(t, J = 8 Hz, overlapping a s, total 9 H); IR (CCl_4) 3300, 3070, 2960, 2900, 1740, 1695 cm^{-1}; n^{25}_D 1.4734 (lit.[1a] n^{25}_D 1.4712). When the DAZD and diene were reacted in comparable concentrations a third compound was isolated from the chromatography after the first two had eluted. On brief standing it crystallized. Recrystallization from hexane gave pure **29**: mp 89–90 °C; NMR (CCl_4) δ 6.8 (broad, 2 H), 4.7–5.1 (m, 6 H), 4.15 (m, 8 H), 1.9 (s, broad, 6 H), 1.25 (t, J = 7 Hz, 12 H); IR (CCl_4) 3300, 3020, 2900, 2850, 1750, 1700, 1640 cm^{-1}. Anal. Calcd for $C_{20}H_{34}N_4O_8$: C, 52.39; H, 7.47; N, 12.22. Found: C, 52.46; H, 7.45; N, 12.24.

Reaction of 10 and DAZD: Diethyl 1-[1-(1-Cyclohexen-1-yl)cyclohexyl]-1,2-hydrazinedicarboxylate (31). After evaporation of the samples of **10** and DAZD used for kinetics there was isolated 130 mg of a colorless oil. Flash chromatography on silica gel with 3:1 hexane:ethyl acetate gave after evaporation at 10^{-2} mm 122 mg of **31** as a viscous colorless oil: NMR ($CDCl_3$) δ 6.3 (s, 1 H, shifts on dilution), 5.7 (m, 1 H), 4.2 (two interlaced q, J = 7 Hz, 4 H), 1.8–2.4 (m, 8 H), 1.3–1.7 (m, 10 H) overlapped by 1.2 (two interlaced t, J = 7 Hz, 6 H); IR (thin film) 3300, 3050, 2970, 2930, 2850, 1760, 1710 cm^{-1}. Anal.[19] Calcd for $C_{18}H_{30}N_2O_4$: C, 63.88; H, 8.94; N, 8.28. Found: C, 62.44; H, 8.59; N, 8.02.

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An Oxyanionic [3,3]-Sigmatropic Approach to the Ophiobolin Ring System

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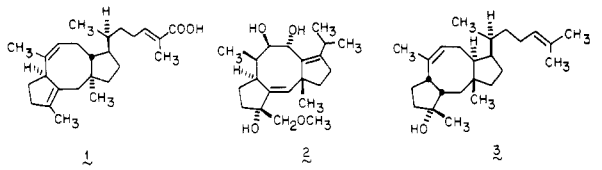
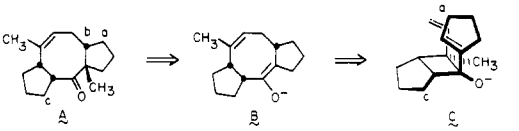
The addition of 1-cyclopentenyllithiums to (7*R**)-7-methyl-7-vinylbicyclo[3.2.0]hept-2-en-6-ones results in spontaneous oxyanionic Cope rearrangement. Addition of methyl iodide traps the resulting regiospecifically positioned enolates to provide highly functionalized *all-cis*-dicyclopenta[*a*,*d*]cyclooctane products such as **5**, **8**, and **11**. Hydride reduction of these ketones proceeds regiospecifically with formation of secondary alcohols which have proven to be exceptionally prone to transannular bond formation. The preparation of **12a–c** is exemplary. Attempts to fully deoxygenate either the ketones or the alcohols were unsuccessful. Epimerization α to the carbonyl group in **5** could be achieved via the silyl enol ether and this stereoisomer (**19**) was found to be susceptible to acid-catalyzed rearrangement.

The dicyclopenta[*a*,*d*]cyclooctane ring system constitutes the fundamental structural element of a large family of diterpenes and sesterterpenes which possess significant, wide-ranging biological activity. Ceroplastols typified by albolic acid (**1**)[1] and fusicoccins such as cotylenol (**2**)[2] are



representative. The ophiobolins comprise the most prevalent subgroup. Ophiobolin F (**3**), a prototypical example, features the characteristic angularly fused 5-8-5 molecular backbone.[3,4] The stereochemical and functional group differences that distinguish these natural products provide structural arrays that are architecturally novel and attractive. Although several approaches to this class of substances have been reported,[5–8] no successful de novo synthesis of any member has yet been achieved.

Two prime considerations behind any strategic planning involving the ophiobolins should be rapid construction of the tricyclic nucleus and appropriate control of those six chiral centers that find themselves clustered in two groups of three about the central cyclooctyl ring. To resolve the first of these issues, we envisioned an anionic rearrangement/ring enlargement sequence that would simultaneously introduce an appropriately positioned cyclooctenyl double bond and associated methyl group. Although the C → B transformation gives rise to an *all-cis* arrangement



of tertiary hydrogens, the enolate anion is suitably disposed for methylation and the resulting carbonyl group allows for additional chemical manipulation in that sector of the molecule. Moreover, suitable placement of functionality

(1) (a) Ceroplastol I and ceroplasteric acid. Iitake, Y.; Watanabe, I.; Harrison, I. T.; Harrison, S. *J. Am. Chem. Soc.* **1968**, *90*, 1092. (b) Ceroplatsol II: Rios, T.; Quijano, L. *Tetrahedron Lett.* **1969**, 1317. (c) Albolic acid: Rios, T.; Gomez, F. *Ibid.* **1969**, 2929.

