I_{50} Values for Compounds 5 (Second Determination), 12, and 13. The I_{50} values for these compounds were determined in the same manner as described above; however, at the time that these inhibitors were evaluated, the observed K_m value for chorismate was 34 μM. The inhibitor concentration ranges used and the I_{50} values obtained were as follows: **5**, 0–0.20 μM, I_{50} = 0.26 ± 0.06 μM; **12**, 0–1700 μM, I_{50} = 4.2 ± 0.3 mM; **13**, 0–120 μM, I_{50} = 67 ± 4 μM.

K_i Value for Compound 5. For determination of the inhibition constant for the endo diacid **5**, four inhibitor concentrations (0–0.20 μM) and six substrate concentrations (15–300 μM) were used. The data was fitted to the equation for linear competitive inhibition,[56] giving a K_i value of 0.121 ± 0.014 μM.

Acknowledgment. We express our appreciation to Prof. Jeremy R. Knowles (Harvard University) for generously providing us with the enzyme, to Dr. Alan Rendina and the other members of the biochemical group at Chevron Chemical Co. for assistance with the spectrophotometric assay, and to Robert Lum and John Bushweller for their assistance in the synthesis of **5** and with 2D NMR experiments, respectively. This project was supported by a grant from the National Institutes of Health (GM-28965). Y.N. and S.H.R. also thank the National Institute of General Medical Sciences for postdoctoral fellowships.

Registry No. **5** (dimethyl ester), 114613-49-9; **5** [bis(dicyclohexylammonium) salt], 114613-48-8; **8** (diethyl ester), 114584-65-5; **8** [bis(dicyclohexylammonium) salt], 114595-89-0; **9** [bis(diethylammonium) salt], 114673-07-3; **11**, 114584-29-1; **12**, 114595-81-2; **13**, 114584-30-4; **14**, 114584-31-5; **15**, 114584-32-6; **16**, 114584-33-7; **17**, 99416-47-4; *exo*-**18**, 114584-34-8; *endo*-**18**, 114584-64-4; *exo*-**19**, 114584-35-9; *endo*-**19**, 114673-08-4; *exo*-**20**, 114613-43-3; *endo*-**20**, 114613-50-2; **21**, 114584-36-0; **22**, 114613-44-4; **23**, 114584-37-1; **24**, 114584-38-2; **25**, 114595-82-3; **26**, 114584-39-3; **27**, 114584-40-6; **28**, 114584-41-7; **29**, 114595-83-4; **30**, 114584-42-8; **31**, 114584-43-9; **32**, 114595-84-5; **33**, 114613-45-5; **34**, 114673-05-1; **35**, 114584-44-0; **35** (*O*-nitrate), 114595-92-5; **36**, 114584-45-1; **37**, 114584-46-2; **38**, 114595-85-6; **39**, 114584-47-3; **40**, 114595-86-7; **41**, 114584-48-4; **42**, 114584-49-5; **43**, 114584-50-8; **44**, 114584-51-9; **45**, 114584-52-0; **46**, 114584-53-1; **47**, 114584-54-2; **48**, 114584-55-3; **49**, 114584-56-4; **50**, 114584-57-5; **51**, 114584-58-6; **52**, 114595-87-8; **53**, 114584-59-7; **54**, 114613-46-6; **55**, 114584-60-0; **56**, 114584-61-1; **57**, 114584-62-2; **58**, 64811-86-5; 3-*exo*,8-*exo*-8-hydroxy-2-oxabicyclo[3.3.1]non-6-ene-3,5-dicarboxylic acid dimethyl ester, 114584-28-0; dimethyl itaconate, 617-52-7; 1-(methoxycarbonyl)-α-[(trimethylsilyl)oxy]-3-cyclohexene-1-propanenitrile, 114595-91-4; 3-*exo*,8-*exo*-8-[1,2-dioxo-2-[2-(trimethylsilyl)ethoxy]-2-oxabicyclo[3.3.1]non-6-ene-3,5-dicarboxylic acid bis[2-(trimethylsilyl)ethyl ester], 114584-63-3; 3-*exo*,8-*exo*-8-hydroxy-2-oxabicyclo[3.3.1]non-6-ene-3,5-dicarboxylic acid bis[2-(trimethylsilyl)ether ester], 114595-90-3; chorismate mutase, 9068-30-8; adamantane 1-phosphonate, 23906-88-9.

Preparation of Functionalized *trans*-Perhydroindans from Substituted Benzoic Acids: Reductive Alkylation–Halolactonization–Free Radical Cyclization

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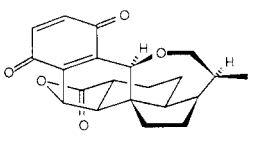
Received December 1, 1987

Reductive alkylation of *m*-toluic acid (**7**), *m*-anisic acid (**8**), benzoic acid (**9**), and 2,3-dimethylbenzoic acid (**31**) with selected alkyl halides followed by iodolactonization and side-chain modification gave free radical precursors **13**, **14**, **19**, **27**, and **34**. Treatment of **13**, **14**, and **19** with tri-*n*-butyltin hydride and AIBN gave mixtures of perhydroindans and perhydronaphthalenes. Similar treatment of **27** and **34** gave *trans*-perhydroindans **28** and **35**, respectively, as the major products. Iodo lactone **47** was also prepared from ethyl *m*-iodobenzoate (**38**) and converted to angularly oxygenated perhydroindans **48** and **49** by using a free radical cyclization.

The preparation of trans-fused perhydroindans has been the focal point of a number of synthetic studies. In large part this is due to the presence of this moiety as a substructure of steroids.[2,3] There are, however, a large number of nonsteroidal natural products that contain *trans*-perhydroindan substructures. The antitumor antibiotic pleurotin (**1**) and the plant growth stimulant gibberellic acid (**2**) serve as examples.[4,5] As part of a program designed to develop free radical cyclizations for use in natural product syntheses, we have examined the route to trans-



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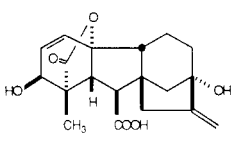
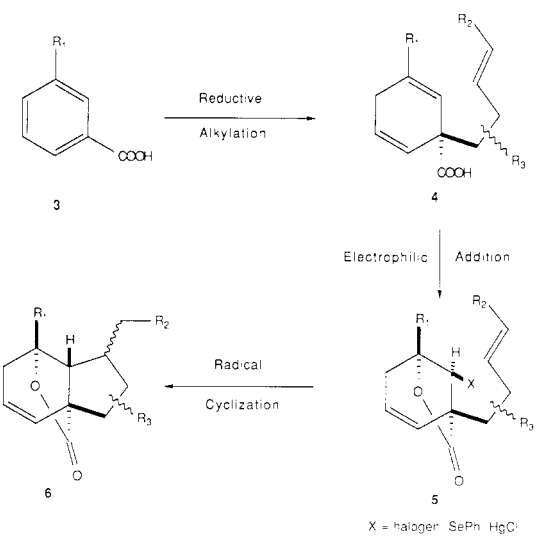


2

Scheme I



(1) Author to whom questions regarding crystal structures should be addressed.

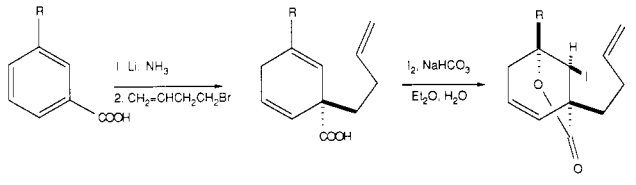
(2) For recent studies directed toward steroidal substructures, see: Denmark, S. E.; Gormanas, J. *Tetrahedron Lett.* **1984**, *25*, 1231. Stork, G.; Winkler, J. D.; Shiner, C. S. *J. Am. Chem. Soc.* **1982**, *104*, 3767.

(3) For a recent study involving free radical cyclizations unrelated to those described here, see: Stork, G.; Kahn, M. *J. Am. Chem. Soc.* **1985**, *107*, 500.

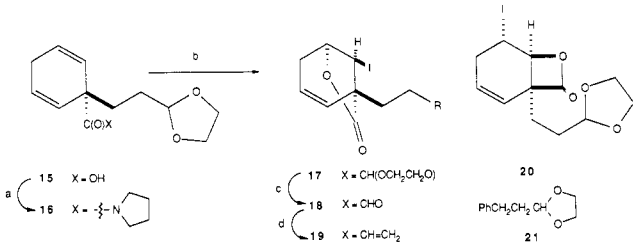
(4) Pleurotin: Dobler, M. *Cryst. Struct. Commun.* **1975**, *4*, 253.

