solution turned cloudy. Chilling at 0 °C furnished a yellow oil which was recrystallized three times from diethyl ether, methanol, and ethyl acetate to give 81 mg (19%); mp 168–170 °C; ^{1}H NMR (D_2O) δ 7.5 (s, 1 H), 7.1 (s, 1 H), 6.4 (q, 1 H, J = 6 Hz), 3.9 (s, 2 H), 3.9 (s, 3 H), 3.8 (s, 3 H), 1.5 (d, 3 H, J = 6 Hz). Anal. Calcd for $C_{12}H_{17}O_6N_2Cl$: C, 44.94; H, 5.31; N, 8.74. Found: C, 44.51; H, 5.41; N, 8.40.

Acknowledgment. This work was supported by a grant (GM04842) awarded to G.P.H. by the National Institute of Health. K.W.J. is grateful for an Olin Fellowship. We are grateful to Dr. David Trentham for helpful comments.

Registry No. 1, 1016-58-6; 2, 53413-67-5; **3a**, 123642-54-6; **3b**, 123642-55-7; **4a**, 123642-56-8; **4b**, 123642-57-9; **5a**, 1131-62-0; **5b**, 4101-32-0; **6a**, 123642-58-0; **6b**, 123642-59-1; **6c**, 123642-60-4; **7**, 123642-61-5; **8a**, 123642-62-6; **8b**, 123642-63-7; **8c**, 123642-64-8; **8d**, 123642-65-9; **9a**, 123642-66-0; **9b**, 123642-67-1; **9c**, 123674-19-1; **9d**, 123642-68-2; 4,5-$(MeO)_2$-2-$O_2NC_6H_2CHO$, 20357-25-9; (BOC)$NH(CH_2)_3COOH$, 57294-38-9; BOC-L-Glu(OBu-*t*)-OH, 13726-84-6; $ClCH_2COOBu$-*t*, 107-59-5; BOC-L-Asp(OBu-*t*)-OH·DCHA, 1913-12-8; BOC-Gly-OH, 4530-20-5.

Regioselective Routes to Nucleophilic Optically Active 2- and 3-Carene Systems

Leo A. Paquette,* Robert J. Ross,[1] and Yao-Jun Shi[2]

Evans Chemical Laboratories, The Ohio State University, Columbus, Ohio 43210

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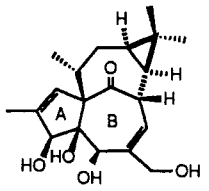
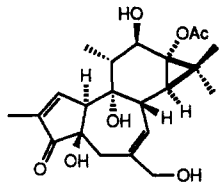
Commercially available (+)-3-carene (**4**) is shown to be capable of efficient conversion to vinyl bromides **28**, **46**, and **49** and to vinyl stannane **44**. All four compounds stem from (+)-3-norcaranone (**23**), an optically pure ketone best prepared by epoxidation of **4**, followed by oxirane ring opening, acetylation, ozonolysis, and $CrCl_2$-promoted reduction. The strong proclivity exhibited by **23** to enolize in the cyclopropyl carbinyl sense is used to advantage to gain entry to **28** and **44**. Remarkably, the tosylhydrazone of (+)-3-norcaranone (**45**) is distinguished from its ketone progenitor **23** by its capacity for highly regioselective deprotonation from the alternative α-position. The crossover has made possible synthetic access to **46** and **49**. Other chemistry of this class of compounds is also presented, including a route to **51**, a vinyl bromide epimeric to **49**. Especially relevant to future work in the ingenol area is the ability of these molecules to serve as nucleophiles. Several reactions involving **28** are provided as exemplary of this property.

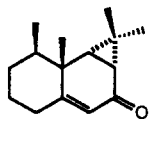
Projected syntheses of the tumor-promoting diterpenes ingenol (**1**)[3,4] and phorbol (**2**)[3,5] share in common with the structurally simpler aristolone (**3**)[6] the necessity of fusing a *gem*-dimethylcyclopropane ring to a six-membered carbocycle. In the Ourisson[6a] and Chan[6c] syntheses of **3**, this structural component was introduced by 1,3-dipolar addition of 2-diazopropane to a suitable enone acceptor and subsequent photoextrusion of nitrogen. The key step in Piers' approach[6b] to **3** was a cupric sulfate catalyzed intramolecular diazo ketone variant of the above.



1



2



3

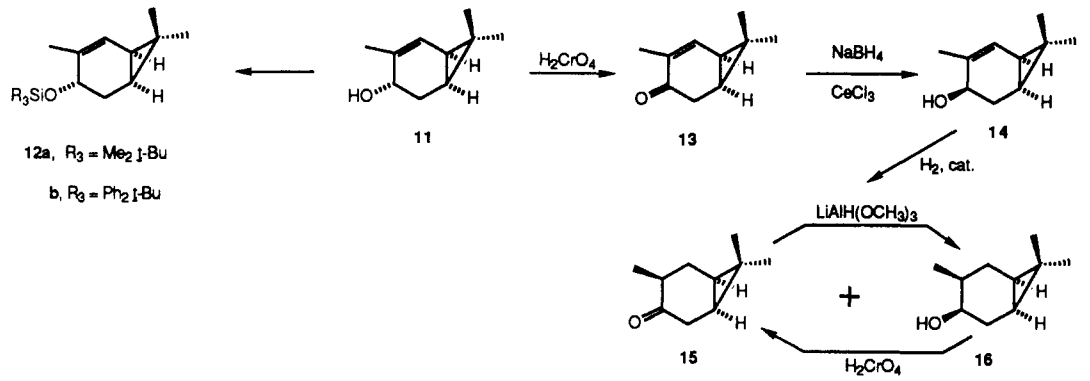
To date, the three-membered rings in **1** and **2** have not been introduced in this manner. Instead, tandem dibromocarbene insertion–$Me_2Cu(CN)Li_2$ substitution has been employed,[5a] and a protocol based on Diels–Alder cycloadditions of carbonyl-activated dimethylcyclopropenes has been developed.[4j,44]

Our program goals in the ingenol area[7] necessitated the utilization of preformed C/D ring subunits, *with strong preference given to optically active intermediates readily available from the chiral pool.* This concept is not new, it having been deployed earlier by Yamakawa[4b] and by Funk[4h] as a tool for arriving at right-hand segments of **1**. However, both of these groups proceeded to rupture the

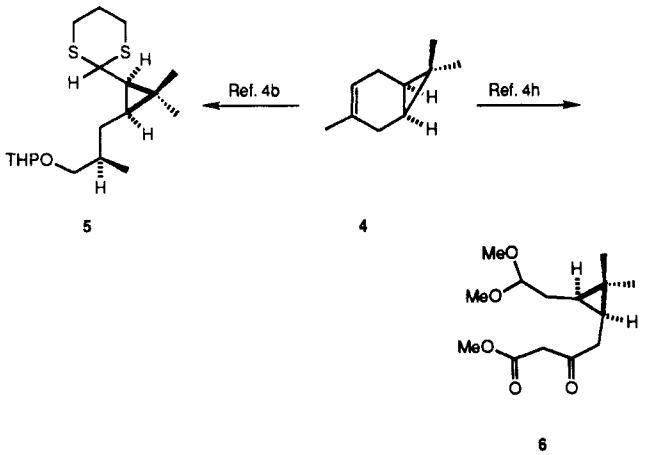
(1) National Science Foundation Graduate Fellow, 1982–1985.
(2) The Ohio State University Postdoctoral Fellow, 1988–1989.
(3) (a) Hecker, E. *Pure Appl. Chem.* **1977**, *49*, 1423. (b) Hecker, E. In *Carcinogenesie*; Slaga, T. S., Sivak, A., Boutwell, R. K., Eds.; Raven: New York, 1978; Vol. 2 (Mechanism of Tumor Promotion and Carcinogenesis), p 11. (c) Evans, F. J.; Coper, C. J. *Lloydia* **1978**, *41*, 193. (d) Adolf, W.; Hecker, E. *Tetrahedron Lett.* **1980**, *21*, 2887. (e) Falsone, G.; Crea, A. E. G.; Noack, E. A. *Arch. Pharm.* **1982**, *315*, 1026. (f) Sorg, B.; Hecker, E. *Z. Naturforsch., B: Anorg. Chem., Org. Chem.* **1982**, *37B*, 1640. (g) Gotta, H.; Adolf, W.; Opferkuch, H. J.; Hecker, E. *Ibid.* **1984**, *39B*, 683. (h) Rizk, A. M.; Hammouda, F.-M.; El-Missiry, M. M.; Radwan, H. M.; Evans, F. J. *Phytochemistry* **1985**, *24*, 1605. (i) *Naturally Occurring Phorbol Esters*: Evans, F. J., Ed.; CRC: Boca Raton, FL, 1986. (j) *Mechanism of Tumor Promotion*; Slaga, T. J., Ed.; CRC: Boca Raton, FL, 1984; Vols. I–IV.
(4) (a) Paquette, L. A.; Nitz, T. J.; Ross, R. J.; Springer, J. P. *J. Am. Chem. Soc.* **1984**, *106*, 1446. (b) Satoh, T.; Okuda, T.; Kaneko, Y.; Yamakawa, K. *Chem. Pharm. Bull.* **1984**, *32*, 1401. (c) Rigby, J. H.; Moore, T. L.; Rege, S. *J. Org. Chem.* **1986**, *51*, 2398. (d) Funk, R. L.; Bolton, G. L. *J. Am. Chem. Soc.* **1986**, *108*, 4655. (e) Winkler, J. D.; Henegar, K. E.; Williard, P. G. *Ibid.* **1987**, *109*, 2850. (f) Mehta, G.; Pathak, V. P. *J. Chem. Soc., Chem. Commun.* **1987**, 876. (g) Ross, R. J.; Paquette, L. A. *J. Org. Chem.* **1987**, *52*, 5497. (h) Funk, R. L.; Olmstead, T. A.; Parvez, M. *J. Am. Chem. Soc.* **1988**, *110*, 3298. (i) Paquette, L. A.; Ross, R. J.; Springer, J. P. *Ibid.* **1988**, *110*, 6192. (j) Rigby, J. H.; Kierkus, P. Ch. *Ibid.* **1989**, *111*, 4125.
(5) (a) Wender, P. A.; Keenan, R. M.; Lee, H. Y. *J. Am. Chem. Soc.* **1987**, *109*, 4390. (b) Wender, P. A. *Pure Appl. Chem.* **1989**, *61*, 469 and earlier references cited therein.
(6) (a) Berger, C.; Franck-Neumann, M.; Ourisson, G. *Tetrahedron Lett.* **1968**, 3451. (b) Piers, E.; Britton, R. W.; de Waal, W. *Can. J. Chem.* **1969**, *47*, 831. (c) Prasad, C. V. C.; Chan, T. H. *J. Org. Chem.* **1987**, *53*, 120.
(7) (a) For the earlier synthetic thrusts from this laboratory, consult ref. 4a,g,i. (b) See also Paquette, L. A.; Shi, Y.-J. *J. Org. Chem.* **1989**, *54*, 5205. (c) Any intended use of carene synthons, requires, of course, that the carene ring be expanded to approach 1 or be functionalized with a bridgehead hydroxyl to arrive at **2**. These tactics will be detailed elsewhere.

0022-3263/90/1955-1589$02.50/0

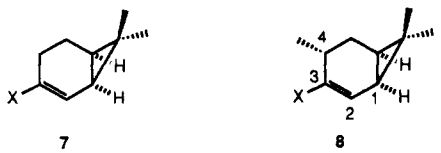
Scheme I



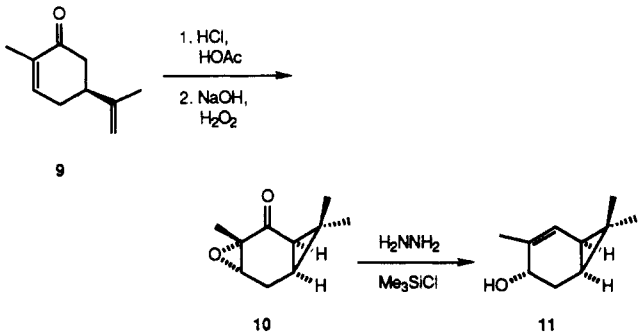
double bond in (+)-3-carene (**4**) so as to achieve electrophilic and nucleophilic differentiation in the two resulting sidechains (e.g. **5** and **6**).