(2) (a) Fusicoccin A: Hough, E.; Hursthouse, M. B.; Neidle, S.; Rodgers, D. *Chem. Commun.* **1968**, 1197. Ballio, A.; Brufani, M.; Casinori, C. G.; Cerrini, S.; Fedeli, W.; Pellicciari, R.; Santurbano, B.; Vaiaga, A. *Experientia* **1968**, *24*, 631. Barrow, K. D.; Barton, D. H. R.; Chain, E.; Ohnsorge, U. F. W.; Thomas, R. *J. Chem. Soc. C* **1971**, 1265. (b) Fusicoccin H: Barrow, K. D.; Barton, D. H. R.; Chain, E.; Ohnsorge, U. F. W.; Sharma, R. P. *J. Chem. Soc., Perkin Trans. 1* **1973**, 159. (c) Fusicoccin J.: Barrow, K. D.; Barton, D. H. R.; Chain, E.; Bageend-Kasujja, D.; Mellows, G. *Ibid.* **1975**, 877. (d) Cotylenol: Sassa, T. *Agric. Biol. Chem.* **1972**, *36*, 2037; **1975**, *39*, 1729.

(3) (a) Ophiobolin A: Ishibashi, K.; Nakamura, R. J. *Agric. Chem. Soc. Jpn.* **1958**, *32*, 739. Nozoe, S.; Morisaki, M.; Tsuda, K.; Iitake, Y.; Takahashi, N.; Tamura, S.; Ishibashi, K.; Shirasaka, M. *J. Am. Chem. Soc.* **1975**, *87*, 4968. (b) Ophiobolins B and C: Nozoe, S.; Hirai, K.; Tsuda, K. *Tetrahedron Lett.* **1966**, 2211. Canonica, L.; Fiecchi, A.; Kinele, M. G.; Scala, A. *Ibid.* **1966**, 1329. Ishibashi, K. *J. Antibiot.* **1962**, *A15*, 88. (c) Ophiobolin D: Itai, A.; Nozoe, S.; Tsuda, K.; Okuda, S.; Iitaka, Y.; Nakayama, Y. *Tetrahedron Lett.* **1967**, 4111. Nozoe, S.; et al. *Ibid.* **1967**, 4113. (d) Ophiobolin F: Nozoe, S.; Morisaki, M.; Fukushima, K.; Okuda, S. *Ibid.* **1968**, 4457. Nozoe, S.; Morisaki, M. *J. Chem. Soc. D* **1968**, 1319.

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(5) (a) Das, T. K.; Gupta, A. D.; Ghosal, P. K.; Dutta, P. C. *Indian J. Chem., Sect. B* **1976**, *14B*, 238. (b) Das, T. K.; Dutta, P. C. *Synth. Commun.* **1976**, *6*, 253. (c) Das, T. K.; Dutta, P. C.; Kartha, G.; Bermassan, J. M. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1287.

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(7) Dauben, W. G.; Hart, D. J. *J. Org. Chem.* **1977**, *42*, 922.

(8) Baker, W. R.; Senter, P. D.; Coates, R. M. *J. Chem. Soc., Chem. Commun.* **1980**, 1011. Coates, R. M.; Senter, P. D.; Baker, W. R. *J. Org. Chem.* **1982**, *47*, 3597.

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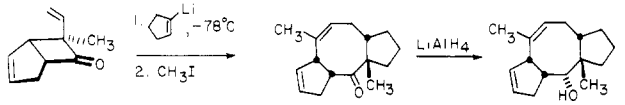
at sites a and c in the starting reagents transcribes into potentially useful activation in A that in turn simplifies the requirement for epimerization at b and side-chain attachment at c. Efforts directed toward the laboratory implementation of this retrosynthetic analysis are detailed in this report.[9]

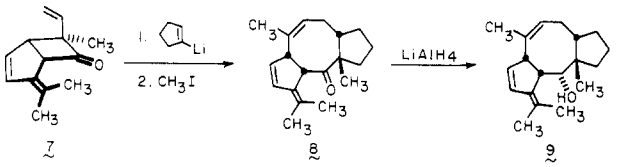
Oxyanionic Cope Studies. Vinyl ketenes, most commonly generated by the dehydrochlorination of α,β-unsaturated acid chlorides,[10] are recognized to enter readily into [2 + 2] cycloaddition with cyclic 1,3-dienes.[11] The process represents a versatile approach to 2-vinylcyclobutanones. When methyl vinyl ketene and cyclopentadiene are involved, a 7:3 mixture of **4** and its epimer results.[11] In our hands, the isolation of epimerically pure **4** could be readily achieved on a preparative scale by high-pressure liquid chromatography on silica gel. For obvious steric reasons, nucleophilic attack on the prochiral carbonyl group of **4** is strongly directed to the exo face. Recourse to a vinyl organometallic sets the stage for oxyanionic Cope rearrangement[12] which, in this instance, should occur with low activation energy because of the strain relief that accompanies rupture of the four-membered ring.[13] Admixture of **4** with 1-cyclopentenyllithium



4 **5** **6**

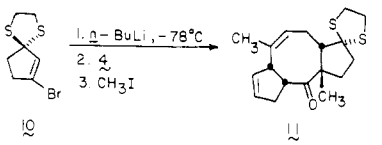
at −78 °C resulted in rapid condensation. Introduction of methyl iodide at this point led to the isolation in 96% yield of a single ketone identified as **5**. The more telling spectral features of **5** are its 1700-cm^{-1} infrared carbonyl absorption and characteristic methyl and olefinic proton signals. The stereochemistry of its four chiral centers follow from the anticipated[14] boat-like transition state of the C → B sigmatropic shift and from steric approach control considerations during methylation of the enolate anion. Confirmatory evidence was gained by hydride reduction to the nicely crystalline alcohol **6** whose complete structural characterization was achieved by X-ray analysis.[9] Thus, the desired tricyclic nucleus can be efficiently elaborated in two laboratory manipulations starting from cyclopentadiene.

Since somewhat more complex substitution patterns are ultimately necessary, the feasibility of extending the scope of the above synthetic sequence was examined to a limited extent. Thus, **7**, an adduct of dimethylfulvene and methyl vinyl ketene,[11b] was analogously processed. In this instance, the resulting tricyclic ketone **8** proved to be particularly labile. Direct hydride reduction to **9** was therefore effected, and this alcohol was isolated in an overall yield of 80%. These substrates provide the opportunity for ultimate ring-A functionalization.