0022-3263/88/1953-3210$01.50/0

Scheme II



Scheme III[a]



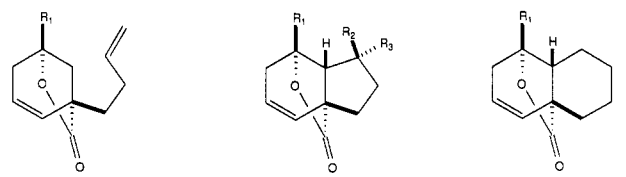
[a] (a) $(PhO)_2PON_3$, pyrrolidine, Et_3N; (b) I_2, THF, H_2O; (c) aqueous HCOOH; (d) $Ph_3P{=}CH_2$.

fused perhydroindans outlined in Scheme I.[6] At the onset of these studies, we felt that attractive features of this scheme were its flexibility in terms of developing different perhydroindan substitution patterns and its predictability from the standpoint of ring juncture stereochemistry (vide infra). Anticipated problems revolved primarily around regioselectivity and stereoselectivity in the electrophilic addition and radical cyclization steps, respectively. This article presents our investigation of this scheme.[7]

Regioselectivity in Lactonizations and Initial Cyclizations. We began our studies by preparing cyclization precursors **13**, **14**, and **19** as shown in Schemes II and III. Thus, reductive alkylation of *m*-toluic acid (**7**) followed by iodolactonization of the resulting dihydrobenzoic acid **10** gave **13** in 56% overall yield.[8-10] The observed chemoselectivity and regioselectivity in the lactonization of triene **10** was determined by olefin substitution patterns. It is notable that bromolactonization of **10** using the procedure of Barnett and Needham gave nearly equal amounts of β-lactone and γ-lactone.[9] Similar reductive alkylation of *m*-anisic acid (**8**) followed by iodolactonization gave **14** (66%).

Iodo lactone **19** was more difficult to prepare. Reductive alkylation of benzoic acid (**9**) gave **12** (90%). Treatment of **12** with iodine or benzeneselenenyl chloride, however, only gave products derived from addition to the monosubstituted olefin.[11] Therefore, it was necessary to perform the halolactonization prior to introducing side-chain unsaturation. Thus, benzoic acid was converted to dienoic acid **15** (94%) by using 2-(2-bromoethyl)-1,3-dioxolane as

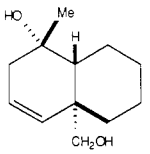
Table I



halo lactone	22	23	24	25	combined yield, %
13	24	48	4	24	87
14	19	29	3	49	85
19		63	7	30	88

the alkylating agent. Attempted iodolactonization of **15** gave the desired γ-lactone **17** (20–25%), β-lactone **20**, and substantial amounts of arene **21**. Since β-lactone **20** could be isolated from the reaction mixture, we imagined that **21** was produced via decarboxylative elimination of an intermediate iodonium carboxylate followed by loss of hydrogen iodide. On the basis of this hypothesis, **15** was converted to amide **16** (74%) in an attempt to eliminate the proposed pathway to **21** (Scheme III).[12] This strategy was successful as iodolactonization of amide **16** gave **17** in 70% yield.[13] Acetal hydrolysis using aqueous formic acid gave aldehyde **18** (91%) and a Wittig reaction completed the preparation of **19** (30%).

We began the cyclization studies by examining the behavior of iodo lactone **13**. Treatment of **13** with tri-*n*-butyltin hydride and AIBN in benzene under reflux gave reduction product **22a** and cyclization products **23a**, **24a**, and **25a** in the yields and ratios shown in Table I. Pure lactone **23a** crystallized directly from the product mixture in 32% yield and its structure was determined by X-ray crystallography.[14] Samples of **24a** and **25a** were obtained by preparative VPC of the mother liquor. The structure of **24a** was consistent with spectral data although we cannot rule out structures that contain a cis-fused perhydroindan nucleus. The structure of **25a** was also consistent with spectral data although ring juncture stereochemistry was initially uncertain. Proof of stereochemistry was obtained by X-ray crystallographic analysis of **26**,



26

prepared by treatment of the cyclization mixture with lithium aluminum hydride.[14] Finally, the presence of **22a** was inferred from vinylic signals at δ 4.8–5.2 in the ^1H NMR spectrum of the product mixture and GC-MS analysis.

Several aspects of this free radical cyclization are notable. The radical derived from **13** gives a 2:1 ratio of exo/endo [(**23a** + **24a**):**25a**] cyclization products, contrary to the much larger (30–50:1) exo/endo ratios usually observed for simply 5-hexenyl radicals.[15] The reasons for

(5) Gibberellic acid: Corey, E. J.; Danheiser, R. L.; Chandrasekaran, S.; Sinet, P.; Keck, G. E.; Gras, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 8031. Corey, E. J.; Danheiser, R. L.; Chandrasekaran, S.; Keck, G.; Gopalan, B.; Larsen, S. D.; Sinet, P.; Gras, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 8034. Mander, L. N. *Acc. Chem. Res.* **1983**, *16*, 48 and references cited therein.

(6) For a preliminary account, see: Chuang, C.-P.; Hart, D. J. *J. Org. Chem.* **1983**, *48*, 1782.

(7) For a route to cis-fused perhydroindans from benzoic acids using a reductive alkylation–radical cyclization sequence, see: Beckwith, A. L. J.; O'Shea, D. M.; Roberts, D. H. *J. Chem. Soc., Chem. Commun.* **1983**, 1445. Beckwith, A. L. J.; Roberts, D. H. *J. Am. Chem. Soc.* **1986**, *108*, 5893.

(8) Van Bekkum, H.; Van Den Bosch, C. B.; Van Minnenpathius, G.; De Mos, J. C.; Van Wijk, A. M. *Recl. Trav. Chim. Pays-Bas* **1971**, *90*, 137.

(9) Barnett, W. E.; Needham, L. L. *J. Org. Chem.* **1975**, *40*, 2843.

(10) Holbert, G. W.; Weiss, L. B.; Ganem, B. *Tetrahedron Lett.* **1976**, 4435.

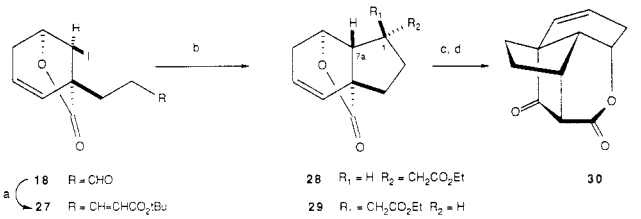
(11) Schmid, G. H.; Garratt, D. G. *Tetrahedron* **1978**, *34*, 2869.

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

(13) Staninets, V. I.; Shilov, E. A. *Russ. Chem. Rev.* (*Engl. Transl.*) **1971**, *40*, 272.

(14) X-ray crystallographic analyses were performed by Dr. Judith C. Gallucci at The Ohio State University Department of Chemistry Crystallographic Facility. Details appear in the supplementary material.

Scheme IV[a]



[a] (a) $Ph_3P{=}CHCO_2Bu$-*t*; (b) *n*-Bu_3SnH, AIBN, PhH; (c) LiN-$(SiMe_3)_2$, Et_2O, hexane, reflux; (d) CF_3COOH.

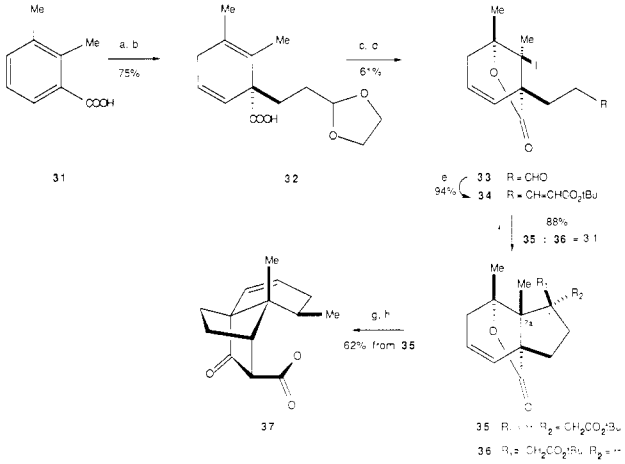
this unusual regiochemistry are unclear, although strain present in the transition state leading to *trans*-perhydroindan **23a** (**24a**) relative to that giving perhydronaphthalene **25a** may be a factor.[16] In terms of stereochemistry, both the endo and exo cyclizations proceed with high selectivity. We anticipated the formation of a *trans*-perhydroindan ring juncture in the exo cyclization (**13** → **23a** + **24a**) and suggest that this selectivity is due to the preference of the oxabicyclo[3.3.0]octane substructure in **23a** and **24a** for a cis ring fusion. The stereochemistry at C(1) in the exo cyclization is consistent with results obtained in simpler carbocyclic systems and is satisfactorally rationalized by steric effects in cyclization transition-state models recently proposed by Beckwith, Curran, and Houk.[17] Finally, the reason for exclusive formation of a *trans*-perhydronaphthalene (**13** → **25a**) is also uncertain. Two reports that appeared after completion of this study indicate that intermolecular reactions of related 6-oxabicyclo[3.2.1]oct-8-yl radicals follow the same stereochemical course observed here (i.e. bond formation syn to the two-atom bridge).[18,19] We have, however, observed exceptions to this behavior and thus remain uncertain as to the origin of the effect.[20,21]

Iodo lactones **14** and **19** were also treated with tri-*n*-butyltin hydride and AIBN to afford **22b–25b** and **23c–25c** as shown in Table I. The gross structures were assigned on the basis of spectroscopic evidence and stereochemical assignments were made by analogy with **23a–25a**. It is apparent that lactones **14** and **19** give results that qualitatively parallel those obtained with **13**. Thus, the incipient C(7) substituent has little effect on the regiochemical or stereochemical course of the cyclizations.

