Diels-Alder Reactions of Cycloalkenones. 12. Reaction of *trans*-$\Delta^{1,2}$-3-Octalone with (*E*)-Piperylene[1]

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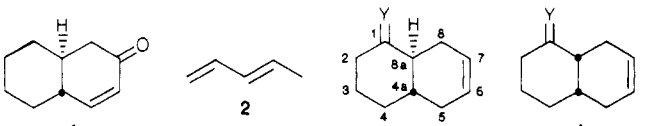
The Diels-Alder reaction of (*E*)-piperylene with *trans*-$\Delta^{1,2}$-3-octalone under aluminum chloride catalysis is described and structure analysis of the adducts by NMR spectroscopy is presented. The diastereofacial selectivity of the reaction is discussed in light of a general hypothesis of the stereochemistry of cycloadditions.

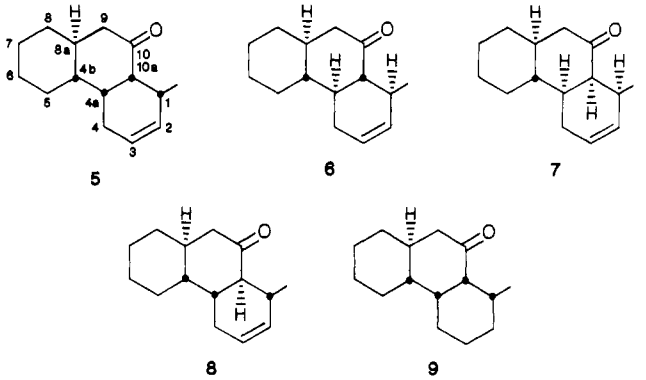
In a recent study of the diastereofacial selectivity of the Diels-Alder reaction of conformationally mobile 2-cyclohexenones,[3] it was shown that the stereochemistry of the products could be explained on the basis of the following considerations. (a) The reaction rate depends both on the reactivity of the cyclohexenone conformers present in the conformational equilibrium and on their concentration. (b) The cycloaddition takes place in a one-step reaction with an unsymmetrical, nonsynchronous transition state, in which the new carbon-carbon single bond at the β-carbon site of the α,β-unsaturated ketone is developed more than that at the α-carbon center. (c) In the absence of strong steric hindrance the diene-dienophile interaction occurs with axial approach of the diene antiparallel to the pseudoaxial substituent at the cyclohexenone γ-carbon, creating a fused cyclohexanone in a chair conformation in the transition state (in preference to a parallel approach leading to a boat conformation). In order to remove criterion (a) from consideration, it was of interest to study the Diels-Alder reaction of a sterically unencumbered, conformationally rigid cyclohexenone and *trans*-$\Delta^{1,2}$-3-octalone (**1**)[4] was chosen for this purpose. (*E*)-Piperylene (**2**) was selected as the diene to determine also the endo-exo diastereoselectivity of the reaction.[5]



a, Y = O
b, Y = H_2
c, Y = *p*-$CH_3C_6H_5SO_2NHN$

The octalone **1** was prepared in the following manner. Interaction of 1,3-butadiene and 2-cyclohexenone under aluminum chloride catalysis at 70 °C for 12 h yielded (96%) a 9:1 mixture of octalones **3a**[6] and **4a**.[7] Wolff-Kishner reduction of the trans ketone **3a** gave a ca. 6:1 mixture (77%) of olefins **3b**[8] and **4b**. To avoid formation of the latter olefin, ketone **3a** was converted into its tosylhydrazone **3c** (87%) and the latter reduced. Reaction with sodium borohydride or with catecholborane[9] led to *trans*-2-octalin (**3b**) in 46% and 70% yields, respectively. Treatment of the latter with *N*-bromosuccinimide in aqueous dioxane, Jones oxidation of the resultant bromohydrin, and dehydrohalogenation of the thus-formed α-bromo ketone with calcium carbonate in refluxing dimethylacetamide produced octalone **1** (50%).