7 **8** **9**

Halogen–metal exchange of dithioketal **10** at −78 °C,[15] followed by sequential addition of **4** and methyl iodide

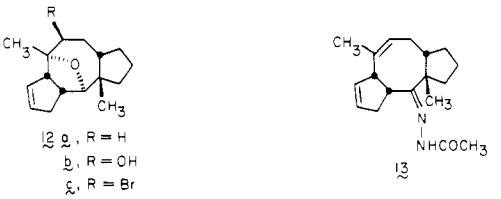


10 **11**

furnished the crystalline ketone **11** in 71% yield. Conveniently, the pair of carbonyl groups within this substrate are chemically differentiated. The task of removing the oxygen atom attached to ring B now had to be addressed.

Predisposition toward Transannular Bonding. Molecular models of **5**, **8**, and **11** reveal that *all-cis* fusion of two five-membered rings to a 4-cyclooctenenone core in this fashion serves to severely restrict the conformational degrees of freedom within the medium ring. The more-stable three-dimensional arrangement appears to be a distorted tub in which the carbonyl group is positioned closely to the inside face of the transannular π bond. For this reason, nucleophilic addition to this functional group was expected to be restricted to the convex face. The exclusive formation of **6** and **9** conforms to this analysis. In these alcohols, the hydroxyl functionality should be additionally compressed against the transannular center of unsaturation.

Therefore, it came as no surprise to find that **6** was quantitatively converted to ether **12a** when allowed to

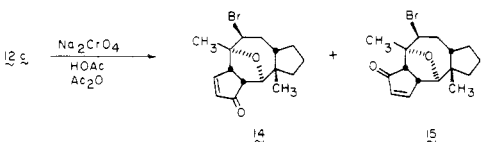


12 a, R = H; b, R = OH; c, R = Br

13

stand in $CDCl_3$ at room temperature. More rapid cyclization occurred when **6** was treated with small amounts of 1 N hydrochloric acid in ether solution. That this cyclization may be an entirely general phenomenon is suggested by the efficient conversion of **6** to **12b** (97%) and **12c** (91%) in the presence of *m*-chloroperbenzoic acid and *N*-bromosuccinimide, respectively.

These chemospecific transformations serve nicely to mask the cyclooctenyl double bond, thereby allowing for purposeful chemical modification of ring A. The chromate oxidation of **12c** to a 3:1 mixture of **14** and **15** illustrates one possibility.



12c → **14** + **15**

This line of investigation was set aside to pursue the more immediate objective of achieving the complete de-

(9) Preliminary report: Paquette, L. A.; Andrews, D. R.; Springer, J. P. *J. Org. Chem.* **1983**, *48*, 1148.

(10) (a) Ozeki, T.; Kusaka, M. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 1232. (b) Iwakura, Y.; Toda, F.; Iwata, R.; Torii, Y. *Ibid.* **1969**, *42*, 841. (c) Payne, G. B. *J. Org. Chem.* **1966**, *31*, 718. (d) Rey, M.; Dunkelblum, E.; Allain, R.; Dreiding, A. S. *Helv. Chim. Acta* **1970**, *53*, 2159. (e) Wuest, J. D.; Madonik, A. M.; Gordon, D. C. *J. Org. Chem.* **1977**, *42*, 2111. (f) Holder, R. W.; Freiman, H. S.; Stefanchik, M. F. *Ibid.* **1976**, *41*, 3303. (g) Danheiser, R.; Sard, H. *Ibid.* **1980**, *45*, 4810. (h) Mohmand, S.; Hirabayashi, T.; Bock, H. *Chem. Ber.* **1981**, *114*, 2609. (i) Jackson, D. A.; Rey, M.; Dreiding, A. S. *Helv. Chim. Chim. Acta* **1983**, *66*, 2330. (j) Danheiser, R. L.; Gee, S. K.; Sard, H. *J. Am. Chem. Soc.* **1982**, *104*, 1670.

(11) (a) Danheiser, R. L.; Martinez-Davila, C.; Sard, H. *Tetrahedron* **1981**, *37*, 3943. (b) Huston, R.; Rey, M.; Dreiding, A. S. *Helv. Chim. Acta* **1982**, *65*, 451.

(12) (a) Evans, D. A.; Golob, A. M. *J. Am. Chem. Soc.* **1975**, *97*, 4765. (b) Evans, D. A.; Nelson, J. V. *Ibid.* **1980**, *102*, 774. (c) Paquette, L. A.; Crouse, G. D.; Sharma, A. K. *Ibid.* **1982**, *104*, 4411 and pertinent references cited therein.

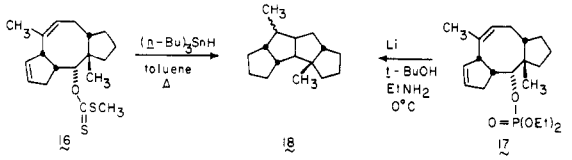
(13) For other examples of 1,2-dialkenylcyclobutanols, see: (a) Kahn, M. *Tetrahedron Lett.* **1980**, *21*, 4547. (b) Levine, S. G.; McDaniel, R. L., Jr. *J. Org. Chem.* **1981**, *46*, 2199. (c) Gadwood, L. C.; Lett, R. M. *Ibid.* **1982**, *47*, 2268.

(14) Maier, G. "Valenziomiesierungen"; Verlag Chemie: Weinheim, FRG, 1972; pp 54–57.

(15) Shih, C.; Swenton, J. S. *J. Org. Chem.* **1982**, *47*, 2825.

oxygenation of **5**. When several modifications of the Wolff–Kishner reduction were shown to provide black tars from which neither a hydrocarbon nor unreacted **6** could be recovered, we opted for a less direct strategy. Notwithstanding the recalcitrance of this ketone toward tosylhydrazone formation,[16] conversion to semicarbazone **13** was successful. However, attempted reduction[17] of this derivative also resulted in complete destruction of the ring system.