Synthesis of Perhydroindans. The preceding discussion shows that the use of a terminal vinyl group in Scheme I gave almost equal partitioning between exo and endo cyclization pathways. This suggested that internal olefin substitution would afford exclusively perhydronaphthalenes while appropriate terminal substituents would give only perhydroindans.[22] Substituent studies have shown that improved exo/endo partitioning can be achieved and our results directed toward perhydroindans are presented here.[23]

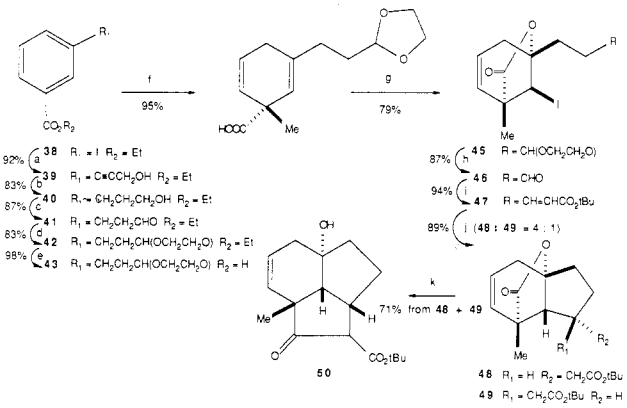
It is possible to divert the radical cyclization (Scheme I) toward perhydroindans by placing electron-withdrawing groups on the olefin terminus. A number of systems were studied, but only three will be presented here.[24]

Scheme V[a]



[a] (a) Li, NH_3; (b) LDA, $BrCH_2CH_2CH(OCH_2CH_2O)$; (c) I_2, $NaHCO_3$, KI, H_2O; (d) HCOOH, H_2O; (e) $Ph_3P{=}CHCO_2$-*t*-Bu, CH_2Cl_2; (f) *n*-Bu_3SnH, AIBN, PhH, reflux; (g) $LiN(SiMe_3)_2$, Et_2O–hexane; (h) CF_3COOH.

Scheme VI[a]



[a] (a) $HC{\equiv}CCH_2OH$, $(Ph_3P)_2PdCl_2$, CuI, Et_2NH; (b) H_2, Pd on C; (c) DMSO, $(COCl)_2$, Et_3N; (d) $HOCH_2CH_2OH$, H^+; (e) NaOH, H_2O; (f) Li, NH_3; MeI; (g) I_2, $NaHCO_3$; (h) HCOOH, H_2O; (i) $Ph_3P{=}CHCO_2$-*t*-Bu; (j) *n*-Bu_3SnH, AIBN, PhH, reflux; (k) LiN-$(SiMe_3)_2$.

(15) Beckwith, A. L. J.; Blair, A. I.; Phillipou, G. *Tetrahedron Lett.* **1974**, 2251. Walling, C.; Cioffari, A. *J. Am. Chem. Soc.* **1972**, *94*, 6059. Also see ref 22.

(16) Clive, D. L. J.; Cheshire, D. R.; Set, L. *J. Chem. Soc., Chem. Commun.* **1987**, 353.

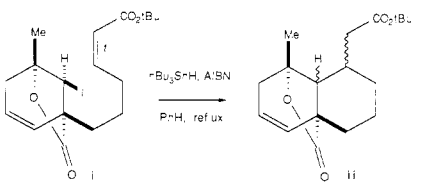
(17) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron Lett.* **1985**, *26*, 373. Curran, D. P.; Rakiewicz, D. M. *Tetrahedron* **1985**, *41*, 3943. Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959.

(18) Keck, G. E.; Yates, J. B. *J. Org. Chem.* **1982**, *47*, 3591.

(19) Coblens, K. E.; Muraldiharan, V. B.; Ganem, B. *J. Org. Chem.* **1982**, *47*, 5041.

(20) Hart, D. J.; Seely, F. L. *J. Am. Chem. Soc.* **1988**, *110*, 1631.

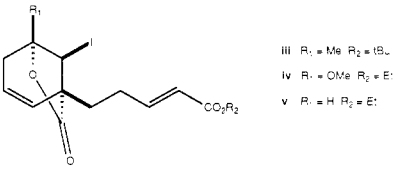
(21) For example, iodo lactone i gives a nearly equal mixture of four diastereomeric perhydronaphthalenes ii (Chuang, C.-P., Ph.D. Thesis, The Ohio State University, 1984).



(22) Julia, M.; Descoins, C.; Baillarge, M.; Jacquet, B.; Uguen, D.; Groeger, F. A. *Tetrahedron* **1975**, *31*, 1737.

(23) Studies directed toward perhydronaphthalenes are presented: Chuang, C.-P.; Gallucci, J. C.; Hart, D. J.; Hoffman, C. *J. Org. Chem.*, following paper in this issue.

(24) The cyclization of radicals derived from iii–v have been reported previously (see ref 6 and Hart, D. J.; Huang, H. C. *Tetrahedron Lett.* **1985**, *26*, 3749). The experimental details for iii appear in the supplementary material of ref 6. The experimental details for iv and v, intermediates in total syntheses underway, will be presented elsewhere.



The protocol for preparing perhydroindans is illustrated by the example shown in Scheme IV. Thus, a Wittig reaction between aldehyde **18** and the appropriate phosphorane gave unsaturated ester **27** in 91% yield. Treatment of **27** with tri-*n*-butyltin hydride gave a 7:1 mixture of diastereomeric esters **28** and **29**, respectively, in 93% yield. The major product (**28**) could be crystallized from the product mixture in 67% yield. The stereochemistry of **28** was established by its conversion to keto lactone **30** (72% from **28** + **29**) upon sequential treatment with lithium hexamethyldisilazide and trifluoroacetic acid. The structure was supported by spectral data including infrared absorptions at 1765 cm^{-1} and 1730 cm^{-1} assigned to the ketone and lactone carbonyls, respectively. No C(1) or C(7a) stereoisomers of **28** are capable of undergoing this Dieckmann condensation–lactonization sequence.

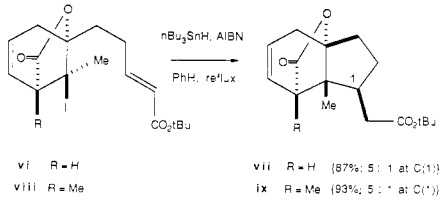
The generality of this approach to *trans*-perhydroindans is underscored by the example outlined in Scheme V. The only notable differences between this sequence and those described earlier are minor changes in the reductive alkylation and halolactonization steps. Thus, conversion of **31** to **32** was best accomplished by isolation of the intermediate dihydrobenzoic acid followed by dianion alkylation in tetrahydrofuran and the iodolactonization of **32** was best performed by using iodine–potassium iodide.

A Variation of Scheme I: Preparation of Angularly Oxygenated Perhydroindans. If one considers structure **5** in Scheme I, it is apparent that transposition of R_1 and the unsaturated side chain would lead to angularly oxygenated perhydroindans. There was reason to expect that everything learned in the studies described above (regiochemistry and stereochemistry) would translate smoothly to such a system. This has been shown to be the case as illustrated in Scheme VI. Ethyl *m*-iodobenzoate (**38**) was coupled with propargyl alcohol to afford **39** in 92% yield.[25] A simple four-step sequence converted **39** to acid **43** in 58% overall yield. Reductive alkylation of **43** afforded **44** (95%) and iodolactonization gave **45** (79%). Acetal hydrolysis yielded aldehyde **46** (87%) and a Wittig reaction gave cyclization precursor **47** (94%). As anticipated, free radical cyclization gave a 4:1 mixture of perhydroindans **48** and **49**, respectively, in 89% yield. Once again, the stereochemistry at C(1) was established by using a Dieckmann condensation (**48** + **49** → **50** in 71% yield). The structure assignment for **50**, which was a single stereoisomer by ^{13}C NMR, was supported by singlets at δ 169.9 and 212.5, indicating the presence of ester and ketone carbonyl groups, respectively. The infrared spectrum of **50** confirmed the presence of these carbonyls (1750 cm^{-1} and 1720 cm^{-1}) and also indicated the presence of the hydroxyl group (3570 cm^{-1}).

Further studies, which will not be reported here, indicate that the aforementioned sequence can be extended to the preparation of other angularly hydroxylated perhydroindans.[26] The end products of Scheme VI (**49** and **50**) are obviously related to the AB ring system of gibberellic acid (**2**) although alternate addends would need to be examined before pursuing this application.

(25) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467.

(26) For the transformation of vi → vii and viii → ix, see: Chuang, C. P., Ph.D. Thesis, The Ohio State University, 1984.



