Synthesis of Polyquinanes. 2. The Total Synthesis of (±)-Silphinene: The Intramolecular Diels–Alder Approach[1]

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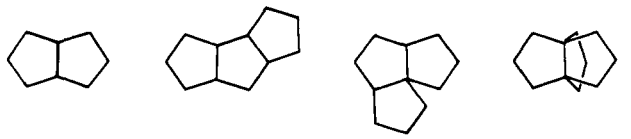
Abstract: A highly efficient (14–19% overall yield) ten-step synthesis of the angularly fused triquinane (±)-silphinene (**11**) is described. The key step in this synthetic sequence is an intramolecular Diels–Alder reaction of the substituted cyclopentadiene **15** to yield tricyclic olefin **16** containing all but one of silphinene's carbons. Compound **16** was elaborated to the key triquinane intermediate **20a** in three steps. (±)-Silphinene was obtained from **20a** through a straightforward four-step sequence. This overall route demonstrates the utility of our intramolecular Diels–Alder strategy for the synthesis of polyquinanes.

An ever increasing number of natural products containing bridged and fused five-membered carbocyclic rings have been isolated in recent times, stimulating efforts directed toward the synthesis of these compounds.[3] We sought to develop a general



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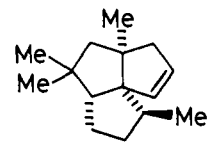
strategy that would be applicable to the synthesis of compounds with the skeletal types depicted in **1–4**.

Strategy. The key element of our strategy is the stereoselective formation of two fused 5-membered carbocyclic rings via an intramolecular Diels–Alder (IMDA) reaction with cyclopentadiene as the diene and a dienophile tethered by a three-carbon chain (Scheme I). It has been shown that cyclopentadienes of this type react exclusively as **5a** when temperatures sufficient for rapid 1,5-hydride shifts are used.[1,4] The stereochemistry of the Diels–Alder product is the result of an exo transition state (i.e., where the bridging chain is exo);[1,4] thus only **6** is formed. Cleavage of the double bond of **6** would lead to a functionalized cis-fused diquinane with defined relative stereochemistry of R_2, R_3, and the aldehyde groups. Our strategy called for the incorporation of a latent acetyl group in the Diels–Alder precursor as R_1, R_2, or R_3. Aldol cyclization of a given acetyl group with one of the aldehydes liberated through cleavage of the double bond in **6** would lead to either **8**, **9**, or **10**, depending on the choice of R groups. Thus this synthetic strategy has potential for the synthesis of all of the possible triquinane skeleta. In this paper we wish to describe the successful implementation of this strategy to the synthesis of (±)-silphinene (**11**).

Results and Discussion

Silphinene was first isolated from the root of silphium perfoliatum L.[5] Its structure was determined by NMR analysis of



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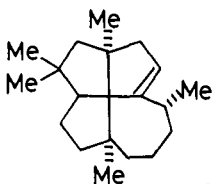

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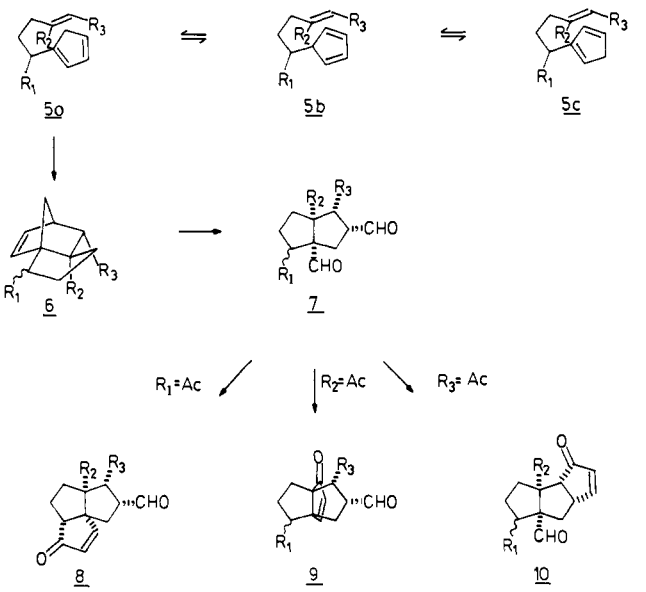
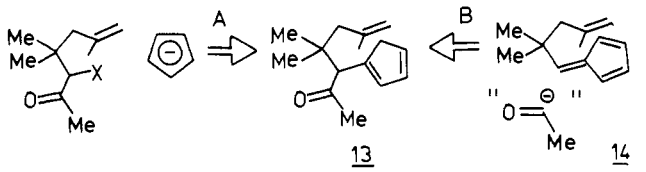
Scheme I. General Strategy for Polyquinane Synthesis



silphinene and several derivatives.[5] Since its isolation, it has been synthesized by three groups.[6] Laurenene[7] (**12**) shares the same triquinane portion as silphinene, so it is anticipated that some of the intermediates described herein may be used for the synthesis of laurenene. Our approach requires **13** or an equivalent as a



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(1)

Diels–Alder precursor. Traditional routes for forming substituted cyclopentadienes by alkylation of cyclopentadiene (eq 1, route A) are not likely to be successful, even if the carbonyl is protected, because of the extremely hindered nature of the electrophilic center (secondary and neopentylic). An alternative strategy (eq 1, route B) that involves prior formation of a fulvene followed by nucleophilic addition of an acyl anion equivalent to the polarized exocyclic double bond proved to be a viable alternative. We have previously shown[8] that a variety of alkyl lithiums may be added to hindered fulvenes. For our purpose the required fulvene was

