Me), 21.1 (ester Me), 22.4 (C-5), 30.2 (C-3), 31.5 (C-8), 34.6 (C-2), 43.5 (C-4a), 46.4 (C-8a), 69.7 (C-4), 123.0 (C-6 or C-7), 123.4 (C-7 or C-6), 170.4 (ester C=O), 212.3 (C=O).

Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 69.98; H, 8.20.

Octalone **3b**: mp 40–42 °C; IR C=CH 3025 (w), C=O 1745 (s), 1715 (s), C=C 1660 (w), C—O 1240 (s) cm^{-1}; ^{1}H NMR δ 1.23 (s, 3, Me), 2.00 (s, 3, acetyl Me), 5.3–5.5 (m, 1, H-4), 5.55 (br s, 2, H-6, H-7); ^{13}C NMR δ 21.2 (ester Me), 23.6 (C-5), 23.7 (Me), 28.2 (C-3), 33.1 (C-8), 33.6 (C-2), 42.6 (C-4a), 47.1 (C-8a), 70.5 (C-4), 123.5 (C-6 or C-7), 124.3 (C-7 or C-6), 170.4 (ester C=O), 212.6 (C=O).

Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.01; H, 8.15.

4aβ-Methyl-3,4,4a,5,8,8aβ-hexahydro-1(2*H*)-naphthalenone (5a). A solution of 267 mg (1.2 mmol) of a 1.3:1 **3a–3b** keto ester mixture and 242 mg (1.3 mmol) of (*p*-tolylsulfonyl)hydrazine in 1 mL of 95% ethanol was heated at 75 °C for 20 min and then cooled and evaporated under reduced pressure. Chromatography of the residue on 7 g of silica gel and elution with 1:1 pentane–ether yielded 350 mg of tosylhydrazones **4a**. A solution of the latter in 1 mL of dry chloroform at 0 °C was treated with 0.16 mL (1.43 mmol) of catecholborane (slow injection by a syringe through a septum) and the mixture kept at 0 °C under nitrogen for 2 h. Upon the addition of 380 mg (2.8 mmol) of sodium acetate trihydrate, the mixture was refluxed for 1 h. It was cooled and filtered and the solid washed with chloroform. The combined filtrate and washings were evaporated and the residue chromatographed on 6 g of silica gel. Elution with 20:1 pentane–ether gave 140 mg of esters **4b**. A mixture of the latter and 150 mg (1.1 mmol) of potassium carbonate in 1 mL of water and 3 mL of methanol was refluxed for 2 h. The cooled mixture was concentrated under reduced pressure and extracted with ether. The extract was washed with 10% hydrochloric acid and with brine, dried, and evaporated. A solution of 1.4 mmol of Jones reagent (prepared from a solution of 7 g of chromium trioxide in 50 mL of water and 6 mL of concentrated sulfuric acid) was added slowly to a stirring solution of the residue in 10 mL of acetone at 0 °C and the stirring continued for 0.5 h. After the usual workup the crude product was chromatographed on 15 g of silica gel and eluted with 100:1 pentane–ether, affording 70 mg (36% overall yield) of colorless, liquid ketone **5a**: IR C=CH 3038 (m), C=O 1715 (s), C=C 1660 (w) cm^{-1}; ^{1}H NMR δ 1.11 (s, 3, Me), 5.58 (br s, 2, H-6, H-7); ^{13}C NMR δ 22.0 (C-8), 22.7 (C-3), 28.2 (Me), 32.6 (C-5), 37.3 (C-4), 37.5 (C-4a), 40.2 (C-2), 53.4 (C-8a), 123.9 (C-6 or C-7), 124.0 (C-7 or C-6), 214.4 (C=O).

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.53; H, 9.80.

4aβ-Methyl-3,4,4a,5,8,8aα-hexahydro-1(2*H*)-naphthalenone (6). A dry, ethanolic, 0.1 M sodium ethoxide solution (7 mL) containing 110 mg (0.67 mmol) of ketone **5a** was stirred at room temperature for 0.5 h. The usual workup furnished 110 mg of a 4:1 **6–5a** mixture (by GC analysis), whose chromatography on 4 g of silica gel and elution with 50:1 pentane–ether gave 60 mg of colorless, liquid ketone **6**: IR C=CH 3025 (m), C=O 1715 (s), C=C 1658 (w) cm^{-1}; ^{1}H NMR δ 0.79 (s, 3, Me), 5.61 (br s, 2, H-6, H-7); ^{13}C NMR δ 18.2 (Me), 21.8 (C-8), 22.8 (C-3), 37.9 (C-4a), 40.1 (C-4), 41.4 (C-5), 41.7 (C-2), 52.9 (C-8a), 124.5 (C-6), 125.5 (C-7), 211.9 (C=O). (2,4-Dinitrophenyl)hydrazone: mp 139–140 °C (EtOH).

Anal. Calcd for $C_{17}H_{20}O_4N_4$: C, 59.29; H, 5.85; N, 16.27. Found: C, 59.60; H, 5.65; N, 15.98.

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Registry No. **1**, 106-99-0; **2**, 118631-94-0; **3a**, 118631-95-1; **3b**, 118631-96-2; **4a** (isomer 1), 118656-37-4; **4a** (isomer 2), 118631-98-4; **4b** (isomer 1), 118631-99-5; **4b** (isomer 2), 118681-75-7; **5a**, 118631-97-3; **6**, 118656-38-5; 2-methyl-2-cyclohexenone, 1121-18-2.

An Efficient Method for Preparation of 3,5-Diamino-6-chloropyrazin-2-yl Alkyl Ketones Using a Novel Acetylene Hydration Method[1]

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In connection with a program directed toward the preparation of new therapeutic agents, we required a