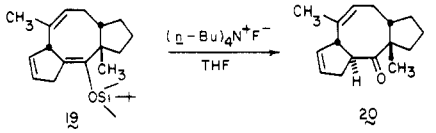
Subsequently, it was adduced that the hydroxyl group in **6** could be converted to its xanthate (**16**, 89%) and diethyl phosphate esters (**17**, 85%) as long as the carbon–oxygen bond was preserved.[18] Of particular interest in this connection is the reputed ease of reduction of both functional groups with resultant deoxygenation.[19,20] Accordingly, **16** was treated with tri-*n*-butyltin hydride in



refluxing toluene. There resulted a mixture of tetraquinane hydrocarbons **18** in which the cyclopentene double bond was also reduced. Curtailment of the reaction prior to complete consumption of **16** did not afford products still containing this double bond. However, full characterization of these less saturated substances was not carried out. In all instances, ^{1}H NMR analysis of the reaction mixtures revealed the absence of signals attributable to an sp^2-bound methyl group.

The same general behavior was encountered during the dissolving metal reduction of **17** in ethylamine, reduction occurring much more rapidly even at temperatures as low as −78 °C. In no case was either double bond seen to survive. Evidently, the transiently generated free radical intermediate (or its derived carbanion) experiences efficient transannular capture by the proximate cyclooctene π system. Although this methodology suggests a potentially useful entry into polyquinane structures, it does not bode well for synthetic access to the ophiobolin series.

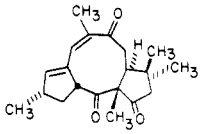
The Epimerization Question. Ultimate elaboration of ophiobolin F (**3**) and its congeners from any of the above intermediates requires epimerization at the tertiary center adjacent to the methyl-substituted quaternary carbon atom. The original projection was to effect this change in **11** following deoxygenation and dethioketalization. However, because no information was available on the relative stabilities of dicyclopenta[*a*,*d*]cyclooctane isomers, a pilot study was carried forward on **5**. Evaluation of Dreiding models suggested that conversion of either of its five-membered rings from cis-locked to trans-fused geometry should relieve nonbonded steric interactions and therefore be thermodynamically favorable. However, treatment of **5** with such bases as $NaHCO_3$, NaOH, and $(C_2H_5)_3N$ led to recovery of the starting ketone. Prolonged exposure to stronger bases ($NaOCH_3$, LDA, etc.) resulted in decomposition. These hurdles were overcome by initial conversion to silyl enol ether **19**. Although this substance



could not be purified due to its sensitivity to adsorbents, unmasking of the new tricyclic ketone **20** was conveniently achieved by treatment with tetra-*n*-butylammonium fluoride in tetrahydrofuran solution. No regeneration of **5** was noted. The spectral differences that distinguish **20** from **5** (see Experimental Section) clearly attest to the configurational change.

Summary

From the practical point of view, the oxyanionic chemistry described herein establishes a short, stereocontrolled, and efficient route to highly functionalized *all-cis*-dicyclopenta[*a*,*d*]cyclooctanes. Although difficulties have been encountered in removal of the β-ring carbonyl group, the flexibility of the scheme should find service in the total synthesis of complex medium-ring natural products where reductive deoxygenation is not an issue. One example is jatrophatrione (**21**)[21] whose possible preparation by related methodology is currently under active investigation.



21

Experimental Section[22]

(7*R)-7-Methyl-7-vinylbicyclo[3.2.0]hept-2-en-6-one.**[11] A solution of cyclopentadiene (75 mL) and triethylamine (29 mL) in refluxing chloroform (300 mL) was treated dropwise during 2 h with tigloyl chloride (21.7 g) in the same solvent (150 mL). After being heated overnight, the reaction mixture was cooled and evaporated to provide an orange slurry which was taken up in ether and filtered. The concentrated filtrate was dissolved in petroleum ether and passed through a plug of silica gel to remove highly polar material. Subsequent HPLC (Waters Prep 500) on silica gel (elution with 2.5% ethyl acetate in petroleum ether) gave after two recycles 8.8 g (32%) of **4** as the less polar isomer: bp 75 °C (1.5 torr); IR (neat, cm^{-1}) 1778, 1628; ^{1}H NMR ($CDCl_3$) δ 5.94 (dd, J = 17.3 and 10.5 Hz, 1 H), 5.87–5.84 (m, 1 H), 5.72–5.68 (m, 1 H), 5.15–5.06 (m, 2 H), 3.96–3.89 (m, 1 H), 3.45–3.41 (m, 1 H), 2.65–2.58 (7, 1 H), 2.42–2.32 (m, 1 H), 1.06 (s, 3 H); ^{13}C NMR ($CDCl_3$) ppm 214.4, 139.6, 134.5, 129.9, 113.8, 71.6, 58.6, 48.7, 34.0, 15.8.

Also isolated was 3 g of the epimer: bp 75 °C (1.5 torr); IR (neat, cm^{-1}) 1778, 1635, ^{1}H NMR ($CDCl_3$) δ 5.85–5.68 (m, 3 H), 5.14–5.06 (m, 2 H), 3.97–3.91 (m, 1 H), 3.30–3.26 (m, 1 H), 2.67–2.60 (m, 1 H), 2.48–2.39 (m, 1 H), 1.41 (s, 3 H); ^{13}C NMR ($CDCl_3$) ppm 215.5, 135.3, 133.8, 130.6, 115.5, 70.1, 57.8, 51.2, 34.2, 21.9.

Conversion of 4 to 5. Method A. Lithium wire (1.4 g, 0.2 mol) was flattened into a foil and scraped clean while submersed in petroleum ether. Following rapid transfer to a dry flask containing anhydrous tetrahydrofuran (20 mL), 1-bromocyclopentene[23] (4.7 g, 32.2 mmol) in the same solvent (10 mL) was added at a rate such that gentle reflux was maintained (ca. 1 h).

(16) For exemplary reductions of tosylhydrazones, consult: (a) Hutchins, R. O.; Milewski, C. A.; Maryanoff, B. E. *J. Am. Chem. Soc.* **1973**, *95*, 3662. (b) Kabalka, G. W.; Baker, J. D. *J. Org. Chem.* **1975**, *40*, 1834.

