mmol) tri-*n*-butyltin hydride in 8 mL of dry benzene via syringe pump at a rate of 1 mL h^{-1}. The solvent was removed in vacuo. The residue was chromatographed over 20 g of silica gel (eluted with ethyl acetate–hexane; 1:6) to give 193 mg (89%) of a 4:1 mixture of **47** and **48**. The ratio of **47**:**48** was determined by integration of peaks at δ 1.44 and 1.41: IR (neat mixture) 1785, 1745 cm^{-1}; ^1H NMR (CCl_4) δ 1.44 (s, 12 H, CH_3 and *t*-Bu), 1.6–2.9 (m, 10 H), 5.63 (dm, J = 9, 3 Hz, 1 H, =CH), 5.82 (dt, J = 9, 3 Hz, 1 H, =CH); mass spectrum, *m/e* (relative intensity) 219 (10, M – OC_4H_9), 192 (83), 133 (51), 131 (100), 117 (50), 105 (39), 91 (30).

***rel*-(1*S*,5*S*,6*S*,7*S*)-10-(*tert*-Butoxycarbonyl)-1-hydroxy-5-methyltricyclo[6.2.1.0^{1,6}]undec-3-en-11-one (50).** To a solution of 994 mg (6.18 mmol) of 1,1,1,3,3,3-hexamethyldisilazane in 10 mL of ether cooled in an ice–water bath was added 3.3 mL (5.28 mmol) of 1.6 M *n*-butyllithium in hexane dropwise over a 10-min period. The reaction temperature was increased to reflux and a solution of 159 mg (0.54 mmol) of **48** and **49** (4:1, respectively) in 50 mL of ether was added dropwise over a 1.5-h period. The reaction mixture was heated under reflux for another 1 h and then cooled to room temperature. To this mixture was added 5 mL of acetic acid dropwise over a 5-min period. The reaction mixture was diluted with 100 mL of ether, washed with three 100-mL portions of brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed over 10 g of silica gel (eluted with ethyl acetate–hexane, 1:4) to give 113 mg (71%) of **50**: mp 99–101 °C; IR (CH_2Cl_2) 3570, 1750, 1720 cm^{-1}; ^1H NMR (CCl_4) δ 1.15 (s, 3 H, CH_3), 1.45 (s, 9 H, *t*-Bu), 1.4–2.4 (m, 8 H), 3.1 (m, 1 H), 3.25 (d, J = 7 Hz, 1 H, COCHCO), 5.73 (dt, J = 9, 3 Hz, 1 H, =CH), 5.97 (dm, J = 9 Hz, 1 H, =CH); ^{13}C NMR ($CDCl_3$) δ 22.6 (q), 28.1 (a), 31.3 (t), 36.5 (overlapping t and d), 38.0 (t), 51.4 (s), 56.2 (d), 64.5 (d), 78.3 (s), 81.5 (s), 125.1 (d), 132.7 (d), 169.9 (s), 212.5 (s); mass spectrum, *m/e* (relative intensity) 236 (8, M – C_4H_8), 201 (9), 132 (100), 117 (46), 105 (22), 91 (20), 57 (23).

Acknowledgment. We thank the National Science Foundation (CHE-8508726) for their generous support. We thank Dr. Charles Cottrell and Mr. Richard Weisenberger for assistance in recording NMR and mass spectra at The Ohio State University Chemical Instrumentation Center.

Supplementary Material Available: Crystallographic details and ORTEP drawings for compounds **23a** and **26** (15 pages). Ordering information is given on any current masthead page.

Observations Regarding the Regiochemical and Stereochemical Course of the Cyclization of Complex 5-Hexenyl Radicals: An Approach to Perhydronaphthalenes

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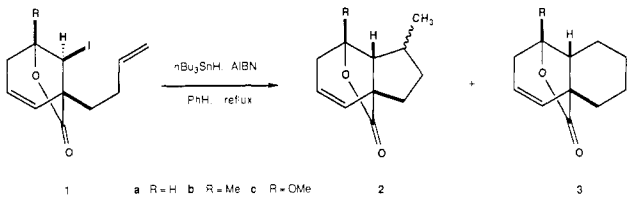
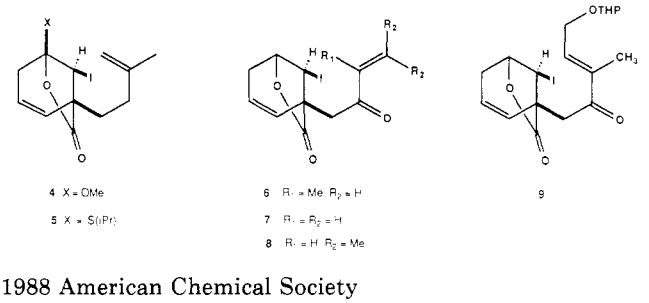
Received December 1, 1987

Iodo lactones **4** and **5** were prepared from *m*-anisic acid (**10**) and *m*-(isopropylthio)benzoic acid (**15**), respectively, by using a reductive alkylation–halolactonization–free radical cyclization sequence. Enones **6–9** were prepared from benzoic acid by way of acid chloride **30** by using a palladium-catalyzed coupling reaction. Tri-*n*-butyltin hydride mediated cyclization of **4–7** and **9** afforded substituted perhydronaphthalenes with good stereoselectivity. The radical derived from enone **8** gave perhydroindan **40**. A transition-state geometry for the cyclization of enones **6–9** is proposed.

It has long been known that the parent 5-hexenyl radical undergoes an irreversible cyclization to afford approximately a 50:1 mixture of cyclopentylmethyl and cyclohexyl radicals, the products derived from exo and endo cyclization, respectively.[2] Studies by Beckwith,[3] Walling,[4] and Julia[5] have shown that C(5) alkyl substituents retard the rate of five-membered ring closure by a factor of about 45 while doubling the rate of six-membered ring formation. Thus, the 5-methyl-5-hexenyl radical affords a 1.6:1 mixture of endo and exo cyclization products, respectively.[3] In the preceding article we reported several examples of 5-hexenyl radical cyclizations that proceed with surprisingly small exo/endo cyclization ratios.[6] For example, tri-*n*-butyltin hydride mediated cyclization of perhydroindans **1a–c** gave nearly equal amounts of perhydroindans



2a–c and perhydronaphthalenes **3a–c**. It was also shown that placing electron-withdrawing groups on the olefin terminus directed the course of cyclization toward perhydroindan formation. This paper describes the effect of internal olefin substituents, including electron-withdrawing groups, on the regiochemical and stereochemical course of the reaction. Specifically, the preparation and cyclization of iodo lactones **4–9** is described.[7]



(1) (a) Author to whom questions regarding crystallographic details should be addressed. (b) Alfred P. Sloan Foundation Fellow, 1983–1987.

(2) For reviews, see: Wilt, J. W. In *Free Radicals*; Kochi, J., Ed.; Wiley-Interscience: New York, 1973; Vol. 1, pp 418–446. Beckwith, A. L. J.; Ingold, K. U. In *Rearrangements in Ground and Excited States*; deMayo, P., Ed.; Academic Press: New York, 1980; Vol. 1, pp 182–219. Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073. Surzur, J.-M. In *Reactive Intermediates*; Abramovitch, R. A., Ed.: Plenum: New York; 1982, pp 121–295.

(3) Beckwith, A. L. J.; Blair, A. I.; Phillipou, G. *Tetrahedron Lett.* **1974**, 2251.

(4) Walling, C.; Cioffari, A. *J. Am. Chem. Soc.* **1972**, *94*, 6059.

(5) Julia, M.; Decoins, C.; Baillarge, M.; Jacquet, B.; Ugen, D.; Groeger, F. A. *Tetrahedron* **1975**, *31*, 1737.

(6) Chuang, C.-P.; Gallucci, J. C.; Hart, D. J. *J. Org. Chem.*, preceding paper in this issue. Also see Chuang, C.-P.; Hart, D. J. *J. Org. Chem.* **1983**, *48*, 1784.

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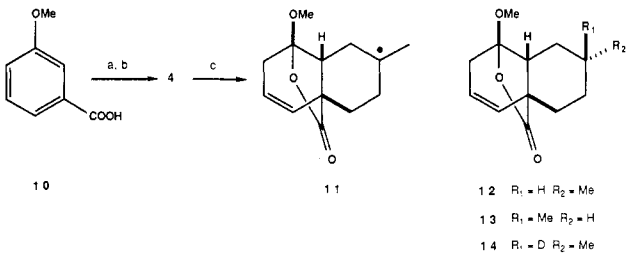
Scheme I[a]

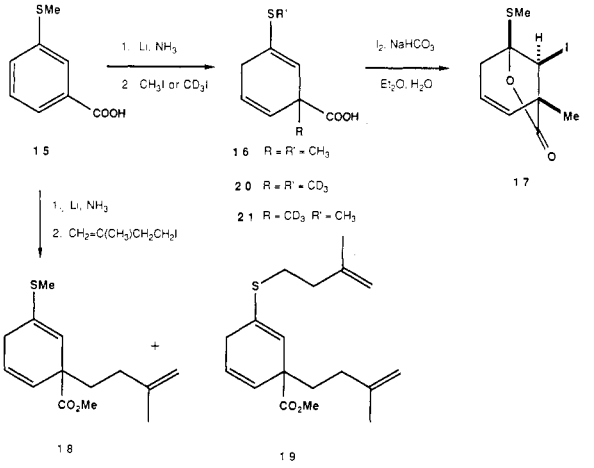


[a] (a) Li, NH_3; $CH_2{=}C(CH_3)CH_2CH_2I$; (b) $NaHCO_3$, I_2, H_2O, Et_2O; (c) *n*-Bu_3SnH, AIBN, PhH, reflux.

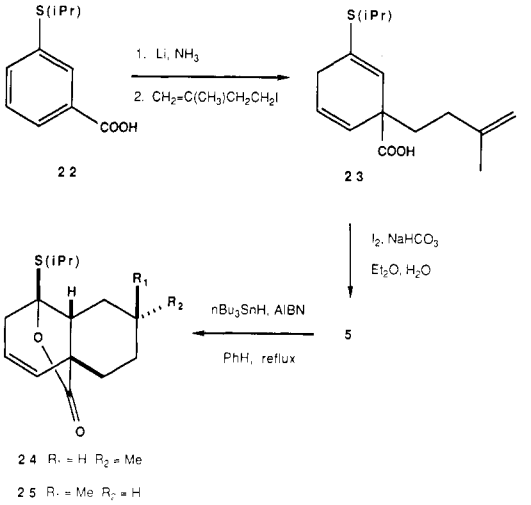
Internal Alkyl Substitution: Preparation and Cyclization of Iodo Lactones 4 and 5. Based on the aforementioned substituent studies[2-5] and the results obtained with **1c**,[6] it was expected that internal alkyl substitution would direct the course of cyclization toward perhydronaphthalenes. This was borne out by the study outlined in Scheme I. Reductive alkylation[8] of *m*-anisic acid with 1-iodo-3-methyl-3-butene[9] followed by halolactonization[10] of the resulting dihydrobenzoic acid gave iodo lactone **4** in 62% overall yield. Treatment of **4** with tri-*n*-butyltin hydride and AIBN in benzene under reflux gave an 85% yield of a 5:1 mixture of **12** and **13**, respectively. Although these compounds could not be separated on a large scale, pure samples of each diastereomer were obtained by preparative gas chromatography. The stereochemistry at C(8a) of **12** was assigned by analogy with the firmly established stereochemical course of the cyclization of **1b**.[6] The stereochemistry at C(7) was established by ^1H NMR. Thus, the C(7) proton was shown to occupy an axial site on the basis of its 13-Hz couplings to H_{6a} and H_{8a}. The preparation of **14**, an isotopically labeled version of **12**, aided in the assignment of signals and couplings.[12] The stereochemical course of this transformation is consistent with initial formation of radical **11** followed by predominant axial delivery of a hydrogen atom by tri-*n*-butyltin hydride. Similar stereochemical results have been reported for the reduction of the 4-*tert*-butyl-1-(acetoxymethyl)cyclohexyl radical.[13]

The preceding study demonstrated that reductive alkylation–halolactonization–free radical cyclization of benzoic acids would provide a route to certain functionalized perhydronaphthalenes. An obvious limitation to this procedure, however, was that the benzoic acid must be substituted such that substituents direct the halolactonization to the six-membered ring rather the unsaturated side chain. For example, the use of benzoic acid itself in this sequence would be problematic because the halolactonization would be expected to occur on the side chain.[6] Since potential applications required routes to 2*H*-1,4a-(epoxymethano)perhydronaphthalenes lacking

Scheme II



Scheme III



C(1) substitution, the use of *m*-(alkylthio)benzoic acids in the annelation sequence was examined (Schemes II and III). It was expected that the alkylthio group would control the regiochemical course of the halolactonization while serving as a latent proton.