Our strategy necessitated instead that the ring system found, for example, in **4** be retained in its intact state.[7c] However, proper implementation of these optically active molecules demanded that they first be transformed into nucleophilic vinyl anion precursors such as **7**. More suitable yet would be **8**, an intermediate that already carries the secondary methyl group in its proper relative and absolute configuration.



We recognized from the outset that commercially available (+)-**4** has a vinylic methyl group positioned at that site where X must ultimately be located. Consequently, excision of this 3-alkyl substituent had to be accomplished, ideally with attachment of another α-methyl group at C-4 (see **8**). While these interconversions have indeed proven straightforwardly feasible (see below), we considered it prudent to evaluate (+)-carvone (**9**) as an alternative possible starting point of the synthesis. Ketone **9** possesses the correct configuration for ultimate arrival at **1**. Furthermore, its totally stereoselective conversion via the hydrochloride[8] to epoxy ketone **10** has been recognized for some time.[9,10] Usefully, when the Wharton rearrangement[11] is subsequently applied to **10**, (+)-*trans*-2-caren-4-ol (**11**) is formed efficiently.[10] In light of the desirable methyl substitution pattern in **11**,[12] preliminary attention was accorded this alcohol.

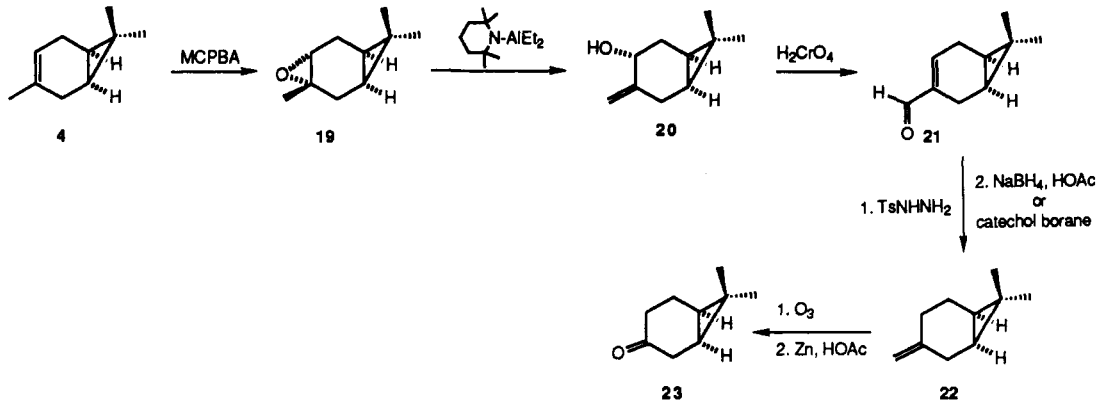


Evaluation of the Suitability of (+)-Carvone as Chiral Precursor. The key facet of any successful approach stemming from **11** must rest on its intrinsic ability to orient the 4-methyl group α as in **8**. Since reagents are driven without exception to approach the double bond in 2-carenes from that surface anti to the dimethylcyclopropane ring, initial efforts were focused on offsetting this obviously strong steric bias. To this end, the derivatization of **11** with bulky silyl groups as in **12a** and **12b** was effected (Scheme I).[13] However, these silyl ethers proved totally inert to diimide reduction and to catalytic hydrogenation under a variety of conditions. Evidently, both approach trajectories to the π bond are now too heavily screened.

These developments led us to consider use of hydroxyl-directed hydrogenation. To explore this approach, the hydroxyl group in **11** had first to be epimerized. This transformation was realized by chromic acid oxidation to **13** and 1,2-reduction with the sodium borohydride–cerium trichloride reagent as reported earlier.[10] Studies were subsequently conducted in the presence of hydrogen and [Rh(nbd)diphos-4]BF_4[14] or [Ir(cod)(py)(PCy_3)]PF_6[15] at both low (50 psi) and moderate pressures (500–1000 psi). In each experiment, the major product isolated was (+)-4-isocaranone (**15**). Lesser amounts of an alcohol identified as (−)-4-neoisocaranol (**16**) were also formed.[13] Standard hydrogenation over platinum oxide produced similar results.

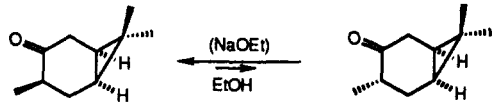
(8) Wolinsky, J.; Hamscher, J. J.; Hutchins, R. O. *J. Org. Chem.* **1970**, *35*, 207.
(9) Burns, W. P. D.; Carson, M. S.; Cocker, W.; Shannon, W. D. P. *J. Chem. Soc. C* **1968**, 3073.
(10) Maas, D. D.; Blagg, M.; Wiemer, D. F. *J. Org. Chem.* **1984**, *49*, 853.
(11) (a) Wharton, P. S.; Bohlen, D. H. *J. Org. Chem.* **1961**, *26*, 3615. (b) Klein, E.; Ohloff, G. *Tetrahedron* **1963**, *19*, 1091.
(12) The enantiomer of **4** would similarly be well suited to our purposes. However, all commercially available carenes uniformly possess the absolute configuration depicted by **4**.
(13) Ross, R. J., unpublished observations.
(14) Evans, D. A.; Morrissey, M. M. *J. Am. Chem. Soc.* **1984**, *106*, 3866.
(15) (a) Crabtree, R. H.; Felkin, H.; Morris, G. E. *J. Organomet. Chem.* **1977**, *141*, 205. (b) Crabtree, R. H. *Acc. Chem. Res.* **1979**, *12*, 331. (c) Crabtree, R. H.; Davis, M. W. *J. Org. Chem.* **1986**, *51*, 2655.

Scheme II



4 19 20 21 23 22

To arrive at **15**, it is necessary only that the particular hydrogenation catalyst be impeded from delivering hydrogen syn to the cyclopropane ring, while finding it possible to promote effective conversion to the enol of **15** by way of 1,3-hydrogen migration on the uncongested α surface. Conversions of this type are well known.[16] Furthermore, Brown and Suzuki, working in the enantiomeric series, demonstrated more than two decades ago that **17** having a cis arrangement of 3-methyl and *gem*-dimethyl substituents is thermodynamically more stable than its epimer **18**.[17,18] In dilute ethanolic sodium ethoxide at room temperature, the isomer distribution is 90:10 in favor of **17**. The preferred tautomerization of the enol to 4-isocaranone (**15**) follows logically from these observations.



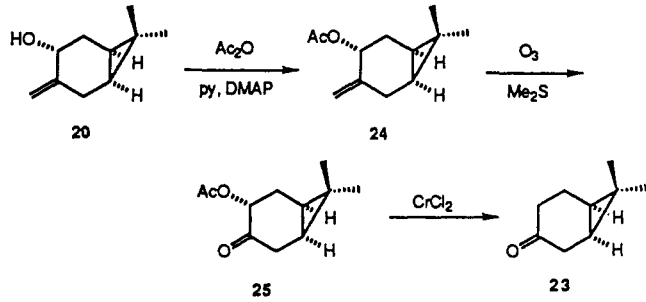
17 18

Rather than pursuing other avenues that might ultimately bypass these complications, we chose instead to investigate (+)-3-carene (**4**) in the belief that it would serve as a more promising starting material.

From (+)-3-Carene to (+)-3-Norcaranone. Regiospecific Enolization of This Ketone in the Cyclopropylcarbinyl Sense. On the strength of structural similarity, 3-norcaranone (**23**) was considered to be a suitable prospective precursor to **7** and/or **8**, depending in large part on the regiochemistry of its enolization. To our knowledge, no definitive study has been made of the deprotonation of bicyclo[4.1.0]heptan-3-ones. The strategy for transforming (+)-**4** into **23** that was explored initially (Scheme II) sought to apply some modern technology to known intermediates. The first two steps, peracid epoxidation of (+)-3-carene[17] and ring opening of the resulting α-epoxide with diethylaluminum tetramethylpiperidide,[19] proceeded with high efficiency (85–100%). Other bases are known to transform **19** into mixtures of all three possible allylic alcohols.[4b]

On the other hand, the chromic acid induced conversion of **20**[20] into **21** as reported by Gollnick and Schade[21] could not be optimized and made reproducible. In addition, while the optical rotations of our samples of **20** (−119.8°) were in good agreement with the literature value (−118.7°),[20] the $[\alpha]_D$ of highly purified (preparative GC) **21** (−131°) was considerably larger in magnitude than that previously recorded (−25.8°).[21]

Scheme III



20 24 25 23

This incident was not an isolated one. Following formation of the tosylhydrazone of **21** and its reduction either with sodium borohydride in acetic acid[22] or catecholborane,[23] β-carene (**22**) was isolated in pure condition, $[\alpha]_D$ +85°. The rotation provided by Gollnick and Schade[21] for this exocyclic olefin is +36°. These discrepancies have not been resolved. Although the ozonolysis of **22** led ultimately to **23**, the overall protocol was deemed less than satisfactory because of the problematic **20** → **21** conversion, the appreciable length of the sequence, and the several questions surrounding enantiomeric purity.

Consequently, the more expedient route outlined in Scheme III was developed. Sequential acetylation and ozonolysis of **20** provided α-acetoxy ketone **25** in 82% overall yield. Chromous chloride reduction[24] of this intermediate was accomplished with 70% efficiency. Satisfyingly, samples of 3-norcaranone prepared by means of this five-step sequence from **4** exhibited an $[\alpha]_D$ value (+256°) identical with that recorded for material derived earlier from **22**.

With (+)-**23** now available in quantity, its intrinsic preference for directed enolization and capacity for stereoselective methylation were examined. In order to maximize kinetic control and thus deter postequilibration of the **17** ⇄ **18** type, **23** was deprotonated with sodium

(16) See for example: (a) $(Ph_3P)_3RhCl$: Corey, E. J.; Suggs, J. W. *J. Org. Chem.* **1973**, *38*, 3224. (b) $Ir(cod)(PMePh_2)_2PF_6$: Oltvoort, J. J.; van Boeckel, C. A. A.; de Koenig, J. H.; van Boom, J. H. *Synthesis* **1981**, 305.

(17) Brown, H. C.; Suzuki, A. *J. Am. Chem. Soc.* **1967**, *89*, 1933.

(18) For a discussion of the conformational factors at play in molecules of this general type, consult: Paquette, L. A.; Fristad, W. E.; Schumann, C. A.; Beno, M. A.; Christoph, G. G. *J. Am. Chem. Soc.* **1979**, *101*, 4645 and pertinent references cited therein.

(19) Yasuda, A.; Yamamato, H.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1705.

(20) Gollnick, K.; Schroeter, S.; Ohloff, G.; Schade, G.; Schenck, G. O. *Chem. Ber.* **1965**, *687*, 14.

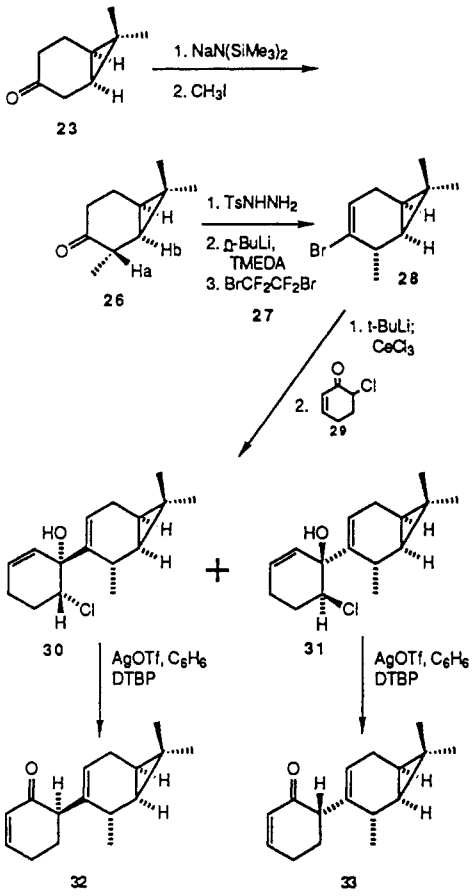
(21) Gollnick, K.; Schade, G. *Tetrahedron* **1966**, *22*, 133.

(22) Hutchins, R. O.; Kache, M.; Rua, L. *J. Org. Chem.* **1975**, *40*, 923.