(1) For part 1 of this series see: Sternbach, D. D.; Hughes, J. W.; Burdi, D. F.; Forstot, R. M. *Tetrahedron Lett.* **1983**, 3295.
(2) Undergraduate research participant.
(3) For a recent review see: Paquette, L. A. *Top. Curr. Chem.* **1984**, *119*, 1.
(4) (a) Corey, E. J.; Glass, R. S. *J. Am. Chem. Soc.* **1967**, *89*, 2600. (b) Breitholle, E. G.; Fallis, A. G. *Can. J. Chem.* **1976**, *54*, 1991. (c) Landry, D. W. *Tetrahedron* **1983**, *39*, 2761. (d) For an example in which the IMDA reaction was carried out at temperatures where 1,5-hydride shifts were slow relative to the IMDA reaction, see: Wallquist, O.; Rey, M.; Dreiding, A. S. *Helv. Chim. Acta* **1983**, *66*, 1891.
(5) Bohlmann, F.; Jakupovic, J. *Phytochemistry* **1980**, *19*, 259.
(6) (a) Leone-Bay, Andrea; Paquette, L. A. *J. Org. Chem.* **1983**, *47*, 4173. (b) Tsunoda, T.; Kodama, M.; Ito, S. *Tetrahedron Lett.* **1983**, *24*, 83. (c) Wender, P., private communication.
(7) Corbett, R. E.; Lauren, D. R.; Weavers, R. T. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1774. Corbett, R. E.; Couldwell, C. M.; Lauren, D. R.; Weavers, R. T. *J. Chem. Soc., Perkin Trans. 1* **1979**, *1791*.
(8) Sternbach, D. D.; Hughes, J. W.; Burdi, D. F. *J. Org. Chem.* **1984**, *49*, 201.

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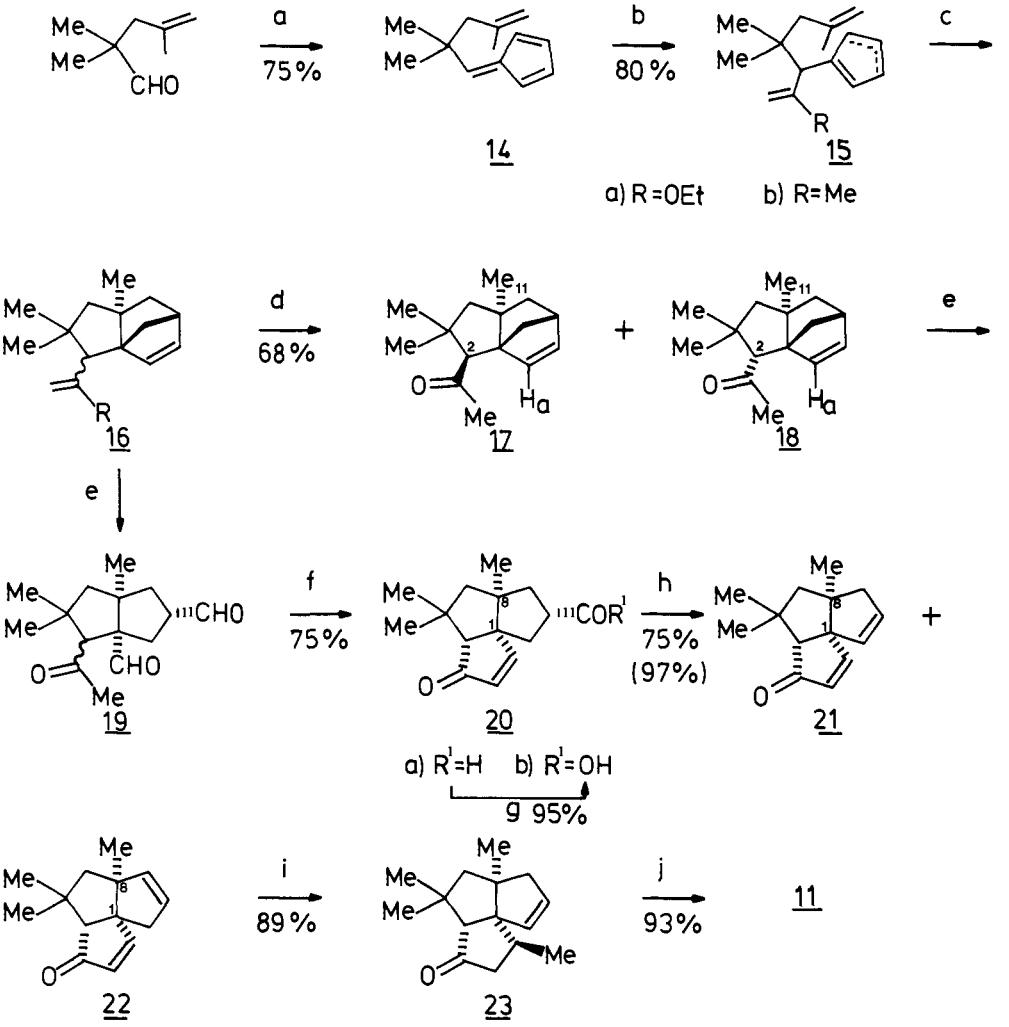
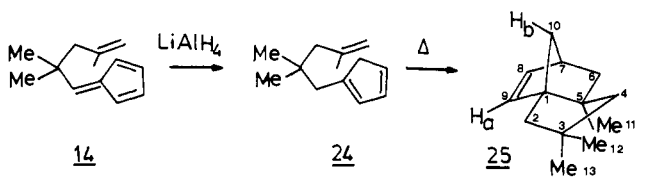
Scheme II. Synthesis of (±)-Silphinene



(a) Na^+Cp^-, THF. (b) $Li(OEt)C{=}CH_2$, THF, 0 °C. (15a); $Li(CH_3)C{=}CH_2$, ether, room temperature (15b). (c) 160 °C, benzene, sealed tube. (d) PyH·OTs, acetone/H_2O. (e) O_3, CH_2Cl_2, −78 °C; DMS, room temperature. (f) KOH, MeOH, room temperature. (g) Jones reagent, acetone. (h) $Pb(OAc)_4$, $Cu(OAc)_2\cdot H_2O$, pyridine, room temperature → reflux. (i) Me_2CuLi, ether, −78 °C → −20 °C. (j) $N_2H_4\cdot H_2O$, K_2CO_3, triethylene glycol, 180 °C → 250 °C.

easily prepared from the known 2,2,4-trimethyl-4-pentenal[9] and sodium cyclopentadienide in 75% yield. The alkenyl lithium derived from ethyl vinyl ether[10] adds to the fulvene in 80% yield. This enol ether will eventually be hydrolyzed to give a ketone. Alternatively, isopropenyllithium[11] adds to fulvene **14** to form **15b** (71%, Scheme II).