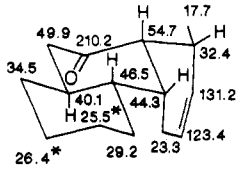
Diels-Alder Reaction and Products. The reaction of octalone **1** with diene **2** in the presence of aluminum chloride at 40 °C for 9 h[10] led in 90% yield to a 45:4:1 mixture of tricyclic ketones **5**, **6**, and **7**. Since the last product was present in the reaction mixture only in a minute amount, its structure could not be determined by direct analysis but depends on the following epimerization data. Treatment of ketones **5** and **6** with ethanolic sodium ethoxide[3] led to their nearly quantitative recovery, while the same treatment of a reaction mixture enriched in ketone **7** caused the disappearance of the latter and enrichment of ketone **6**. Thus ketones **5** and **7** are the primary products of the Diels-Alder reaction, both having been derived from cis addition across the double bond of enone **1**, and hydrophenanthrone **5** survived the reaction because of its much greater stability than its 10a epimer **8**, while isomer **7** was transformed in part into its 10a epimer **6**.[11] Base-induced equilibration[3] of perhydrophenahthrone **9**, prepared by the hydrogenation of ketone **5** over platinum in ethanol,[3] also led to nearly quantitative recovery of starting material.[12]



(1) For the previous paper, see: Angell, E. C.; Fringuelli, F.: Minuti, L.; Pizzo, F.; Taticchi, A.; Wenkert, E. *J. Org. Chem.* **1986**, *51*, 5177.
(2) (a) University of California. (b) Università di Perugia.
(3) Angell, E. C.; Fringuelli, F.; Pizzo, F.; Porter, B.; Taticchi, A.; Wenkert, E. *J. Org. Chem.* **1986**, *51*, 2642.
(4) (a) Mühle, H.; Tamm, Ch. *Helv. Chim. Acta* **1962**, *45*, 1475. (b) Corey, E. J.; Boger, D. L. *Tetrahedron Lett.* **1978**, 4597.
(5) Angell, E. C.; Fringuelli, F.; Minuti, L.; Pizzo, F.; Porter, B.; Taticchi, A.; Wenkert, E. *J. Org. Chem.* **1986**, *51*, 2649.
(6) Fringuelli, F.; Pizzo, F.; Taticchi, A.; Halls, T. D. J.; Wenkert, E. *J. Org. Chem.* **1982**, *47*, 5056.
(7) The reaction was reported first in 1982,[6] but now has been modified slightly (see Experimental Section).
(8) (a) Hückel, W.; Sowa, W. *Ber.* **1941**, *74*, 57. (b) Johnson, W. S.; Bauer, V. J.; Margrave, J. L.; Frisch, M. A.; Dreger, L. H.; Hubbard, W. N. *J. Am. Chem. Soc.* **1961**, *83*, 606.
(9) cf. Kabalka, G. W.; Hutchins, R.; Natale, N. R.; Yang, D. T. C.; Broach, V. *Org. Synth.* **1979**, *59*, 42.
(10) Cf. Fringuelli, F.; Pizzo, F.; Taticchi, A.; Wenkert, E. *J. Org. Chem.* **1983**, *48*, 2802.
(11) The 10a epimeric relationship of ketones **6** and **7** was evident also from the observation of a concentration decrease of product **7** with time in the cycloaddition process, commensurate with a concentration increase of its isomer **6**.
(12) For equilibrations of related perhydrophenanthrones, see (a) Linstead, R. P.; Davis, S. B.; Whetstone, R. R. *J. Am. Chem. Soc.* **1942**, *64*, 2009. (b) Johnson, W. S.; Rogier, E. R.; Ackerman, J. *Ibid.* **1956**, *78*, 6322.

0022-3263/88/1953-1424$01.50/0

The stability data of the primary Diels–Alder adducts, ketones **5** and **7**, fit their conformational analysis. As can be seen from conformation **10** for ketone **5**, isomerization of H(10a) and formation of ketone **8** would require the creation of a boat conformation for the central, ketonic ring—an energetically highly unfavorable alteration. Thus ketone **8** is observed neither in the cycloaddition nor in the equilibration. On the other hand, Diels–Alder adduct **7**, depicted by conformation **11**, is unstable with respect to its 10a epimer **6**, portrayed conformationally by formula **12**, in view of the presence of a cis bridgehead arrangement and an axial methyl group in the octalone portion of the compound. Hence hydrophenanthrone **7** is transformed nearly completely into ketone **6** on equilibration and remains only a trace component in the Diels–Alder reaction mixture because of the unfavorable stereoelectronic relationship in the acid-induced enolization (i.e. H(10a) being equatorial in the ketonic ring in the chair conformation) causing a relatively low rate of H(10a) isomerization.