(23) Kabalka, G. W.; Yang, D. T. C.; Baker, J. D., Jr. *J. Org. Chem.* **1976**, *41*, 574.

(24) Rosenkranz, G.; Mancera, O.; Gatica, J.; Djerassi, C. *J. Am. Chem. Soc.* **1950**, *72*, 4077.

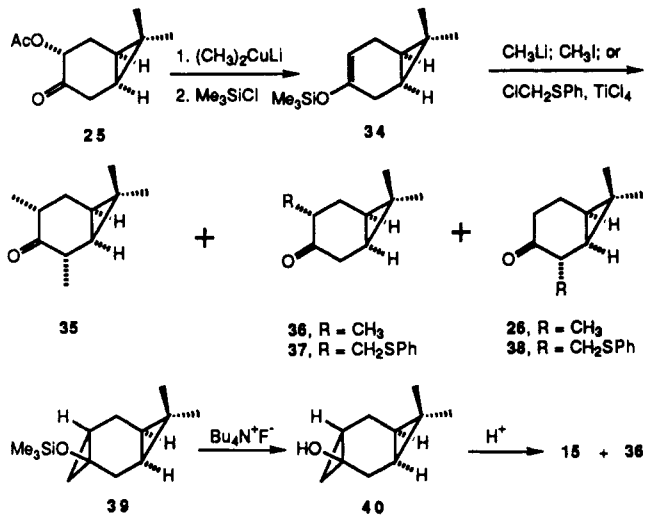
Scheme IV



hexamethyldisilazide in tetrahydrofuran at −78 °C, and the enolate anion was quenched with excess methyl iodide prior to warming to 0 °C. Although a single monomethylated product was obtained, two early observations hinted that this material was not the desired enantiomer of **18** (viz., **36**). Firstly, the methyl ketone was not at all subject to equilibration. Nor was it the 4β-methyl isomer **15**. Also, a 2D COSY NMR analysis showed the proton geminal to methyl to be strongly coupled to a cyclopropyl hydrogen. The H_a–H_b combination depicted in **26** was considered best accountable for these spin interactions. No doubt persisted following preparation of the tosylhydrazone as a prelude to Shapiro degradation[25] and in situ trapping of the derived vinyl anion with 1,2-dibromotetrafluoroethane (**27**).[26,27] Since an α-alkyl group directs introduction of the double bond to the α′ flank, the olefinic proton in **28** would be expected to reflect its close proximity to the allylic methylene group. This is indeed the case (see Experimental Section). In contrast, the vinyl bromide that would have arisen from **36** should be characterized by pronounced olefinic cyclopropyl proton coupling, but multiplicities of this type are absent.

Consequently, **23** undergoes deprotonation exclusively by abstraction of its (presumably) endo cyclopropylcarbinyl proton to deliver a vinylcyclopropane species. In contrast to nonstabilized cyclopropylmethyl carbanions,[28,29] the reactive intermediate generated in the present study is not prone to fragmentation of the strained ring. Instead, it enters conveniently into reaction with electrophiles, capturing then from the less hindered α face.

Scheme V

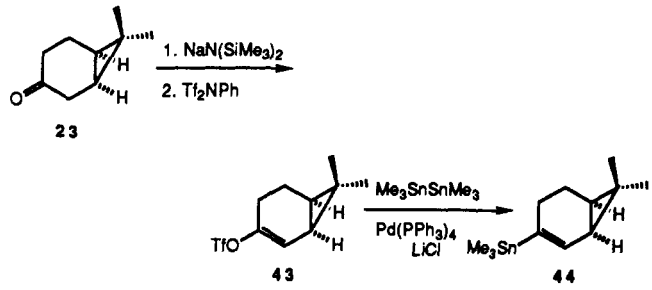


The nucleophilic potential of bromide **28** (and by analogy the functionalized compounds **44**, **46**, **48**, and **50** that follow) was demonstrated by transmetalation with *tert*-butyllithium, conversion to the dichlorocerate,[30] and condensation of this organometallic with 6-chloro-2-cyclohexen-1-one (**29**). The latter polyfunctional reagent was prepared by quenching the kinetic enolate of 2-cyclohexenone with trifluoromethanesulfonyl chloride.[31] Two chromatographically separable chlorohydrins (**30** and **31**) were produced, the absolute stereochemistries of which were not distinguished.[32] Each of the chlorohydrins was separately treated with silver triflate and 2,6-di-*tert*-butylpyridine in benzene for the purpose of accomplishing pinacol rearrangement to **32** and **33**, respectively.[33] No interconversion of these β,γ-unsaturated ketones was encountered under these conditions.[34]

Studies Involving (+)-3-((Trimethylsilyl)oxy)-3-carene. Since 3-norcaranone (**23**) enolizes strictly in the cyclopropylcarbinyl sense, the problem of directing deprotonation to the alternative α-site had to be resolved. Some time ago, Bull and Tuinman demonstrated that lithium dimethylcuprate has the capacity for reducing α-acetoxy ketones with resultant regiospecific enolate generation.[35] This expeditious process was therefore extended to **25**. Whereas attempted direct methylation of the intermediate with methyl iodide led only to the isolation of **23**, utilization of the more reactive chlorotrimethylsilane did give rise to silyl enol ether **34** (76%, Scheme V). Regeneration of the enolate ion by treatment of **34** with methyllithium was found to proceed more slowly than usual in tetrahydrofuran.[36] When recourse was made

(25) Shapiro, R. H. *Org. React. (N.Y.)* **1975**, *23*, 405.
(26) Habata, Y.; Akabori, S.; Sato, M. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 3540.
(27) (a) Paquette, L. A.; Pierre, F.; Cottrell, C. E. *J. Am. Chem. Soc.* **1987**, *109*, 5731. (b) Paquette, L. A.; DeRussy, D. T.; Gallucci, J. C. *J. Org. Chem.* **1989**, *54*, 2278.
(28) Hoffmann, R. W.; Eicken, K. R. *Chem. Ber.* **1967**, *100*, 1465.
(29) Paquette, L. A.; Maynard, G. D. *J. Org. Chem.* **1989**, *54*, 5054 (and pertinent references cited therein).
(30) (a) Imamoto, T.; Sugiura, Y.; Takiyama, N. *Tetrahedron Lett.* **1984**, *25*, 4233. (b) Imamoto, T.; Sugiura, Y. *J. Organomet. Chem.* **1985**, *285*, C21. (c) Imamoto, T.; Takiyama, N.; Nakamura, K. *Tetrahedron Lett.* **1985**, *26*, 4763. (d) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392.
(31) Hakimelahi, G. H.; Just, G. *Tetrahedron Lett.* **1979**, 3643.
(32) For a comparable synthetic application of 2-chlorocyclohexanone, consult: (a) Wender, P. A.; Holt, D. A. *J. Am. Chem. Soc.* **1985**, *107*, 7772. (b) Wender, P. A.; Sieburth, S. M.; Petraitis, J. J.; Singh, S. K. *Tetrahedron* **1981**, *37*, 3967.
(33) Review: Collins, R. *Q. Rev. Chem. Soc.* **1960**, *14*, 357.
(34) Attempts to effect the **30** → **32** and **31** → **33** conversions under basic conditions were unsuccessful.
(35) Bull, J. R.; Tuinman, A. *Tetrahedron Lett.* **1973**, 4349.
(36) House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1969**, *34*, 2324.

Scheme VI



instead to 1,2-dimethoxyethane as solvent and to somewhat more elevated temperatures (viz., 0 °C) for the purpose of accelerating this process, and methyl iodide was subsequently introduced, a 1:1 mixture of monomethylated ketones **26** and **36** was formed (35%) alongside dimethylated product **35** (10%). Unfortunately, clean conversion to **36** could not be realized in this direct manner.

Alkaline conditions were therefore skirted altogether by implementation of Paterson's methodology involving chloromethyl phenyl sulfide as electrophile and titanium tetrachloride as Lewis acid catalyst.[37] Once again, the formation of **37** and **38** in modest yield signaled an inability to achieve reliable regiocontrol in those condensations involving **34**. Furthermore, the tosylhydrazone of **37** was observed to epimerize slowly on standing.

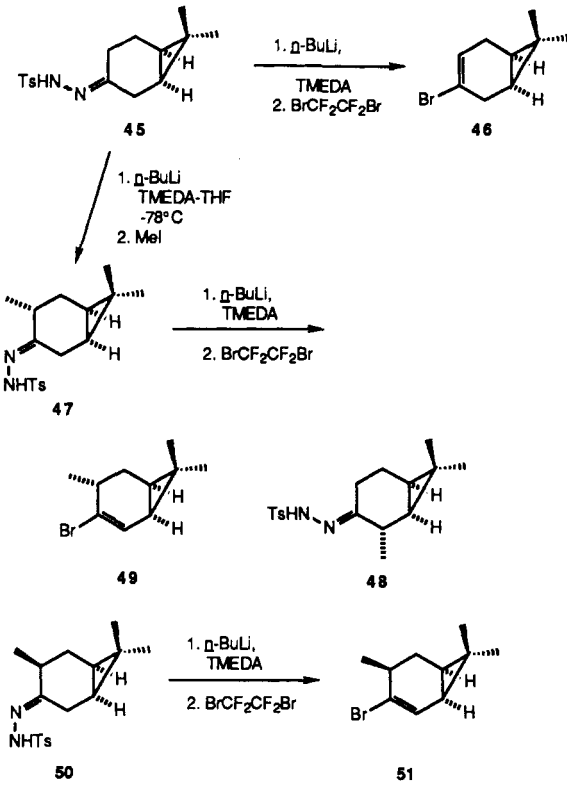
Accordingly, silyl enol ether **34** was transformed into **39** by Simmons–Smith cyclopropanation.[38] This reaction proceeds with complete regio- and stereocontrol. Desilylation of **39** with tetra-*n*-butylammonium fluoride furnished cyclopropanol **40** efficiently (96%). Expectedly, acid-promoted ring opening within **40** proceeded more slowly than the equilibration of **15** to **36**.[39] As a result, the undesired β-epimer invariably predominated, and by a wide margin.

Contrasting Deprotonation Pathways for (+)-3-Norcaranone and Its Tosylhydrazone. In an effort to turn the exceptional regiocontrol exhibited by **23** in our favor, enol triflate **43** was prepared and transformed subsequently into vinyl stannane **44**[40] (Scheme VI). The unoptimized yield for this two-step conversion is good (51%). In our experience, this sequence represents the most direct and efficient pathway to optically active 2-norcarenes having nucleophilic potential at C-3.

Next, we focused on the tosylhydrazone derivative **45** of 3-norcaranone. Submission of this intermediate to standard Shapiro conditions and subsequent trapping of the vinyl anion thereby generated with 1,2-dibromotetrafluoroethane[26,27] led uniquely to (+)-3-bromo-3-norcarene (**46**) in 73% yield (Scheme VII). In contrast to 3-substituted 2-norcarenes such as **43** whose vinyl protons appear as clean doublets, the olefinic absorptions in **28**, **34**, and **46** occur as multiplets, the result of more extensive spin interaction with the neighboring methylene group. Evidently, steric factors operate on **45** (initially a 1:1 mixture of *E*/*Z* isomers) to direct the rate-determining deprotonation step[25] to the less hindered environment.

This crossover in regioselective proton abstraction that distinguishes **23** from **45** has made possible a convenient

Scheme VII



preparation of bromide **49**. Deprotonation of **45** following a literature method (deprotonation with *n*-BuLi in THF at −78 °C)[41] and in situ methylation afforded a 1:1 mixture of tosylhydrazones **47** and **48** in 61% yield. In contrast, when the *n*-butyllithium (2.2 equiv) was premixed with TMEDA and methylation conducted in a solvent system consisting of TMEDA and THF (2:1),[42] **47** was found to predominate widely (49% isolated). Accompanying **47** was its epimer **50** (4%) and only a trace of **48** (300-MHz ^{1}H NMR analysis). Interestingly, use of the same solvent system but without advance premixing was found to give **47** and **48** in a ratio of 3:2. These results implicate an important role for the TMEDA if given adequate time to deaggregate the alkyllithium species. Relevantly, the TMEDA-chelated base is capable of particularly efficient regioselective deprotonation at the less sterically hindered site.