At the onset of this study there was concern that treatment of *m*-(alkylthio)benzoic acids with lithium in ammonia would simply afford the dianion of 1,4-dihydrobenzoic acid due to expulsion of alkylthioate or alkylthiyl radical from an intermediate radical anion.[14] Fortunately this was not the case as sequential treatment of 3-(methylthio)benzoic acid (**15**)[15] with lithium in ammonia and methyl iodide gave dihydrobenzoic acid **16** in 62% yield.[16] Furthermore, treatment of **16** with iodine in ether gave iodo lactone **17** in 51% yield. We next examined the reductive alkylation of **15** with 1-iodo-3-methyl-3-butene. It was a surprise to find that an inseparable mixture of two carboxylic acids was obtained in 60% yield. The mixture was treated with diazomethane

(7) Portions of this work are taken from the Ph.D. Theses of C.-P. Chuang (1984) and C. Hoffman (1987), The Ohio State University.

(8) Birch, A. J.; Smith, H. *Q. Rev. Chem. Soc.* **1958**, *12*, 17. vanBekkum, H.; van den Bosch, C. B.; van Minnenpathius, G.; de Moss, J. C.; van Wijk, A. M. *Recl. Trav. Chim. Pays-Bas* **1971**, *90*, 137.

(9) Trost, B. M.; Kunz, R. A. *J. Am. Chem. Soc.* **1975**, *97*, 7152.

(10) Staninets, V. I.; Shilov, E. A. *Russ. Chem. Rev. (Engl. Transl.)* **1971**, *40*, 272. Barnett, W. E.; Needham, L. L. *J. Org. Chem.* **1975**, *40*, 2843. Holbert, G. W.; Weiss, L. B.; Ganem, B. *Tetrahedron Lett.* **1976**, 4435.

(11) Kuivila, H. G. *Acc. Chem. Res.* **1968**, *1*, 299. Kuivila, H. G. *Synthesis* **1970**, 499.

(12) Treatment of **4** with triphenyltin hydride[11] gave a 6:1 mixture of **12** and **13**, respectively.

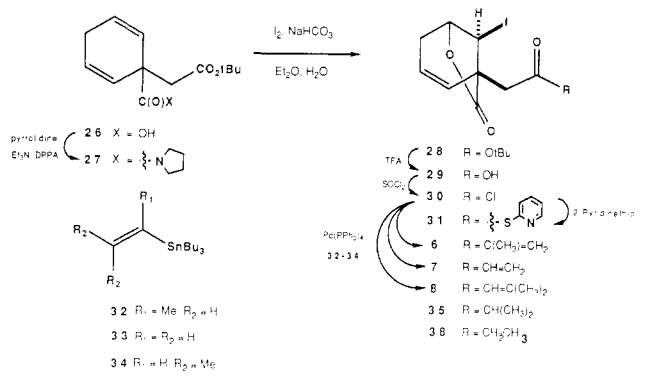
(13) Baumberger, F.; Vasella, A. *Helv. Chim. Acta* **1983**, *66*, 2210.

(14) Bunnett, J. F. *Acc. Chem. Res.* **1978**, *11*, 413.

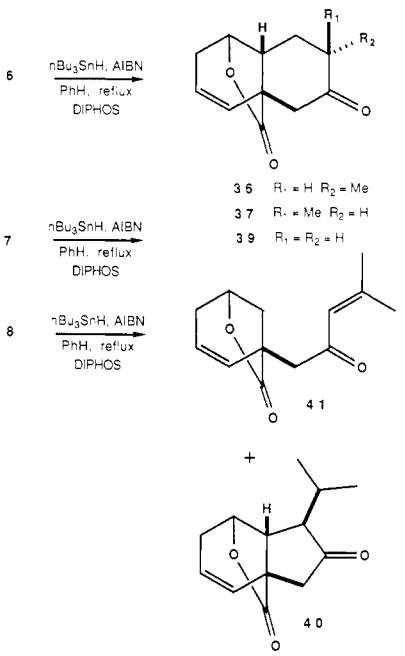
(15) Prepared in 45% yield from 3-aminobenzoic acid by using a modification of the procedure of Senning, A.; Lawesson, S. *Acta Chem. Scand.* **1960**, *14*, 2230.

(16) Treatment of either 2-(methylthio)benzoic acid (Arndt, F.; Kirsch, A.; Nachtwey, P. *Ber. Deutsch. Chem. Ges.* **1926**, *59*, 1074) or 2-(isopropylthio)benzoic acid (Gilman, H.; Webb, F. J. *J. Am. Chem. Soc.* **1949**, *71*, 4062. Oae, S.; Numata, T. *Tetrahedron* **1974**, *30*, 2641) with lithium in ammonia followed by methyl iodide (as described for **15** in the Experimental Section) gave 1-methylcyclohexa-2,5-diene-1-carboxylic acid in good yield. Thus, reductive alkylation of 2-(alkylthio)benzoic acids with retention of sulfur is problematic.

Scheme IV



Scheme V



to afford a separable 4:1 mixture of esters **18** and **19**, respectively. Apparently cleavage of the S–methyl bond occured to some extent during the course of the reduction.[17] In fact, reexamination of the conversion of **15** to **16** using methyl iodide-d_3 as the alkylating agent gave an 8:1 mixture of **20** and **21**, respectively, indicating once again that S–methyl cleavage was taking place.

Fortunately, it was quickly discovered that 3-(isopropylthio)benzoic acid (**22**)[18] underwent clean reductive alkylation to afford carboxylic acid **23** in 84% yield.[19] Halolactonization of **23** proceeded smoothly to give radical precursor **5** (67%) and the radical cyclization also went as expected to give an 80% yield of an 8:1 mixture of **24** and **25**, respectively. Unfortunately, attempts to reduce the carbon–sulfur bond in **24** without disturbing other functional groups met with failure.[20]

Internal Electron-Withdrawing Groups: Preparation and Cyclization of Iodo Lactones 6–8. In an attempt to introduce additional functionality into the perhydronaphthalene nucleus and determine the effect of an electron-withdrawing substituent on the course of cyclization, enones **6–8** were examined. The syntheses of **6–8** were initially problematic, but a suitable route was eventually developed as outlined in Scheme IV. Reductive alkylation of benzoic acid with *tert*-butyl bromoacetate gave acid **26**. Treatment of **26** with pyrrolidine and diphenyl phosphorazidate[21] gave amide **27**, which was converted to iodo lactone **28** (40% from benzoic acid) by using iodine in aqueous tetrahydrofuran. Ester **28** was then converted to acid **29** (97%) and subsequently acid chloride **30** (97%) and thioester **31** (65%) by using straightforward procedures.

Initial attempts to convert **30** and **31** to **6–8** were discouraging. For example, treatment of **31** and **30** with isopropenylmagnesium bromide at low temperatures did afford **6**, but in only 32% and 11% yields, respectively.[22] Furthermore, **30** and **31** failed to give **7** upon exposure to vinylmagnesium bromide. The Stille enone synthesis was ultimately used to prepare **6**, **7**, and **8** in modest yields.[23]

Thus, treatment of acid chloride **30** with vinylic stannanes **32**, **33**, and **34** in the presence of 1–3 mol % of tetrakis(triphenylphosphine)palladium(0) gave enones **6** (40%), **7** (65%), and **8** (34%).[24]

The operational details of accomplishing the free radical cyclization of enones **6–8** proved to be quite interesting. When iodo lactone **6**, prepared by using the Stille procedure, was subjected to typical radical cyclization conditions (n-Bu_3SnH, AIBN, benzene, reflux), only reduction product **35** (76%) was obtained. The retention of iodine in **35** suggested that free radical chemistry was somehow being inhibited. Furthermore, this result (**6** → **35**) was surprising in that treatment of **6** prepared from acid chloride **30** and isopropenylmagnesium bromide did afford cyclization products and no **35** under the same conditions. These results, and others,[25] implied that a palladium impurity was promoting enone hydrostannylation of **6** at the expense of free radical chemistry.[26] This was occuring even though the **6** being employed had been chromatographed and recrystallized to analytical purity. A trivial solution to this problem was ultimately developed. When 1–3 mol % of 1,2-bis(diphenylphosphino)ethane (DIPHOS) was added to the cyclization media, only trace amounts of **35** were produced and a 6:1 mixture of **36** and **37**, respectively, was obtained in 80% yield (Scheme V).[27] This result was satisfying from an operational standpoint and also supported the notion that a palladium impurity was the culprit in early attempts to effect the free radical cyclization of **6**.

(17) Lithium–ammonia reduction of the S–alkyl bond in alkyl vinyl sulfides is known: Brandsma, L.; Schuijl, P. J. W. *Recl. Trav. Chim. Pays-Bas* **1969**, *88*, 513.

(18) Prepared in 50% yield from 3-aminobenzoic acid via the following sequence: (i) $NaNO_2$, HCl, H_2O; (ii) $EtOC(S)S^-K^+$; (iii) KOH; (iv) 2-iodopropane.

(19) The reasons behind the difference in behavior of **15** and **22** are unclear.

(20) It was possible to reduce the C–S bond with W-2 Raney nickel in modest yield, but this was accompanied by reduction of the double bond.

(21) Shioiri, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.* **1972**, *94*, 6203.

(22) Araki, M.; Sakata, S.; Takei, H.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1974**, 1777.

(23) Labadie, J. W.; Tueting, D.; Stille, J. K. *J. Org. Chem.* **1983**, *48*, 4634. Kosugi, M.; Shimizu, Y.; Migita, T. *Chem. Lett.* **1977**, 1423.