(17) Cram, D. J.; Sahyun, M. R. V.; Knox, G. R. *J. Am. Chem. Soc.* **1962**, *84*, 1734.

(18) In a related pilot experiment, treatment of **6** with thionyl chloride in the presence of 2,6-lutidine was found to give a tertiary tetraquinanyl chloride (Andrews, D. A., unpublished work). Efficient transannular involvement of a double bond under similar ionizing conditions is precedented [e.g., Garratt, P. G.; White, J. F. *J. Org. Chem.* **1977**, *42*, 1733].

(19) Barrett, A. G. M.; Barton, D. H. R.; Bielski, R.; McOmbie, S. W. *J. Chem. Soc., Chem. Commun.* **1977**, 866.

(20) Ireland, R. E.; Muchmore, D. C.; Hengartner, U. *J. Am. Chem. Soc.* **1972**, *94*, 5098.

(21) Torrance, S. J.; Wiedhopf, R. M.; Cole, J. R.; Arora, S. K.; Bates, R. B.; Beavers, W. A.; Cutler, R. S. *J. Org. Chem.* **1978**, *41*, 1855.

(22) Except where noted, all compounds were purified chromatographically to the point where they provided a single spot on TLC analysis and gave ^{1}H NMR, ^{13}C NMR, and mass spectra in complete agreement with their structural assignment.

(23) Giacomoni, J. C.; Cambon, A.; Rouvier, E. *Bull. Soc. Chim. Fr.* **1970**, 3097.

After the olive-green solution had cooled to room temperature, transfer to a separate dry flask was accomplished via cannula. The residual lithium fragments were washed with dry tetrahydrofuran (5 mL) and this rinse solution was also transferred. The organometallic solution was cooled to −78 °C and treated dropwise with a solution of **4** (2.0 g, 13.5 mmol) in the same solvent (5 mL). After 1 h at −78 °C, freshly filtered (basic Al_2O_3) methyl iodide (9.0 g, 64 mmol) was added dropwise and stirring was maintained as the reaction mixture was allowed to warm to room temperature during 2–3 h. Water (50 mL) was added and the aqueous layer was extracted with ether (3 × 50 mL). The combined organic layers were dried and concentrated to provide a yellow oil that was purified by flash chromatography (silica gel, petroleum ether elution). There was obtained 3.0 g (96%) of **5** as a clear colorless oil: IR (neat, cm^{-1}) 1690, 1440, 1370; ^1H NMR ($CDCl_3$) δ 5.86–5.83 (m, 1 H), 5.62–5.59 (m, 1 H), 5.29 (br t, J = 7 Hz, 1 H), 4.04–3.92 (m, 1 H), 2.78–2.65 (m, 1 H), 2.24–2.16 (m, 1 H), 2.07–1.99 (m, 1 H), 1.86–1.22 (m, 9 H), 1.51 (s, 3 H), 1.33 (s, 3 H); ^{13}C NMR ($CDCl_3$) ppm 215.5, 140.2, 131.6, 130.3, 122.6, 57.0, 53.5, 49.6, 47.6, 38.3, 35.1, 30.7, 27.2, 26.1, 22.9 (one signal not seen); m/z calcd (M^+) 230.1671, obsd 230.1697.

Method B. A solution of *n*-butyllithium in hexane (5.0 mL of 1.27 N, 7.5 mmol) in dry tetrahydrofuran (10 mL) was cooled to −78 °C, treated dropwise with 1-bromocyclopentene (1.11 g, 7.5 mmol) in the same solvent (5 mL) and stirred for 1 h. To the resulting white slurry was added a solution of **4** (740 mg, 5.0 mmol) in dry tetrahydrofuran (2 mL), and stirring was continued at −78 °C for 1 h at which point freshly filtered methyl iodide (1.41 g, 10.0 mmol) was introduced dropwise. The clear yellow reaction mixture was allowed to warm to room temperature during 2–3 h and worked up in the predescribed manner. Chromatography as before gave 770 mg (49%) of **5**, identical in all respects with the ketone described above.

Hydride Reduction of 5. A solution of **5** (2.32 g, 10.0 mmol) in dry ether (5 mL) was added to a stirred suspension of lithium aluminum hydride (1.0 g, 26.2 mmol) in the same solvent (25 mL) at 0 °C. The reaction mixture was stirred at room temperature for 1 h and worked up according to Fieser.[24] HPLC purification (silica gel, elution with 2% ethyl acetate in petroleum ether) furnished 2.25 g (97%) of **6** as a colorless crystalline solid: mp 41–42 °C (from methanol); IR (CCl_4, cm^{-1}) 3420, 2950, 1820, 1455; ^1H NMR ($CDCl_3$) δ 5.93–5.90 (m, 1 H), 5.71–5.63 (m, 2 H), 3.71 (d, J = 8 Hz, 1 H), 3.51–3.45 (m, 1 H), 2.85–2.61 (m, 2 H), 2.29–1.22 (series of m, 1 H), 1.69 (s, 3 H), 1.06 (s, 3 H); ^{13}C NMR ($CDCl_3$) ppm 142.5, 132.9, 132.5, 130.6, 83.9, 52.9, 50.0, 49.5, 45.2, 44.6, 37.0, 32.1, 27.4, 26.2, 23.6, 23.5, m/z calcd (M^+) 232.1827, obsd 232.1834.

The 3,5-dinitrobenzoate was prepared in conventional fashion, mp 163–166 °C dec.

Anal. Calcd for $C_{23}H_{26}N_2O_6$: C, 64.78; H, 6.15. Found: C, 64.73; H, 6.18.