Submission of **47** to the Shapiro process and bromination made available the pivotal vinyl bromide **49** (87%). Its 300-MHz ^{1}H NMR spectrum (in C_6D_6) features key signals for the vinyl [δ 6.02 (d, J = 3.6 Hz)] and methyl protons [δ 1.12 (d, J = 6.9 Hz)]. In order to substantiate the stereochemical assignment to **49**, tosylhydrazone **50** was prepared from **15** and analogously transformed into **51**. The corresponding absorptions for this vinyl bromide epimer in C_6D_6 [δ 6.14 (t, J = 3.1 Hz) and 1.03 (d, J = 7.0 Hz)] are distinctively different from those observed for **49**.

In summary, this study establishes straightforward syntheses from (+)-3-norcaranone of several 2- and 3-carene systems suitably functionalized at C-3 for use as nucleophilic species. Particular attention is called to **49** and **51**, molecules which we anticipate will find utility in

(37) Paterson, I. *Tetrahedron* **1988**, *44*, 4207.
(38) Denis, J. M.; Conia, J. M. *Synthesis* **1972**, 549.
(39) Ireland, R. E.; Kowalski, C. J.; Tilley, J. W.; Walba, D. M. *J. Org. Chem.* **1975**, *40*, 990.
(40) (a) Wulff, W. D.; Peterson, G. A.; Bauta, W. E.; Chan, K.-S.; Faron, K. L.; Gilbertson, S. R.; Kaesler, R. W.; Yang, D. C.; Murray, C. K. *J. Org. Chem.* **1986**, *51*, 277. (b) Taylor, R. T.; Degenhardt, C. R.; Melega, W. P.; Paquette, L. A. *Tetrahedron Lett.* **1977**, 159.
(41) (a) Caille, J. C.; Bellamy, F.; Guilard, R. *Tetrahedron Lett.* **1984**, *25*, 2345. (b) Caille, J. C.; Farnier, M.; Guilard, R. *Can. J. Chem.* **1986**, *64*, 824.
(42) Nakai, T.; Mimura, T. *Tetrahedron Lett.* **1979**, 531. These authors utilize a 1:2 TMEDA–THF solvent system, which has proven less advantageous for our purposes.

the elaboration of certain cocarcinogenic diterpenes. Studies along these lines are in progress.

Experimental Section[43]

(+)-(1*S*,3*S*,4*R*,6*R*)-3,4-Epoxy-3,7,7-trimethylbicyclo[4.1.0]heptane (19). In accordance with the procedure of Brown and Suzuki,[17] 68 g (500 mmol) of (+)-3-carene (Chemical Samples Co.) was epoxidized with *m*-chloroperbenzoic acid (109 g of 85% purity, 540 mmol). Distillation provided 60 g (85%) of **19** as a sweet-smelling colorless oil: bp 95–101 °C (20 Torr); IR (neat, cm^{-1}) 3000, 2960, 2920, 2870, 1450, 1430, 1380, 1210, 1070, 1035, 1000, 950, 845, 765, 720; ^1H NMR (300 MHz, $CDCl_3$) δ 2.83 (s, 1 H), 2.29 (ddd, J = 16.4, 8.6, 2.2 Hz, 1 H), 2.14 (dd, J = 16.2, 8.9 Hz, 1 H), 1.64 (dt, J = 16.4, 2.3 Hz, 1 H), 1.49 (dd, J = 16.2, 2.2 Hz, 1 H), 1.26 (s, 3 H), 1.00 (s, 3 H), 0.73 (s, 3 H), 0.56–0.42 (m, 2 H); MS m/z (M^+) calcd 152.1201, obsd 152.1202; $[\alpha]^{20}_D$ +13.95° (neat) [lit.[17] $[\alpha]^{20}_D$ +13.3° (neat)].

(−)-(1*R*,3*R*,6*S*)-4-Methylene-7,7-dimethylbicyclo[4.1.0]heptan-3-ol (20). *n*-Butyllithium (118 mL of 1.6 M in hexanes, 300 mmol) was added to a solution of 2,2,6,6-tetramethylpiperidine (51 mL, 300 mmol) and benzene (600 mL) at 0 °C. After 15 min, a solution of diethylaluminum chloride (302 mL of 1.0 M in hexane, 302 mmol) was introduced, and the resulting white suspension was stirred for 30 min. A solution of **19** (22.3 g, 150 mmol) in benzene (10 mL) was added, and the reaction mixture was stirred for 30 min at 0 °C, cautiously quenched with ice-cold 10% hydrochloric acid (600 mL), and extracted with ether (2 × 600 mL). The combined organic phases were dried and evaporated to provide 22 g (98%) of **20** as an oily solid. Sublimation of a small sample at 40–50 °C and 0.5 Torr furnished colorless crystals: mp 53–54 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 4.82 (s, 1 H), 4.75 (s, 1 H), 4.09 (t, J = 3.1 Hz, 1 H), 2.75 (ddt, J = 16.4, 8.1, 2.6 Hz, 1 H), 2.26 (d, J = 16.3 Hz, 1 H), 2.23 (ddd, J = 15.0, 9.5, 2.3 Hz, 1 H), 1.70 (br s, 1 H), 1.55 (dt, J = 15.2, 3.6 Hz, 1 H), 1.01 (s, 3 H), 0.88 (s, 3 H), 0.82 (t, J = 8.3 Hz, 1 H), 0.69 (dt, J = 8.3, 4.0 Hz, 1 H); $[\alpha]^{20}_D$ −119.8° (*c* 2.47, $CHCl_3$) [lit.[20] −118.7° (*c* 3.4, $CHCl_3$)].

Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 78.70; H, 10.54.

(−)-(1*S*,6*R*)-7,7-Dimethylbicyclo[4.1.0]hept-3-ene-3-carboxaldehyde (21). In accordance with the procedure of Gollnick and Schade,[21] a solution of 1.0 g (6.6 mmol) of **20** was treated with 2 M aqueous chromic acid (6.6 mL, 13.1 mmol) for 2 h at 60 °C. The best crude yield of **21** realized was 770 mg (70%). A small sample was purified by preparative GC (5 ft × 0.25 in., 5% SE-30 on Chromosorb W, 120 °C): ^1H NMR (300 MHz, $CDCl_3$) δ 9.40 (s, 1 H), 6.70–6.68 (m, 1 H), 2.84–2.65 (m, 1 H), 2.60–2.45 (m, 1 H), 2.38–2.24 (m, 1 H), 2.22–2.10 (m, 1 H), 1.07 (s, 3 H), 0.90–0.75 (m, 2 H), 0.70 (s, 3 H); $[\alpha]^{20}_D$ −131° (*c* 2.1, C_6H_6) [lit.[21] $[\alpha]^{20}_D$ −25.8° (*c* 2.3, C_6H_6)].

The tosylhydrazone of **21** was a colorless foamy solid: IR ($CHCl_3$, cm^{-1}) 3270, 3190, 3020, 3000, 2940, 2920, 2860, 1640, 1590, 1490, 1440, 1420, 1365, 1345, 1310, 1300, 1185, 1160, 1090, 1070, 1045, 950, 925, 810; ^1H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, J = 8.2 Hz, 2 H), 7.58 (s, 1 H), 7.32 (s, 1 H), 7.30 (d, J = 8.2 Hz, 2 H), 5.88 (s, 1 H), 2.60–2.40 (m, 2 H), 2.42 (s, 3 H), 2.25–2.05 (m, 2 H), 1.04 (s, 3 H), 0.95–0.60 (m, 2 H), 0.67 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 151.91, 143.68, 136.31, 135.26, 132.84, 129.40, 127.90, 28.18, 21.67, 21.53, 18.09, 17.29, 17.18, 17.14, 13.36; MS m/z (M^+) calcd 318.1402, obsd 318.1386; $[\alpha]^{20}_D$ −46.4° (*c* 1.19, CH_2Cl_2).

(+)-(1*S*,6*R*)-7,7-Dimethylbicyclo[4.1.0]hept-3(8)-ene (22). A. Sodium Borohydride Reduction. Sodium borohydride (1.89 g, 50 mmol) was added to a solution of **21** tosylhydrazone (1.62 g, 5.1 mmol) in acetic acid (20 mL) at room temperature over 1 h. The reaction mixture was heated to 70 °C for 1 h, poured onto ice, and extracted with pentane (3 × 100 mL). Drying and solvent removal left a yellow oil, chromatography of which on silica gel (pentane solution) gave 180 mg (26%) of clear colorless **22**: ^1H NMR (300 MHz, $CDCl_3$) δ 4.63 (s, 1 H), 4.59 (d, J = 1.5 Hz, 1 H), 2.49 (dd, J = 16.0, 7.2 Hz, 1 H), 2.30 (d, J = 16 Hz, 1 H), 2.20–1.8 (m, 3 H), 1.40–1.20 (m, 1 H), 0.98 (s, 3 H), 0.92 (s, 3 H), 0.76–0.59 (m, 2 H); $[\alpha]^{23}_D$ +85.9° (*c* 3.6, C_6H_6) [lit.[21] $[\alpha]^{25}_D$ +36° (*c* 2.3, C_6H_6)].

B. Catecholborane Reduction. Catecholborane (714 mg, 6.0 mmol) was added to a solution of **21** tosylhydrazone (1.67 g, 5.2 mmol) in chloroform (16 mL) at 0 °C. Following 1.5 h of stirring, sodium acetate (2.12 g, 15.6 mmol) was introduced, and the reaction mixture was heated at reflux for 1 h, filtered through Celite with ether (40 mL), and evaporated. Chromatography of the residue (silica gel, elution with petroleum ether) gave 470 mg (66%) of **22**, identical in all respects with the material obtained above.

(+)-(1*S*,6*R*)-7,7-Dimethylbicyclo[4.1.0]heptan-3-one (23). A solution of **22** (180 mg, 1.32 mmol) in dichloromethane (2.5 mL) and methanol (2.5 mL) was ozonolyzed at −78 °C for approximately 30 min until a blue color formed. The reaction mixture was purged with nitrogen for 30 min, treated with zinc (400 mg) followed by acetic acid (1.5 mL), and stirred at −78 °C for 30 min and at room temperature for 1 h. The mixture was filtered through Celite with ether (200 mL), and the filtrate was washed with water, sodium bicarbonate solution, and brine prior to drying and evaporation. The residual oil was chromatographed on silica gel (elution with 5% ethyl acetate in petroleum ether) to give 150 mg (83%) of colorless **23**: IR (neat, cm^{-1}) 2950, 2870, 1710, 1460, 1380, 1240, 1170, 980, 960, 780, 740; ^1H NMR (300 MHz, $CDCl_3$) δ 2.52 (dd, J = 18, 8 Hz, 1 H), 2.34–2.09 (m, 4 H), 1.57–1.43 (m, 1 H), 1.07 (s, 3 H), 1.06–0.94 (m, 2 H), 0.93 (s, 3 H); $[\alpha]^{20}_D$ +256° (*c* 1.3, $CHCl_3$).

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.13; H, 10.23.

(−)-(1*R*,3*R*,6*S*)-4-Methylene-7,7-dimethylbicyclo[4.1.0]heptan-3-ol Acetate (24). A solution of **20** (22 g, 150 mmol) and 4-(dimethylamino)pyridine (100 mg) in acetic anhydride (19 mL) and pyridine (15 mL) was stirred at room temperature for 12 h, diluted with ether (1000 mL), and washed consecutively with saturated cupric sulfate solution (3 × 100 mL), 2% hydrochloric acid (500 mL), and brine (2 × 300 mL). The organic phase was dried and evaporated to give 28 g (96%) of **24** as a yellowish oil. A small sample was further purified by distillation: bp 95–105 °C (20 Torr); IR (neat, cm^{-1}) 3080, 2990, 2940, 2870, 1735, 1655, 1440, 1370, 1245, 1185, 1025, 985, 975, 905, 840; ^1H NMR (300 MHz, $CDCl_3$) δ 5.16 (t, J = 3.4 Hz, 1 H), 4.90 (d, J = 2 Hz, 1 H), 4.85 (d, J = 2 Hz, 1 H), 2.66 (ddt, J = 16, 8, 2.5 Hz, 1 H), 2.34–2.25 (m, 2 H), 2.06 (s, 3 H), 1.54 (dt, J = 3.7 Hz, 1 H), 1.00 (s, 3 H), 0.90 (s, 3 H), 0.80 (t, J = 8.5 Hz, 1 H), 0.67 (td, J = 9.3, 3.9 Hz, 1 H); $[\alpha]^{20}_D$ −70° (*c* 3.05, C_6H_6).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.30; H, 9.50.