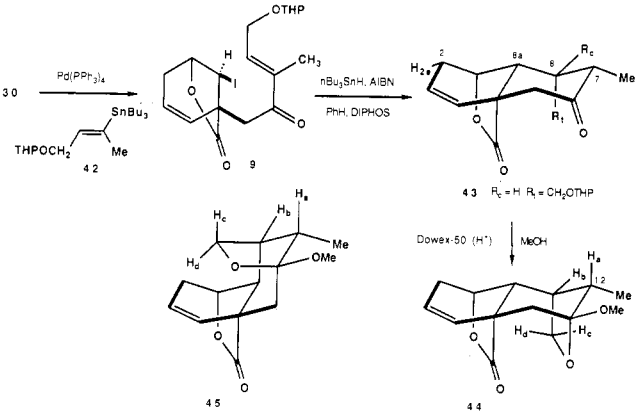
(24) Vinylstannane **32** was commercially available. Compound **33** was prepared in 82% yield from isopropenylmagnesium bromide and tri-n-butyltin chloride. Vinylstannane **34** (Saihi, M. L.; Pereyre, M. *Bull. Soc. Chim. Fr.* **1977**, 1251) was prepared in 85% yield by treating 1-bromo-2-methylpropene with *tert*-butyllithium and tri-n-butyltin triflate in sequence. For the preparation and use of organotin reagents, see: Stille, J. K. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508.

(25) For example, treatment of a mixture of **5** and **6** (from **30** + **32**) with n-Bu_3SnH–AIBN gave **35** and returned **5** unchanged. The possibility of glassware contamination was considered and attempts to cyclize **6** in virgin glassware also failed.

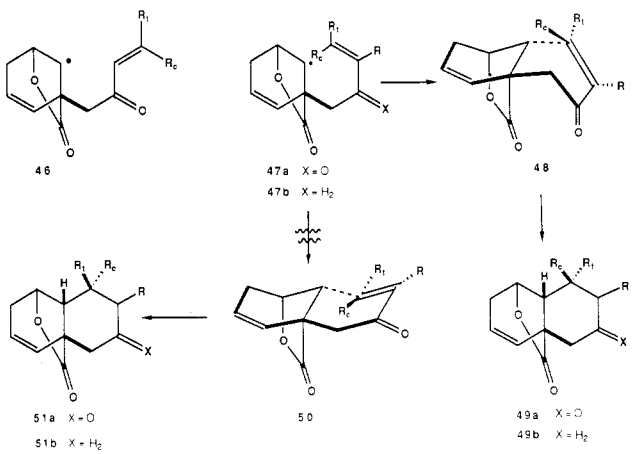
(26) Gleize, P. A.; Keinan, E. *Tetrahedron Lett.* **1982**, *23*, 477. Kogure, T.; Nagai, Y.; Ojima, I. *Tetrahedron Lett.* **1972**, 5035.

(27) The structure of **36** was confirmed by X-ray crystallography. Details are reported in the supplementary material.

Scheme VI



Scheme VII



The aforementioned observations were not restricted to **6**. Treatment of iodo lactone **7** with tri-*n*-butyltin hydride and AIBN gave no cyclization product as ketone **38** was obtained in 52% yield. When DIPHOS was added to the reaction mixture, **38** was not detected and perhydronaphthalene **39** was obtained in 30% yield. It is notable that no exo cyclization product was found in the product mixture. Thus, it appears that the carbonyl group does influence exo–endo partitioning in this system.

Finally, the cyclization of **8** gave perhydroindan **40** (36%) and reduction product **41** (16%), an indication that the influence of the carbonyl group is not strong enough to override steric effects already documented for simple 5-hexenyl radicals.[28]

Stereochemical Observations: Cyclization of 9. As part of a larger synthetic problem, and to gain insight into stereochemical aspects of the aforementioned cyclizations, the preparation and cyclization of iodo lactone **9** was examined as shown in Scheme VI. Vinylstannane **42** was coupled with acid chloride **30** to give enone **9** in a 26% yield.[29] Free radical cyclization of **9** gave perhydronaphthalene **43** in 60% yield as a 1:1 mixture of isomers, suspected to be epimeric at the tetrahydropyranyl group. It was shown that $J_{8,8a}$ was 6 Hz and $J_{7,8}$ was 5 Hz in each diastereomer, consistent with the assigned stereochemistry at C(7), C(8), and C(8a). The ring-juncture stereochemistry was assigned by analogy with the stereochemical results established for the cyclizations of **1b** and **6** and was supported by the absence of W coupling between H_{8a} and H_{2e}, a coupling frequently observed in 6-oxabicyclo[3.2.1]oct-2-en-7-ones bearing 8-substituents anti to the lactone bridge.[30] Further evidence for the structure of **43** was obtained when hydrolysis of the tetrahydropyranyl group with acidic Dowex-50 in methanol gave an 86% yield of ketal **44** as a single stereoisomer. Difference NOE experiments conducted on **44** also supported the assignment of stereochemistry at C(7) and C(8a) in **43**.[31] Thus, irradiation of the C(12) methyl group produced enhancement of the signals due to H_a, H_b, and H_c, all of which are expected if the methyl group is equatorial. Furthermore, irradiation of H_d resulted in enhancement only at H_c, a result that is consistent with **44** but inconsistent with alternative structure **45**.[32]

Discussion and Conclusions. A unified picture of the cyclizations of enones **6–9** is represented in Scheme VII. First, it appears that the enone carbonyl group plays a role in determining the cyclization regiochemistry. This conclusion is based on the fact that **1a** affords a 2:1 ratio of exo and endo cyclization products, respectively, while **7** gives only the endo cyclization product **39**. Data were not obtained to determine that the change in exo/endo partitioning was due to an enhancement of the endo cyclization rate. Nonetheless, we tentatively attribute the observed change to the known acceleration of radical addition by electron-withdrawing groups[33] and assume that overlap is being maintained between the olefin and carbonyl π-bonds in the cyclization transition state. Such overlap is possible in two enone conformations.[34] The cis conformation **46** cannot undergo endo cyclization with maintenance of overlap. On the other hand, the trans conformation **47a** could afford either exo or endo cyclization products. It appears that as long as R_c is a hydrogen, perhydronaphthalene formation will be observed. As stated before, we suggest that this occurs via a transition state which maintains π-overlap. From the one stereochemically defined system examined here (**9** → **43**), it seems transition state **48**, which ultimately gives **49a**, is preferred over transition state **50**. Perhaps the reason that systems were R_c is an alkyl group fail to afford perhydronaphthalenes is due to the development of a transannular interaction in transition state **48**.[35]

Finally, current models proposed for endo 5-hexenyl radical cyclization of systems related to **4** and **5** suggest that these substrates cyclize via chair-like transition states.[36] This leads to the testable prediction that ap-

(28) For other relevant studies that probe the influence of a carbonyl group on the cyclization of a 5-hexenyl radical, see: Danishefsky, S.; Chackalamannil, S.; Uang, B.-J. *J. Org. Chem.* **1982**, *47*, 2231. Danishefsky, S.; Tamiyama, E. *Tetrahedron Lett.* **1983**, *24*, 15. Clive, D. L. J.; Beaulieu, P. L. *J. Chem. Soc., Chem. Commun.* **1983**, 307.

(29) Stannane **42** was prepared from the corresponding vinyl bromide (Corey, E. J.; Bock, M. G.; Kozikowski, A. P.; Rao, A. V. R.; Floyd, D.; Lipshutz, B. *Tetrahedron Lett* **1978**, 1051) in 81% yield as described in the Experimental Section.

(30) For some examples, see ref 6, 7, and Ganem, B.; Holbert, F. W.; Weiss, L. B.; Ishizumi, K. *J. Am. Chem. Soc.* **1978**, *100*, 6483.

(31) For an appropriate discussion, see: Derome, A. E. *Modern NMR Techniques for Chemistry Research*; Pergamon Press: New York, 1987; pp 113–118.

(32) Structure **45** would result from cyclization of the radical derived from **9** on the ring face opposite the lactone bridge followed by subsequent transformations. Compound **45** and its tetrahydropyranyl ether precursor are reasonably consistent with the spectral data observed for **43**. As mentioned, however, the ring juncture stereochemistry would be an exception to what has been observed for similar systems (**1b** and **6**) and couplings and NOE effects expected for **45** are absent.

(33) Park, S.-U.; Chung, S.-K.; Newcomb, M. *J. Am. Chem. Soc.* **1986**, *108*, 240. Giese, B. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 753.

(34) For a discussion of conformational preferences of unsaturated carbonyl compounds, see: Montaudo, G.; Librando, V.; Caccamese, S.; Maravigna, P. *J. Am. Chem. Soc.* **1973**, *95*, 6365.

(35) Compounds of type **49a** prefer a chair cyclohexanone conformation (for example see the crystal structure of **36**). We imagine, however, that the α-keto radicals resulting from cyclization of **47a** are borne in boat conformations. This results in a transannular interaction between R_c and the β-C(5) hydrogen in transition state **48**.

propriately substituted substrates of type **47b** would products of type **51b** rather than **49b**.

Experimental Section

All melting points were taken with a Thomas-Hoover capillary melting point apparatus and are uncorrected as are all boiling points. Proton nuclear magnetic resonance spectra were recorded on a Varian Associates EM-360, Varian Associates EM-390, Bruker WP-200, Bruker AM-250, Bruker WM-300, or Bruker AM-500 spectrometers and are recorded in parts per million from internal tetramethylsilane on the δ scale. The ^{1}H NMR spectra are reported as follows: [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants in hertz, integration, interpretation]. ^{13}C NMR data were obtained with a Bruker WP-80, a Bruker AM-250, or a Bruker AM-500 spectrometer. Infrared spectra were taken with a Perkin-Elmer 457 instrument. Mass spectra were obtained on a Kratos MS-30 or Kratos VG 70-250S instrument at an ionization energy of 70 eV or by fast atom bombardment (FAB). Compounds for which exact mass is reported exhibited no significant peaks at m/e greater than that of the parent. Gas chromatograph/mass spectrometry was performed on a Finnigan 4021 GC/MS instrument. Combustion analyses were performed by Micro-Analysis, Inc., Wilmington, DE.

Solvents and reagents were dried and purified prior to use when deemed necessary: tetrahydrofuran, diethyl ether, and benzene were distilled from sodium metal; dichloromethane was distilled over calcium hydride. Thionyl chloride was freshly distilled through a Vigreux column. Diazomethane was prepared from *N*-methyl-*N*-nitrosourea[37] and used immediately. Anhydrous magnesium bromide solutions were prepared by addition of ethylene dibromide to magnesium in tetrahydrofuran. Reactions requiring an inert atmosphere were run under argon. Analytical thin-layer chromatography was conducted on EM Laboratories 0.25-mm-thick precoated silica gel 60F-254 plates. Column chromatography was performed over EM Laboratories silica gel (70–230 mesh). Medium pressure liquid chromatography (MPLC) was performed on EM Laboratories Lobar prepacked silica gel columns. All organometallic reagents (Grignard, organolithiums) were titrated prior to use with *s*-butanol using 1,10-phenanthroline as the indicator.[38]

***rel*-(1*S*,5*S*,8*S*)-8-Iodo-1-(3-methyl-3-butenyl)-5-methoxy-6-oxabicyclo[3.2.1]oct-2-en-7-one (4).** To a solution of 502 mg (3.3 mmol) of *m*-anisic acid (**10**) in 6 mL of tetrahydrofuran and 50 mL of ammonia was added 93 mg (13.3 mmol) of lithium metal in small portions. The reaction mixture was stirred for 10 min followed by the addition of 2.25 g (11.5 mmol) of 4-iodo-2-methyl-1-butene[9] in one portion. The reaction mixture was stirred for 30 min and then quenched with 945 mg (17.8 mmol) of ammonium chloride. The ammonia was allowed to evaporate. The residue was dissolved in 100 mL of water, acidified with 3 N aqueous hydrochloric acid, and extracted with three 75-mL portions of dichloromethane. The combined dichloromethane layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was dissolved in 20 mL of saturated aqueous sodium bicarbonate. To the resulting solution cooled in an ice–water bath was added 1.21 g (4.78 mmol) of iodine in 20 mL of ether in one portion. The mixture was stirred at 0 °C for 2 h, diluted with 150 mL of ether, washed with three 100-mL portions of saturated aqueous sodium bisulfite and three 100-mL portions of brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed over 15 g of silica gel (eluted with ethyl acetate–hexane, 1:5) to give 714 mg (62%) of **4**: IR (CH_2Cl_2) 1780 cm^{-1}; NMR (CCl_4) δ 1.81 (s, 3 H, CH_3), 1.5–2.4 (m, 4 H, CH_2), 2.66–2.93 (m, 2 H, $=CCH_2$), 3.53 (s, 3 H, OCH_3), 4.53 (s, 1 H, CHI), 4.80 (s, 2 H, $=CH_2$), 5.45 (dm, J = 9, 1 H, =CH), 5.99 (dt, J = 9, 3, 1 H, =CH). Iodo lactone **4** was unstable and used immediately in subsequent reactions.