The intramolecular Diels–Alder reaction of both **15a** and **15b** occurred smoothly at 160 °C (benzene, sealed tube) to yield **16**. The enol ethers **16a** were hydrolyzed directly to **17** and **18** (10:1) in 68% yield from **15a**. The stereochemistry of the acetyl group in the major epimer (**17**) was assigned the β configuration on the basis of ^1H NMR evidence. To aid in the NMR assignments a model compound **25**, without an acetyl group, was synthesized (eq 2). The olefinic proton H_a appears as a doublet at 5.96 ppm



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in the major isomer **17** comparable to the chemical shift exhibited by the model **25** (5.99 ppm). In the minor isomer **18** this proton exhibited a more deshielded absorption at 6.23 ppm, indicative of the influence of the proximal carbonyl.[12] In addition, the C-11 methyl group had a similar chemical shift in both **17** and the model **25** (**17**; 0.85 ppm; **25**, 0.82 ppm) and was more deshielded in **18** (1.00 ppm), once again showing the influence of the neighboring carbonyl. The proton H_b, on the one carbon bridge, was dramatically deshielded in **17** (1.91 ppm) compared with that in the model **25** (1.24 ppm). Unfortunately, the absorption of this proton was obscured in the spectrum of the minor isomer **18** but could not have been further downfield than 1.8 ppm.

Epimerization studies performed on **17** and **18** showed that **18** was slowly converted to **17** (MeO^-/CD_3OD, 45 °C) while **17** remained unchanged except for incorporation of deuterium at the sites adjacent to the carbonyl. Although the exact ratio of Diels–Alder products **16a** could not be accurately determined by ^1H NMR,[13] it was shown (in a separate experiment) that the conditions necessary to hydrolyze the enol ethers **16a** were not sufficient to epimerize the ketones **17** and **18**. Therefore, the isomer ratio of the methyl ketones (**17**, **18**) was most likely a

(9) Brannock, K. C. *J. Am. Chem. Soc.* **1959**, *81*, 3379. Prepared according to: Diefl, H. K.; Brannock, K. C. *Tetrahedron Lett.* **1973**, 1273.
(10) Boeckman, R. K., Jr.; Braza, K. J. *J. Org. Chem.* **1979**, *44*, 4781.
(11) Luche, J.-L.; Damiano, J.-C. *J. Am. Chem. Soc.* **1980**, *102*, 7926.
(12) Jackman, L. M.; Sternhell, S. "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry"; 2nd ed.; Pergamon Press: Oxford, 1969; p 91.
(13) The crude Diels–Alder products contained some **17** and **18** presumably resulting from hydrolysis by adventitious water.

reflection of the stereospecificity of the IMDA reaction. In addition, cyclization of **15b** yielded essentially one Diels–Alder product **16b**, presumed to have the β configuration on the basis of a comparison of the ^{1}H NMR spectra of **16b**, **17**, and **25**. The fact that the major Diels–Alder products have the undesired stereochemistry is of no consequence since epimerization can occur during the aldol reaction (vide infra).

It is interesting that the Diels–Alder reaction of **15** is stereoselective with respect to the substitutent at C-2 (see structures **25** for numbering). This stereoselectivity is probably due to the presence of the C-11 methyl which sterically disfavors the transition state leading to the α configuration at C-2. Other similar Diels–Alder precursors, without substituents at C-5, give mixtures of C-2 epimers.[1,4c]

Ozonolytic cleavage of **17**, **18**, or **16b** led to the dialdehyde **19** after reductive workup. This dialdehyde was present as a mixture of hydrates and was therefore carried on without purification. Aldolization of the epimeric mixture **19** (KOH, MeOH) led to the cyclopentenone **20** in 75% yield from **17**, thus forming the triquinane skeleton. Interestingly, about 10% of the acid **20b** was also present (presumably the result of a Cannizzaro reaction or oxidation by adventitious oxygen). Jones oxidation[14] of **20a** afforded **20b** in 95% yield. (Combined with the **20b** produced on aldolization, the yield of **20b** from **17** and **18** is 81%.)

Now the stage was set for introduction of the double bond present in silphinene. Oxidative decarboxylation of **20** could lead to two possible olefins (**21** and **22**). We reasoned that if the product ratio was determined by the accessibility of the protons β to the carboxyl group, than **21** should predominate, since models show that the steric hindrance of proton abstraction owing to the angular methyl group outweighs that of the β sp^2 carbon of the enone. In the event, oxidative decarboxylation ($Pb(OAc)_4$, $Cu(OAc)_2$)[15] of **20b** afforded **21** and **22** in 75% yield (97% based on recovered starting material) in a 7:3 ratio. The major isomer was assigned structure **21** on the basis of its ^{13}C NMR. In particular, the chemical shift of C-8 in **21** (50.3 ppm) was about the same as that in **20b** (50.2 ppm), while the same carbon in **22** was considerably more deshielded (58.7 ppm), indicating the presence of an adjacent sp^2 center. Conversely C-1 in **21** was deshielded (74.6 ppm) while the shifts of the analogous carbons were similar in **22** and **20b** (66.6 and 67.5 ppm, respectively). These isomers could be separated by flash chromatography. Addition of $(CH_3)_2CuLi$ to the major isomer (**21**) occurred smoothly, producing only **23** (89%) as judged by ^{13}C NMR. This was not surprising since one face of the enone is shielded by the angular methyl group.[16] Some kinetic selection for **21** was possible when cuprate addition was attempted on the mixture of **21** and **22**, but for preparative purposes separation prior to cuprate addition was preferred.

Conversion of **23** to (±)-silphinene (**11**) could be accomplished in high yield (93%) through a Wolff–Kishner reduction of the carbonyl.[16] A small amount (<7%) of a related compound, assumed to be dihydrosilphinene (GC–MS analysis), was also produced in this reaction. The 250-MHz ^{1}H NMR of our synthetic silphinene was superimposable on the spectrum of an authentic sample.[17] In addition, the ^{13}C NMR spectrum matched the data reported for natural silphinene.[5]

In summary, we have described an efficient (14% overall yield or 19% if one counts recycling in the conversion of **20** to **21**) 10-step synthesis of (±)-silphinene that demonstrates the utility of the intramolecular Diels–Alder strategy for the synthesis of angularly fused triquinanes.