(+)-(1*S*,4*R*,6*R*)-4-Acetoxy-7,7-dimethylbicyclo[4.1.0]heptan-3-one (25). A solution of **24** (28 g, 144 mmol) in methanol (200 mL) and dichloromethane (50 mL) was ozonolyzed at −78 °C for approximately 2 h until a blue color was observed. The reaction mixture was purged with nitrogen, and dimethyl sulfide (50 mL) was added. This solution was stirred at −78 °C for 1 h, then slowly warmed to room temperature over 2 h. Following the evaporation of solvent, the residue was dissolved in ether (800 mL), washed with brine (2 × 200 mL), dried, and concentrated in vacuo. Purification by preparative HPLC (silica gel, elution with 7% ethyl acetate in petroleum ether) furnished 24 g (85%) of **25** as a colorless oil: bp 160–170 °C (20 Torr); IR (neat, cm^{-1}) 3000, 2950, 2870, 1745, 1730, 1455, 1375, 1235, 1160, 1065, 1040, 960, 915, 805, 760; ^1H NMR (300 MHz, $CDCl_3$) δ 4.79 (t, J = 5.2 Hz, 1 H), 2.73 (dd, J = 17, 9 Hz, 1 H), 2.54–2.44 (m, 1 H), 2.30 (dd, J = 17, 2.6 Hz, 1 H), 2.13 (s, 3 H), 2.10–2.04 (m, 1 H), 1.16

(43) Melting points are uncorrected. ^1H NMR spectra were recorded at 300 MHz and the ^{13}C NMR spectra at either 75 or 20 MHz as indicated. 2D COSY NMR were obtained at 500 MHz. The preparative GC work made use of a Varian Series 2700 unit. All MPLC separations were conducted on Merck Lobar columns (Lichroprep Si-60) with the help of a Fluid Metering INC pump and a Waters Associates Model R403 differential refractometer detector. All reactions were performed under an inert atmosphere (dry nitrogen or argon). Solvents were reagent grade and dried prior to use. The purity of all title compounds was judged to be ≥97% by TLC, GC (where relevant, ^1H NMR and ^{13}C NMR determinations).

(44) **Note Added in Proof.** A recent synthesis of phorbol has been accomplished by capitalizing on the proper facial selectivity of $Ph_2S^+C^-(CH_3)_2$ addition to an α-acetoxy enone for generating the dimethylcyclopropane subunit [Wender, P. A.; et al. *J. Am. Chem. Soc.* **1989**, *111*, 8957].

(dt, J = 2.6, 9 Hz, 1 H), 1.06 (s, 3 H), 1.02 (s, 3 H), 0.85 (dt, J = 4.1, 9 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 208.30, 169.79, 73.36, 34.46, 27.94, 27.86, 23.40, 20.59, 19.11, 17.01, 14.63; $[\alpha]^{20}_D$ +89° (c 2.85, C_6H_6).

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.33; H, 8.35.

(+)-(1*S*,6*R*)-7,7-Dimethylbicyclo[4.1.0]heptan-3-one (23). An aqueous solution of chromous sulfate (500 mL of 0.55 M, 275 mmol) and concentrated hydrochloric acid (20 mL) was added dropwise under argon to a solution of **25** (27 g, 138 mmol) in acetone (300 mL) and water (300 mL) and stirred at room temperature for 28 h. The product was extracted into ether (4 × 300 mL), and the combined organic phases were washed with brine (400 mL) and dried. Removal of solvent and distillation (bp 65–67 °C (20 Torr)) afforded 14.6 g (77%) of **23** as a colorless oil, identical in all respects to the ketone derived earlier from **22**.

(+)-(1*S*,2*S*,6*R*)-2,7,7-Trimethylbicyclo[4.1.0]heptan-3-one (26). A solution of **23** (3.0 g, 22 mmol) in anhydrous tetrahydrofuran (15 mL) was added during 40 min to a cold (−78 °C) solution of sodium hexamethyldisilazide (26 mL of 1.0 M, 26 mmol) in the same solvent. After an additional 30 min, methyl iodide (5 mL) was introduced in one portion. The reaction mixture was warmed to 0 °C and quenched with water (50 mL). The mixture was extracted with ether (3 × 50 mL), and the combined organic layers were washed with brine (50 mL), dried, and evaporated. Purification was achieved by HPLC (silica gel, elution with 5% ethyl acetate in petroleum ether) to give pure **26** as a colorless oil (2.24 g, 67%): bp 80–85 °C (20 Torr); IR (neat, cm^{-1}) 2940, 2870, 1710, 1460, 1400, 1375, 1330, 1250, 1180, 1160, 1125, 1030, 890, 835, 780; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.41–2.27 (m, 3 H), 1.56–1.42 (m, 1 H), 1.17 (d, J = 7 Hz, 3 H), 1.08 (s, 3 H), 0.97–0.85 (m, 1 H), 0.52 (dd, J = 9, 6 Hz, 1 H); $[\alpha]^{20}_D$ +323° (c 2.3, C_6H_6).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 78.50; H, 10.59.

The tosylhydrazone of **26** was obtained as a white crystalline solid: mp 109–110 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87–7.78 (m, 2 H), 7.33–7.26 (m, 2 H), 2.41 (s, 3 H), 2.25–1.89 (m, 4 H), 1.13 (d, J = 6.6 Hz, 3 H), 1.12–1.04 (m, 1 H), 1.00 (s, 3 H), 0.98 (s, 3 H), 0.65 (dd, J = 16, 9 Hz, 1 H), 0.50 (s, 1 H), 0.29 (dd, J = 9, 7.6 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 165.86, 144.88, 137.00, 130.22, 128.94, 33.81, 29.41, 28.53, 26.52, 22.60, 21.66, 19.90, 18.27, 17.83, 14.69; $[\alpha]^{20}_D$ +112° (c 1.39, methanol).

Anal. Calcd for $C_{17}H_{24}N_2O_2S$: C, 63.72; H, 7.55. Found: C, 63.46; H, 7.59.

(1*S*,2*S*,6*R*)-2,7,7-Trimethyl-3-bromobicyclo[4.1.0]hept-3-ene (28). A solution of the tosylhydrazone of **26** (3.3 g, 10.5 mmol) in dry *N,N,N′,N′*-tetramethylethylenediamine (20 mL) was added to *n*-butyllithium (26 mL of 1.6 M in hexanes, 42 mmol) in the same solvent (25 mL) during 30 min at −78 °C. After 30 min at −78 °C, the deep red solution was warmed to room temperature whereupon the color faded to a pale orange with the evolution of gas. One hour later, the reaction mixture was recooled to −78 °C and 1,2-dibromotetrafluoroethane (**27**, 11.7 g, 45 mmol) was introduced. The solution was warmed to room temperatue, quenched with water (50 mL), and diluted further with brine (100 mL). The product was extracted into petroleum ether (3 × 100 mL), and the combined organic phases were washed with 10% hydrochloric acid (2 × 100 mL), saturated sodium bicarbonate solution (2 × 50 mL), and brine prior to drying. Solvent removal provided a yellow oil, chromatography of which on neutral alumina (elution with petroleum ether) afforded 1.4 g (65%) of **28**, which was approximately 88% pure based on ^{1}H NMR (300 MHz, C_6D_6) δ 5.73–5.70 (m, 1 H), 2.45–2.35 (m, 1 H), 2.20–2.07 (m, 1 H), 1.79 (d, J = 20, 4.3 Hz, 1 H), 1.33 (d, J = 7.1 Hz, 3 H), 0.85 (s, 3 H), 0.84 (s, 3 H), 0.50–0.40 (m, 2 H). This vinyl bromide was not allowed to stand for prolonged periods and was utilized without further purification.

6-Chloro-2-cyclohexen-1-one (29). A solution of 2-cyclohexen-1-one (2.88 g, 30 mmol) in anhydrous tetrahydrofuran (10 mL) was added dropwise during 30 min to a solution of lithium hexamethyldisilazide (36 mmol) in the same solvent (46 mL) at −78 °C. The enolate solution was stirred for 30 min and transfered via cannula to a magnetically stirred solution of trifluoromethanesulfonyl chloride (3.84 mL, 36 mmol) in 10 mL of cold (−78 °C), dry tetrahydrofuran. The reaction mixture was stirred for 15 min, the cooling bath was removed, and water (10 mL) was introduced. Following partitioning between ether (100 mL) and water (100 mL), the aqueous layer was extracted with ether (100 mL) and the combined organic phases were washed with brine (100 mL) and dried. Removal of solvent in vacuo and chromatography on silica gel (elution with 5% ethyl acetate in petroleum ether) provided 2.9 g (73%) of **29** as a colorless oil: IR (neat, cm^{-1}) 3040, 2930, 1675, 1620, 1425, 1390, 1385, 1300, 1255, 1220, 1195, 1125, 1020, 885, 840, 800, 720, 695; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05–6.99 (m, 1 H), 6.08 (dt, J = 10, 2 Hz, 1 H), 4.43–4.37 (m, 1 H), 2.73–2.60 (m, 1 H), 2.58–2.30 (m, 3 H); MS m/z (M$^+$) calcd 130.0185, obsd 130.0216.

Chlorohydrins 30 and 31. *tert*-Butyllithium (6.11 mL of 1.7 M, 10.4 mmol) was added dropwise to a solution of **28** (1.4 g of 88% purity, 5.7 mmol) in anhydrous tetrahydrofuran (18 mL) at −78 °C. After 30 min, this solution was transferred via cannula to a suspension of anhydrous cerium trichloride (1.48 g, 6 mmol) in the same solvent (10 mL) at −78 °C, and the mixture was stirred for 1 h. A solution of 6-chloro-2-cyclohexen-1-one (**29**, 780 mg, 6.0 mmol) in tetrahydrofuran (5 mL) was introduced slowly via cannula during 20 min, and stirring was maintained at −78 °C for 2 h prior to removal of the cooling bath and addition of 10 mL of water. This mixture was partitioned between water (100 mL) and ether (75 mL), and the aqueous layer was extracted with ether (2 × 75 mL). The combined organic phases were filtered through Celite, washed with brine (80 mL), and dried. Removal of solvent and MPLC on silica gel (elution with 2% ethyl acetate in petroleum ether) provided 510 mg (34%) of one diastereomeric chlorohydrin and 540 mg (36%) of the other. Their absolute stereochemistries have not been determined.

For the less polar isomer: IR (neat, cm^{-1}) 3540, 3010, 2980, 2940, 2870, 1450, 1380, 1325, 1290, 1250, 1235, 1180, 1100, 1015, 935, 900, 870, 805, 770, 725; ^{1}H NMR (300 MHz, C_6D_6) δ 5.48–5.44 (m, 2 H), 5.35–5.32 (m, 1 H), 4.09 (dd, J = 6, 3 Hz, 1 H), 2.60–2.50 (m, 1 H), 2.49–2.40 (m, 2 H), 2.15–1.73 (m, 4 H), 1.64–1.49 (m, 1 H), 1.47 (d, J = 6.7 Hz, 3 H), 1.00 (s, 3 H), 0.99 (s, 3 H), 0.75–0.57 (m, 2 H); MS m/z (M$^+$) calcd 266.1438, obsd 266.1424.

For the more polar isomer: IR (neat, cm^{-1}) 3550, 3450, 3020, 2920, 2850, 1445, 1425, 1095, 1000, 860, 790, 730, 710; ^{1}H NMR (300 MHz, C_6D_6) δ 5.91 (t, J = 4 Hz, 1 H), 5.56–5.35 (m, 2 H), 4.26 (dd, J = 10.7, 3.2 Hz, 1 H), 2.60–2.49 (m, 1 H), 2.42–2.32 (m, 1 H), 2.25–2.06 (m, 3 H), 1.92–1.76 (m, 2 H), 1.67–1.50 (m, 1 H), 1.14 (d, J = 7.1 Hz, 3 H), 1.02 (s, 3 H), 1.02 (s, 3 H), 0.67 (dd, J = 9, 7.2 Hz, 1 H), 0.50 (d, J = 9 Hz, 1 H); MS m/z (M$^+$) calcd 266.1438, obsd 266.1426.