Experimental Section

General. All melting points were taken with a Thomas-Hoover capillary melting point apparatus and are uncorrected as are melting points. ^1H nuclear magnetic resonance spectra were recorded on Varian Associates EM-390, Varian Associates EM-360, or Brucker WP-200 FT instruments. NMR data are reported as follows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants, integration, interpretation]. ^{13}C nuclear magnetic resonance spectra were recorded on a Brucker WP-80 spectrometer and are reported in parts per million from internal tetramethylsilane. Infrared spectra were taken with a Perkin-Elmer 457 instrument. Mass spectra were recorded with either Finnigan 4021 GC-MS or Kratos MS-30 mass spectrometers. 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 (distilled from sodium metal); benzene, dichloromethane, *N,N*-dimethylformamide, dimethyl sulfoxide, pyridine, toluene (distilled from calcium hydride). Reactions requiring an inert atmosphere were run under a blanket of nitrogen or argon. Analytical thin-layer chromatography was performed with EM Laboratories 0.25-mm-thick precoated silica gel 60 F-254 plates. Column chromatography was performed over EM Laboratories silica gel (70–230 mesh). Medium pressure liquid chromatography (MPLC) was performed using EM Laboratories Lobar prepacked silica gel columns and a FMI RPSY Lab pump. GLC analysis was done on a Varian Aerograph Series 1400 instrument equipped with a thermal conductivity detector.

1-(3-Butenyl)-3-methyl-2,5-cyclohexadiene-1-carboxylic Acid (10). To a solution of 6.63 g (46.5 mmol) of *m*-toluic acid (**7**) in 60 mL of tetrahydrofuran and 500 mL of ammonia was added 983 mg (0.14 mol) of lithium metal in small portions. The solution was stirred for 10 min followed by the addition of 12.95 g (95.9 mmol) of 3-butenyl bromide. The resulting solution was stirred under reflux for 45 min followed by the addition of 10.6 g (0.2 mol) of ammonium chloride in small portions. The ammonia was allowed to evaporate and traces were removed under house vacuum. The residue was dissolved in 100 mL of water and acidified with 3 N aqueous hydrochloric acid. The resulting mixture was extracted with three 150-mL portions of ether. The combined ether extracts were washed with three 200-mL portions of brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over 70 g of silica gel (eluted with ethyl acetate–hexane, 1:4) to give 8.14 g (91%) of **10** as a colorless oil suitable for use in the following reaction: IR (CH_2Cl_2) 3300–2500 (br), 1705, 925 cm^{-1}; ^1H NMR (CCl_4) δ 1.5–2.01 (m with broad singlet at δ 1.8, 7 H, CH_3, and CH_2CH_2), 2.50 (br s, 2 H, $=CCH_2$), 4.63–5.01 (m, 2 H, $=CH_2$), 5.33–5.97 (m, 4 H, =CH), 11.8 (br s, 1 H, CO_2H); mass spectrum, *m/e* (relative intensity) 145 (21, $M^+ - HCO_2H$), 121 (18), 105 (100), 91 (18), 79 (11), 77 (14).

***rel*-(1*S*,5*S*,8*S*)-1-(3-Butenyl)-8-iodo-5-methyl-6-oxabicyclo[3.2.1]oct-2-en-7-one (13).** To a solution of 96.1 g (0.38 mol) of iodine in 250 mL of ether cooled in an ice–water bath was added a solution of 6.64 g (34.6 mmol) of **10** in 100 mL of saturated aqueous sodium bicarbonate. The reaction mixture was stirred at 0 °C for 5 h, diluted with 350 mL of ether, washed with two 400-mL portions of saturated aqueous sodium bisulfite and two 400-mL portions of brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over 100 g of silica gel (eluted with ethyl acetate–hexane, 1:25) to give 6.75 g (61%) of **13** as a white solid: mp 63–64 °C; IR (CH_2Cl_2) 1790 cm^{-1}; ^1H NMR (CCl_4) δ 1.6–2.33 (m with s at δ 1.45, 7 H, CH_3, and CH_2CH_2), 2.3–2.5 (m, 2 H, $=CCH_2$), 4.2 (br s, 1 H, CHI), 4.8–6.3 (m, 5 H, =CH and $=CH_2$); mass spectrum, *m/e* (relative intensity) 147 (27, $M^+ - CO_2I$), 105 (100), 91 (26), 77 (13), 55 (33). Anal. Calcd for $C_{12}H_{15}O_2I$: C, 45.30; H, 4.75. Found: C, 45.03; H, 4.59.

Cyclization of Iodo Lactone 13: *rel*-(1*R*,3a*R*,7*S*,7a*R*)-1,2,3,6,7,7a-Hexahydro-1,7-dimethyl-7,3a-(epoxymethano)-3a*H*-inden-9-one (23a), *rel*-(1*S*,3a*R*,7*S*,7a*R*)-1,2,3,6,7,7a-Hexahydro-1,7-dimethyl-7,3a-(epoxymethano)-3a*H*-inden-9-one (24a), and *rel*-(1*S*,4a*R*,8a*R*)-1,5,6,7,8,8a-Hexahydro-

1-methyl-2*H*-1,4a-(epoxymethano)naphthalen-9-one (25a). To a solution of 5.67 g (17.8 mmol) of **13** in 300 mL of dry benzene under reflux in an argon atmosphere was added a solution of 11 g (37.9 mmol) of tri-*n*-butyltin hydride[27] and 5 mg of AIBN in 30 mL of dry benzene via syringe pump at a rate of 1.67 mL h^{-1}. The resulting solution was heated under reflux for 1 h and the solvent was removed in vacuo. The residue was chromatographed over 100 g of silica gel (eluted with ethyl acetate–hexane; 1:15) to give 3.0 g (87%) of a mixture of **22a–25a**. The ratio of **22a**:**23a**:**24a**:**25a** was 12:2:6:1 by VPC (6 ft × $^1/_8$ in. 10% OV-101, injector temperature 270 °C, detector temperature 280 °C, column temp 180 °C).

The mixture was recrystallized from hexane to give 1.1 g (32%) of **23a** as a white solid: mp 105–107 °C; IR (CH_2Cl_2) 1770 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.97 (d, J = 7.4 Hz, 3 H, CH_3), 1.58 (s, 3 H, CH_3), 1.36–2.49 (m, 8 H), 5.63 (dt, J = 9.2, 3.2 Hz, 1 H, =CH), 6.00 (dt, J = 9.2, 2 Hz, 1 H, =CH); ^{13}C NMR ($CDCl_3$) δ 16.1 (q), 21.1 (q), 27.0 (t), 33.9 (d), 34.9 (t), 41.91 (t), 55.2 (s), 58.1 (d), 83.6 (s), 127.0 (d), 132.0 (d), 180.0 (s); mass spectrum, m/e (relative intensity) 148 (26, $M^+ - CO_2$), 133 (41), 106 (44), 105 (43), 91 (100), 79 (15), 77 (14), 65 (9), 55 (10); t_R(VPC) 8 min. Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.96; H, 8.41. Found: C, 75.50; H, 8.32.

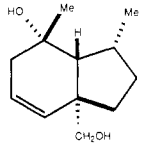
Pure samples of **24a** and **25a** were prepared by gas chromatography.

Lactone **24a**: ^1H NMR ($CDCl_3$) δ 1.09 (d, J = 6.1 Hz, 3 H, CH_3), 1.48 (s, 3 H, CH_3), 1.2–2.48 (m, 8 H), 5.65 (dt, J = 9.3, 3.3 Hz, 1 H, =CH), 5.6 (dt, J = 9.3, 2.1 Hz, 1 H, =CH); mass spectrum, m/e (relative intensity) 148 (24, $M^+ - CO_2$), 133 (46), 106 (39), 105 (33), 91 (100), 79 (13), 77 (12); t_R(VPC) 7 min.

Lactone **25a**: ^1H NMR ($CDCl_3$) δ 1.36 (s, 3 H, CH_3), 0.85–2.28 (m, 9 H), 2.32–2.40 (m, 2 H, CH_2), 5.59 (dt, J = 9.3, 1.7 Hz, 1 H =CH), 5.71 (dt, J = 9.3, 3.0 Hz, 1 H, =CH); mass spectrum, m/e (relative intensity) 148 (28, $M - CO_2$), 133 (38), 119 (15), 106 (37), 105 (52), 91 (100), 79 (16), 77 (14), 65 (8), 55 (7); t_R(VPC) 9 min.

The presence of **22a** was inferred from the signal at δ 4.8–5.18 (=CH_2) in the 60-MHz NMR spectrum of the product mixture and GC-MS: m/e (relative intensity) 148 (3, $M^+ - CO_2$), 133 (11), 107 (57), 91 (100), 79 (32), 65 (6), 55 (19); t_R(VPC) 6 min.