(7*R)-7-Methyl-7-vinyl-3-isopropenylbicyclo[3.2.0]hept-2-en-6-one (7).**[11b] A solution of 6,6-dimethylfulvene (20 g, 189 mmol) and tigloyl chloride (19 g, 101 mmol) in dry chloroform (200 mL) was cooled to 0 °C and treated dropwise with triethylamine (10.7 g, 106 mmol). The resulting black reaction mixture was stirred overnight, concentrated under reduced pressure, and treated with ether (20 mL). The dark solids were separated by filtration and the filtrate was evaporated under reduced pressure. In rapid succession, **7** was precolumned on silica gel (elution with petroleum ether) and further purified by HPLC (elution with 2% ethyl acetate in petroleum ether). This ketone was carried forward as quickly as it was isolated; IR (neat, cm^{-1}) 2940, 1775, 1450; ^1H NMR ($CDCl_3$) δ 6.50 (d, J = 5 Hz, 1 H), 6.01–5.87 (m, 2 H), 5.21–5.03 (m, 2 H), 4.44 (d, J = 8 Hz, 1 H), 3.53 (d, J = 8 Hz, 1 H), 1.83 (s, 3 H), 1.78 (s, 3 H), 1.10 (s, 3 H); ^{13}C NMR ($CDCl_3$) ppm 211.4, 139.4, 135.4, 135.0, 132.2, 126.6, 113.8, 70.1, 63.0, 47.5, 22.2, 20.8, 16.7; m/z calcd (M^+) 188.1197, obsd 118.1174.

Conversion of 7 to 9. Reaction of 1-cyclopentenyllithium [prepared by method A from lithium metal (1.5 g, 0.25 mol) and 1-bromocyclopentene (962 mg, 6.5 mmol)] with freshly prepared **7** (940 mg, 5.0 mmol) followed by the addition of methyl iodide (1.41 g, 10.0 mmol) and workup provided a pale yellow oil. This material was immediately dissolved in ether (2 mL) and added at 0 °C to a stirred slurry of lithium aluminum hydride (900 mg, 23.6 mmol) in dry ether (20 mL). After 1 h, the product alcohol was isolated in the predescribed manner. There was obtained 90 mg (80% overall) of **9** as a pale yellow oil which decomposed to a red tar relatively rapidly at room temperature and more slowly in a freezer: IR (CCl_4, cm^{-1}) 3400, 2940, 1450, 1370; ^1H NMR ($CDCl_3$) δ 6.58–5.88 (m, 2 H), 5.13–4.95 (m, 1 H), 4.0–3.5 (m, 2 H), 2.55–0.95 (series of m, 1 H), 1.15 (s, 6 H), 1.0 (s, 3 H), 0.95 (s, 3 H); ^{13}C NMR ($CDCl_3$) ppm 145.9, 140.5, 134.9, 132.4, 126.5, 120.2, 86.1, 53.2, 50.0, 40.8, 40.2, 33.0, 30.6, 26.2, 24.7, 24.2, 22.3, 21.8; m/z calcd (M^+) 272.2133, obsd 272.2137.

Conversion of 10 to 11. A 250-mg (1.07 mmol) sample of **10**[15] was treated with *n*-butyllithium (0.8 mL of 1.27 N in hexane, 1.0 mmol) according to method B. Following the addition of **4** (104 mg, 0.67 mmol) and subsequently methyl iodide (282 mg, 2.0 mmol), there was isolated a solid which was recrystallized from chloroform–ether (8:1) to give 155 mg (71%) of **11** as colorless crystals: mp 178–180 °C; IR ($CHCl_3$, cm^{-1}) 2930, 1690, 1440; ^1H NMR ($CDCl_3$) δ 5.83–5.79 (s, 1 H), 5.68–5.64 (m, 1 H), 5.49–5.41 (m, 1 H), 4.08–4.02 (m, 2 H), 3.26 (s, 4 H), 2.79–2.43 (m, 7 H), 2.07 (t, J = 6 Hz, 2 H), 1.60 (s, 3 H), 1.32 (s, 3 H); ^{13}C NMR ($CDCl_3$) ppm 214.0, 141.9, 131.0, 129.9, 122.0, 77.6, 58.4, 56.7, 50.5, 49.8, 45.2, 39.5, 38.5, 37.4, 35.1, 28.2 (2C), 22.8; m/z calcd (M^+) 320.1263, obsd 320.1296.

Anal. Calcd for $C_{18}H_{24}OS_2$: C, 67.47; H, 7.56. Found: C, 67.80; H, 7.99.

Acid-Promoted Cyclization of 6. A solution of **6** (116 mg, 0.5 mmol) in ether (10 mL) was stirred with 1 drop of 1 N hydrochloric acid at room temperature for 1 h. The reaction mixture was washed with brine (10 mL), dried, and concentrated to leave a yellowish oil. Flash chromatographic purification (silica gel, elution with 2% ethyl acetate in petroleum ether) gave **12a** as a colorless oil: IR ($CHCl_3$, cm^{-1}) 2930, 2870, 1095; ^1H NMR ($CDCl_3$) δ 5.74–5.71 (m, 1 H), 5.64–5.61 (m, 1 H), 3.51 (d, J = 4.5 Hz, 1 H), 3.06–3.02 (m, 1 H), 2.96–2.93 (m, 1 H), 2.72–2.64 (m, 1 H), 2.23 (br d, J = 4.5 Hz, 1 H), 2.01–1.25 (series of m, 11 H), 1.23 (s, 3 H), 0.91 (s, 3 H); ^{13}C NMR ($CDCl_3$) ppm 131.2, 130.2, 97.1, 84.1, 74.9, 61.1, 48.1, 44.0, 42.9, 40.1, 39.8, 33.4, 26.7, 25.4, 25.3, 23.4; m/z calcd (M^+) 232.1821, obsd 232.1867.