(14) Bowers, A.; Halsall, T. G.; Jones, E. R. H.; Lemin, A. J. *J. Chem. Soc.* **1953**, 2548.

(15) Bacha, J. D.; Kochi, J. K. *Tetrahedron* **1968**, *24*, 2215. Ito, T.; Tomiyoshi, N.; Nokamura, K.; Azuma, S.; Izawa, M. Maruyamz, F.; Yanagiya, M.; Shirahama, H.; Matsumoto, T. *Tetrahedron* **1984**, *40*, 255.

(16) For addition of $(CH_3)_2CuLi$ to a similarly substituted triquinane see Paquette's isocomene synthesis; Paquette, L. A.; Han, Y.-K.; *J. Am. Chem. Soc.* **1981**, *103*, 1835.

(17) We thank Prof. L. A. Paquette for kindly providing a ^{1}H NMR spectrum of (±)-silphinene.

Experimental Section

All NMR chemical shifts are reported as δ values in ppm relative to Me_4Si or $CHCl_3$. When ^{13}C NMR multiplicities are given, they were determined by application of the INEPT pulse sequence.

Preparation of [1-(1-Ethoxyvinyl)-2,2,4-trimethyl-4-pentenyl]cyclopentadiene (15a). To a solution of 8.8 mL (0.091 mol) of ethyl vinyl ether in 44 mL of dry THF at −78 °C under N_2 was added dropwise 19 mL of 2.4 M *t*-BuLi in pentane. After addition was complete, the yellow suspension was warmed slowly to 0 °C, at which point a clear, colorless solution was obtained.[10] To this solution was added a solution of fulvene **14**[8] (0.0228 mol, 4.00 g) in 24 mL of dry THF. After 30 min at 0 °C, saturated NH_4Cl was added and the mixture was extracted with ether. The ether extract was washed sequentially with saturated NH_4Cl, water, and brine and dried with $MgSO_4/K_2CO_3$. Concentration gave 4.50 g (80%) of nearly pure **15a**, which was used directly for the subsequent Diels–Alder reaction. **15a**: ^{1}H NMR ($CDCl_3$, 80 MHz) 0.96 (s, 3 H), 0.98 (s, 3 H), 1.34 (t, J = 7.0 Hz, 3 H), 1.76 (br s, 3 H), 2.0–2.1 (m, 2 H), 2.9–3.1 (m, 2 H), 3.72 (q, J = 7.0 Hz, 2 H), 3.86–3.92 (m, 2 H), 4.64–4.87 (m, 2 H), 6.15–6.72 (m, 3 H).

Diels–Alder Reaction of 15a: Preparation of 2-Acetyl-3,3,5-trimethyltricyclo[5.2.1.0^{1,5}]dec-8-enes 17 and 18. A solution of 4.50 g (18.2 mmol) of cyclopentadiene **15a** in 155 mL of dry benzene was placed in a thick-walled, resealable glass tube which has been previously washed with alcoholic KOH and distilled water and then oven-dried. The solution was subjected to 3 freeze–pump–thaw sequences, and the tube was then sealed under vacuum. The tube was heated to 160 °C for 2 h. The solvent was then evaporated to give 4.5 g of a dark oil (**16a**). This oil was dissolved in a mixture of 90 mL of acetone and 30 mL of water and treated with 0.45 g (1.8 mmol) of pyridinium tosylate. This solution was stirred for 24 h and then diluted with ether, washed successively with water and brine, and dried ($MgSO_4$). Concentration gave 4.25 g of crude **17** and **18**, a 10:1 mixture as determined by ^{1}H NMR. Flash chromatography (silica gel, hexane/ether, 25:1) gave 1.68 g of pure **17** (major isomer, low-melting solid), 0.88 g of mixed isomers, and 0.14 g of **18** (minor isomer, oil) admixed with a small amount of an unidentified, inseparable impurity (total yield, 68%.) In normal practice, the isomers were not separated but were used as a mixture for subsequent reactions.

17: ^{1}H NMR ($CDCl_3$, 250 MHz) 0.85 (dd, J = 11.4, 3.0 Hz, 1 H), 0.85 (s, 3 H), 1.00 (s, 3 H), 1.38 (s, 3 H), 1.65 (dd, J = 8.6, 0.5 Hz, 1 H), 1.70–1.81 (m, 3 H), 1.91 (dt, J = 8.6, 2.4 Hz, 1 H) 2.21 (s, 3 H), 2.88 (br s, 1 H), 3.16 (s, 1 H), 5.96 (d, J = 5.7 Hz, 1 H), 6.05 (dd, J = 5.6, 3.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 22.5 MHz) 25.9 (q), 29.4 (q). 33.2 (q), 34.1 (q), 42.1 (s), 42.6 (t), 44.9 (d), 48.4 (s), 50.9 (t), 56.6 (t), 60.2 (d), 67.5 (s), 135.4 (d), 137.5 (d), 209.6 (s); IR ($CDCl_3$ 3050 (w), 2955 (s), 2860 (m), 1705 (s), 1465 (w), 1370 (m), 1160 (m), 760 cm^{-1} (w). Anal. ($C_{15}H_{22}O$) C, H.

18: ^{1}H NMR ($CDCl_3$, 80 MHz) 0.88 (dd, J = 11.6, 3.2 Hz, 1 H), 1.00 (s, 3 H), 1.10 (s, 3 H), 1.30 (s, 3 H), 1.25–1.90 (m, 5 H), 2.18 (s, 3 H), 2.79 (br s, 1 H), 3.05 (s, 1 H), 5.98 (dd, J = 5.6, 3.0 Hz, 1 H), 6.23 (d, J = 5.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 22.5 MHz) 26.7, 28.7, 34.4, 36.3, 44.1, 44.3, 45.4, 50.8, 56.7, 57.3, 63.4, 68.3, 133.8, 137.7, 209.7.