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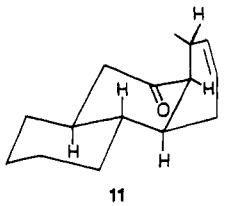

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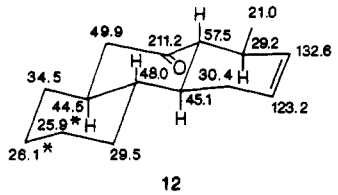

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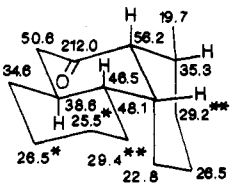

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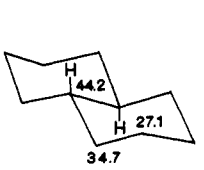
The configurational assignments of hydrophenanthrones **5**, **6**, and **9** (conformations **10**, **12** and **13**, respectively) were based on ^{13}C NMR spectroscopy. The carbon shifts are detailed on the conformational formulas[13] and their designation was helped by the known δ values for *trans*-decalin (**14**) as well as octalones **15** and **16** and decalone **17**.[14] Carbons 6, 7, and 8 of all three hydrophenanthrones and C(8a) of ketone **6** (**12**) reveal chemical shifts only minimally different from those of like carbons in *trans*-decalin (**14**). Carbon 8a of the two *trans-syn-cis*-hydrophenanthrones (**5**–**10** and **9**–**13**) is shielded appreciably due to a γ-effect by C(4). This shift perturbation is felt also by C(5) of all three ketones. Finally, C(4b) is deshielded in the three ketones by (inter alia) a β-effect of C(4).

The chemical shifts of the methylcyclohexene carbons of the hydrophenanthrones are in perfect agreement with those of like carbons in models **15**, **16**, and **17** except for the slight variation of C(4), probably due to the difference of a γ-shift exerted by a rigidly held methylene group, i.e. C(5) of the hydrophenanthrones, vs the cyclohexanone methyl function of the models. The carbonyl carbon shift of the ketones and the proper models are surprizingly similar and the C(9) signal of the hydrophenanthrones is strongly downfield from that of the proper models, exhibiting a β-effect of C(8).

Discussion. The orientation of the methyl group in the two Diels–Alder adducts **5** and **7** (as revealed in its isolated epimer **6**) shows the cycloaddition of octalone **1** and



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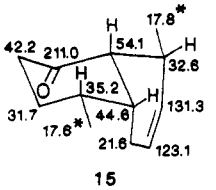

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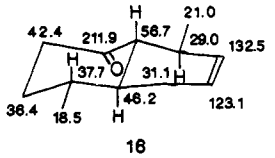

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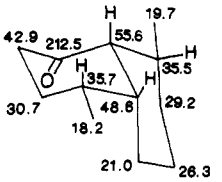

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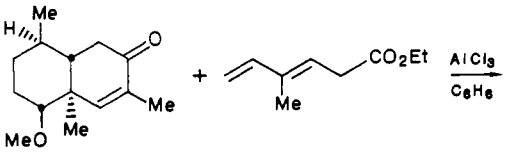
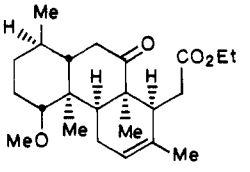
(*E*)-piperylene (**2**) to have proceeded exclusively in an endo fashion. Furthermore, the 9:1 **5**/[**6** + **7**] ratio reveals high diastereofacial selectivity, i.e., the reaction being a 9:1 anti/syn addition with respect to the axial, bridgehead hydrogen γ to the keto group of the starting ketone. This result thus supports the hypothesis of the diene–dienophile interaction at the enone β-carbon taking place preferentially by axial approach of the diene antiparallel to the pseudoaxial substituent at the enone γ-carbon. It is noteworthy that, were this substituent a methyl group instead of a hydrogen as in enone **1**, the anti/syn addition ratio should increase—an argument in consonance with the observation of the exclusive formation of tricycle **18** in the following Diels–Alder reaction.[15]