Peracid Oxidation of 6. To a cold (0 °C), magnetically stirred slurry of *m*-chloroperbenzoic acid (95 mg, 0.55 mmol) and sodium bicarbonate (84 mg, 1.0 mmol) in dichloromethane (1 mL) was added a solution of **6** (116 mg, 0.5 mmol) in the same solvent (1 mL). The reaction mixture was stirred for 1 h and diluted with water. The aqueous phase was extracted with dichloromethane (3 × 5 mL), and the combined organic layers were dried and concentrated. Recrystallization of the solid residue from ether gave 120 mg (97%) of **12b** as colorless crystals: mp 113–114 °C; IR ($CHCl_3$, cm^{-1}) 3460, 2940, 1445, 1305, 1045, 1015; ^1H NMR ($CDCl_3$) δ 5.76–5.72 (m, 1 H), 5.61–5.55 (m, 1 H), 3.72 (dd, J = 12 and 5 Hz, 1 H), 3.39–3.33 (m, 1 H), 2.93–2.66 (m, 2 H), 2.32–1.27 (series of m, 12 H), 1.27 (s, 3 H), 0.95 (s, 3 H); ^{13}C NMR ($CDCl_3$) ppm 131.0, 130.1, 97.2, 74.9, 54.6, 45.2, 44.5, 43.8, 43.2, 41.5, 34.6, 34.4, 27.2, 24.5, 22.7; m/z calcd (M^+) 248.1803, obsd 248.1773.

Anal. Calcd for $C_{16}H_{24}O_3$: C, 77.36; H, 9.75. Found: C, 77.09; H, 9.72.

Reaction of 6 with *N*-Bromosuccinimide. To a solution of *N*-bromosuccinimide (245 mg, 1.38 mmol) in 80% aqueous acetone (2 mL) at room temperature was added **6** (320 mg, 1.38 mmol) in portions. The resulting clear reaction mixture was stirred for 30 min and diluted with ether. The organic phase was washed with water (2 × 10 mL), dried, and concentrated to provide **12c** as a colorless, heat-sensitive oil (390 mg, 91%); IR ($CHCl_3$, cm^{-1}) 2940, 1445, 1370; ^1H NMR ($CDCl_3$) δ 5.76–5.72 (m, 1 H), 5.61–5.57 (m, 1 H), 4.18 (dd, J = 12.3 and 3.9 Hz, 1 H), 3.67–3.63 (m, 1 H), 2.98–2.91 (m, 1 H), 2.77–2.68 (m, 1 H), 2.46–2.23 (m, 4 H), 1.91–1.60 (m, 7 H), 1.46 (s, 3 H), 0.96 (s, 3 H); m/z calcd (M^+) 310.0932, obsd 310.0897.

Semicarbazone 13. A solution of **5** (200 mg, 0.87 mmol), semicarbazide hydrochloride (200 mg, 1.8 mmol), and sodium acetate (300 mg, 3.66 mmol) in 80% aqueous ethanol (8 mL) was stirred at room temperature overnight, extracted with chloroform (3 × 20 mL), dried, and concentrated. The resulting greenish colored crystals of **13** (220 mg, 88%), mp 163–170 °C dec, proved

(24) Fieser, L. F.; Fieser, M. "Reagents for Organic Synthesis"; Wiley: New York, 1967; Vol. I, p 583.

difficult to purify by recrystallization and were therefore utilized in this condition; IR ($CHCl_3$, cm^{-1}) 3420, 1700, 1572; ^1H NMR ($CDCl_3$) δ 6.24 (br s, 2 H), 5.72–5.57 (m, 1 H), 4.96–4.82 (m, 1 H), 3.09–2.98 (m, 1 H), 2.72–1.06 (series of m, 12 H), 1.94 (s, 3 H), 1.64 (br s, 2 H), 1.42 (s, 3 H); m/z calcd (M^+) 242.1545, obsd 242.1506.

Oxidation of 12c. To a cold (0 °C) stirred slurry of sodium chromate (183 mg, 1.12 mmol) in acetic acid (1.25 mL) and acetic anhydride (0.75 mL) was added under nitrogen 100 mg (0.33 mmol) of **12c**. The reaction mixture was allowed to warm to room temperature overnight, water (10 mL) was added, and the green solution was extracted with ether (3 × 20 mL). The combined organic layers were washed with saturated sodium bicarbonate solution (50 mL) and brine (50 mL) prior to drying and evaporation. The colorless oil, an inseparable 3:1 mixture of **14** and **15**, proved to be very sensitive to chromatographic adsorbents; IR ($CHCl_3$, cm^{-1}) 2963, 1720, 1457; ^1H NMR ($CDCl_3$) δ 6.96–6.89 and 6.75–6.68 (m, 1 H), 5.96–5.88 (m, 1 H), 4.17–3.88 (m, 2 H), 3.49–3.22 (m, 1 H), 2.91 (br s, 1 H), 2.53 (dd, J = 5.0 and 2.5 Hz, 1 H), 2.22–1.09 (series of m, 8 H), 1.41 (s, 3 H), 0.91 (s, 3 H); ^{13}C NMR ($CDCl_3$) ppm major peaks at 210.3, 165.7, 163.9, 134.3, 133.5, 90.0, 89.4, 86.8, 58.5, 58.1, 52.2, 51.0, 48.0, 41.6, 35.9, 33.6, 27.0, 25.1, 24.2; m/z calcd (M^+) 324.0719, obsd 324.0701.

Xanthate 16. A solution of **6** (116 mg, 0.5 mmol) in dry ether (5 mL) was allowed to react for 1 h with *n*-butyllithium (0.4 mL of 1.27 N in hexane, 0.5 mmol), where-upon freshly distilled carbon disulfide (76 mg, 1.0 mmol) was added and the resulting red solution was heated at reflux for 1 h. Upon cooling, methyl iodide (141 mg, 1.0 mmol) was introduced and heating was resumed for an additional hour. Water (10 mL) was added and the aqueous phase was extracted with ether (3 × 15 mL). The combined organic layers were washed with brine (20 mL), dried, and evaporated. The residue was purified by chromatography on silica gel (elution with 2% ethyl acetate in petroleum ether) to give **16** as a colorless solid (150 mg, 89%), mp 100–101 °C; IR ($CHCl_3$, cm^{-1}) 2970, 2930, 1450, 1375, 1045; ^1H NMR ($CDCl_3$) δ 6.18 (br s, 1 H), 5.85–5.82 (m, 1 H), 5.68–5.59 (m, 1 H), 3.76 (d, J = 9.6 Hz, 1 H), 2.98–2.88 (m, 1 H), 2.71–2.63 (m, 1 H), 2.55 (s, 3 H), 2.16–1.89 (series of m, 8 H), 1.60 (s, 3 H), 1.52–1.38 (m, 3 H), 1.18 (s, 3 H); ^{13}C NMR ($CDCl_3$) ppm 139.1, 133.5, 131.2, 125.1, 91.9, 52.9, 51.0, 50.1, 44.8, 42.8, 36.0, 30.0, 26.6, 25.4, 23.4, 21.2, 19.2 (C=S not observed); m/z 322, 137, 125, 95, 81, 69, 57 (base).