Base Equilibration of Ketones 17 and 18. Ketones **17** and **18** (10 mg each) were dissolved in MeOH-d_4 (0.6 ml) and treated with excess NaOMe. These solutions were heated at 45 °C in NMR tubes and the reactions monitored by ^{1}H NMR. After 46 days, the olefin pattern in the ^{1}H NMR of the minor isomer (**18**) had been completely replaced by the pattern of the major isomer (**17**). In addition, the signals at 3.05 and 2.18 had completely disappeared. The major isomer, however, suffered no change other than the loss of the NMR signals at 3.16 and 2.88. After workup (ether–water), the NMR spectra in $CDCl_3$ were compared and found to be identical with each other and with the original spectrum of **17** (except, of course, for the signals lost by deuterium exchange).

Preparation of [1-(2-Propenyl)-2,2,4-trimethyl-4-pentenyl]cyclopentadiene (15b). To a solution of isopropenyllithium[11] (8.6 mmol) in 25 mL of dry ether was added a solution of fulvene **14** (500 mg, 2.9 mmol) in 8 mL of ether. After 1 h at room temperature, the reaction was quenched with saturated NH_4Cl. The mixture was diluted with ether, the layers were separated, and the ether layer was washed sequentially with saturated NH_4Cl and brine and dried with $MgSO_4/K_2CO_3$. Evaporation gave 558 mg of crude **15b**. Chromatography on activity II–III neutral alumina (hexane elution) afforded 442 mg (71%) of pure **15b** (oil). ^{1}H NMR ($CDCl_3$, 80 MHz) 1.00 (s, 6 H), 1.78 (m, 6 H), 2.09 (br s, 2 H), 2.94–3.08 (m, 3 H), 4.61–4.91 (m, 4 H), 6.11–6.60 (m, 3 H).

Diels–Alder Cyclization of 15b: Preparation of 16b. A solution of 442 mg (2.05 mmol) of **15b** in 16 mL of dry benzene was subjected to the same conditions used for Diels–Alder cyclization of **15a**. Flash chromatography (silica gel, hexane) of the crude product gave 300 mg (68%) of pure **16b** (oil), a single isomer by ^{1}H NMR. ^{1}H NMR ($CDCl_3$, 250

mHZ) 0.79–0.87 (m, 1 H), 0.83 (s, 3 H), 0.93 (s, 3 H), 1.17 (s, 3 H), 1.62–1.80 (m, 8 H), 2.72 (s, 1 H), 2.84 (br, s, 1 H), 4.78–4.89 (m, 2 H), 5.96–6.02 (m, 2 H).

Further confirmation of the structure of **16b** was obtained by its conversion to **19** (vide infra).

Preparation of 3,3,5-Trimethyltricyclo[5.2.1.0^{1,5}]dec-8-ene (25). $LiAlH_4$ (57 mg, 1.5 mmol) was suspended in 3 mL of THF, and a solution of fulvene **14** (174 mg, 1.0 mmol) in 1 mL of THF was added dropwise. After addition was complete, the mixture was stirred for 5 min. The reaction was quenched by sequential addition of 75 μL of water, 75 μL of 10% NaOH, and 150 μL of water. The suspension was filtered, the solids were washed well with ether, and the ether solution was dried with $MgSO_4$. Careful concentration gave 149 mg of crude **24** (84%). Crude **24** (30 mg, 0.17 mmol) was dissolved in 1.0 mL of benzene-d_6, and the solution placed in a thick-walled NMR tube. The solution was subjected to 3 freeze–pump–thaw sequences and then sealed under vacuum. The tube was heated to 160 °C and the reaction progress monitored by ^1H NMR. After 69 h the reaction was complete. The tube was cooled and the solvent removed by rotary evaporation. Preparative GLC (125 °C oven temperature) of the residue gave 16 mg of pure **25** (53%, oil): ^1H NMR ($CDCl_3$, 250 MHz) 0.82 (s, 3 H), 0.86 (dd, J = 11.6, 2.9 Hz, 1 H), 1.06 (s, 3 H), 1.13 (s, 3 H), 1.24 (dt, J = 8.0, 2.2 Hz, 1 H), 1.61–1.68 (m, 4 H), 1.81 (dd, J = 11.6, 3.6 Hz, 1 H), 1.88 (d, J = 13.4 Hz, 1 H), 2.80 (br s, 1 H), 5.97–6.02 (m, 2 H); ^{13}C NMR ($CDCl_3$, 22.5 MHz) 26.2 (q), 34.0 (q), 34.3 (q), 39.6 (s), 41.9 (t), 43.7 (t), 45.3 (d), 50.7 (s), 54.0 (t), 55.7 (t), 66.3 (s), 134.9 (d), 139.5 (d); IR ($CDCl_3$) 3050 (w), 2950 (s), 2855 (s), 1450 (m), 1365 (m), 1245 cm^{-1} (w).

Preparation of 6,6,8-Trimethyl-10-formyltricyclo[6.3.0.0^{1,5}]undec-2-en-4-one (20a). (A) From 17. A solution of 1.31 g (6.0 mmol) of ketone **17** in 60 mL of methylene chloride was cooled to −78 °C and treated with ozone until a blue color persisted. The excess ozone was discharged by bubbling oxygen through the solution, 2.64 mL (36.0 mmol) of dimethyl sulfide was added, and the solution was allowed to warm slowly to room temperature. After being stirred overnight, the mixture was diluted with ether. The ether solution was washed successively with water and brine and dried ($MgSO_4$). Concentration gave 1.55 g of crude **19**, which was assumed to exist largely as a cyclic hydrate of the two aldehyde groups, based on the low intensity of the aldehyde resonances in the ^1H NMR.