***rel*-(1*R*,4a*S*,7*R*,8a*R*)-1,5,6,7,8,8a-Hexahydro-1-methoxy-7-methyl-2*H*-1,4a-(epoxymethano)naphthalen-9-one (12) and *rel*-(1*R*,4*S*,7*S*,8a*R*)-1,5,6,7,8,8a-Hexahydro-1-methoxy-7-methyl-2*H*-1,4a-(epoxymethano)naphthalen-9-one (13).** To a solution of 541 mg (1.55 mmol) of **4** and 10 mg of azobis(isobutyronitrile) in 20 mL of benzene heated at reflux was added 660 mg (2.24 mmol) of tri-*n*-butyltin hydride in benzene via a syringe pump at a rate of 1.2 mL h^{-1}. The solvent was removed in vacuo and the residue was chromatographed over 20 g of silica gel (eluted with ethyl acetate–hexane, 1:12) to give 293 mg (85%) of a 5:1 mixture of **12** and **13**. The ratio of **12**:**13** was determined by VPC (5% OV-101, injector temperature 280 °C, column temperature 190 °C).

Pure samples of **12** and **13** were prepared by VPC. Lactone **12**: ^{1}H NMR ($CDCl_3$) δ 0.84–0.90 (m, 1 H, H_{8a}), 0.92 (d, J = 6.5, 3 H, CH_3), 0.98–1.04 (m, 1 H, H_{6a}), 1.24–1.36 (m, 1 H, H_7), 1.45 (dt, J = 13.9, 4.5, 1 H, H_{5a}), 1.61 (ddt, J = 13.6, 4.5, 2.3, 1 H, H_{6e}), 1.77 (dm, J = 14, 1 H, H_{8e}), 2.06 (dd, J = 12.2, 5.2, 1 H, H_{8a}), 2.24 (ddd, J = 13.9, 3.8, 2.3, 1 H, H_{5e}), 2.45 (dt, J = 17.9, 2.7, 1 H, =CCH), 2.87 (ddd, J = 17.9, 3.8, 1.7, 1 H, =CCH), 3.52 (s, 3 H, OCH_3), 5.62 (dt, J = 9, 1.7, 1 H, =CH), 5.81 (dt, J = 9, 3.8, 1 H, =CH); mass spectrum, m/e (relative intensity) 178 (52, M – CO_2), 135 (31), 121 (35), 105 (22), 91 (100), 77 (27); t_R (VPC) 6.4 min. Lactone **13**: ^{1}H NMR ($CDCl_3$) δ 0.93 (d, J = 6.5, 3 H, CH_3), 1.35–1.81 (m, 1 H), 2.0–2.15 (m, 6 H), 2.22 (dd, J = 11.5, 5, 1 H), 2.45 (dt, J = 18, 2.4, 1 H), 2.87 (ddd, J = 18, 3.8, 1.7, 1 H), 3.53 (s, 3 H, OCH_3), 5.63 (dt, J = 9, 1.7, 1 H, =CH), 5.8 (dt, J = 9, 3.9, 1 H, =CH); mass spectrum, m/e (relative intensity) 178 (58, M – CO_2), 147 (2), 135 (37), 121 (38), 105 (24), 91 (100), 77 (27), t_R (VPC) 7.1 min.

Treatment of **4** with tri-*n*-butyltin deuteride gave a sample of **14** from which the following coupling constants were easily obtained: $J_{5a,5e}$ = 13.9 Hz, $J_{5a,6a}$ = 13.6 Hz, $J_{5a,6e}$ = 4.5 Hz, $J_{5e,6a}$ = 2.3 Hz, $J_{5e,6e}$ = 4.5 Hz, $J_{6e,6a}$ = 13.6 Hz, $J_{6e,8e}$ = 2.3 Hz, $J_{8e,8ax}$ = 14 Hz, $J_{8e,8a}$ = 5.2 Hz, $J_{8ax,8a}$ = 12.2 Hz. From these coupling constants and the spectrum of compound **12**, $J_{7,8ax}$ and $J_{6a,7}$ were determined to be 13 Hz.

1-Methyl-3-(methylthio)cyclohexa-2,5-diene-1-carboxylic Acid (16). To a solution of 1.90 g (11.3 mmol) of 3-(methylthio)benzoic acid (**15**)[15] in 10 mL of dry tetrahydrofuran and 50 mL of liquid ammonia was added 314 mg (45.2 mmol) of lithium in one portion. The resulting blue solution was stirred for a 10-min period and 4.82 g (34.0 mmol) of methyl iodide was added. The mixture was stirred for 20 min and 1.90 g (35.5 mmol) of solid ammonium chloride was added slowly. The ammonia was allowed to evaporate. The solid residue was dissolved in 50 mL of water and the aqueous solution was acidified to pH 3 with 3 N aqueous hydrochloric acid. The mixture was extracted with three 70-mL portions of dichloromethane and the combined extracts were washed with 150 mL of water, dried ($MgSO_4$), and concentrated in vacuo. The residual oil was chromatographed over 50 g of silica gel (eluted with ethyl acetate–hexane, 1:3) to yield 1.30 g (62%) of **16** as a yellow oil which crystallized upon cooling: mp 60–64 °C; IR (CCl_4) 2500–3000 (br), 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.33 (s, 3 H, CH_3), 2.23 (s, 3 H, SCH_3), 2.75 (br s, 2 H, CH_2), 5.33 (br s, 1 H, =CH), 5.70 (m, 2 H, =CH), 11.20 (br s, 1 H, COOH); exact mass calcd for $C_9H_{12}O_2S$ m/e 184.0558, found m/e 184.0575.

***rel*-(1*S*,5*R*,8*S*)-8-Iodo-1-methyl-5-(methylthio)-6-oxabicyclo[3.2.1]oct-2-en-7-one (17).** To a solution of 195 mg (0.77 mmol) of iodine in 8 mL of ether cooled to 0–5 °C was added a solution of 113 mg (0.61 mmol) of **16** in 2.5 mL of saturated aqueous sodium bicarbonate. The mixture was stirred for 1.5 h, washed with two 2-mL portions of 10% aqueous sodium thiosulfate and two 2-mL portions of water, and dried ($MgSO_4$). The solution was concentrated in vacuo to give a light brown solid. The material was chromatographed over 5 g of silica gel (eluted with ethyl acetate–hexane, 1:12) to yield 97 mg (51%) of **17** as a white crystalline solid. The compound was thermally unstable and decomposed without melting above 70 °C: IR (CCl_4) 1780 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 3 H, CH_3), 2.15 (s, 3 H, SCH_3), 2.70 (m, 2 H, CH_2), 4.30 (br s, 1 H, CHI), 5.35 (br d, J = 10, 1 H, =CH), 5.80 (dt, J = 10, 3, 1 H, =CH); exact mass calcd for $C_9H_{11}O_2SI$ m/e 309.9525, found m/e 309.9543.

1-(Trideuteriomethyl)-3-[(trideuteriomethyl)thio]cyclohexa-2,5-diene-1-carboxylic Acid (20) and 1-(Trideuteriomethyl)-3-(methylthio)cyclohexa-2,5-diene-1-carboxylic Acid (21). To a solution of 100 mg (0.60 mmol) of 3-(methylthio)benzoic acid (**15**) in 2 mL of dry tetrahydrofuran and 20 mL of liquid

(36) Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959 and references cited therein.
(37) Arndt, F. *Organic Synthesis*; Wiley: New York, 1943; Collect. Vol. II, p 165.
(38) Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165.

ammonia was added 26 mg (3.74 mmol) of lithium. The mixture was stirred for 10 min after all of the lithium dissolved and a dark blue color persisted. To the solution was added 0.11 mL (1.70 mmol) of methyl iodide-d_3, and the mixture was stirred for 40 min. Solid ammonium chloride (150 mg, 2.80 mmol) was added, followed by stirring for 5 min. The ammonia was allowed to evaporate and the residual solid was dissolved in 20 mL of water. The resulting aqueous solution was acidified with 3 N aqueous hydrochloric acid and the mixture was extracted with two 20-mL portions of dichloromethane. The combined extracts were washed with 20 mL of water, dried ($MgSO_4$), and concentrated in vacuo to yield 110 mg of a colorless oil which crystallized upon cooling (mp 60–65 °C). A mass spectrum of the solid showed that the product was a mixture of **20** and **21** in a ratio of 8.8:1, respectively; mass spectrum, m/e (relative intensity) 190 (14), 187 (1.6), 145 (100), 126 (28), 94 (20); exact mass calcd for $C_9H_6O_2D_6S$ m/e 190.0934, found m/e 190.0931; exact mass calcd for $C_9H_9O_2D_3S$ m/e 187.0747, found m/e 187.0742.

The ^1H NMR spectrum showed virtually no SCH_3 at δ 2.33. The ratio of the allylic protons at δ 2.75 to the peak at δ 2.33 was approximately 5.2:1, indicating that the **20**:**21** ratio was about 8:1.

Methyl 1-(3-Methyl-3-buten-1-yl)-3-(methylthio)cyclohexa-2,5-diene-1-carboxylate (18) and Methyl 1-(3-Methyl-3-buten-1-yl)-3-[(3-methyl-3-buten-1-yl)thio]cyclohexa-2,5-diene-1-carboxylate (19). To a solution of 504 mg (3.00 mmol) of 3-(methylthio)benzoic acid (**15**) in 5 mL of tetrahydrofuran and 25 mL of liquid ammonia was added 88 mg (12.7 mmol) of lithium over a 45-min period. To the dark blue solution was added 1.09 g (5.60 mmol) of 4-iodo-2-methyl-1-butene[9] in one portion, and the mixture was stirred for 30 min. Solid ammonium chloride (700 mg, 13.0 mmol) was added followed by stirring for 5 min. The ammonia was allowed to evaporate and the residual solid was dissolved in 50 mL of water. The aqueous solution was acidified with 3 N aqueous hydrochloric acid and the mixture was extracted with three 50-mL portions of ether. The combined extracts were washed with two 50-mL portions of water, dried ($MgSO_4$), and concentrated in vacuo. The residual oil (650 mg) was chromatographed over 35 g of silica gel (eluted with ethyl acetate–hexane, 1:4) to yield 450 mg of an inseparable mixture of acids as a colorless oil.