Silver Ion Promoted Rearrangement of 30 and 31. A. Less Polar Chlorohydrin. Silver trifluoromethanesulfonate (820 mg, 3.2 mmol) was added to a solution of the less polar chlorohydrin (780 mg, 2.9 mmol) in benzene (40 mL) containing 2,6-di-*tert*-butylpyridine (0.89 mL, 4 mmol), and the mixture was stirred at room temperature for 48 h. At this time, ether (150 mL) and brine (50 mL) were added, and the mixture was filtered to remove silver chloride. The ether phase was again washed with brine prior to drying and solvent evaporation. The residue was purified by MPLC (silica gel, elution with 7% ethyl acetate in petroleum ether) to give 300 mg (45%) of either **32** or **33** and 93 mg (12%) of unreacted starting material.

For the β,γ-unsaturated ketone: colorless oil; IR (neat, cm^{-1}) 3050, 2950, 2850, 1680, 1450, 1385, 1255, 1215, 1125, 1050, 850, 770, 715; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.91–6.85 (dt, J = 10, 4 Hz, 1 H), 6.03–5.99 (dt, J = 10, 2 Hz, 1 H), 5.09 (t, J = 3.5 Hz, 1 H), 2.94 (t, J = 5.6 Hz, 1 H), 2.48–2.35 (m, 1 H), 2.28–2.12 (m, 3 H), 2.08–1.92 (m, 3 H), 1.18 (d, J = 7.1 Hz, 3 H), 0.99 (s, 3 H), 0.86 (s, 3 H), 0.70–0.65 (m, 1 H), 0.52 (d, J = 8.3 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 200.80, 149.52, 137.59, 130.45, 121.70, 50.83, 28.91, 27.91, 27.62, 27.57, 23.98, 21.89, 21.58, 17.33, 16.80, 13.74; MS m/z (M$^+$) calcd 230.1671, obsd 230.1696; $[\alpha]^{20}_D$ +105° (c 1.07, C_6H_6).

Anal. Calcd for $C_{16}H_{22}O$: C, 83.43; H, 9.63. Found: C, 83.52; H, 9.66.

B. More Polar Chlorohydrin. By means of the exact procedure described above, the more polar chlorohydrin (710 mg, 2.66 mmol) was converted into the other diastereomeric β,γ-unsaturated ketone (470 mg, 78%) after only 4 h: IR (neat, cm^{-1}) 3040, 2940, 2875, 2825, 1680, 1450, 1430, 1380, 1220, 1210, 1120, 850, 710; ^{1}H NMR (300 MHz, C_6D_6) δ 6.20–6.13 (m, 1 H), 5.91

(d, J = 8.7 Hz, 1 H), 5.20–5.17 (m, 1 H), 2.68–2.63 (m, 1 H), 2.44–2.35 (m, 2 H), 2.10 (dt, J = 19.5, 4.3 Hz, 1 H), 1.80–1.56 (m, 4 H), 1.24 (s, 3 H), 1.14 (d, J = 7 Hz, 3 H), 1.05 (s, 3 H), 0.69 (dd, J = 9.1, 7.4 Hz, 1 H), 0.53 (d, J = 9 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 199.75, 149.74, 137.89, 130.03, 122.46, 52.11, 28.96, 27.93, 27.78, 25.70, 21.84, 21.53, 17.58, 17.04, 13.61 (one carbon signal not observed); MS m/z (M^+) calcd 230.1670, obsd 230.1661; $[\alpha]^{20}_D$ +60° (c 1.2, C_6H_6).

(+)-(1*S*,6*R*)-3-((Trimethylsilyl)oxy)-7,7-dimethylbicyclo[4.1.0]hept-3-ene (34). Methyllithium (114.8 mL of 1.4 M in ether, 161 mmol) was added to a suspension of copper(I) iodide (15.44 g, 81 mmol) in 150 mL of cold (0 °C), dry tetrahydrofuran during 5 min. After 30 min of stirring at 0 °C, a solution of **25** (7.84 g, 40 mmol) in the same solvent (10 mL) was added dropwise. The resulting orange-green suspension was stirred for 10 min, treated with trimethylsilyl chloride (15.2 mL, 120 mmol), and 10 min later poured into 200 mL of saturated sodium bicarbonate solution. The suspension was filtered through neutral alumina, and the filter cake was rinsed with ether. The organic phase in the filtrate was washed with brine, dried, and evaporated. Chromatography of the residue on silica gel (elution with petroleum ether) afforded 4.10 g (49%) of **34** as a colorless oil: IR (neat, cm^{-1}) 2980, 2940, 2880, 2820, 1672, 1440, 1420, 1360, 1245, 1180, 900, 885, 750; ^{1}H NMR (300 MHz, C_6D_6) δ 4.79–4.77 (m, 1 H), 2.53–2.36 (m, 2 H), 2.12–1.97 (m, 2 H), 0.96 (s, 3 H), 0.93 (s, 3 H), 0.75–0.68 (m, 1 H), 0.53 (t, J = 8.4 Hz, 1 H), 0.23 (s, 9 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 149.54, 102.39, 28.47, 25.09, 20.95, 20.47, 17.37, 16.99, 13.58, 0.54; MS m/z (M^+) calcd 210.1439, obsd 210.1457; $[\alpha]^{20}_D$ +107° (c 1.48, C_6H_6).

Lithiation–Methylation of 34. Methyllithium (1.70 mL of 1.5 M in ether, 2.55 mmol) was added to a solution of **34** (500 mg, 2.38 mmol) in cold (0 °C), dry 1,2-dimethoxyethane. The mixture was stirred at 20 °C for 1 h, treated in one portion with methyl iodide (1.0 mL, 16.38 mmol) at −78 °C, and stirred at that temperature for 40 min and at room temperature for 1 h before being poured into water. The products were extracted into ether, and the combined organic layers were washed with brine, dried, and evaporated. MPLC of the residue (silica gel, elution with 3% ethyl acetate in petroleum ether) furnished 39 mg (10%) of **35** and 127 mg (35%) of a 1:1 mixture of **26** and **36**.

For **26**/**36**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.58 (dd, J = 18.2, 8.5 Hz, 1 H, **36**), 2.36–1.98 (m, **26** and **36**), 1.73 (dt, J = 14.9, 5.7 Hz, 1 H, **36**), 1.60–1.40 (m, 1 H, **26**), 1.23 (d, J = 7.2 Hz, 3 H, **36**), 1.17 (d, J = 6.9 Hz, 3 H, **26**), 1.15–1.00 (m, 1 H, **36**), 1.08 (s, 3 H, **26**), 1.07 (s, 3 H, **26**), 1.07 (s, 3 H, **36**), 0.93 (s, 3 H, **36**), 0.95–0.70 (m, 2 H, **26** and **36**), 0.52 (dd, J = 9.1, 6.0 Hz, 1 H, **26**); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 217.30, 215.86, 41.57, 39.81, 36.74, 33.85, 28.68, 28.02, 27.84, 26.71, 21.58, 21.53, 19.84, 19.22, 18.95, 16.81, 16.59, 15.86, 14.53, 14.53.

For **35**: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.23–2.18 (m, 1 H), 1.97–1.80 (m, 2 H), 1.73–1.64 (m, 1 H), 1.17 (d, J = 7.4 Hz, 3 H), 1.11 (d, J = 6.8 Hz, 3 H), 1.10 (s, 3 H), 1.09 (s, 3 H), 0.87–0.79 (m, 1 H), 0.44 (dd, J = 9.0, 6.8 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 217.52, 40.62, 39.15, 28.26, 27.98, 26.10, 20.00, 19.32, 17.58, 15.38, 14.43; MS m/z calcd 166.1358, obsd 166.1361; $[\alpha]^{20}_D$ +252° (c 2.29, C_6H_6).

Phenylthiomethylation of 34. A solution of titanium tetrachloride in dichloromethane (14.7 mL of 1.0 M, 14.7 mmol) was added dropwise to a solution of **34** (2.66 g, 12.7 mmol) and chloromethyl phenyl sulfide (1.70 mL, 12.7 mmol) in 35 mL of dry dichloromethane at −23 °C. The reaction mixture was stirred at −23 °C for 1.5 h, poured in saturated sodium bicarbonate solution (50 mL), and extracted with ether (3 × 25 mL). The combined organic layers were washed with brine, dried, and evaporated. The residual oil was chromatographed on silica gel (elution with 5% ethyl acetate in petroleum ether) to give a mixture of **37** and **38**. These isomers were separated by MPLC (silica gel, elution with 3% ethyl acetate in petroleum ether). There was isolated 793 mg (24%) of **37** and 470 mg (14%) of **38**.

For **37**: colorless crystals; mp 52–53 °C (from petroleum ether); IR (film, cm^{-1}) 3040, 2980, 2920, 2870, 1710, 1560, 1480, 1450, 1440, 1410, 1375, 1305, 1230, 1150, 1130, 1090, 1025, 1000, 740, 690; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86–7.14 (m, 5 H), 3.31 (dd, J = 13.2, 6.3 Hz, 1 H), 3.09 (dd, J = 13.2, 9.4 Hz, 1 H), 2.56 (dd, J = 18.1, 8.5 Hz, 1 H), 2.48–2.39 (m, 1 H), 2.33–2.26 (m, 1 H), 2.16–2.00 (m, 1 H), 1.68–1.52 (m, 1 H), 1.07 (s, 3 H), 1.04–1.00 (m, 1 H), 0.93 (s, 3 H), 0.86–0.78 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 214.77, 135.23, 130.05, 128.96, 126.48, 46.26, 34.95, 34.72, 27.99, 23.63, 21.76, 19.88, 16.83, 14.71; MS m/z (M^+) calcd 260.1235, obsd 260.1240; $[\alpha]^{20}_D$ +21° (c 2.58, C_6H_6).

Anal. Calcd for $C_{16}H_{20}OS$: C, 73.87; H, 7.75. Found: C, 73.86; H, 7.74.

For **38**: colorless oil; IR (neat, cm^{-1}) 2980, 2940, 2920, 2870, 1705, 1580, 1476, 1455, 1435, 1400, 1372, 1328, 1295, 1255, 1235, 1220, 1085, 1025, 993, 950, 905, 740, 690; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34–7.11 (m, 5 H), 3.53 (dd, J = 13.0, 4.6 Hz, 1 H), 2.90 (dd, J = 13.0, 9.4 Hz, 1 H), 2.38–2.02 (m, 3 H), 1.55–1.33 (m, 1 H), 1.07 (s, 3 H), 1.00 (s, 3 H), 1.1–0.85 (m, 1 H), 0.61 (t, J = 7.4 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 212.95, 136.59, 128.64, 128.31, 125.48, 44.83, 37.39, 33.55, 27.65, 26.29, 22.12, 20.69, 18.30, 14.74; MS m/z (M^+) calcd 260.1235, obsd 260.1249; $[\alpha]^{20}_D$ +207° (c 2.84, C_6H_6).

Tosylhydrazone Formation Involving 37. A mixture of **37** (319 mg, 1.23 mmol) and tosylhydrazine (227 mg, 1.23 mmol) in 0.5 mL of methanol was allowed to stand at room temperature with occasional swirling during 2.5 h. In the process, a clear solution developed, and crystallization of a white solid occurred. The methanol was evaporated under high vacuum to leave tosylhydrazone **41** in pure condition (515 mg, 98%): IR ($CHCl_3$, cm^{-1}) 3400, 3280, 3210, 3020, 3000, 2970, 2940, 2860, 1620, 1595, 1580, 1490, 1475, 1435, 1380, 1330, 1300, 1180, 1160, 1090, 1025, 1000, 955, 910, 810; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84–7.77 (m, 2 H), 7.37–7.14 (m, 7 H), 3.00 (dd, J = 8.0, 2.5 Hz, 2 H), 2.53–2.42 (m, 1 H), 2.40 (s, 3 H), 2.28–2.05 (m, 3 H), 1.56–1.40 (m, 2 H), 1.00 (s, 3 H), 0.93–0.67 (m, 2 H), 0.70 (s, 3 H); $[\alpha]^{20}_D$ +11.2° (c 1.21, CH_2Cl_2).