This product was dissolved in 5 mL of MeOH and added dropwise to a solution of 1.74 g (31.0 mmol) of KOH in 75 mL of MeOH. After being stirred for 6 h, the solution was diluted with ether and washed with water. The water layer was extracted with ether, and the combined ether layers were washed with brine and dried with $MgSO_4$. Concentration gave 1.05 g (75%) of nearly pure **20a**, which was used directly without further purification. A sample for combustion analysis was prepared by flash chromatography (silica gel, hexane/ether, 1:1). ^1H NMR ($CDCl_3$, 250 MHz) 0.91 (s, 3 H), 1.19 (s, 3 H), 1.21 (s, 3 H), 1.56–2.00 (m, 6 H), 2.24 (s, 1 H), 2.94 (dtt, J = 2.9, 6.1, 12.1 Hz, 1 H), 5.95 (d, J = 5.6 Hz, 1 H), 7.46 (d, J = 5.7 Hz, 1 H), 9.63 (d, J = 2.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 22.5 MHz) 25.7 (q), 25.9 (q), 31.5 (q), 39.7 (s), 42.4 (d), 43.6 (t), 47.4 (t), 50.1 (s), 59.9 (t), 67.4 (s), 69.4 (d), 132.6 (d), 167.7 (d), 179.9 (s), 210.7 (s); IR ($CDCl_3$) 3050 (w), 2955 (s), 2860 (m), 1720 (s), 1690 (s), 1580 (w), 1440 (m), 1265 cm^{-1} (s). Anal. ($C_{15}H_{20}O_2$) C, H.

In another run of the above reaction sequence, starting with 0.88 g (40 mmol) of **17**, the aqueous layer from the reaction workup was acidified with concentrated HCl and extracted with ether. The ether extract was washed with brine and dried ($MgSO_4$). Evaporation gave 0.25 g of a mixture of carboxylic acids. This mixture was dissolved in 10 mL of dry ether, cooled to 0 °C, and treated with an excess of diazomethane in ether. After being warmed to room temperature, acetic acid was added to consume excess CH_2N_2. The solution was washed sequentially with saturated $NaHCO_3$ and brine and dried with $MgSO_4$. Evaporation and flash chromatography (silica gel, hexane/ether, 2:1) of the residue afforded 103 mg of **20b**-Me ester, identified by saponification (K_2CO_3/MeOH) to **20b**, and comparison with authentic material (vide infra). This represents a 10% yield of **20b** from **17**.

(B) **From 18: 18** (44 mg, 0.2 mmol) was subjected to the same reaction conditions as in (A) to afford 28 mg (60%) of **20a**.

(C) From 16b: A solution of 63 mg (0.3 mmol) of **16b** in 3 mL of CH_2Cl_2 was ozonolyzed at −78 °C and then treated with 1 mL of acetic acid and 117 mg of Zn dust (1.8 mmol). After being warmed to room temperature, the mixture was diluted with ether. The ether solution was washed twice with saturated $NaHCO_3$ and once with brine and then dried with $MgSO_4$. The residue after evaporation was treated with KOH/MeOH as in (A) to give 42 mg (60%) of **20a**.

Jones Oxidation of Aldehyde 20a: Preparation of Acid 20b. Aldehyde **20a** (285 mg, 1.2 mmol) in acetone (12 mL) at 0 °C was treated dropwise with 5 mL of Jones reagent. After the mixture was stirred for 30 min at 0°, isopropyl alcohol was added and the solution was warmed to room temperature. The mixture was diluted with water and extracted with ether (3×). The ether extracts were combined, washed with brine, and dried ($MgSO_4$). Evaporation gave 287 mg of **20b** (95%, white solid), which was used without further purification. For combustion analysis a sample was recrystallized from hexane/ether (white crystals, mp 168–169 °C). ^1H NMR ($CDCl_3$, 250 MHz) 0.88 (s, 3 H), 1.16 (s, 3 H), 1.19 (s, 3 H), 1.63–2.06 (m, 6 H), 2.23 (s, 1 H), 2.90 (tt, J = 12.2, 6.1 Hz, 1 H), 5.94 (d, J = 5.6 Hz, 1 H), 7.48 (d, J = 5.6 Hz, 1 H), carboxylic acid resonance not observed below 12 ppm; ^{13}C NMR ($CDCl_3$, 22.5 MHz) 25.7 (q), 25.9 (q), 31.5 (q), 39.7 (s), 42.5 (d), 43.6 (t), 47.4 (t), 50.2 (s), 59.9 (t), 67.5 (s), 69.4 (d), 132.6 (d), 167.6 (d), 179.8 (s), 210.6 (s); IR ($CDCl_3$) 3400–2300 (br s), 2950 (s), 2860 (m), 1705 (s), 1690 (s), 1580 (w), 1460 (m), 1300 (m), 1190 cm^{-1} (m). Anal. ($C_{15}H_{20}O_3$) C, H.

Oxidative Decarboxylation of 20b:[15] Preparation of 6,6,8-Trimethyltricyclo[6.3.0.0^{1,5}]undeca-2,10-dien-4-one (21) and 6,6,8-Trimethyltricyclo[6.3.0.0^{1,5}]undeca-2,9-dien-4-one (22). To a solution of acid **20b** (53 mg, 0.21 mmol) in 2 mL of dry benzene were added 27 μL (0.34 mmol) of pyridine and 1 mg (0.005 mmol) of $Cu(OAc)_2H_2O$. This solution was stirred for 30 min in the dark. $Pb(OAc)_4$ (149 mg, 0.34 mmol) was added, and the solution was stirred for another 3 h in the dark. The solution was then heated to reflux for 1 h (no longer in the dark). After the mixture was cooled, aqueous ethylene glycol was added and the mixture was extracted with ether. The ether solution was washed sequentially with water, saturated $NaHCO_3$, and brine and then dried ($MgSO_4$). Careful evaporation yielded 32 mg (75%) of oily product (**21**/**22**), containing only very small amounts of impurities as demonstrated by ^1H NMR and capillary GLC analysis. The GLC analysis revealed the ratio of **21** to **22** to be 7:3. After acidification of the combined aqueous washes from above, followed by ether extraction, 12 mg of starting acid **20b** could be recovered. This represents a 77% conversion of **20b**; thus the yield of **21**/**22** based on recovered starting material was 97%. In larger runs (up to 2 mmol of **20b**), the isomers **21** and **22** were separated by flash chromatography (silica gel, hexane/ether, 25:1), although some losses due to decomposition were incurred. After a single pass, yields of pure **21** (based on recovered **20b**) ranged from 25 to 31%, with another 22–28% of pure **22** and mixed fractions. One recycle of the mixed fractions gave essentially complete separation of **21** and **22**.