For characterization of these products, a 48-mg portion of the acid mixture in 2 mL of dichloromethane was treated with a solution of diazomethane [prepared by addition of 195 mg (1.89 mmol) of *N*-methyl-*N*-nitrosourea to a mixture of 1.5 mL of 40% aqueous potassium hydroxide solution and 5 mL of dichloromethane at 0–2 °C] until no starting material was seen by TLC. The solution was dried ($MgSO_4$) and concentrated in vacuo. The crude ester mixture (51 mg) was separated by MPLC over a Lobar size A column (eluted with ethyl acetate–hexane, 1:20) to give a pure sample of **18**: IR (neat) 1725 cm^{-1}; ^1H NMR (CCl_4) δ 1.66 br s, 3 H, CH_3), 1.73 (br s, 4 H, CH_2CH_2), 2.20 (s, 3 H, SCH_3), 2.66 (br s, 2 H, $=CH_2$), 3.60 (s, 3 H, $COOCH_3$), 4.57 (br s, 2 H, $=CH_2$), 5.26 (br s, 1 H, =CH), 5.73 (br s, 1 H, =CH); exact mass calcd for $C_{14}H_{20}O_2S$ m/e 252.1184, found m/e 252.1150. Pure **19** was also obtained: IR (neat) 1725 cm^{-1}; ^1H NMR (CCl_4) δ 1.70 (br s, 3 H, CH_3), 1.76 (br s, 3 H, CH_3), 1.83 (br s, 4 H, CH_2CH_2), 2.15–2.50 (m, 2 H, SCH_2), 2.66–3.00 (m, 4 H, $=CCH_2$), 3.66 (s, 3 H, $COOCH_3$), 4.63 (br s, 2 H, $=CH_2$), 4.73 (br s, 2 H, $=CH_2$), 5.53 (br s, 1 H, =CH), 5.76 (br s, 2 H, =CH); exact mass calcd for $C_{18}H_{26}O_2S$ m/e 306.1654, found m/e 306.1654. The ratio of **18** to **19** in the mixture was determined to be 4:1, respectively, by NMR. The yields of the corresponding acids were estimated at 48% and 12%, respectively, by this analysis.

3-[(1-Methylethyl)thio]-1-(3-methyl-3-buten-1-yl)cyclohexa-2,5-diene-1-carboxylic Acid (23). To a solution of 4.00 g (20.4 mmol) of 3-(isopropylthio)benzoic acid (**22**)[16] in 40 mL of dry tetrahydrofuran and 120 mL of liquid ammonia was added 480 mg (69.2 mmol) of lithium. The mixture was stirred for a 15-min period after all of the lithium dissolved and a dark blue color persisted. To the blue solution was added 4-bromo-2-methylbutene dropwise until the blue color disappeared followed by 3.05 g (20.4 mmol) of the bromide in one portion. The mixture was stirred for 25 min and 4.20 g (78.5 mmol) of solid ammonium chloride was added. The mixture was stirred for 5 min and the ammonia was allowed to evaporate. The residual solid was dissolved in 70 mL of water and the solution was adjusted to pH 3 with 3 N aqueous hydrochloric acid. The mixture was extracted with three 70-mL portions of dichloromethane and the combined extracts were washed with 150 mL of water, dried ($MgSO_4$), and concentrated in vacuo to yield 4.60 g (84%) of **23** as a yellow oil. This material could be purified by chromatography over silica gel (eluted with ethyl acetate–hexane, 1:3) but was suitable for use in subsequent reactions: IR (neat) 2500–3300 (br), 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.33 (d, J = 6, 6 H, CH_3), 1.75 (br s, 3 H, $=CCH_3$), 1.90 (br s, 4 H, CH_2CH_2), 2.80 (br s, 2 H, $=CCH_2$), 3.90 (quintet, J = 6, 1 H, SCH), 4.65 (br s, 2 H, $=CH_2$), 5.80 (m, 3 H, =CH), 11.10 (br s, 1 H, COOH); exact mass calcd for $C_{15}H_{22}O_2S$ m/e 266.1340, found m/e 266.1363.

***rel*-(1*S*,5*R*,8*S*)-8-Iodo-5-[(1-methylethyl)thio]-1-(3-methyl-3-buten-1-yl)-6-oxabicyclo[3.2.1]oct-2-en-7-one (5).** To a solution of 1.10 g (4.30 mmol) of iodine in 40 mL of ether cooled to 0–5 °C was added a solution of 840 mg (3.15 mmol) of **23** in 16 mL of saturated aqueous sodium bicarbonate over an 8-min period. The mixture was stirred for 1 h and washed with two 30-mL portions of 10% aqueous sodium thiosulfate and two 40-mL portions of water. The ethereal phase was dried ($MgSO_4$) and concentrated in vacuo. The residual oil (1.10 g) was chromatographed over 30 g of silica gel (eluted with ethyl acetate–hexane, 1:20) to yield 820 mg (67%) of pure iodo lactone **5** as a yellow oil: IR (neat) 1780 cm^{-1}; ^1H NMR (CCl_4) δ 1.35 (d, J = 6, 3 H, CH_3), 1.40 (d, J = 6, 3 H, CH_3), 1.80 (br s, 3 H, $=CCH_3$), 1.8–2.2 (m, 4 H, CH_2CH_2), 2.75 (m, 2 H, $=CCH_2$), 3.20 (quintet, J = 6, 1 H, SCH), 4.45 (br s, 1 H, CHI), 4.75 (br s, 2 H, $=CH_2$), 5.45 (br d, J = 9, 1 H, =CH), 5.85 (dt, J = 9, 2, 1 H, =CH). This material decomposed on standing and was used directly in subsequent reactions.

***rel*-(1*R*,4a*S*,7*R*,8a*R*)-1,5,6,7,8,8a-Hexahydro-7-methyl-1-[(1-methylethyl)thio]-2*H*-1,4a-(epoxymethano)-naphthalen-9-one (24).** To a solution of 1.49 g (3.80 mmol) of iodo lactone **5** in 75 mL of dry benzene under reflux was added a solution of 2.00 mL (7.60 mmol) of tri-*n*-butyltin hydride and 18 mg of azobis(isobutyronitrile) in 20 mL of benzene over a 6-h period. The benzene was removed in vacuo. The residual pale yellow oil (3.50 g) was chromatographed over 120 g of silica gel (eluted with ethyl acetate–hexane, 1:12) to yield 800 mg (80%) of a clear oil which crystallized upon cooling to 0 °C. This material was predominantly lactone **24** and its C(7) diastereomer by NMR, but a small amount (5% by NMR) of noncyclized reduction product derived from **5** was apparent from a weak signal at δ 4.7 ($=CH_2$). A pure sample of lactone **24** was obtained by recrystallization from hexane: mp 85–86 °C; IR (CCl_4) 1780 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85–1.70 (m with d's, J = 6 at 0.92, J = 7 at 1.30, 1.44, 14 H), 1.85 (br d, J = 14, 1 H, CH), 2.14 (dd, J = 12, 5, 1 H, CH), 2.25 (br d, J = 14, 1 H, CH), 2.75 and 2.95 (AB q, J_{AB} = 19, 2 H, $=CCH_2$), 3.35 (quintet, J = 7, 1 H, SCH), 5.63 (br d, J = 9, 1 H, =CH), 5.75 (dt, J = 9, 3, 1 H, =CH); ^{13}C NMR ($CDCl_3$) δ 22.37 (q), 23.76 (q), 25.86 (q), 28.13 (t), 30.48 (d), 31.05 (t), 32.32 (t), 32.65 (d), 39.22 (t), 46.96 (s), 49.78 (d), 92.86 (s), 126.17 (d), 132.50 (d), 176.48 (s); mass spectrum, m/e (relative intensity) 266 (3), 147 (40), 146 (32), 961 (100); exact mass calcd for $C_{15}H_{22}O_2S$ m/e 266.1341, found m/e 266.1314.

A pure sample of the C(7) diastereomer (**25**) was not isolated. The ratio of **24**:**25** was estimated to be 8:1 by GC (10% OV-101, column temperature 220 °C, He 30 mL/min). Under these conditions, **24** had t_R 8.5 min and **25** had t_R 9.5 min. The assignment of the peak with t_R 9.5 min was made on the basis of its mass spectrum: mass spectrum, m/e (relative intensity) 266 (M^+, 3), 147 (43), 146 (38), 91 (100).

1,1-Dimethylethyl [*rel*-(1*S*,5*S*,8*S*)-8-Iodo-7-oxo-6-oxabicyclo[3.2.1]oct-2-en-1-yl]acetate (28). To a solution of 5.05 g (41.4 mmol) of benzoic acid in 25 mL of tetrahydrofuran and 250 mL of liquid ammonia was added 768 mg (111 mmol) of lithium over a 40-min period. The resulting blue solution was stirred for 25 min after all of the lithium had been added. To the mixture was added 0.12 mL of isoprene, followed by 10.0 g (51.3 mmol) of *tert*-butyl bromoacetate, and the solution was stirred at reflux for 50 min. Solid ammonium chloride (6.50 g, 121 mmol) was added followed by stirring for 5 min. The ammonia was allowed to evaporate and the residual solid was dissolved in 100 mL of water. The resulting aqueous solution was acidified to pH 1–2 with 3 N aqueous hydrochloric acid and the mixture was extracted with three 50-mL portions of ether. The combined extracts were

dried ($MgSO_4$) and concentrated in vacuo.

To a solution of the crude acid **26** (12.6 g) in 85 mL of dimethylformamide was added 5.0 mL (60.0 mmol) of pyrrolidine, and the mixture was cooled to 0 °C. To the mixture was added 11.8 mL (54.8 mmol) of diphenyl phosphorazidate followed by 13.0 mL (93.4 mmol) of triethylamine over a 5-min period. The mixture was stirred at 0 °C for 20 min, warmed to room temperature, and stirred for 20 h. The mixture was diluted with 1000 mL of ether and the resulting solution was washed with three 300-mL portions of brine, dried ($MgSO_4$), and concentrated in vacuo.

To a solution of the crude amide **27** (16.6 g) in 200 mL of tetrahydrofuran and 200 mL of water was added 30.9 g (121 mmol) of iodine, and the mixture was stirred for 23 h. The mixture was diluted with 800 mL of ether and the resulting solution was washed with two 400-mL portions of saturated sodium bisulfite and 300 mL of brine, dried ($MgSO_4$), and concentrated in vacuo. The residual orange oil (16.7 g) was chromatographed over 100 g of silica gel (eluted with ethyl acetate–hexane, 1:10) to yield 6.80 g of a yellow oil. This oil was crystallized from hexane to give 5.99 g (40%) of pure **28** as a white solid: mp 53–55 °C; IR (CH_2CH_2) 1780, 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.46 (s, 9 H, *t*-Bu), 2.58, 2.81 (AB q with fine coupling, J_{AB} = 18, 2 H, $=CCH_2$), 2.61, 2.82 (AB, q, J_{AB} = 18, 2 H, CH_2CO_2), 4.75 (m, 1 H, OCH), 5.23 (dd, J = 5, 2, 1 H, CHI), 5.35 (dq, J = 9, 2, 1 H, =CH), 5.87 (br d, J = 9, 1 H, =CH); ^{13}C NMR ($CDCl_3$) δ 23.89 (d), 28.05 (q), 30.31 (t), 34.89 (t), 47.26 (s), 76.38 (d), 81.85 (s), 127.47 (d), 128.86 (d), 168.78 (s), 170.94 (s); mass spectrum, m/e (relative intensity) 309 (4), 290 (9), 137 (54), 91 (78), 57 (100). Anal. Calcd for $C_{13}H_{17}IO_4$: C, 42.87; H, 4.70. Found: C, 42.97; H, 4.80.