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Experimental Section

Melting points were determined on a Büchi melting point apparatus and are uncorrected. Infrared spectra of CCl_4 solutions were recorded on a Perkin-Elmer 257 spectrophotometer. ^1H NMR spectra were observed on CCl_4 solutions, containing Me_4Si as internal standard (δ 0), on a Varian EM-390 spectrometer. The ^{13}C NMR spectra of $CDCl_3$ 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. For the carbon shifts see ref 13. GC analyses were performed on Carlo Erba 4100 (2 m 10% Carbowax 20M column) and Hewlett-Packard 5880A (with an "on-column" injection system; 25 m 10% Carbowax 20M column) chromatographs. Absorption chromatography was carried out on Merck silica gel (0.040–0.063 mm, 230–400 mesh ASTM). All hydrazones were crystallized from 95% ethanol and all other solid products from pentane. All extracts were dried over anhydrous Na_2SO_4.

Octalones 3a and 4a. A suspension of 6.67 g (50 mmol) of anhydrous aluminum chloride and 9.60 g (0.10 mmol) of 2-cyclohexenone in 700 mL of dry toluene, prepared in a previously described manner,[6] was stirred under nitrogen at room temperature for 40 min. A solution of 0.90 mol of 1,3-butadiene in 300 mL of dry toluene was added, the system was closed, and the

(13) In ppm downfield from Me_4Si: $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm. Asterisked carbon shifts on each formula may be interchanged.

(14) Angell, E. C.; Fringuelli, F.; Halls, T. D. J.; Pizzo, F.; Porter, B.; Taticchi, A.; Tourris, A. P.; Wenkert, E. *J. Org. Chem.* **1985**, *50*, 4691.

(15) Grieco, P. A.; Vidari, G.; Ferrino, S.; Haltiwanger, R. C. *Tetrahedron Lett.* **1980**, *21*, 1619.

mixture was heated at 70 °C for 12 h. It then was cooled and poured into ice water, and the layers were separated. The aqueous layer was extracted with ether and the combined extract and organic layer were washed with 10% sodium bicarbonate solution, dried, and evaporated under vacuum. Chromatography of the residue on 150 g of silica gel and elution with 20:1 petroleum ether–ether afforded 12.0 g of octalone **3a** and 2.40 g of a 1.5:1 mixture of octalones **3a** and **4a** (96% total yield of a 9:1 mixture). Base-induced equilibration of the **3a–4a** mixture by a previously described procedure,[16] followed by chromatography on silica gel, afforded 1.50 g more of ketone **3a**, spectrally identical in all respects with an authentic sample.[6]

An analytical sample of octalone **4a** was prepared by chromatography of a **3a–4a** mixture (from a run different from that above, enriched in **4a**). Elution with 20:1 petroleum ether–ether gave colorless, liquid octalone **4a**: IR 3032 (m, olefinic CH), 1716 (s, C=O), 1660 (w, C=C) cm^{-1}; ^1H NMR δ 5.59 (br s, 2, H-6, H-7); ^{13}C NMR δ 23.3 (C-3), 23.6 (C-8), 26.7 (C-5), 28.2 (C-4), 35.4 (C-4a), 39.6 (C-2), 47.8 (C-8a), 123.9 (C-7), 124.4 (C-6), 211.4 (C-1). Anal. Calcd for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 79.80; H, 9.34.

Octalin 3b. A solution of 5.0 g (33 mmol) of octalone **3a** and 22.3 mL of 85% hydrazine in 7.9 mL of ethylene glycol was heated at 140 °C for 1 h. Potassium hydroxide (26.2 g) was added to the cooled mixture and the latter refluxed for 3 h. It then was cooled, diluted with 200 mL of pentane, washed with 10% hydrochloric acid and saturated sodium bicarbonate solutions, dried, and evaporated under vacuum. Chromatography of the residue on 80 g of silica gel and elution with pentane afforded 3.5 g (77%) of a ca. 6:1 mixture of olefins **3b** and **4b** (by GC analysis).