***rel*-(1*R*,3a*R*,7*S*,7a*R*)-1,2,3,6,7,7a-Hexahydro-7-hydroxy-3a-(hydroxymethyl)-1,7-dimethyl-3a*H*-indene (x) and *rel*-(1*S*,4a*R*,8a*R*)-1,5,6,7,8,8a-Hexahydro-1-hydroxy-4a-(hydroxymethyl)-1-methyl-2*H*-naphthalene (26).** To a suspension of 453 mg (11.9 mmol) of lithium aluminum hydride in 10 mL of tetrahydrofuran was added a solution of 1.12 g (5.85 mmol) of **22a–25a** (1:2:3.5:5.8, from mother liquor of cyclization of **13**) in 25 mL of tetrahydrofuran over a 30-min period. The resulting solution was heated under reflux for another 1 h and cooled to room temperature. To the reaction were added 0.4 mL of water, 0.4 mL of 3 N aqueous sodium hydroxide, and 1 mL of water, followed by filtration. The ether solution was dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over 25 g of silica gel (eluted with ethyl acetate–hexane, 1:1) followed by medium pressure chromatography over a Lobar size B column (eluted with ethyl acetate–hexane, 1:1.3) to give 310 mg (27%) of x as a white solid: mp 135–136 °C; IR (CH_2Cl_2) 3390 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (d, J = 7.8 Hz, 3 H, CH_3), 1.17–2.54 (m with s at δ 1.43, 11 H), 3.0–3.2 (br s, 2 H, OH), 3.35 and 3.93 (AB q, J = 12.5 Hz, 2 H, CH_2O), 5.71 (dt, J = 9.1, 1.7 Hz, 1 H, =CH), 5.81 (dt, J = 9.1, 2.9 Hz, 1 H, =CH). Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.41; H, 10.27. Found: C, 73.25; H, 10.24. Continued elution gave 723 mg of a mixture of alcohols, which was recrystallized from ethyl acetate and hexane to give 312 mg (27%) of pure **26**: mp 136–137 °C; IR (CH_2Cl_2) 3640, 3480 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (s, 3 H, CH_3), 1.3–1.98 (m, 9 H), 2.15–2.43 (m, 2 H, =CCH_2), 2.67–2.95 (br s, 2 H, OH), 3.2 and 4.19 (AB q, J = 11.4 Hz, 2 H, CH_2O), 5.49 (dt, J = 9.5, 1.7 Hz, 1 H, =CH), 5.83 (dt, J = 9.5, 3.3 Hz, 1 H, =CH); ^{13}C NMR ($CDCl_3$) δ 20 (q), 21 (t), 27 (t), 29 (t), 40 (t), 41 (s), 43 (t), 51 (d), 63 (t), 69 (s), 128 (d), 132.5 (d); exact mass calcd for $C_{12}H_{20}O_2$ m/e 196.1545, found m/e 196.1504. Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.41; H, 10.27. Found: C, 72.84; H, 9.95.



x

***rel*-(1*S*,5*S*,8*S*)-1-(3-Butenyl)-8-iodo-5-methoxy-6-oxabicyclo[3.2.1]oct-2-en-7-one (14).** To a solution of 3.0 g (19.7 mmol) of *m*-anisic acid (**8**) in 35 mL of tetrahydrofuran and 250 mL of ammonia was added 543 mg (77.6 mmol) of lithium metal in small portions. The solution was stirred for 10 min followed by the addition of 8.0 g (59.3 mmol) of 3-butenyl bromide. The resulting solution was stirred under reflux for 1 h followed by the addition of 4.14 g (78.1 mmol) of ammonium chloride. The ammonia was allowed to evaporate. The residue was dissolved in 100 mL of water and acidified with 3 N aqueous hydrochloric acid. The resulting oil was extracted with three 100-mL portions of ether. The ether extracts were washed with three 20-mL portions of brine, dried (Na_2SO_4), and concentrated until about 150 mL of ether remained. [On one occasion, a portion of the solution was concentrated to afford crude **11** as an oil: IR (CH_2Cl_2) 3300–2500 (br), 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.2–2.3 (m, 4 H), 2.7 (m, 2 H, =CCH_2), 3.4 (s, 3 H, OCH_3), 4.7 (br s, 1 H, =CH), 5.0 (m, 2 H, =CH_2), 5.8 (m, 3 H, CH=CH and =CH), 9.5 (br s, 1 H, COOH); exact mass calcd for $C_{12}H_{16}O_3$ m/e 208.1099, found m/e 208.1053].

To the solution of crude acid **11** was added 50 mL of aqueous saturated sodium bicarbonate. The resulting mixture was stirred for 10 min followed by the addition of 5.51 g (2.18 mmol) of iodine. The reaction mixture was stirred at 0 °C for 2.5 h, diluted with 100 mL of ether, washed with two 250-mL portions of saturated aqueous sodium bisulfite and two 250-mL portions of brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed over 30 g of silica gel to give 4.36 (66%) of **14** as a colorless oil: IR (CH_2CH_2) 1785 cm^{-1}; ^1H NMR (CCl_4) δ 1.4–2.3 (m, 4 H, CH_2CH_2), 2.7 (m, 2 H, =CCH_2C=), 3.43 (s, 3 H, OCH_3), 4.43 (br s, 1 H, CHI), 4.9–6.0 (m, 5 H, =CH and =CH_2). Lactone **14** darkened quickly on standing and was used directly in the following reaction.

Cyclization of Iodo Lactone 14: *rel*-(1*R*,3a*R*,7*S*,7a*R*)-1,2,3,6,7,7a-Hexahydro-7-methoxy-1-methyl-7,3a-(epoxymethano)-3a*H*-inden-9-one (23b), *rel*-(1*S*,3a*R*,7*S*,7a*R*)-1,2,3,6,7,7a-Hexahydro-7-methoxy-1-methyl-7,3a-(epoxymethano)-3a*H*-inden-9-one (24b), and *rel*-(1*S*,4a*R*,8a*R*)-1,5,6,7,8,8a-Hexahydro-1-methoxy-2*H*-1,4a-(epoxymethano)naphthalen-9-one (25b). To a solution of 2.0 g (5.9 mmol) of **14** in 100 mL of dry benzene heated under reflux was added a solution of 4.4 g (15.1 mmol) of tri-*n*-butyltin hydride and 5 mg of AIBN in 50 mL of dry benzene via a syringe pump at a rate of 5.1 mL h^{-1}. The solvent was removed in vacuo. The residue was chromatographed over 40 g of silica gel (eluted with ethyl acetate–hexane, 1:10) to give 1.05 g (85%) of a mixture of **22b**, **23b**, **24b**, and **25b** in an 8:9:1:14 ratio by VPC (10% OV-101, injector temperature 190 °C) and the NMR integration of the signals at δ 4.77–5.23 and δ 5.33–6.1.

Pure samples of **23b**, **24b**, and **25b** were prepared by VPC: IR (CH_2Cl_2, mixture) 1770 cm^{-1}. Lactone **23b**: ^1H NMR ($CDCl_3$) δ 1.04 (d, J = 6.5 Hz, 3 H, CH_3), 1.1–3.0 (m, 8 H), 3.53 (s, 3 H, OCH_3), 5.75 (dt, J = 9, 3 H, 1 H, =CH), 6.02 (dm, J = 9 Hz, 1 H, =CH); t_R(VPC) 5.4 min. Lactone **24b**: ^1H NMR ($CDCl_3$) δ 1.09 (d, J = 6 Hz, 3 H, CH_3), 1.26–3.0 (m, 8 H), 3.55 (s, 3 H, OCH_3), 5.78 (dt, J = 9, 3 Hz, 1 H, =CH), 5.96 (dm, J = 9 Hz, 1 H, =CH); mass spectrum, m/e (relative intensity) 164 (16, $M - CO_2$), 149 (6), 133 (6), 121 (41), 109 (100), 94 (46); t_R(VPC) 4.6 min. Lactone **24c**: ^1H NMR ($CDCl_3$) δ 1.0–3.0 (m, 11 H), 3.54 (s, 3 H, OCH_3), 5.67 (dm, J = 9 Hz, 1 H, =CH), 5.80 (dt, J = 9, 3 Hz, 1 H, =CH); mass spectrum, m/e (relative intensity) 164 (72, $M - CO_2$), 133 (32), 121 (56), 104 (27), 91 (100), 79 (32), 67 (11); t_R(VPC) 6.2 min.

The presence of lactone **22a** was inferred by signals at δ 4.77–5.17 in the product mixture. A sample of lactone **22a** was obtained in one case merely by allowing acid **12** to stand overnight: IR (CH_2Cl_2) 1775 cm^{-1}; ^1H NMR (CCl_4) δ 1.5–2.33 (m, 6 H), 2.43–2.66 (m, 2 H, =CCH_2), 3.42 (s, 3 H, OCH_2), 4.77–5.17 (m, 2 H, =CH_2), 5.56–6.03 (m, 3 H, =CH); mass spectrum, m/e (relative intensity) 162 (43, $M - CO_2H$), 147 (13), 121 (100), 109

(27) Kuivila, H. G. *Synthesis* **1970**, 499.

(27), 91 (56), 77 (18); t_R(VPC) 4.6 min.