[*rel*-(1*S*,5*S*,8*S*)-8-Iodo-7-oxo-6-oxabicyclo[3.2.1]oct-2-en-1-yl]acetic Acid (29). To a solution of 2.50 g (6.87 mmol) of **28** in 7.5 mL of dichloromethane was added 1.0 mL of trifluoroacetic acid, and the mixture was stirred for 21 h. The mixture was concentrated in vacuo and the residual solid was washed with three 10-mL portions of dichloromethane to give 1.85 g (87%) of **29** as a white solid. The combined organic washes were concentrated and washed as before to yield an additional 210 mg (10%) of pure **29**: mp 180 °C dec; IR (KBr) 3200–2700 (br), 1755, 1685 cm^{-1}; ^1H NMR (acetone-d_6) δ 2.35–3.00 (m, 2 H, $=CCH_2$), 2.74, 2.95 (AB q, J_{AB} = 18, 2 H, CH_2COO), 4.95 (m, 1 H, OCH), 5.35 (d, J = 6, 1 H, CHI), 5.50 (br d, J = 9, 1 H, =CH), 5.97 (br d, J = 9, 1 H, =CH), 9.0 (br s, 1 H, COOH); ^{13}C NMR (acetone-d_6) δ 24.5 (d), 31.0 (t), 33.5 (t), 47.5 (s), 77.0 (d), 128.5 (d), 130.0 (d), 171.2 (s), 171.3 (s); exact mass calcd for $C_9H_9IO_4$ m/e 308.9624, found m/e 308.9582. Anal. Calcd for $C_9H_9IO_4$: C, 35.09; H, 2.94. Found: C, 34.79;; H, 2.85.

[*rel*-(1*S*,5*S*,8*S*)-8-Iodo-7-oxo-6-oxabicyclo[3.2.1]oct-2-en-1-yl]acetyl Chloride (30). To 1.00 g (3.25 mmol) of **29** was added 9 mL of freshly distilled thionyl chloride, and the mixture was heated at 40 °C for 2.5 h, followed by 60 °C for an additional 2.5 h. The mixture was concentrated in vacuo to give 1.03 g (97%) of **30** as a white solid: mp 70 °C dec; IR (CH_2Cl_2) 1785 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.62, 2.85 (AB q, J_{AB} = 20, 2 H, $=CCH_2$), 3.32, 3.55 (AB q, J_{AB} = 19, 2 H, CH_2COCl), 4.85 (m, 1 H, CH), 5.00 (d, J = 6, 1 H, CHI), 5.35 (br d, J = 9, 1 H, =CH), 5.97 (br d, J = 9, 1 H, =CH). This material was used in subsequent reactions without further purification.

***S*-2-Pyridyl [*rel*-(1*S*,5*S*,8*S*)-8-Iodo-7-oxo-6-oxabicyclo-[3.2.1]oct-2-en-1-yl]thioacetate (31).** To a solution of 103 mg (9.20 mmol) of 2-mercaptopyridine and 0.13 mL (9.35 mmol) of triethylamine in 7 mL of tetrahydrofuran at 0 °C was added 300 mg (9.20 mmol) of **30** in 7 mL of tetrahydrofuran over a 5-min period. The solution was warmed to room temperature and stirred for 4 h. The mixture was diluted with 20 mL of dichloromethane and the resulting solution was washed with 10 mL of water, dried ($MgSO_4$), and concentrated in vacuo. The residual oil was chromatographed over 6 g of silica gel (eluted with ethyl acetate–hexane, 1:3) to give 240 mg (65%) of **31** as a green solid. This material was pure enough for subsequent reactions but could be recrystallized (ethyl acetate–hexane, 1:10) to give a slightly green crystalline compound: mp 138–139 °C; IR (CH_2Cl_2) 1785, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.60, 2.80 (AB q, J_{AB} = 20, 2 H, $=CCH_2$), 3.13, 3.33 (AB q, J_{AB} = 17, 2 H, $CH_2C=O$), 4.25 (m, 1 H, OCH), 5.09 (dd, J = 5, 2, 1 H, CHI), 5.40 (dq, J = 9.5, 2, 1 H, =CH), 5.90 (dtd, J = 10, 5, 1.5, 1 H, =CH), 7.30 (ddd, J = 14, 5, 1.5, 1 H, ArH_5), 7.63 (dt, J = 7, 1, 1 H, ArH_3), 7.75 (td, J = 7.5, 2, 1 H, ArH_4), 8.62 (d with fine coupling, J = 5, 1 H, ArH_6); ^{13}C NMR ($CDCl_3$) δ 23.44 (d), 30.24 (t), 42.65 (t), 48.00 (s), 76.55 (d), 123.75 (d), 127.85 (d), 128.25 (d), 130.31 (d), 137.15 (d), 150.46 (d), 150.65 (s), 170.43 (s), 193.20 (s); exact mass calcd for $C_{14}H_{12}INO_2S$ m/e 400.9587, found m/e 400.9585. Anal. Calcd for $C_{14}H_{12}INO_2S$: C, 41.91; H, 3.01. Found: C, 42.19; H, 3.04.

***rel*-(1*S*,5*S*,8*S*)-1-(3-Methyl-2-oxobut-3-en-1-yl)-8-iodo-6-oxabicyclo[3.2.1]oct-2-en-7-one (6). (A) From Vinylstannane 32.** To a solution of 500 mg (1.53 mmol) of **30** and 517 mg (1.53 mmol) of isopropenyltributylstannane (**32**)[24] in 3 mL of benzene was added 26 mg (0.0225 mmol) of tetrakis(triphenylphosphine)palladium(0) in 1 mL of benzene, and the mixture was heated in a sealed tube at 55 °C for 17 h. The gray precipitate was removed by filtration and the filtrate was concentrated in vacuo. The residual oil was dissolved in 5 mL of dichloromethane and the resulting solution was washed with two 5-mL portions of 10% aqueous potassium fluoride solution, using filtration to remove the white solid that was formed with each wash. The organic phase was concentrated in vacuo and the residual oil was chromatographed over 5 g of silica gel (eluted with ethyl acetate–hexane, 1:10) to give 330 mg of a white solid. This material was recrystallized (ethyl acetate–hexane) to yield 200 mg (40%) of pure **6**: mp 123–124 °C; IR (CH_2Cl_2) 1780, 1675 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.90 (s, 3 H, CH_3), 2.60, 2.80 (AB q, J_{AB} = 17, 2 H, $=CCH_2$), 3.12, 3.28 (AB q, J_{AB} = 18, 2 H, $CH_2C=O$), 4.82 (m, 1 H, CH), 5.30 (d, J = 6, 1 H, CHI), 5.41 (dq, J = 10, 2, 1 H, =CH), 5.85 (s, 1 H, CH=CC=O), 5.90 (br d, J = 10, 1 H, =CH), 6.06 (s, 1 H, CH=CC=O); ^{13}C NMR ($CDCl_3$) δ 17.30 (q), 24.20 (d), 30.48 (t), 36.70 (t), 47.13 (s), 76.39 (d), 125.45 (t), 127.64 (d), 129.17 (d), 144.22 (s), 171.21 (s), 197.32 (s); mass spectrum, m/e (relative intensity) 161 (13), 143 (42), 131 (21), 91 (100), 69 (93), 41 (96). Anal. Calcd for $C_{12}H_{13}IO_3$: C, 43.39; H, 3.94. Found: C, 43.50; H, 4.03.

(B) From Thioester 31. To a solution of 0.50 mL of 0.30 M (0.150 mmol) 2-propenylmagnesium bromide in 2 mL of tetrahydrofuran at −78 °C was added 57 mg (0.142 mmol) of **31** in 3 mL of tetrahydrofuran in one portion, and the resulting mixture was stirred for 1 h. The mixture was quenched with 1 mL of saturated aqueous ammonium chloride, warmed to room temperature, and diluted with dichloromethane (40 mL). The resulting solution was washed with saturated aqueous ammonium chloride (15 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over 6 g of silica gel (eluted with ethyl acetate–hexane, 1:10) to yield 15 mg (32%) of **6** as a white solid.

***rel*-(1*S*,5*S*,8*S*)-8-Iodo-1-(3-methyl-2-oxobutyl)-6-oxabicyclo[3.2.1]oct-2-en-7-one (35).** To a solution of 21 mg (0.0633 mmol) of **6** in 10 mL of benzene were added 40 mg (0.137 mmol) of tri-*n*-butyltin hydride and 3 mg of azobis(isobutyronitrile) in 2 mL of benzene. The mixture was degassed with argon and warmed under reflux for 25–30 min. The benzene was evaporated and the residue was chromatographed over 6 g of silica gel (eluted with ethyl acetate–hexane, 1:10) to give 16 mg (76%) of **35** as a white solid: mp 59–61 °C; IR (CH_2Cl_2) 1780, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15 (d, J = 7, 6 H, CH_3), 2.55, 2.75 (AB q, J_{AB} = 20, 2 H, $=CCH_2$), 2.60 (quintet, 1 H, $CHMe_2$), 2.80, 3.05 (AB q, J_{AB} = 18, 2 H, $CH_2C=O$), 4.75 (m, 1 H, OCH=O), 5.22 (br d, J = 5, 1 H, CHI), 5.30 (br d, J = 9, 1 H, =CH), 5.80–5.90 (m, 1 H, =CH); exact mass calcd for $C_{12}H_{16}O_3I$ (M + 1) m/e 335.0144, found m/e 335.0175.

***rel*-(1*S*,4a*S*,7*S*,8a*R*)-1,7,8,8a-Tetrahydro-7-methyl-2*H*-1,4a-(epoxymethano)naphthalene-6,9(5*H*)-dione (36).** To a solution of 197 mg (0.593 mmol) of **6** and 5 mg of 1,2-bis(diphenylphosphino)ethane in 116 mL of benzene were added 303 mg (1.06 mmol) of tri-*n*-butyltin hydride and 14 mg of azobis(isobutyronitrile) in 4 mL of benzene. The mixture was degassed with argon and warmed under reflux for 1 h. The benzene was evaporated and the residue was dissolved in 25 mL of dichloromethane. The resulting solution was washed with two 5-mL portions of 10% aqueous potassium fluoride solution (the white precipitate was removed by filtration), dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over 6 g of silica gel (eluted with ethyl acetate–hexane, 1:10 to 1:2) to give 98 mg (80%) of **36** as a white solid. This material was a 6:1 mixture of C(7) diastereomers by capillary GC (Ph Me Silicone,

220 °C) and was recrystallized (ethyl acetate–hexane) to give the major diastereomer: mp 114–115 °C; IR (CH_2Cl_2) 1780, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05 (d, J = 6, 3 H, CH_3), 1.45 (q, J = 14, 1 H, CH), 2.11 (dt, J = 14, 5, 1 H, CH), 2.35–2.60 (m with d, J = 15 at 2.45, 4 H, =CCH_2, 2 CHC=O) 3.05 (d, J = 15, 1 H, CHC=O), 4.50 (br s, 1 H, CHOC=O), 5.65 (dt, J = 9, 2, 1 H, =CH), 5.78 (m, 1 H, =CH); ^{13}C NMR ($CDCl_3$) δ 14.12 (q), 32.09 (t), 34.39 (t), 41.84 (t), 42.93 (d), 44.25 (d), 48.63 (s), 77.25 (d), 126.70 (d), 131.11 (d), 176.21 (s), 207.33 (s); exact mass calcd for $C_{12}H_{15}O_3$ (M + 1) m/e 207.1021, found m/e 207.1040 (FAB).