21: ^1H NMR ($CDCl_3$, 250 MHz) 1.00 (s, 3 H), 1.06 (s, 3 H), 1.11 (s, 3 H), 1.66 (d, J = 13.3 Hz, 1 H), 1.81 (d, J = 13.3 Hz, 1 H), 2.14 (s, 1 H), 2.27 (dt, J = 17.5, 2.3 Hz, 1 H), 2.54 (dt, J = 17.4, 2.3 Hz, 1 H), 5.38 (dt, J = 5.7, 2.3 Hz, 1 H), 5.65 (dt, J = 5.7, 2.3 Hz, 1 H), 5.94 (d, J = 5.6 Hz, 1 H), 7.31 (d, J = 5.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 22.5 MHz) 26.5 (q), 26.7 (q), 32.1 (q), 40.0 (s), 50.2 (t), 50.3 (s), 58.5 (t), 66.0 (d), 74.6 (s), 130.3 (d), 132.9 (d), 134.2 (d), 167.0 (d), 210.5 (s); IR ($CDCl_3$) 3050 (m), 2955 (s), 2920 (s), 2860 (m), 2850 (m), 1690 (s), 1580 (m), 1450 (m), 1340 (m), 1190 cm^{-1} (m). Anal. ($C_{14}H_{18}O$) C, H.

22: ^1H NMR ($CDCl_3$, 250 MHz) 0.96 (s, 3 H), 1.00 (s, 3 H), 1.11 (s, 3 H), 1.47 (d, J = 13.4 Hz, 1 H), 1.73 (d, J = 13.5 Hz, 1.H), 2.06 (s, 1 H), 2.35 (br d, J = 16.9 Hz, 1 H), 2.66 (ddd, J = 16.9, 2.3, 1.8 Hz, 1 H), 5.56–5.65 (m, 2 H), 6.03 (d, J = 5.6 Hz, 1 H), 7.48 (d, J = 5.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 22.5 MHz) 23.3 (q), 28.2 (q), 32.5 (q), 39.8 (s), 44.0 (t), 53.5 (t), 58.7 (s), 66.6 (s), 70.0 (d), 126.4 (d), 133.9 (d), 142.4 (d), 167.9 (d), 211.2 (s); IR ($CDCl_3$) 3040 (w), 2950 (s), 2925 (s), 2855 (m), 2825 (m), 1690 (s), 1585 (m), 1445 (w), 1365 (w), 1185 cm^{-1} (m). A sample for combustion analysis was prepared by preparative GLC (175 °C oven temperature). Anal. ($C_{14}H_{18}O$) C, H.

Conjugate Addition of Me_2CuLi to Enone 21: Preparation of 2,6,6,8-Tetramethyltricyclo[6.3.0.0^{1,5}]undec-10-en-4-one (23). To a suspension of CuI (254 mg, 1.3 mmol) in 0.5 mL of dry ether at 0 °C was added 1.8 mL (2.7 mmol) of MeLi (1.5M in ether). After 15 min at 0 °C the solution was cooled to −78 °C, at which point a solution of enone **21** (54 mg, 0.27 mmol) in 2 mL of dry ether was added. After being warmed to −20 °C the reaction was stirred for 1 h. Saturated NH_4Cl was then added and the mixture warmed to room temperature. The reaction mixture was extracted with ether, and the ether extract was washed with brine and dried over $MgSO_4$. Evaporation gave 52 mg (89%) of essentially pure **23** (oil). A sample for combustion analysis was prepared by preparative GLC (180 °C oven temperature). ^1H NMR ($CDCl_3$, 250 MHz) 0.89 (d, J = 6.7 Hz, 3 H), 0.97 (s, 3 H), 1.07 (s, 3 H), 1.16 (s, 3 H), 1.65 (d, J = 13.1 (Hz, 1 H), 1.74 (d, J = 13.1 Hz, 1 H), 2.00–2.48 (m, 6 H), 5.57 (dt, J = 5.9, 2.2 Hz, 1 H), 5.68 (dt, J = 5.9, 2.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 22.5 MHz) 18.2 (q), 25.7 (q), 26.8 (q), 31.8 (q), 33.8 (d), 42.2 (s), 50.0 (t), 50.9 (s), 51.3 (t), 59.8 (t), 69.4 (d), 71.3 (s), 127.6 (d), 135.5 (d), 219.5 (s); IR ($CDCl_3$) 3050 (w), 2960 (s), 2925 (s), 2870 (m), 2850 (m), 1720 (s), 1450 (m), 1380 (m), 1360 (m), 1200 cm^{-1} (m). Anal. ($C_{15}H_{22}O$) C, H.

Wolff–Kishner Reduction of 23: Preparation of (±)-Silphinene (11). A sample of ketone **23** (11 mg, 0.05 mmol) was dissolved in 0.3 mL of

triethylene glycol. To this solution were added 23 mg of K_2CO_3 and 25 μL of hydrazine hydrate. This mixture was heated at 180 °C (bath temperature) under N_2 for 1 h, at which point another 25 μL of hydrazine hydrate was added and the temperature was raised to 200 °C. After 30 min, the solution was heated to 250 °C for 2 h. The mixture was cooled and diluted with water. This mixture was extracted with ether, and the ether solution was washed with 1 N HCl followed by brine and dried (Mg_4SO_4). Concentration gave 10 mg of crude product consisting of a 93:7 mixture of two compounds, as determined by capillary GLC analysis. The minor product was tentatively identified by GC–MS analysis as dihydrosilphinene (M^+ 206). The major product was silphinene (M^+ 204). The identity of the major product was confirmed by comparison of a high-field ^1H NMR spectrum with the spectrum of authentic silphinene.[17] In addition, the ^{13}C NMR matched the reported spectrum.[5] MS, *m/e* calcd for $C_{15}H_{24}$, 204.1878; found 204.1876. The yield of (±)-silphinene was 93%.