1-[2-(1,3-Dioxolan-2-yl)ethyl]-2,5-cyclohexadiene-1-carboxylic Acid (15). To a solution of 12.2 g (0.1 mol) of benzoic acid (**9**) in 100 mL of dry tetrahydrofuran and 1000 mL of ammonia was added 2.1 g (0.3 mol) of lithium metal in small portions. The solution was stirred for 10 min followed by the addition of 45 g (0.25 mol) of 2-(2-bromoethyl)-1,3-dioxolane.[28] The resulting solution was stirred under reflux for 1 h followed by the addition of 15.3 g (0.29 mmol) of ammonium chloride. The ammonia was allowed to evaporate and traces were removed in vacuo. The residue was dissolved in 300 mL of water and extracted with two 200-mL portions of dichloromethane. The water layer was acidified with 3 N aqueous hydrochloric acid and extracted with three 300-mL portions of dichloromethane. The combined dichloromethane extracts were washed with three 500-mL portions of brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed over 100 g of silica gel (eluted with ethyl acetate–hexane, 1:1) to give 21.1 g (94%) of acid **15** as a pale yellow oil: IR (neat) 3300–2500 (br), 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27–2.0 (m, 4 H, CH_2), 2.45–2.67 (m, 2 H, $=CCH_2$), 3.63–4.05 (m, 4 H, OCH_2), 4.77 (t, J = 4.5 Hz, 1 H, OCHO), 5.4–6.05 (m, 4 H, =CH), 11.05 (br s, 1 H, CO_2H); exact mass calcd for $C_{12}H_{16}O_4$ m/e 224.1055, found m/e 224.1051.

***N*-[(1-[2-(1,3-Dioxolan-2-yl)ethyl]-2,5-cyclohexadien-1-yl)carbonyl]pyrrolidine (16).** To a solution of 21.1 g (94.2 mmol) of acid **15**, 8.67 g (122 mmol) of pyrrolidine, and 31.0 g (113 mmol) of diphenyl phosphorylaziate in 200 mL of *N*,*N*-dimethylformamide cooled in an ice–water bath was added 20.9 g (207 mmol) of triethylamine dropwise over a 20-min period. The reaction mixture was stirred at 0 °C for 3 h, diluted with 600 mL of ether, washed with three 450-mL portions of brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was filtered through 100 g of silica gel (eluted with 500 mL of dichloromethane and ethyl acetate–hexane, 1:1) to give 19.2 g (74%) of amide **16** as a white solid: mp 79–80 °C; IR (CH_2Cl_2) 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.4–2.1 (m, 8 H), 2.53–2.83 (m, 2 H, $=CCH_2$), 3.33–3.66 (m, 4 H, NCH_2), 3.66–4.1 (m, 4 H, OCH_2), 4.87 (t, J = 5.4 Hz, 1 H, OCHO), 5.48 (dt, J = 9.2, 1.2 Hz, 1 H, =CH), 5.93 (dt, J = 9.2, 3 Hz, 1 H, =CH); mass spectrum, m/e (relative intensity) 173 (29), 142 (26), 117 (98), 98 (93), 91 (100), 73 (74), 55 (84). Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.28; H, 8.36. Found: C, 69.13; H, 8.36.

***rel*-(1*S*,5*S*,8*R*)-1-[2-(1,3-Dioxolan-2-yl)ethyl]-8-iodo-6-oxabicyclo[3.2.1]oct-2-en-7-one (17).** To a mixture of 16.2 g (58.5 mmol) of amide **16** in 350 mL of tetrahydrofuran and 350 mL of water was added 44.3 g (0.17 mol) of iodine in one portion. The reaction mixture was stirred at room temperature for 18 h, diluted with 250 mL of ether, washed with three 450-mL portions of saturated aqueous sodium bisulfite and three 450-mL portions of brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed over 100 g of silica gel (eluted with dichloromethane) to give 14.3 g (70%) of **17** as a white solid: mp 116–117 °C; IR (CH_2Cl_2) 1780 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.3–2.43 (m, 4 H, CH_2), 2.5–2.8 (m, 2 H, $=CCH_2$), 3.66–4.2 (m, 4 H, OCH_2), 4.47 (dd, J = 4.8, 1.6 Hz, 1 H, CHI), 4.6–4.97 (m, 2 H, OCH, and OCHO), 5.38 (dm, J = 10 Hz, 1 H, =CH), 5.85 (dm, J = 10 Hz, 1 H, =CH). Anal. Calcd for $C_{12}H_{15}O_4I$: C, 41.16; H, 4.34. Found: C, 41.34; H, 4.31.

***rel*-(1*S*,5*S*,8*R*)-8-Iodo-1-(3-oxopropyl)-6-oxabicyclo[3.2.1]oct-2-en-7-one (18).** A solution of 4.98 g (15.2 mmol) of acetal **17** in 100 mL of 80% formic acid–water was stirred at 0 °C for 4.5 h. The reaction mixture was diluted with 400 mL of dichloromethane, washed with three 200-mL portions of brine, three 150-mL portions of saturated aqueous sodium bicarbonate, and two 150-mL portions of brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed over 100 g of silica gel (eluted with dichloromethane) to give 3.95 g (91%) of **18** as a white solid: mp 77–78 °C; IR (CH_2Cl_2) 1785, 1730 cm^{-1}; ^1H NMR (CCl_4) δ 1.5–2.8 (m, 6 H, CH_2CH_2, and $=CCH_2$), 4.38 (dd, J = 6, 1.7 Hz, 1 H, CHI), 4.57–4.89 (m, 1 H, CHO), 5.2–6.1 (m, 2 H, =CH), 9.8 (br s, 1 H, CH=O); mass spectrum, m/e (relative intensity) 135 (6, M – CO_2I), 128 (6), 119 (100), 105 (11), 91 (28), 85 (54), 67 (11). Anal. Calcd for $C_{10}H_{11}O_3I$: C, 39.22; H, 3.62. Found: C, 39.15; H, 3.37.

***rel*-(1*S*,5*S*,8*R*)-1-(3-Butenyl)-8-iodo-6-oxabicyclo[3.2.1]-oct-2-en-7-one (19).** To a solution of 0.4 mL of dimethyl sulfoxide in 1 mL of tetrahydrofuran cooled in an ice–water bath was added 0.33 mL (0.54 mmol) of *n*-butyllithium dropwise over a 10-min period. The resulting solution was stirred for another 10 min. To a mixture of 226 mg (0.63 mmol) of methyltriphenylphosphonium bromide in 1 mL of tetrahydrofuran was added the solution of dimsyllithium dropwise via syringe over a 10-min period. The resulting mixture was stirred for another 15 min and cooled in a dry ice–ether bath. To the mixture was added a solution of 140 mg (0.46 mmol) of aldehyde **18** in 2 mL of tetrahydrofuran dropwise over a 5-min period. The reaction mixture was stirred until the yellow color disappeared. The resulting 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, 1:20) to give 41 mg (30%) of **19** as a white solid: mp 50–52 °C; IR (CH_2Cl_2) 1790, 930 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.9–2.3 (m, 4 H, CH_2CH_2), 2.35–3.05 (m, 2 H, $=CCH_2$), 4.43 (dd, J = 6, 1.6 Hz, 1 H, CHI), 4.55–4.78 (m, 1 H, OCH), 4.78–6.2 (m, 5 H, =CH and $=CH_2$); mass spectrum, m/e (relative intensity) 133 (20, M – CO_2I), 123 (25), 77 (47), 65 (43), 55 (10).

Cyclization of Iodo Lactone 19: *rel*-(1*R*,3a*R*,7*S*,7a*R*)-1,2,3,6,7,7a-Hexahydro-1-methyl-7,3a-(epoxymethano)-3a*H*-inden-9-one (23c), *rel*-(1*S*,3a*R*,7*S*,7a*R*)-1,2,3,6,7,7a-Hexahydro-1-methyl-7,3a-(epoxymethano)-3a*H*-inden-9-one (24c), and *rel*-(1*S*,4a*R*,8a*R*)-1,5,6,7,8,8a-Hexahydro-2*H*-1,4a-(epoxymethano)naphthalen-9-one (25c). To a solution of 151 mg (0.50 mmol) of **19** in 8 mL of dry benzene under reflux in an argon atmosphere was added a solution of 275 mg (0.94 mmol) of tri-*n*-butyltin hydride and 5 mg of AIBN in 10 mL of dry benzene via syringe pump at a rate of 1.2 mL h^{-1}. The resulting solution was heated under reflux for another 1 h. The solvent was removed under vacuum. The residue was chromatographed over 10 g of silica gel (eluted with ethyl acetate–hexane, 1:20) to give 78 mg (88%) of **23c**, **24c**, and **25c** in a 63:7:30 ratio, respectively, by VPC (3% SE-30, injector temperature 270 °C, detector temperature 280 °C, column temperature 150 °C).

Pure samples of **23c** and **25c** were prepared by VPC. Lactone **23c**: ^1H NMR ($CDCl_3$) δ 0.93 (d, J = 7.1 Hz, 3 H, CH_3), 0.9–1.62 (m, 2 H), 1.97–2.55 (m, 6 H), 4.69 (m, 1 H, OCH), 5.6 (dtd, J = 9.0, 3.2, 1.3 Hz, 1 H, =CH), 5.98 (dt, J = 9.0, 1.9 Hz, 1 H, =CH); mass spectrum, m/e (relative intensity) 134 (24, M – CO_2), 119 (86), 92 (57), 91 (100), 79 (16), 77 (16), 41 (27), 39 (23); t_R(VPC) 3.8 min. Lactone **25c**: ^1H NMR ($CDCl_3$) δ 0.89–2.14 (m, 9 H), 2.37–2.38 (m, 2 H, $=CCH_2$), 4.27–4.30 (m, 1 H, OCH), 5.53 (dt, J = 9.2, 1.7 Hz, 1 H, =CH), 5.62 (dtd, J = 9.2, 3.0, 1.5 Hz, 1 H, =CH); mass spectrum, m/e (relative intensity) 134 (25, M – CO_2), 119 (18), 105 (19), 92 (55), 91 (100), 78 (13), 41 (12), 39 (13): t_R(VPC) 4.5 min.