Anal. Calcd for $C_{18}H_{26}OS_2$: C, 67.02; H, 8.13. Found: C, 66.75; H, 8.12.

Diethyl Phosphate 17. Freshly distilled diethylchlorophosphate (430 mg, 2.50 mmol) was added to a solution of **6** (116 mg, 0.5 mmol) in tetrahydrofuran–tetramethylethylenediamine (4:1, 2 mL) and stirring was maintained overnight. Water (5 mL) was added, and the combined organic layers were dried and evaporated. Final purification by MPLC (silica gel, elution with 2% ethyl acetate in petroleum ether) provided 152 mg (85%) of **17** as a colorless oil: IR ($CHCl_3$, cm^{-1}) 2930, 2870, 1440, 1275, 1025; ^1H NMR ($CDCl_3$) δ 5.86–5.83 (m, 1 H), 5.63–5.56 (m, 2 H), 4.21–4.12 (m, 4 H), 3.64 (d, J = 9.5 Hz, 1 H), 2.78–2.58 (m, 2 H), 2.13–1.25 (series of m, 15 H), 1.62 (s, 3 H), 1.29 (t, J = 8.5 Hz, 6 H); m/z calcd (M^+) 262.9792, obsd 263.0492.

Tetraquinanes 18. Method A. A solution of **16** (169 mg, 0.5 mmol) and tri-*n*-butyltin hydride (320 mg, 1.1 mmol) in dry toluene (10 mL) was heated at reflux until no xanthate remained (TLC analysis, 9 h). The reaction mixture was cooled, concentrated in vacuo, diluted with petroleum ether, and filtered. Solvent removal left a clear oil which was purified by MPLC (silica gel, petroleum ether elution) to give 73 mg (67%) of **18** as a mixture of isomers: IR ($CHCl_3$, cm^{-1}) 2940, 2870, 2860, 1460; ^1H NMR ($CDCl_3$) δ 1.67–1.58 (m, 7 H), 1.39–1.24 (m, 13 H), 1.04–0.86 (m, 6 H); m/z calcd (M^+) 218.2028, obsd 218.2057.

Method B. Phosphate **17** (179 mg, 0.5 mmol) was added to a cold (0 °C) solution of lithium (500 mg, 71 g-at) and *tert*-butyl alcohol (370 mg, 5.0 mmol) in ethylamine (10 mL). The reaction mixture was stirred at this temperature for 2 h, poured into 10% ammonium chloride solution (20 mL), and extracted with ether (3 × 20 mL). The combined organic layers were dried and evaporated to give 83 mg (76%) of a hydrocarbon mixture similar to that obtained in A.

Epimerization of 5. Ketone **5** (460 mg, 2.0 mmol) in dry tetrahydrofuran (0.5 mL) was added to a cold (−78 °C), magnetically stirred solution of lithium diisopropylamide [from 252 mg (2.5 mmol) of diisopropylamine and 1.33 mL of 1.88 N *n*-butyllithium in hexane (2.5 mmol)] in the same solvent (10 mL). The resulting yellow solution was stirred at −78 °C for 1 h, treated with *tert*-butyldimethylsilyl triflate (528 mg, 2.5 mmol) in dry tetrahydrofuran (0.5 mL), and allowed to warm to room temperature. Stirring was continued for 1.5 h, the yellow solution was poured into 10% ammonium chloride solution (30 mL), and the mixture was extracted with ether (3 × 30 mL). The combined organic layers were dried, filtered, and concentrated to leave an orange oil, further purification of which was achieved by MPLC on silica gel (elution with petroleum ether). There was isolated a total of 176 mg (51%) of **19** as labile pale yellow oil. The purest fraction (ca. 80% of **19**) was utilized for spectral analysis and conversion to **20**: ^1H NMR ($CDCl_3$) δ 5.84–4.87 (m, 3 H), 3.93–3.78 (m, 1 H), 2.82–1.10 (m, 11 H), 1.50 (s, 3 H), 1.33 (s, 3 H), 0.83 (s, 9 H), 0.2–0.0 (m, 6 H).

A solution of **19** (100 mg, 0.292 mmol) in tetrahydrofuran (0.5 mL) was treated with wet tetra-*n*-butylammonium fluoride (157 mg) and the reaction mixture was stirred at room temperature for 1 h and poured into brine (10 mL). The product was extracted into ether (3 × 20 mL), the combined organic layers were dried, and the solvent was evaporated. There was obtained 55 mg (82%) of **20** as a pale yellow oil, which was homogeneous by TLC: IR ($CHCl_3$, cm^{-1}) 2930, 1690, 1455, 1360; ^1H NMR ($CDCl_3$) δ 5.83–5.81 (m, 1 H), 5.43 (t, J = 9.0 Hz, 1 H), 5.27–5.25 (m, 1 H), 4.84–4.81 (m, 1 H), 3.01–2.93 (m, 1 H), 2.48–2.41 (m, 1 H), 2.23–2.14 (m, 2 H), 2.03–1.87 (m, 2 H), 1.82 (s, 3 H), 1.76–1.09 (series of m, 6 H), 1.35 (s, 3 H); ^{13}C NMR ($CDCl_3$) ppm 216.6, 151.5, 133.4, 127.5, 125.8, 56.8, 53.3, 50.5, 35.6, 35.1, 27.1, 25.9, 25.1, 24.98, 23.5, 23.03; m/z calcd (M^+) 230.1691, obsd 239.1506 (with decomposition in MS probe).

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