A solution of 13.5 g (90 mmol) of octalone **3a** and 18.9 g (102 mmol) of *p*-toluenesulfonylhydrazine in 58 mL of 95% ethanol was stirred and refluxed for 20 min. The mixture was permitted to return to room temperature and then was cooled at 0 °C for an extended time. Filtration of the resultant precipitate gave 24.9 g (87%) of colorless hydrazone **3c**, mp 147–148 °C. Sodium borohydride (11.9 g, 31.4 mmol) was added slowly to a stirring solution of 10.0 g (31.4 mmol) of the hydrazone in 525 mL of glacial acetic acid at 40–50 °C and the mixture then stirred at room temperature for 3 h. It was diluted with 300 mL each of pentane and cold water. The organic phase was washed with sodium bicarbonate solution, dried, and evaporated under reduced pressure. Chromatography of the residue on 40 g of silica gel and elution with pentane yielded 1.97 g (46%) of colorless, liquid octalin **3b**:[8] IR 3030 (m, olefinic CH), 1655 (w, C=C) cm^{-1}; ^1H NMR δ 5.53 (m, 2, H-6, H-7); ^{13}C NMR δ 26.7 (C-2, C-3), 33.4 (C-1, C-4), 34.2 (C-5, C-8), 38.5 (C-4a, C-8a), 126.6 (C-6, C-7). Anal. Calcd for $C_{10}H_{16}$: C, 88.17; H, 11.83. Found: C, 87.95; H, 12.05.

The best procedure for the production of octalin **3b** is as follows. Catecholborane (1.27 mL, 11.3 mmol) was injected slowly through a septum into a stirring solution of 3.00 g (9.43 mmol) of hydrazone **3c** in 40 mL of chloroform at 0 °C under nitrogen and the stirring continued at the same temperature for 2 h. Sodium acetate trihydrate (2.60 g, 19.1 mmol) was added and the mixture refluxed for 1 h. The mixture was brought to room temperature and filtered. The solid material was washed with 30 mL of chloroform and the combined filtrates were evaporated under vacuum. Chromatography of the residue on 100 g of silica gel and elution with pentane afforded 900 mg (70%) of pure, liquid octalin **3b**.

4aβ,5,6,7,8,8aα-Hexahydro-2(1*H*)-naphthalenone (1). A solution of 3.04 g (16.3 mmol) of *N*-bromosuccinimide and 5 mL of 60% perchloric acid in 30 mL of dioxane and 30 mL of water was added to a solution of 1.80 g (13.2 mmol) of octalin **3b** and 6 mL of water in 61 mL of dioxane and 115 mL of *tert*-butyl alcohol, and the mixture was kept at room temperature for 4 h. It then was diluted with 200 mL of ether, washed with sodium bicarbonate, dried, and evaporated under vacuum. Chromatography of the residue on 40 g of silica gel and elution with 4:1 pentane–ether yielded 2.50 g of bromohydrin, whose oxidation with Jones reagent in acetone at 7–10 °C gave 2.40 g of crude bromo ketone. A mixture of the latter and 3.6 g of calcium carbonate in 72 mL of dimethylacetamide was was stirred and refluxed under nitrogen for 0.5 h. The cooled mixture was filtered and the filtrate diluted with pentane and washed with 1.5 M hydrochloric acid. The washings were extracted with pentane and the combined extract and filtrate washed with sodium bicarbonate solution, dried, and evaporated under vacuum. Chromatography of the residue on 30 g of silica gel and elution with 4:1 pentane–ether afforded 1.00 g (50% total yield) of colorless, liquid octalone 1:[4] IR 3019 (w, olefinic CH), 1685 (s, C=O), 1655 (w, C=C) cm^{-1}; ^1H NMR δ 5.96 (dq, 1, J = 10, 2, 1 Hz, H-3), 6.74 (dd, 1, J = 10, 2 Hz, H-4); ^{13}C NMR δ 25.4 (C-7 or C-6), 26.4 (C-6 or C-7), 31.3 (C-5 or C-8), 32.6 (C-8 or C-5), 41.8 (C-4a or C-8a), 42.3 (C-8a or C-4a), 45.3 (C-1), 129.0 (C-3), 155.2 (C-4), 199.9 (C=O). (2,4-Dinitrophenyl)hydrazone: mp 194–195 °C (lit.[4a] mp 193–195 °C). Anal. Calcd for $C_{16}H_{18}O_4N_4$: C, 58.18; H, 5.49; N, 16.96. Found: C, 58.06; H, 5.39; N, 16.84.