The presence of **24c** was inferred from its GC-MS: mass spectrum, m/e (relative intensity) 134 (16, M – CO_2), 119 (67), 91 (100), 77 (10), 41 (16); t_R(VPC) 3.0 min.

1,1-Dimethylethyl 5-[*rel*-(1*S*,5*S*,8*S*)-8-Iodo-7-oxo-6-oxabicyclo[3.2.1]oct-2-en-1-yl]-2(*E*)-pentenoate (27). To a solution of 4.01 g (13.1 mmol) of aldehyde **18** in 60 mL of benzene was added 5.88 g (15.6 mmol) of [(*tert*-butoxycarbonyl)-methylene)]triphenylphosphorane.[29] The reaction mixture was heated at 60 °C for 3.5 h. The solvent was removed in vacuo. The residue was chromatographed over 100 g of silica gel (eluted with dichloromethane) to give 4.83 g (91%) of **27** as a pale yellow oil: IR (CH_2Cl_2) 1785, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.3–2.33 (m with s at δ 1.43, 13 H, CH_2CH_2 and CH_3), 2.4–2.76 (m, 2 H, $=CCH_2$), 4.38 (dd, J = 6, 1.6 Hz, 1 H, CHI), 4.5–4.83 (m, 1 H, CHO), 5.15–5.97 (m, 3 H, =CH and $=CHCO_2$), 6.83 (dt, J = 16, 6 Hz, 1 H, $CH=CCO_2$); mass spectrum, m/e (relative intensity) 331 (9, M – OC_4H_9), 177 (29), 159 (27), 128 (14), 117 (29), 91 (100), 56 (17).

***rel*-(1*S*,3a*S*,7*S*,7a*R*)-1,1-Dimethylethyl 1,2,3,6,7,7a-Hexahydro-9-oxo-7,3a-(epoxymethano)-3a*H*-indene-1-acetate (28).** To a solution of 4.49 g (11.1 mmol) of **27** and 5 mg of AIBN

(28) Büchi, G.; Wüest, H. *J. Org. Chem.* **1969**, *34*, 1122.

(29) Griffiths, G. F.; Kenner, G. W.; McCombie, S. W.; Smith, K. M. *Tetrahedron* **1976**, *32*, 275.

in 80 mL of dry benzene was added 5.5 g (18.9 mmol) of tri-*n*-butyltin hydride in one portion. The reaction mixture was heated under reflux for 2 h and the solvent was removed in vacuo. The residue was partitioned between 100 mL of hexane and 100 mL of acetonitrile. The hexane layer was extracted with two 75-mL portions of acetonitrile. The combined acetonitrile extracts were concentrated in vacuo. The residue was chromatographed over 40 g of silica gel (eluted with ethyl acetate–hexane, 1:7) to give 2.95 g (91%) of a 7:1 mixture of esters **28** and **29**, respectively. The ratio of **28** and **29** was determined by the integration of peaks at δ 4.71–4.76. The mixture was recrystallized to give 2.07 g (67%) of pure **28**: mp 75–76 °C; IR (CH_2Cl_2) 1770, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.44 (s, 9 H, $C(CH_3)_3$), 1.17–2.66 (m, 10 H), 4.71–4.74 (m, 1 H, CHO), 5.57 (dt, J = 10, 2.4 Hz, 1 H, =CH), 6.06 (dt, J = 10, 1.4 Hz, 1 H, =CH). Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 68.63; H, 8.16.

***rel*-(3*S*,3a*R*,5a*R*,8a*S*,8b*R*)-3a,4,5,8,8a,8b-Hexahydro-3,5a-methano-5a*H*-cyclopenta[*de*]-1-benzopyran-2,9(3*H*)-dione (30).** To a solution of 994 mg (6.1 mmol) of 1,1,1,3,3,3-hexamethyldisilazane in 15 mL of ether cooled in an ice–water bath was added 3.3 mL (5.4 mmol) of 1.64 M *n*-butyllithium in hexane, dropwise over a 10-min period. To the resulting solution of lithium hexamethyldisilazide heated under reflux was added a solution of 250 mg (0.90 mmol) of **28** and **29** (7:1, respectively) in 50 mL of ether dropwise over a 1.5-h period. The reaction mixture was heated under reflux for another 1 h and cooled to room temperature. To the resulting solution was added 12 mL of acetic acid dropwise over a 5-min period. The reaction mixture was diluted with 75 mL of ether, washed with three 100-mL portions of brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed over 20 g of silica gel (eluted with ethyl acetate–hexane, 1:4) to give an inseparable mixture of β-keto esters.

To a solution of the mixture of keto esters in 1 mL of dichloromethane was added 90 μL of trifluoroacetic acid in one portion. The reaction mixture was stirred at room temperature for 18 h, diluted with 100 mL of ether, washed with two 100-mL portions of brine, and concentrated in vacuo. The residue was chromatographed over 20 g of silica gel (eluted with ethyl acetate–hexane, 1:2) to give 155 mg (72%) of **30** as a white solid: mp 111–112 °C; IR (CH_2Cl_2) 1765, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.0–2.67 (m, 7 H), 2.8 (m, 1 H), 3.3 (d, J = 2.3 Hz, 1 H, COCHCO), 4.8–5.25 (m, 1 H, OCH), 5.65 (dt, J = 9.5, 2.7 Hz, 1 H, =CH), 6.05 (dm, J = 9.5 Hz, 1 H, =CH); mass spectrum, m/e (relative intensity) 204 (18), 131 (28), 120 (18), 117 (100), 104 (22), 91 (94); exact mass calcd for $C_{12}H_{12}O_3$ m/e 204.0786, found m/e 204.0783.

1-[2-(1,3-Dioxolan-2-yl)ethyl]-2,3-dimethyl-2,5-cyclohexadiene-1-carboxylic Acid (32). To a solution of 0.3 mL (1.82 mmol) of diisopropylamine in 3 mL of tetrahydrofuran cooled in a dry ice–carbon tetrachloride bath was added 1 mL (1.63 mmol) of *n*-butyllithium dropwise over a 10-min period. The resulting solution was stirred for another 10 min followed by the addition of a solution of 122 mg (0.8 mmol) of 2,3-dimethylcyclohexa-2,5-diene-1-carboxylic acid[9] and 0.15 mL (0.84 mmol) of HMPA in 3 mL of tetrahydrofuran dropwise over a 10-min period. The resulting solution was stirred for another 30 min followed by the addition of 192 mg (1.07 mmol) of 2-(2-bromoethyl)-1,3-dioxolane in 2 mL of tetrahydrofuran dropwise over a 5-min period. The reaction mixture was stirred at room temperature for 2 h, diluted with 50 mL of ether, acidified with 3 N aqueous hydrochloric acid, washed with three 50-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, 1:1.2) to give 163 mg (80%) of **32**: IR (CH_2Cl_2) 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.0–2.3 (m, 10 H, CH_2CH_2, and CH_3), 2.4–2.8 (s, 2 H, $=CCH_2C=$), 3.7–4.2 (m, 4 H, CH_2O), 4.8 (t, J = 4 Hz, 1 H, CHO), 5.41 (dm, J = 9 Hz, 1 H, =CH), 5.9 (dt, J = 9, 3 Hz, 1 H, =CH), 11.21 (s, 1 H, CO_2H); mass spectrum, m/e (relative intensity) 251 (2, M – H), 145 (93), 119 (100), 107 (30), 105 (26), 99 (94), 91 (31), 73 (51).

***rel*-(1*S*,5*S*,8*S*)-5,8-Dimethyl-8-iodo-1-(3-oxopropyl)-6-oxabicyclo[3.2.1]oct-2-en-7-one (33).** To a solution of 1.6 g (6.3 mmol) of iodine and 3.2 g (19.3 mmol) of potassium iodide in 20 mL of water cooled in an ice–water bath was added a solution of 820 mg (3.3 mmol) of **32** in 20 mL of saturated aqueous sodium bicarbonate. The reaction mixture was stirred at 0 °C for 5 h, diluted with 150 mL of ether, washed with three 100-mL portions of saturated aqueous sodium bisulfite and two 100-mL portions of brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed over 20 g of silica gel (eluted with ethyl acetate–hexane, 1:8).

The resulting mixture of **33** and the corresponding acetal was dissolved in 20 mL of 80% aqueous formic acid. The reaction mixture was stirred at 0 °C for 4 h, diluted with 150 mL of ether, washed with four 100-mL portions of brine, three 100-mL portions of saturated aqueous sodium bicarbonate, and three 100-mL portions of brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed over 20 g of silica gel (eluted with ethyl acetate–hexane, 1:6) to give 665 mg (61%) of **33** as a white solid: mp 103–104 °C; IR (CH_2Cl_2) 1780, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.43 (s, 3 H, $OCCH_3$), 1.63–3.1 (m with s at δ 2.01, 9 H, CH_2CH_2, $=CCH_2$ and CH_3), 5.6 (dt, J = 9, 1 Hz, 1 H, =CH), 5.93 (dt, J = 9, 3 Hz, 1 H, =CH), 9.83 (s, 1 H, CHO). Anal. Calcd for $C_{12}H_{15}O_3I$: C, 43.13; H, 4.52. Found: C, 43.44; H, 4.62.