Upon standing in ether or $CDCl_3$ solution at room temperature, **41** underwent spontaneous equilibration with **42** (ratio 3:2). The characteristic ^{1}H NMR signals of **42** (in $CDCl_3$) appear at δ 3.5–3.4 (m, 2 H), 2.41 (s, 3 H), 0.97 (s, 3 H), and 0.66 (s, 3 H).

(+)-(1*S*,3*R*,5*S*,7*R*)-3-((Trimethylsilyl)oxy)-7,7-dimethyltricyclo[5.1.0.0^{3,5}]octane (39). The zinc–silver couple was prepared according to Denis[38] from 2 mg of silver acetate and 169 mg (2.6 mmol) of granulated zinc. The couple was added to a solution of diiodomethane (352 mg, 1.30 mmol) in dry ether (5 mL) and stirred at room temperature for 1 h. Following the addition of **34** (210 mg, 1.0 mmol), the mixture was heated at reflux for 14 h. Pyridine (129 μL, 1.60 mmol) was introduced, the solids were removed by filtration, and the solvent was evaporated. The residue was purified by silica gel chromatography (elution with 1.5% ethyl acetate in petroleum ether) to give 69 mg (31%) of **39** as a colorless oil: IR (neat, cm^{-1}) 2980, 2940, 2900, 2850, 1445, 1430, 1365, 1320, 1245, 1180, 1085, 1015, 995, 975, 855, 835; ^{1}H NMR (300 MHz, C_6D_6) δ 2.31 (dd, J = 14.1, 9.6 Hz, 1 H), 1.92 (ddd, J = 11.7, 9.5, 2.2 Hz, 1 H), 1.59–1.46 (m, 2 H), 1.05–0.96 (m, 1 H), 0.90 (s, 3 H), 0.81 (s, 3 H), 0.80–0.74 (m, 1 H), 0.57 (t, J = 5.5 Hz, 1 H), 0.38–0.30 (m, 1 H), 0.14 (s, 9 H), 0.14–0.07 (m, 1 H); MS m/z (M^+) calcd 224.1596, obsd 224.1607; $[\alpha]^{20}_D$ +97° (c 1.75, C_6H_6).

(1*S*,3*R*,5*S*,7*R*)-7,7-Dimethyltricyclo[5.1.0.0^{3,5}]octan-3-ol (40). A solution of tetra-*n*-butylammonium fluoride in tetrahydrofuran (1.0 M, 103 μL) was added to a solution of **39** (23 mg, 0.103 mmol) in 3 mL of tetrahydrofuran at 0 °C and stirred for 1.5 h. The reaction mixture was diluted with ether, washed with water and brine, dried, and evaporated. Chromatography of the residue on silica gel (elution with 10% ethyl acetate in petroleum ether) afforded 16 mg (96%) of **40** as a colorless oil; IR (neat, cm^{-1}) 3300, 3000, 2990, 2935, 2860, 1470, 1450, 1415, 1375, 1345, 1230, 1200, 1180, 1135, 1110, 1085, 1020, 975, 935, 925, 890, 825; ^{1}H NMR (300 MHz, C_6D_6) δ 2.15 (dd, J = 14.1, 9.6 Hz, 1 H), 1.87 (ddd, J = 14.8, 9.5, 2.0 Hz, 1 H), 1.47–1.10 (m, 4 H), 0.89 (s, 3 H), 0.76 (s, 3 H), 0.64 (dd, J = 9.9, 4.8 Hz, 1 H), 0.46 (t, J = 5.5 Hz, 1 H), 0.37–0.29 (m, 1 H), 0.09–0.03 (m, 1 H).

This cyclopropanol was used without further manipulation.

Acid-Catalyzed Cleavage of 40. To a solution of **40** (20 mg, 0.123 mmol) in 6 mL of methanol was added 5 drops of concentrated hydrochloric acid. After 2 h of stirring at room temperature, much of **40** had remained intact. The mixture was therefore refluxed for 15 min, poured into saturated sodium bicarbonate solution, and extracted with ether. The combined organic layers were washed with brine, dried, and evaporated. Chromatography of the residue on silica gel (elution with 3% ethyl acetate in

petroleum ether) furnished 5 mg of **15** and 10 mg of a mixture of **15** and **27** (total yield 78%). The overall isomer ratio was 3:1. The characteristic ^{1}H NMR peaks for **27** (in $CDCl_3$) appear at δ 1.23 (d, J = 7.2 Hz, 3 H), 1.07 (s, 3 H), and 0.93 (s, 3 H).

(+)-(1*R*,6*R*)-3-(((Trifluoromethyl)sulfonyl)oxy)-7,7-dimethylbicyclo[4.1.0]hept-2-ene (43). A solution of **23** (1.38 g, 10.0 mmol) in cold (−78 °C), anhydrous tetrahydrofuran (10 mL) was treated dropwise with a solution of sodium hexamethyldisilazide in the same solvent (12.2 mL of 0.8 M, 11.0 mmol) and stirred for 1.5 h. To this reaction mixture was introduced dropwise a solution of *N*-phenyltriflimide (3.59 g, 10.5 mmol) in 10 mL of tetrahydrofuran at −78 °C. After 10 min of stirring at this temperature, the cold bath was replaced by an ice bath and agitation was continued for 3 h. The solvent was removed in vacuo, and the residue was eluted in 1% ethyl acetate/petroleum ether through a short silica gel column. Final purification was realized by MPLC (silica gel, elution with petroleum ether) to give **43** as a colorless liquid (1.49 g, 55%); IR (neat, cm^{-1}) 3000, 2940, 2860, 1675, 1450, 1415, 1240, 1205, 1140, 1050, 1000, 925, 880, 870; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.91 (d, J = 5.2 Hz, 1 H), 2.45–2.25 (m, 1 H), 2.20–1.90 (m, 3 H), 1.30–1.15 (m, 1 H), 1.12 (s, 3 H), 1.10–0.85 (m, 1 H), 0.97 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 148.52, 117.68, 28.28, 26.95, 25.28, 22.72, 21.67, 18.62, 14.90; MS m/z (M^+) calcd 270.0537, obsd 270.0551; $[\alpha]^{20}_D$ +10° (*c* 2.08, hexane).

(−)-(1*R*,6*R*)-3-(Trimethylstannyl)-7,7-dimethylbicyclo[4.1.0]hept-2-ene (44). A 50-mL three-necked flask was charged with **43** (1.40 g, 5.51 mmol), lithium chloride (1.58 g, 37.2 mmol), tetrakis(triphenylphosphine)palladium(0) (72.2 mg, 0.062 mmol), hexamethylditin (1.81 g, 5.51 mmol), and tetrahydrofuran (20 mL). The mixture was deoxygenated for 30 min by bubbling argon through and then stirred at 60 °C under argon overnight. The solids were removed by filtration through Celite and rinsed with ether. The filtrate was washed with water and brine, dried, and evaporated. The residue was chromatographed on Florisil (elution with petroleum ether) to give 1.44 g (92%) of **44** as a colorless liquid. Molecular distillation gave a bp of 58–60 °C (0.8 Torr): IR (neat, cm^{-1}) 2980, 2940, 2900, 2850, 1600, 1445, 1370, 1185, 1120, 1060, 980, 865; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.19–6.05 (m, 1 H), 2.22–2.17 (m, 2 H), 1.97–1.80 (m, 2 H), 1.78–1.60 (m, 3 H), 1.09 (s, 3 H), 1.08–1.00 (m, 1 H), 0.91 (s, 3 H), 0.08 (s, 9 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 139.29, 136.17, 28.94, 28.33, 24.50, 24.10, 23.22, 18.07, 15.93, −4.78; MS m/z (M^+) calcd 284.0739, obsd 284.0778; $[\alpha]^{20}_D$ −10.0° (*c* 1.7, hexane).

Anal. Calcd for $C_{12}H_{22}Sn$: C, 20.55; H, 7.78. Found: C, 50.67; H, 7.81.

(+)-(1*S*,6*R*)-7,7-Dimethylbicyclo[4.1.0]heptan-3-one Tosylhydrazone (45): colorless crystals; mp 128 °C (from methanol); IR ($CHCl_3$, cm^{-1}) 3290, 3210, 3000, 2950, 2920, 2860, 1594, 1490, 1455, 1375, 1340, 1320, 1160, 1090, 1020, 920; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, J = 7.9 Hz, 2 H), 7.81 (d, J = 7.9 Hz, 2 H), 7.30 (d, J = 7.9 Hz, 2 H), 7.28 (d, J = 7.9 Hz, 2 H), 2.58–1.77 (m, 12 H), 2.42 (s, 6 H), 1.40–0.75 (m, 6 H), 1.00 (s, 3 H), 0.98 (s, 3 H), 0.93 (s, 3 H), 0.67 (s, 3 H) indicative of an approximate 1:1 ratio of isomers.

Anal. Calcd for $C_{16}H_{22}N_2O_2S$: C, 62.72; H, 7.24. Found: C, 62.86; H, 7.29.

(+)-(1*S*,6*R*)-3-Bromo-7,7-dimethylbicyclo[4.1.0]hept-2-ene (46). Tosylhydrazone **45** (1.00 g, 3.27 mmol) was added in one portion to a cold (−78 °C), mechanically stirred solution of *n*-butyllithium (8.72 mL of 1.5 M in hexanes, 13.1 mmol) in TMEDA (30 mL). Stirring was maintained for 1 h before the cooling bath was removed, and the mixture was allowed to warm slowly to room temperature. After 1 h, the solution was recooled to −78 °C, and 1,2-dibromotetrafluoroethane (3.40 g, 13.1 mmol) was added dropwise. The solution was stirred at −78 °C for 1.5 h, quenched with water (15 mL), and diluted with brine (30 mL). The product was extracted into petroleum ether (3 × 50 mL), and the combined organic phases were washed with 10% hydrochloric acid (2 × 50 mL), saturated sodium bicarbonate solution (2 × 50 mL), and brine prior to drying and evaporation. Chromatography of the residue on Florisil (elution with petroleum ether) afforded 480 mg 73%) of **46** as a colorless oil: IR (neat, cm^{-1}) 3000, 2950, 2920, 2860, 2820, 1660, 1460, 1445, 1435, 1370, 1330, 1280, 1220, 1200, 1130, 1078, 1015, 980, 940, 930, 785; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.91–5.87 (m, 1 H), 2.73–2.62 (m, 1 H), 2.52–2.40 (m, 1 H), 2.35–2.25 (m, 1 H), 2.12–2.03 (m, 1 H), 1.03 (s, 3 H), 0.96–0.75 (m, 1 H), 0.85 (s, 3 H), 0.74–0.62 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 126.59, 121.29, 29.93, 27.95, 23.36, 20.85, 17.12, 15.79, 13.21; MS m/z (M^+) calcd 200.0200, obsd 200.0205; $[\alpha]^{20}_D$ +6.1° (*c* 2.35, C_6H_6).

4-Caranone Tosylhydrazone (47). *n*-Butyllithium (2.30 mL of 1.5 M in hexane, 3.45 mmol) was dissolved in dry TMEDA (10 mL) at −30 °C, stirred for 15 min, and transferred via cannula into a solution of **45** (478 mg, 1.56 mmol) in a cold (−60 °C) mixture of TMEDA (10 mL) and tetrahydrofuran (5 mL). The reaction mixture was stirred at −60 °C for 45 min, at which point methyl iodide (0.48 mL, 7.82 mmol) in 5 mL of dry tetrahydrofuran was introduced. After 1.5 h at −60 to −30 °C, water was added, and the products were extracted into ether (3 × 100 mL). The combined organic phases were washed sequentially with 10% hydrochloric acid (3 × 50 mL), saturated sodium bicarbonate solution (2 × 50 mL), and brine (50 mL) prior to drying and solvent evaporation. Flash chromatography on silica gel (elution with 10–15% ethyl acetate in petroleum ether) afforded 15.4 mg (4%) of **50**, 207 mg (38%, 49% based on recovered **45**) of **47**, and 71 mg (15%) of unreacted **45**.