***rel*-(1*S*,5*S*,8*S*)-8-Iodo-1-(2-oxobut-3-en-1-yl)-6-oxabicyclo[3.2.1]oct-2-en-7-one (7).** To a solution of 501 mg (1.54 mmol) of **30** and 533 mg (1.68 mmol) of vinyltri-*n*-butylstannane (**33**)[24] in 5 mL of dichloromethane was added 25 mg (0.022 mmol) of tetrakis(triphenylphosphine)palladium(0) in 1 mL of dichloromethane, and the mixture was heated at 45 °C in a sealed tube for 4.5 h. The solution was concentrated in vacuo and the residual solid was washed with 20 mL of ether. The ethereal solution was washed with an equal volume of 10% aqueous potassium fluoride solution (the white precipitate was removed by filtration), dried ($MgSO_4$), and added to the above solid. The resulting solution was concentrated and the residual oil was chromatographed over 12 g of silica gel (eluted with ethyl acetate–hexane, 1:10) to yield 320 mg (65%) of **7** as a white solid: mp 134–135 °C; IR (CH_2Cl_2) 1780, 1675 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.60, 2.82 (AB q, J_{AB} = 20, 2 H, =CCH_2), 2.97, 3.17 (AB q, J_{AB} = 20, 2 H, CH_2C=O), 4.80 (m, 1 H, CH), 5.30 (dd, J = 6, 2, 1 H, CHI), 5.40 (dq, J = 9, 2, 1 H, =CH), 5.90 (m, 2 H, =CH), 6.25–6.45 (m, 2 H, CH_2=CC=O); ^{13}C NMR ($CDCl_3$) 23.96 (d), 30.42 (t), 38.71 (t), 47.05 (s), 76.50 (d), 127.69 (d), 129.01 (d), 129.20 (t), 136.02 (d), 171.06 (s), 176.05 (s); exact mass calcd for $C_{11}H_{12}IO_3$ m/e 318.9831, found m/e 318.9893. Anal. Calcd for $C_{11}H_{12}IO_3$: C, 41.53; H, 3.49; I, 39.89. Found: C, 41.30, H, 3.20; I, 39.92.

***rel*-(1*S*,5*S*,8*R*)-8-Iodo-1-(2-oxobutyl)-6-oxabicyclo[3.2.1]oct-2-en-7-one (38).** To a solution of 21 mg (0.066 mmol) of enone **7** in 10 mL of benzene were added 35 mg (0.120 mmol) of tri-*n*-butyltin hydride and 4 mg of azobis(isobutyronitrile) in 3 mL of benzene. The mixture was degassed with argon and warmed under reflux for 1 h. The benzene was evaporated and the residue was chromatographed over 7 g of silica gel (eluted with ethyl acetate–hexane, 1:10) to give 11 mg (52%) of **38** as a white solid: mp 96–98 °C; IR (CH_2Cl_2) 1775, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05 (t, J = 7, 3 H, CH_3), 2.35–3.13 (m with dd at 2.50, J = 18, 9, and AB q at 2.75, 3.03, J_{AB} = 18, 6 H, =CCH_2, CH_2C=O), 4.80 (m, 1 H, OCHC=O), 5.23–5.43 (m, 2 H, CHI, =CH), 5.80–6.00 (m, 1 H, =CH), exact mass calcd for $C_{11}H_{14}O_3I$ (M + 1) m/e 320.9988, found m/e 320.9997 (FAB).

***rel*-(1*S*,4a*S*,8a*R*)-1,7,8,8a-Tetrahydro-2*H*-1,4a-(epoxymethano)naphthalene-6,9(5*H*)-dione (39).** To a solution of 199 mg (0.626 mmol) of **7** and 2.1 mg of 1,2-bis(diphenylphosphino)ethane in 116 mL of benzene were added 306 mg (1.05 mmol) of tri-*n*-butyltin hydride and 14 mg of azobis(isobutyronitrile) in 4 mL of benzene. The mixture was degassed with argon and warmed under reflux for 1.5 h. The benzene was evaporated and the residue was dissolved in dichloromethane (20 mL). The resulting solution was washed with two 5-mL portions of 10% aqueous potassium fluoride solution (the white precipitate was removed by filtration), dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over 6 g of silica gel gel (eluted with ethyl acetate–hexane, 1:2) to yield 36 mg (30%) of **39** as a white solid: mp 127–128 °C; IR (CH_2Cl_2) 1765, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.70 (dq, J = 13, 4, 1 H, CH), 2.15 (ddt, J = 16, 5, 3, 1 H, CH), 2.31 (td, J = 16, 5, 1 H, CHC=O), 2.38 (dd, J = 12, 4, 1 H, CH), 2.41 (d, J = 16, 1 H, CHC=O), 2.45 (br d, J = 16, 1 H, CHC=O), 2.55 (br s, 2 H, =CCH_2), 3.05 (br d, J = 16, 1 H, CHC=O), 4.50 (br s, 1 H, CHOC=O), 5.60 (br d, J = 9, 1 H, =CH), 5.75 (br d, J = 9, 1 H, =CH); ^{13}C NMR ($CDCl_3$) δ 25.45 (t), 32.14 (t), 39.25 (t), 41.63 (t), 43.65 (d), 47.90 (s), 77.50 (d), 126.77 (d), 131.33 (de, 176.33 (s), 206.12 (s); exact mass calcd for $C_{11}H_{12}O_3$ m/e 192.0796, found m/e 192.0763.

***rel*-(1*S*,5*S*,8*S*)-8-Iodo-1-(4-methyl-2-oxopent-3-en-1-yl)-6-oxabicyclo[3.2.1]oct-2-en-7-one (8).** To a solution of 496 mg (1.52 mmol) of **30** and 24 mg (0.021 mmol) of tetrakis(triphenylphosphine)palladium(0) in 3 mL of tetrahydrofuran was added 545 mg (1.58 mmol) of isobutenyltri-*n*-butyltin (**34**)[24] in 1 mL of tetrahydrofuran, and the mixture was heated in a sealed tube at 55 °C for 30 min, followed by 65 °C for 1.5 h. The mixture was concentrated in vacuo. The residue was chromatographed over 25 g of silica gel (eluted with ethyl acetate–hexane, 1:10) to yield 180 mg (34%) of **8** as a pale yellow solid. This material was recrystallized to give a white crystalline solid: mp 144–145 °C; IR (CH_2Cl_2) 1780, 1680 (weak), 1615 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.90 (d, J = 1, 3 H, CH_3), 2.15 (d, J = 1, 3 H, CH_3), 2.59, 2.81 (AB q, J_{AB} = 18, 2 H, =CCH_2), 3.08, 3.80 (AB q, J_{AB} = 18, 2 H, CH_2C=O), 4.80 (m, 1 H, CHOC=O), 5.33 (d, J = 6, 1 H, CHI), 5.35 (dq, J = 9, 2, 1 H, =CH), 5.85 (m, 1 H, =CH), 6.10 (quintet, J = 1, 1 H, CH=CC=O); ^{13}C NMR ($CDCl_3$) δ 20.94 (q), 24.40 (d), 27.74 (q), 30.43 (t), 42.51 (t), 47.12 (s), 76.35 (d), 123.00 (d), 127.37 (d), 129.24 (d), 157.67 (s), 171.27 (s), 195.74 (s); exact mass calcd for $C_{13}H_{15}IO_3$ m/e 346.0036, found m/e 346.0051. Anal. Calcd for $C_{13}H_{15}IO_3$: C, 45.11; H, 4.37. Found: C, 45.26; H, 4.48.

***rel*-(1*R*,3a*S*,7*S*,7a*R*)-1,2,3,6,7,7a-Hexahydro-1-(1-methylethyl)-7,3a-(epoxymethano)-3a*H*-indene-2,9-dione (40).** To a solution of 100 mg (0.290 mmol) of **8** and 2.3 mg of 1,2-bis(diphenylphosphino)ethane in 50 mL of benzene were added 147 mg (0.505 mmol) of tri-*n*-butyltin hydride and 6.0 mg of azobis(isobutyronitrile) in 5 mL of benzene. The mixture was degassed with argon and warmed under reflux for 50 min. The benzene was removed in vacuo and the resulting residue was chromatographed over 6 g of silica gel (eluted with ethyl acetate–hexane, 1:10 to 1:15) to yield 58 mg of colorless oil. This material was further purified by MPLC (Lobar size A column, eluted with ethyl acetate–hexane, 1:10) to give 23 mg (36%) of pure **40** as a white solid: mp 114–115 °C; IR (CH_2Cl_2) 1770, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (d, J = 6.5, 3 H, CH_3), 1.05 (d, J = 6.5, 3 H, CH_3), 2.05 (dd, J = 11, 5, 1 H, CH), 2.18–2.32 (m with d, J = 18 at 2.26, 2 H, CHMe, CHC=O), 2.50 (d, J = 11, 1 H, CH), 2.65 (m, 2 H, =CCH_2), 2.96 (d, J = 18, 1 H, CHC=O), 4.75 (br s, 1 H, CHOC=O), 5.80 (dtd, J = 9, 3, 1.5, 1 H, =CH), 6.05 (dt, J = 9, 3, 1 H, =CH); ^{13}C NMR ($CDCl_3$) δ 18.60 (q), 20.93 (q), 27.24 (d), 33.05 (t), 41.68 (t), 47.61 (s), 49.17 (d), 55.12 (d), 77.26 (d), 127.61 (s), 128.71 (d), 177.38 (s), 213.57 (s); exact mass calcd for $C_{13}H_{17}O_3$ m/e 221.1178 (M + 1), found m/e 221.1201 (FAB).

The reduction product **41** was also isolated in a 16% yield (10 mg): IR (CH_2Cl_2) 1770, 1685, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.90 (s, 3 H, CH_3), 2.15 (s, 3 H, CH_3), 2.40 (m, 2 H, =CCH_2), 2.80, 3.00 (AB q, J_{AB} = 18, 2 H, CH_2C=O), 4.80 (m, 1 H, CHOC=O), 5.75 (br s, 2 H, =CH), 6.10 (br s, 1 H, =CH); exact mass calcd for $C_{13}H_{17}O_3$ m/e 221.1178 (M + 1), found 221.1185 (FAB).

Tetrahydropyran-2-yl (*E*)-3-(Tributylstannyl)but-2-en-1-yl Ether (42). To a solution of 1.49 g (6.34 mmol) of (*E*)-2-bromo-4-[(tetrahydro-2*H*-pyran-2-yl)oxy]but-2-ene[29] in 12 mL of tetrahydrofuran at −78 °C was added 10.4 mL of 1.25 M (13.0 mmol) *t*-butyl lithium in pentane over 5–10 min, and the mixture was stirred for 1 h. To the yellow solution was added 30 mL of 0.22 M (6.60 mmol) anhydrous magnesium bromide in tetrahydrofuran followed by stirring for 1 h. To the mixture was added 1.44 g (4.43 mmol) of tri-*n*-butyltin chloride in 10 mL of tetrahydrofuran, and the suspension was stirred 15 min, warmed to room temperature, and stirred for 19 h. The mixture was quenched with 1 mL of saturated aqueous ammonium chloride, washed with 30 mL of saturated aqueous sodium bicarbonate and 30 mL of saturated aqueous sodium chloride, dried ($MgSO_4$), and concentrated in vacuo. The residual oil (2.25 g) was chromatographed over 50 g of silica gel (eluted with ethyl acetate–hexane, 1:30) to give 1.60 g (81%) of **42** as a liquid: ^1H NMR (CCl_4) δ 0.7–1.70 (m, 33 H, *n*-Bu_3), 1.83 (s, 3 H, =CCH_3), 3.30–4.30 (m, 4 H, OCH_2), 4.60 (br t, J = 3, 1 H, OCHO), 5.65 (m, 1 H, =CH).