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Registry No. (±)-**11**, 83057-81-2; **14**, 87937-90-4; (±)-**15a**, 87648-96-2; (±)-**15b**, 95121-99-6; (±)-(2α)-**16a**, 87649-04-5; (±)-(2β)-**16a**, 87680-59-9; (±)-(2β)-**16b**, 95122-00-2; (±)-**17**, 95190-94-6; (±)-**18**, 87649-02-3; (±)-(2α)-**19**, 95122-01-3; (±)-(2β)-**19**, 95122-02-4; (±)-**20a**, 95122-03-5; (±)-**20b**, 95122-04-6; (±)-**21**, 95122-05-7; (±)-**22**, 95122-06-8; (±)-**23**, 95122-07-9; **24**, 95122-08-0; (±)-**25**, 95122-09-1; $EtOCH{=}CH_2$, 109-92-2; $Li(CH_3)C{=}CH_2$, 6386-71-6.

Functional Group Diversity in Enzymatic Oxygenation Reactions Catalyzed by Bacterial Flavin-Containing Cyclohexanone Oxygenase

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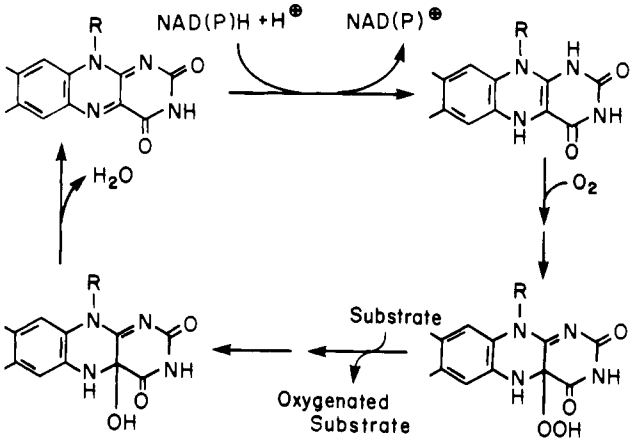
Abstract: The bacterial flavoprotein monooxygenase cyclohexanone oxygenase was found by spectrophotometric NADPH consumption assays and product analysis studies to perform oxygenation reactions on ketones, aldehydes, sulfides, selenides, boronic acids, a phosphite ester, and an iodide ion. Kinetic parameters (K_m, V_{max}) are reported for these substrates. The relevance of these results to possible active oxygen-transfer species in this enzyme is discussed. The potential utility of boronic acids as general probes for nucleophilic oxygen-transfer capability in oxygenases and in model chemistry is analyzed. The potential utility of cyclohexanone oxygenase as an enatioselective and/or chemoselective oxidant for organic molecules is assessed. Unsuccessful attempts at exploiting the 2,3-sigmatropic rearrangement of allyl sulfoxides and allyl selenoxides for mechanism-based inactivation of cyclohexanone oxygenase are reported. The use of the facile 2,3-sigmatropic rearrangement of allyl selenoxides to generate electrophilic allyl selenates for the design of mechanism-based inactivators for other enzymes is proposed.

The set of enzymes classified as monooxygenases,[2] transferring one atom from O_2 to specific cosubstrates, utilize various cofactors, including flavins, pterins, copper, and iron-containing heme (cytochromes P-450). In the past decade much progress has been made in the analysis of the nature of the enzyme-bound active oxygen-transfer species in these enzymes.[3]

A variety of flavoprotein monooxygenases are known which oxygenate various substrate molecules by catalyzing the four-electron reduction of dioxygen with two electrons derived from reduced nicotinamide cofactor and two electrons derived from substrate. Flavoprotein monooxygenases can be classified according to the "natural" substrates oxygenated and include phenolic aromatic α-hydroxylases (conversion of phenols to catechols),[4] mammalian microsomal sulfur–nitrogen oxygenases,[5] bacterial luciferases (conversion of straight-chain aliphatic aldehydes to straight-chain aliphatic carboxylic acids + light),[6] and cyclic ketone oxygenases such as cyclohexanone oxygenase (conversion of cyclic ketones to lactones) (eq 1).[7]

Scheme I



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(2) Walsh, C. "Enzymatic Reaction Mechanisms"; W. H. Freeman: San Francisco, 1979; pp 411–431, 458–485.

(3) Recent reviews include: (a) White, R. E., Coon, M. J. *Annu. Rev. Biochem.* **1980**, *49*, 315–356. (b) Malmstrom, B. G. *Annu. Rev. Biochem.* **1982**, *51*, 21–59. (c) Ballou, D. P. In "Flavins and Flavoproteins"; Massey, V., Williams, C. H., Jr., Eds.; Elsevier: New York, 1982; pp 301–310.

(4) (a) Detmer, K.; Massey, V.; Ballou, D. P.; Neujahr, H. Y. In "Flavins and Flavoproteins"; Massey, V., Williams, C. H., Jr., Eds.; Elsevier: New York, 1982; pp 335–358 and references therein. (b) References in ref 8. (c) Entsch, B.; Ballou, D. P.; Massey, V. *J. Biol. Chem.* **1976**, *251*, 2550–2563. (d) Husain, M.; Massey, V. *J. Biol. Chem.* **1979**, *254*, 6657–6666.

(5) Beatty, N.; Ballou, D. P. *J. Biol. Chem.* **1981**, *256*, 4611–4618, 4619–4625 and references therein.

(6) Hastings, J. W.; Balny, C.; LePeuch, C.; Douzou, P. *Proc. Natl. Acad. Sci. U.S.A.* **1973**, *70*, 3468–3472. (b) Ghisla, S.; Hastings, J. W.; Favaudon, V.; Lhoste, J. M. *Proc. Natl. Acad. Sci. U.S.A.* **1978**, *75*, 5860–5863. (c) Hastings, J. W.; Nealson, K. H. *Annu. Rev. Microbiol.* **1977**, *31*, 549–595. (d) Nealson, K. H.; Hastings, J. W. *Microbiol. Rev.* **1979**, 496–518. (e) Ziegler, M. M.; Baldwin, T. O. *Curr. Top. Bioenerg.* **1981**, *12*, 65–113.

0002-7863/85/1507-2153$01.50/0