For **47**: colorless foamy solid; IR ($CHCl_3$, cm^{-1}) 3660, 3440, 3290, 3220, 3020, 3000, 2960, 2930, 2860, 1625, 1595, 1490, 1455, 1375, 1340, 1330, 1305, 1290, 1275, 1230, 1185, 1160, 1095, 1020, 985, 960, 910; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, J = 8.3 Hz, 2 H), 7.29 (d, J = 8.1 Hz, 2 H), 2.44–1.70 (series of m, 3 H), 2.42 (s, 3 H), 1.42 (dt, J = 5.0, 9.6 Hz, 1 H), 1.15–0.9 (m, 2 H), 1.05 (d, J = 7.1 Hz, 3 H), 0.99 (s, 3 H), 0.90–0.65 (m, 2 H), 0.61 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 166.40, 143.72, 135.55, 129,34, 127.85, 35.70, 27.90, 26.13, 21.52, 19.58, 19.05, 18.79, 18.69, 16.77, 14.38; MS m/z (M^+) calcd 320.1558, obsd 320.1541.

(+)-(1*R*,4*R*,6*R*)-3-Bromo-4,7,7-trimethylbicyclo[4.1.0]hept-2-ene (49). *n*-Butyllithium (1.72 mL of 1.5 M in hexane, 2.52 mmol) was added dropwise to a solution of **47** (179 mg, 0.56 mmol) in dry TMEDA (15 mL) at −55 °C. The red solution was stirred at this temperature for 45 min and then allowed to warm to 20 °C during 1.5 h. After recooling to −60 °C, 1,2-dibromotetrafluoroethane (0.296 mL, 2.52 mmol) was introduced quickly, and stirring was continued for 1 h at −60 °C and 1 h at room temperature. The reaction mixture was quenched with water at −30 °C and extracted with petroleum ether. The combined organic extracts were washed with 10% hydrochloric acid, saturated sodium bicarbonate solution, and brine prior to drying and filtration through a small column of alumina. There was isolated 105 mg (87%) of **49** as a colorless liquid. Purification for analysis was achieved by preparative GC (5 ft × 0.25 in., 5% SE 30 on Chromosorb W, 80 °C): IR (neat, cm^{-1}) 2990, 2950, 2930, 2860, 1625, 1450, 1375, 1330, 1235, 1195, 1130, 1040, 980, 965, 940, 920, 870, 810; ^{1}H NMR (300 MHz, C_6D_6) δ 6.02 (d, J = 3.6 Hz, 1 H), 2.20–2.10 (m, 1 H), 1.69 (dt, J = 5.3, 14.4 Hz, 1 H), 1.48 (ddd, J = 3.1, 8.7, 14.4 Hz, 1 H), 1.12 (d, J = 6.9 Hz, 3 H), 0.84 (s, 3 H), 0.82 (s, 3 H), 0.74 (dd, J = 3.8, 8.5 Hz, 1 H), 0.57 (dd, J = 5.1, 8.5 Hz, 1 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 130.56, 127.01, 37.66, 28.23, 27.60, 26.03, 24.25, 20.52, 17.70, 15.29; MS m/z (M^+) calcd 216.0336, obsd 216.0352; $[\alpha]^{20}_D$ +77.2° (*c* 1.70, hexane).

Anal. Calcd for $C_{10}H_{15}Br$: C, 55.81; H, 7.03. Found: C, 56.16; H, 7.16.

4-Isocaranone Tosylhydrazone (50). The hydrogenation of **13** (200 mg, 1.33 mmol) was carried out following a literature method[9] for its enantiomer to give 160 mg (80%) of **15**: IR (neat, cm^{-1}) 3000, 2950, 2920, 2860, 1710, 1455, 1410, 1380, 1290, 1170, 1080, 1040, 990, 920, 810; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.50 (dd, J = 8.2, 17.9 Hz, 1 H), 2.40–2.23 (m, 3 H), 1.29–1.17 (m, 1 H), 1.13–0.80 (m, 3 H); 1.01 (s, 3 H), 0.92 (dd, J = 1.2, 6.5 Hz, 3 H), 0.82 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 216.4, 41.9, 36.8, 29.7, 27.9, 22.8, 20.3, 19.4, 14.8, 14.1; MS m/z (M^+) calcd 152.1201, obsd 152.1189; $[\alpha]^{20}_D$ +101° (*c* 4.01, hexane).

In accordance with a literature procedure,[17] **15** (429 mg, 2.83 mmol) and tosylhydrazide (523 mg, 2.83 mmol) were heated in dry methanol (15 mL) at reflux for 3 h. Following solvent evaporation and silica gel chromatography (elution with 10% ethyl acetate in petroleum ether), there was isolated 425 mg (47%) of **50** and 38 mg (4%) of **47**.

For **50**: colorless crystals, mp 128 °C dec; IR ($CHCl_3$, cm^{-1}) 3295, 3215, 3025, 3005, 2960, 2925, 2865, 1700, 1625, 1600, 1495, 1455, 1380, 1335, 1310, 1295, 1190, 1170, 1095, 1050, 1010, 920;

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, J = 8.2 Hz, 2 H), 7.28 (d, J = 8.1 Hz, 1 H), 2.42 (s, 3 H), 2.31–2.06 (m, 3 H), 1.25–0.70 (series of m, 3 H), 0.97 (s, 3 H), 0.97 (d, J = 6.1 Hz, 3 H), 0.62 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 164.08, 143.67, 135.30, 129.15, 128.15, 36.14, 29.18, 27.83, 22.30, 21.52, 20.58, 19.48, 18.58, 16.22, 14.48; MS m/z (M^+) calcd 320.1559, obsd 320.1527; $[\alpha]^{20}_D$ +127° (c 1.27, CH_2Cl_2).

(+)-(1*R*,4*S*,6*R*)-3-Bromo-4,7,7-trimethylbicyclo[4.1.0]hept-2-ene (51). *n*-Butyllithium (1.32 mL of 1.5 M in hexane, 1.98 mmol) was added dropwise to a solution of **50** (141 mg, 0.44 mmol) in dry TMEDA (10 mL) at −55 °C. The reaction mixture was stirred at this temperature for 45 min and allowed to warm to 20 °C during 2 h. Following cooling to −60 °C, 1,2-dibromotetrafluoroethane (0.233 mL, 1.98 mmol) was introduced in one portion, and stirring was maintained at −60 °C for 1 h and at 20 °C for 1 h. The usual workup was applied (see **49**) to give 47 mg (50%) of **51** as a colorless liquid. Purification for analysis was accomplished by preparative GC as before: IR (neat, cm^{-1}) 3030, 3000, 2965, 2950, 2930, 2860, 1625, 1450, 1380, 1335, 1235, 1130, 1050, 1005, 990, 970, 950, 870, 835; ^{1}H NMR (300 MHz, C_6D_6) δ 6.14 (t, J = 3.1 Hz, 1 H), 2.46–2.30 (m, 1 H), 1.90–1.79 (m, 1 H), 1.25–1.05 (m, 1 H), 1.03 (d, J = 7.0 Hz, 3 H), 0.85 (s, 3 H), 0.83 (s, 3 H), 0.78–0.60 (m, 2 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 128.58, 127.47, 33.30, 30.48, 27.32, 26.58, 24.71, 22.30, 20.46, 15.35; MS m/z (M^+) calcd 216.0337, obsd 216.0349; $[\alpha]^{20}_D$ +80° (c 0.82, hexane).

Anal. Calcd for $C_{10}H_{15}Br$: C, 55.81; H, 7.03. Found: C, 55.93; H, 7.07.

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Registry No. **4**, 498-15-7; **13**, 88390-11-8; **15**, 52153-58-9; **19**, 936-91-4; **20**, 4017-83-8; **21**, 5114-01-2; **21** (tosylhydrazone), 124719-01-3; **22**, 6909-01-9; **23**, 22327-37-3; **24**, 10309-64-5; **25**, 73582-90-8; **26**, 124719-02-4; **26** (tosylhydrazone), 124719-03-5; **27**, 124-73-2; **28**, 124719-04-6; (±)-**29**, 124719-05-7; **30**, 124719-06-8; **31**, 124817-19-2; **32**, 124719-07-9; **33**, 124719-08-0; **34**, 124719-09-1; **35**, 124817-20-5; **36**, 52153-58-9; **37**, 124719-10-4; **38**, 124719-11-5; **39**, 124719-13-7; **40**, 124719-14-8; **41**, 124719-12-6; **43**, 124719-15-9; **44**, 124719-16-0; (*E*)-**45**, 124719-17-1; (*Z*)-**45**, 124719-21-7; **46**, 124719-18-2; **47**, 124817-22-7; **48**, 124817-23-8; **49**, 124719-19-3; **50**, 124817-21-6; **51**, 124719-20-6; $ClCH_2SPh$, 7205-91-6; 2-cyclohexen-1-one, 930-68-7.

Supplementary Material Available: ^{1}H NMR and ^{13}C NMR spectra for compounds **15**, **21**, **26–35**, **38–41**, **43**, **46**, **47**, and **50** (31 pages). Ordering information is given on any current masthead page.

[4.4.4]Propellahexaene by Triple Shapiro Degradation. Structural and Electronic Properties of This Maximally Unsaturated Hydrocarbon and Consequences of O-Methylation of Its [4.4.4]Propellatrienetrione Precursors

Leo A. Paquette,* Shaowo Liang, Liladhar Waykole, George DeLucca, Heiner Jendralla, Robin D. Rogers,[1a] Detlef Kratz,[1b] and Rolf Gleiter[1b]

Evans Chemical Laboratories, The Ohio State University, Columbus, Ohio 43210, Department of Chemistry, Northern Illinois University, DeKalb, Illinois 60115, and Institut für Organische Chemie der Universität Heidelberg, D-6900 Heidelberg, West Germany

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The trienetriones **6** and **7** were prepared and transformed into their tris(phenylsulfonyl)hydrazones to arrive at the title hydrocarbon (**5**). These derivatives were subjected in turn to triple Shapiro degradation. The D_3 symmetric nature of the resulting hexaene was suggested by its NMR spectra and corroborated by X-ray crystallographic analysis. When this molecule is viewed down its central C–C bond, its dramatic propeller-like shape is made evident. Thermochemical experiments established **5** to be a rather stable substance. Photoelectron spectroscopic studies involving **5** and its less unsaturated analogues **24** and **25** are also detailed. By this means, the electronic structure of **5** was shown to be such that there are no σ-MO's amid its high-lying π MO's. MNDO calculations for **5** predict the central bond to be 1.61 Å (experimental value = 1.57 Å). Also described are experiments detailing the fate of both **7** and its C_{3v} symmetric isomer **6** on attempted 3-fold O-methylation. In the first instance, the major product happens to be 3,6,9-trimethoxyphenanthrene (**42**). Skeletal rearrangement is not encountered with **6**. Rather, the major product is dimethoxy enone **39**, which is accompanied by lesser amounts of 2,7-dimethoxynaphthalene (**40**). On further processing of **39**, fragmentation to **40** occurs to a major extent, although it has proven possible to acquire limited amounts of the trimethoxy hexaene **41**. The interesting divergence in chemical response exhibited by **6** and **7** has no parallel. Finally, the relative rates and stereochemical course (where relevant) of the Diels–Alder reaction of *N*-methyltriazolinedione (MTAD) with **5**, **24**, and **25** are reported. The reactivity order is **5** > **24** > **25**, the hexaene being consumed instantaneously on mixing at room temperature. The facial selectivity exhibited by **24** during its initial capture by MTAD is best rationalized in terms of steric control. Like considerations apply to the pathways followed by **44**, **45** and **5** in their reactions with the same dienophile. Consequently, orbital symmetry considerations do not appear to play a major role in these processes.

The larger fully unsaturated propellanes constitute a formidable challenge to those who would undertake their synthesis. At the purely chemical level, an increase in the extent of functionalization in any or all of the three constituent rings often results in the immediate onset of reactions seriously detrimental to acquisition of the particular target molecule. The intramolecular [4 + 2] capture of the cyclohexadiene subunit in **1**, a relatively rapid process at room temperature, is illustrative of the problem.[2]

(1) (a) Northern Illinois University. Author to whom inquiries regarding the X-ray crystallographic analysis should be directed. (b) Institut für Organische Chemie Heidelberg. Authors responsible for the photoelectron spectroscopy studies and associated calculations.

(2) (a) Paquette, L. A.; Jendralla, H.; DeLucca, G. *J. Am. Chem. Soc.* **1984**, *106*, 1518. (b) Jendralla, H.; Jelich, K.; DeLucca, G.; Paquette, L. A. *Ibid.* **1986**, *108*, 3731.

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