***rel*-(1*S*,5*S*,8*R*)-8-Iodo-1-[3-methyl-5-[(tetrahydro-2*H*-pyran-2-yl)oxy]-2-oxopent-3-en-1-yl]-6-oxabicyclo[3.2.1]oct-2-en-7-one (9).** To a solution of 350 mg (1.07 mmol) of **30** in 1 mL of tetrahydrofuran were added 484 mg (1.09 mmol) of **42** and 20 mg (0.017 mmol) of tetrakis(triphenylphosphine)palladium(0) in 1 mL of tetrahydrofuran, and the mixture was heated in a sealed tube at 55–60 °C for 18 h. The mixture was concentrated and the residue dissolved in dichloromethane (20 mL). The resulting solution was washed with two 5-mL portions of 10% aqueous potassium fluoride solution (the white precipitate was removed by filtration) and concentrated in vacuo. The residual oil was chromatographed over 10 g of silica gel (eluted with ethyl acetate–hexane, 1:10) to give 208 mg (43%) of **9** as an orange solid.

This material was recrystallized (ethyl acetate–hexane) to give 125 mg (26%) of pure **9**: mp 123–125 °C; IR (CH_2Cl_2) 1780, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.50–1.95 (m, with s at 1.78, 9 H, $CH_2CH_2CH_2$, CH_3), 2.59, 2.81 (AB q, J_{AB} = 20, 2 H, $=CCH_2$), 3.12, 3.31 (AB q, J_{AB} = 18, 2 H, $CH_2C=O$), 3.50–3.60 (m, 1 H, OCH), 3.82–3.92 (m, 1 H, OCH), 4.25, 4.51 (d of AB q, J_{AB} = 13, J = 5, 2 H, OCH_2), 4.67 (m, 1 H, OCHO), 4.81 (m, 1 H, CHOC=O), 5.31 (d, J = 6, 1 H, CHI), 5.41 (br d, J = 9, 1 H, =CH), 5.90 (br d, J = 9, 1 H, =CH), 6.80 (br t, J = 10, 1 H, CH=CC=O); ^{13}C NMR ($CDCl_3$) δ 11.46 (q), **19.45** (t), 24.40 (t), 25.32 (d), 30.54 (t), 36.52 (t), 47.22 (s), 62.30 (s), **62.49** (t), 64.47 (t), 76.39 (d), **98.88** (d), 127.61 (d), 129.28 (d), 137.10 (s), 139.70 (d), 171.26 (s), 196.55 (s) (the boldfaced signals were slightly doubled, indicating the presence of compounds diastereomeric at the THP methine); exact mass calcd for $C_{18}H_{24}IO_5$ (M + 1) m/e 447.0670, found m/e 447.0669 (FAB). Anal. Calcd for $C_{18}H_{23}IO_5$: C, 48.44; H, 5.19. Found: C, 48.21; H, 4.61.

***rel*-(1*S*,4a*S*,7*S*,8*S*,8a*R*)-1,7,8,8a-Tetrahydro-7-methyl-8-[[(tetrahydro-2*H*-pyran-2-yl)oxy]methyl]-2*H*-1,4a-(epoxymethano)naphthalene-6,9(5*H*)-dione (43).** To a solution of 115 mg (0.258 mmol) of **9** and 3 mg of 1,2-bis(diphenylphosphino)ethane in 49 mL of benzene was added 134 mg (0.460 mmol) of tri-*n*-butyltin hydride and 6 mg of azobis(isobutyronitrile) in 4 mL of benzene. The mixture was degassed with argon and warmed under reflux for 1 h. The benzene was evaporated and the residue was dissolved in 20 mL of dichloromethane. The resulting solution was washed with two 5-mL portions of 10% aqueous potassium fluoride solution (the white precipitate was filtered off), dried ($MgSO_4$), and concentrated in vacuo. The residual oil was chromatographed over 6 g of silica gel (eluted with ethyl acetate–hexane, 1:3 to 1:1) to give 44 mg (53%) of pure **43** and 12 mg of a less pure sample, which was recrystallized to afford 6 mg (7%) of additional **43**: mp 135–137 °C. This material was a 1:1 mixture of tetrahydropyranyl diastereomers that could be separated by MPLC (Lobar size A column, eluted with ethyl acetate–hexane, 1:10): IR (CH_2Cl_2, mixture) 1775, 1710 cm^{-1}; ^1H NMR ($CDCl_3$, less polar diastereomer) δ 1.21 (d, J = 6, 3 H, CH_3), 1.30–1.70 (m, 6 H, $CH_2CH_2CH_2$), 2.28 (m, 1 H, CH), 2.35 (d, J = 18, 1 H, $CH_2C=O$), 2.42 (quintet, J = 5, 1 H, C*H*Me), 2.58 (br s, 2 H, $=CCH_2$), 2.62 (d, J = 6, 1 H, CH), 3.25 (d, J = 18, 1 H, $CH_2C=O$), 3.32 (d, J = 10, 1 H, OCH), 3.50 (br d, J = 11, 1 H, OCH), 3.65 (td, J = 10, 3, 1 H, OCH), 3.89 (dd, J = 10, 4, 1 H, OCH), 4.55 (br s, 1 H, CHOC=O), 4.75 (br s, 1 H, OCHO), 5.75 (br d, J = 9, 1 H, =CH), 5.82 (br d, J = 9, 1 H, =CH); ^1H NMR ($CDCl_3$, more polar diastereomer) δ 1.10 (d, J = 6, 3 H, CH_3), 1.15–1.90 (m, 6 H, $CH_2CH_2CH_2$), 2.25 (q, J = 4, 1 H, CH), 2.35 (d, J = 18, 1 H, CHC=O), 2.42 (quintet, J = 5, 1 H, C*H*Me), 2.57 (m, 2 H, $=CCH_2$), 2.63 (d, J = 6, 1 H, CH), 3.25 (d, J = 18, 1 H, CHC=O), 3.33 (dd, J = 10, 4, 1 H, OCH), 3.48 (dt, J = 10, 3, 1 H, OCH), 3.79 (m, 1 H, OCH), 3.88 (d, J = 10, 1 H, OCH), 4.45 (br s, 1 H, CHOC=O), 4.80 (br s, 1 H, OCHO), 5.70–5.85 (m, 2 H, =CH); ^{13}C NMR ($CDCl_3$, mixture) δ 11.81 (q), 11.95 (q), 17.91 (t), 18.09 (t), 25.17 (t), 25.48 (t) 28.60 (t), 29.12 (t), 33.54 (t), 41.21 (t), 41.34 (t), 42.68 (d), 42.92 (d), 45.04 (d), 45.35 (d), 45.98 (s), 48.20 (d), 48.28 (d), 61.53 (t), 61.75 (t), 61.86 (t), 63.66 (t), 75.79 (d), 75.92 (d), 98.27 (d), 101.16 (d), 126.02 (d), 135.46, 135.57 (d), 175.77 (s), 176.04 (s), 205.94 (s), 206.42 (s); exact mass calcd for $C_{18}H_{24}O_5$ m/e 320.1623, found m/e 320.1676. Anal. Calcd for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55. Found: C, 66.91; H, 7.22.

***rel*-(1*S*,4*R*,5a*S*,9*S*,9a*R*,12*S*)-1,4,5,8,9,9a-Hexahydro-4-methoxy-2-methyl-2*H*-9,5a-(epoxymethano)-1,4-methano-3-benzoxepin-11-one (44).** To a solution of 4.9 mg (0.0153 mmol) of **43** in 3 mL of methanol was added 3.7 mg of Dowex-50 (H^+), and the mixture was heated at reflux for 3.5 h. The resin was removed by filtration and the solvent was removed in vacuo. The residue (4 mg) was chromatographed over 0.5 g of silica gel (eluted with ethyl acetate–hexane, 1:5) to give 3.3 mg (86%) of **44** as a colorless oil: IR (CH_2Cl_2) 1775 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05 (d, J = 6, 3 H, CH_3), 1.62 (d, J = 14, 1 H, CHC(OMe)O), 1.85 (q, J = 7, 1H, $CHCH_3$), 2.12 (t, J = 4, 1 H, CH), 2.31 (d, J = 4, 1 H, CH), 2.50 (m, 2 H, $=CCH_2$), 3.05 (d, J = 14, 1 H, CHC(OMe)O), 3.45 (s, 3 H, OCH_3), 3.95 (d, J = 10, 1 H, OCH), 4.02 (dd, J = 10, 3, 1 H, OCH), 4.58 (br s, 1 H, CHOC=O), 5.67 (br d, J = 10, 1 H, =CH), 5.81 (dt, J = 10, 3, 1 H, =CH); exact mass calcd for $C_{14}H_{18}O_4$ m/e 250.1179, found m/e 250.1192.

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Supplementary Material Available: Crystallographic details and ORTEP drawing for compound **36** (6 pages). Ordering information is given on any current masthead page.

Stereochemistry of Hexakis(dimethylamino)benzene and Its Dication

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The crystal structures of hexakis(dimethylamino)benzene (**4**) and its dication bis(triiodide) (**8**) have been determined. Crystals of **4** are monoclinic, space group $C2/c$, a = 18.440 (6) Å, b = 9.461 (3) Å, c = 12.017 (4) Å, β = 104.74 (3)°, Z = 4. Like hexaisopropylbenzene, hexakis(dimethylsilyl)benzene, and hexakis(dichloromethyl)benzene, molecules of **4** adopt approximate C_{6h} symmetry in the crystal, but, unlike these otherwise closely related compounds, **4** does not manifest an orientational disorder. Reaction of **4** with iodine yields **8**, crystals of which belong to the monoclinic system, space group $P2/c$, a = 16.243 (5) Å, b = 11.051 (4) Å, c = 20.358 (7) Å, β = 112.02 (3)°, Z = 4. Molecules of **8** have crystallographic C_2 symmetry and approximate D_2 symmetry, with the benzene ring in a twist conformation. Variable-temperature NMR studies on 1,3,5-tris(diethylamino)-2,4,6-tris(dimethylamino)benzene (**9**) and hexakis(diethylamino)benzene, two molecules that are structurally related to **4**, show that pyramidal inversion of the nitrogen atoms requires 8.2 and 10.0 kcal mol^{-1}, respectively. As shown by the interconversion of the diastereomers of 1,3,5-tris(ethylmethylamino)-2,4,6-tris(dimethylamino)benzene, which requires 16.0 kcal mol^{-1}, barriers to rotation about the C_{ar}–N bonds in this class of compounds are substantially higher than barriers to pyramidal inversion. According to AM1 calculations, the homomerization (topomerization) of **4** is not concerted but involves stepwise inversion of the dimethylamino groups. The calculated activation energy, 10.5 kcal mol^{-1}, is in reasonable agreement with the experimentally observed barrier of 8.2 kcal mol^{-1} for **9**. Variable-temperature NMR studies on **8** reveal a site exchange of the methyl groups which is rationalized by a pseudorotational motion of the twisted benzene ring.

Hexaisopropylbenzene (**1**),[2] hexakis(dimethylsilyl)-benzene (**2**),[3] and hexakis(dichloromethyl)benzene (**3**)[4] assume ground-state conformations of approximate C_{6h} symmetry in which the α-hydrogen in each side chain is

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