1α-Methyl-1,4,4aβ,4bβ,5,6,7,8,8aα,10aβ-decahydro-10(9*H*)-phenanthrenone (5) and 1β-Methyl-1,4,4aα,4bβ,5,6,7,8,8aα,10aβ-decahydro-10(9*H*)-phenanthrenone (6). A suspension of 245 mg (1.84 mmol) of anhydrous aluminum chloride and 1.10 g (7.34 mmol) of octalone **1** in 40 mL of dry toluene, prepared in a previously described manner,[6] was stirred under nitrogen at room temperature for 40 min. A solution of 2.2 mL (22.0 mmol) of (*E*)-piperylene (**2**) in 34 mL of dry toluene was added, the system closed, and the mixture warmed at 40 °C for 9 h. It then was cooled, poured into ice water, and extracted with ether. The extract was washed with sodium bicarbonate solution, dried, and evaporated under reduced pressure. Chromatography of the residue on 50 g of silica gel and gradient elution with 200:1 to 50:1 petroleum ether–ether mixtures led to 1.26 g of crystalline ketone **5**, 120 mg of crystalline ketone **6**, and 60 mg of a mixture of ketones **5**, **6**, and **7** (90% total yield).

Hydrophenanthrone **5**: mp 81–82 °C; IR 3022 (w, olefinic CH), 1719 (s, C=O) cm^{-1}; ^1H NMR δ 1.17 (d, 3, J = 7 Hz, Me), 5.41 (s, 2, H-2, H-3). (2,4-Dinitrophenyl)hydrazone: mp 176–177 °C. Anal. Calcd for $C_{21}H_{26}O_4N_4$: C, 63.30; H, 6.57; N, 14.06. Found: C, 63.73; H, 6.48; N, 13.95.

Hydrophenanthrone **6**: mp 45–46 °C; IR 3023 (w, olefinic CH), 1715 (s, C=O), 1662 (w, C=C) cm^{-1}; ^1H NMR δ 0.93 (d, 3, J = 7 Hz, Me), 5.43 (m, 2, H-2, H-3). (2,4-Dinitrophenyl)hydrazone: mp 201–202 °C. Anal. Calcd for $C_{21}H_{26}O_4N_4$: C, 63.30; H, 6.57; N, 14.06. Found: C, 63.12; H, 6.60; N, 13.91.

1α-Methyl-1,2,3,4,4aβ,4bβ,5,6,7,8,8aα,10aβ-dodecahydro-10(9*H*)-phenanthrenone (9). A mixture of 300 mg of hydrophenanthrone **5** and 30 mg of platinum oxide in 15 mL of dry ethanol was hydrogenated at room temperature and atmospheric pressure and then worked up in the usual manner, leading to 300 mg of crystalline ketone **9**: mp 61–62 °C; IR 1715 (s, C=O) cm^{-1}; ^1H NMR δ 1.10 (d, 3, J = 6 Hz, Me). (2,4-Dinitrophenyl)-hydrazone: mp 179–180 °C. Anal. Calcd for $C_{21}H_{28}O_4N_4$: C, 62.97; H, 7.06; N, 13.99. Found: C, 62.65; H, 7.18; N, 13.79.

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(16) Angell, E. C.; Fringuelli, F.; Minuti, L.; Pizzo, F.; Porter, B.; Taticchi, A.; Wenkert, E. *J. Org. Chem.* **1985**, *50*, 4686.