***rel*-(1*S*,5*S*,8*S*)-1,1-Dimethylethyl 5-(8-Iodo-7-oxo-5,8-dimethyl-6-oxabicyclo[3.2.1]oct-2-en-1-yl)-2(*E*)-pentenoate (34).** A solution of 124 mg (0.37 mmol) of aldehyde **33** and 167 mg (0.44 mmol) of [(*tert*-butoxycarbonyl)methylene]triphenylphosphorane in 5 mL of benzene was heated at 55 °C under argon for 4 h. The solvent was removed in vacuo and the residue was chromatographed over 10 g of silica gel (eluted with dichloromethane) to give 151 mg (94%) of iodo ester **34** as a white solid: mp 89–90 °C; IR (CH_2Cl_2) 1780, 1710 cm^{-1}; NMR ($CDCl_3$ δ 1.44 (s, 3 H, CH_3), 1.46 (s, 9 H, *t*-Bu), 1.65–2.9 (m with s at δ 1.97, 9 H, CH_2CH_2, $=CCH_2$ and $ICCH_3$), 5.5–6.1 (m, 3 H, CH=CH, and $=CHCO_2$), 6.6–7.02 (m, 1 H, $CH=CCO_2$); mass spectrum, m/e (relative intensity) 359 (15, M – OC_4H_9), 205 (40), 145 (26), 119 (100), 105 (15), 57 (37).

***rel*-(1*S*,3a*S*,7*S*,7a*R*)-1,1-Dimethylethyl 1,2,3,6,7,7a-Hexahydro-7,7a-dimethyl-9-oxo-7,3a-(epoxymethano)-3a*H*-indene-1-acetate (35).** To a solution of 602 mg (1.39 mmol) of ester **34** in 20 mL of dry benzene under reflux was added a solution of 825 mg (2.8 mmol) of tri-*n*-butyltin hydride and 5 mg of AIBN in 10 mL of dry benzene via syringe pump at a rate of 1.2 mL h^{-1}. The solvent was removed in vacuo. The residue was chromatographed over 30 g of silica gel (eluted with ethyl acetate–hexane, 1:7) to give 376 mg (88%) of a 3:1 mixture of ester **35** and **36**, respectively. The ratio of **35**:**36** was determined by the integration of singlets at δ 0.97 and 0.91. The mixture was recrystallized from hexane–ethyl acetate to give 162 mg of pure **35** as a white solid: mp 88–89 °C; IR (CH_2Cl_2) 1775, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.97 (s, 3 H, CH_3), 1.4 (s, 9 H, *t*-Bu), 1.43 (s, 3 H, CH_3CO), 1.5–2.8 (m, 9 H), 5.65–5.85 (m, 2 H, =CH); mass spectrum, m/e (relative intensity) 233 (16, M – OC_4H_9), 206 (90), 191 (22), 173 (22), 147 (31), 145 (65), 131 (100), 119 (41), 57 (19). Anal. Calcd for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Foundb C, 70.75; H, 8.69.

***rel*-(3*S*,3a*R*,5a*R*,8a*S*,8b*R*)-3a,4,5,8,8a,8b-Hexahydro-8a,8b-dimethyl-5a*H*-cyclopenta[*de*]-1-benzopyran-2,9-(3*H*)-dione (37).** To a solution of 994 mg (6.18 mmol) of 1,1,1,3,3,3-hexamethyldisilazane in 15 mL of ether cooled in an ice–water bath was added 3.3 mL (5.0 mmol) of 1.5 M *n*-butyllithium in hexane dropwise over a 10-min period. The reaction temperature was increased to reflux and a solution of 130 mg (0.42 mmol) of **35** 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 the reaction mixture was added 5 mL of acetic acid dropwise over a 5-min period. The resulting solution 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 an inseparable mixture of β-keto esters.

To a solution of the β-keto esters in 1 mL of dichloromethane was added 0.15 mL (1.95 mmol) of trifluoroacetic acid dropwise over a 5-min period. The reaction mixture was stirred at room temperature for 12 h. The reaction was diluted with 75 mL of ethyl acetate, washed with three 75-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, 1:2) to give 61 mg (61%) of **37**: mp 137–138 °C; IR (CH_2Cl_2) 1765, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.2–2.8 (m, 7 H),

1.4 (s, 3 H, CH_3), 1.53 (s, 3 H, CH_3CO), 3.17 (s, 1 H, COCHCO), 5.89 (dt, J = 10, 3 Hz, 1 H, =CH), 5.95 (dm, J = 10 Hz, 1 H, =CH); mass spectrum, m/e (relative intensity) 232 (16), 188 (27), 173 (23), 144 (49), 131 (54), 129 (21), 119 (100), 105 (69), 91 (28); exact mass calcd for $C_{14}H_{16}O_3$ m/e 232.1099, found m/e 232.1081.

Ethyl 3-(3-Hydroxyprop-1-yn-1-yl)benzoate (39). To a mixture of 3.9 g (14.18 mmol) of ethyl *m*-iodobenzoate, 214 mg of bis(triphenylphosphine)palladium(II) chloride, and 20 mg of cuprous iodide in 60 mL of diethylamine was added 1.03 g (18.45 mmol) of propargyl alcohol in one portion. The reaction mixture was stirred at room temperature for 1.5 h. The solvent was removed in vacuo. The residue was chromatographed over 30 g of silica gel (eluted with ethyl acetate–hexane, 1:3) to give 2.64 g (92%) of **39**: mp 48–50 °C; IR (neat) 3600, 3350, 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.32 (t, J = 7 Hz, 3 H, $OCCH_3$), 3.9 (s, 1 H, OH), 4.25 (q, J = 7 Hz, 2 H, CO_2CH_2), 4.43 (s, 2 H, $=CCH_2$), 7.17 (t, J = 8 Hz, 1 H, Ar H), 7.43 (dt, J = 8, 1.5 Hz, 1 H, Ar H), 7.83 (dt, J = 8, 1.5 Hz, 1 H, Ar H), 7.88 (d, J = 1.5 Hz, 1 H, Ar H); mass spectrum, m/e (relative intensity) 204 (41), 159 (66), 131 (100), 130 (25), 103 (39), 102 (20), 77 (50); exact mass calcd for $C_{12}H_{12}O_3$ m/e 204.0787, found m/e 204.0776.

Ethyl 3-(3-Hydroxypropyl)benzoate (40). A solution of 2.55 g (12.5 mmol) of ester **39** in 25 mL of ethanol was hydrogenated at 1 atm over 100 mg of 5% palladium on charcoal as a catalyst for 3 h. The solution was filtered and the solvent was removed in vacuo. The residue was chromatographed over 40 g of silica gel (eluted with ethyl acetate–hexane, 1:3) to give 2.37 g (91%) of **40**: IR (neat) 3620, 3330, 1710 cm^{-1}; ^1H NMR (CCl_4) δ 1.33 (t, J = 7 Hz, 3 H, $OCCH_3$), 1.5–2.2 (m, 2 H, CH_2), 2.66 (t, J = 7 Hz, 2 H, CH_2), 3.53 (t, J = 7 Hz, 2 H, CH_2), 3.77 (s, 1 H, OH), 4.24 (q, J = 7 Hz, 2 H, CO_2CH_2), 7.03–7.45 and 7.53–7.97 (m, 4 H, Ar H); mass spectrum, m/e (relative intensity) 208 (34), 190 (27), 163 (87), 162 (78), 145 (77), 135 (41), 117 (89), 105 (41), 91 (100), 77 (49); exact mass calcd for $C_{12}H_{16}O_3$ m/e 208.1100, found m/e 208.1109.

Ethyl 3-[2-(1,3-Dioxolan-2-yl)ethyl]benzoate (42). To a suspension of 3.67 g (17.1 mmol) of pyridinium chlorochromate[30] in 20 mL of dry dichloromethane was added a solution of 2.32 g (11.2 mmol) of **40** in 5 mL of dry dichloromethane in one portion. The reaction mixture was stirred at room temperature for 4 h, diluted with 50 mL of ether, and filtered through Florisil. The residue was washed with four 100-mL portions of ether. The combined organic solutions were concentrated in vacuo. The residue was chromatographed over 5 g of silica gel (eluted with ethyl acetate–hexane, 1:5) to give 1.28 g (55%) of aldehyde **41** which was used directly in the next reaction: NMR (CCl_4) δ 1.37 (t, J = 7 Hz, 3 H, CH_3), 2.5–3.1 (m, 4 H, CH_2), 4.23 (q, J = 7 Hz, 2 H, OCH_2), 7.15–7.45 (m, 2 H, Ar H), 7.6–7.9 (m, 2 H, Ar H), 9.73 (d, J = 1 Hz, 1 H, CHO).

A mixture of 1.28 g (6.2 mmol) of **41**, 3 mL of ethylene glycol, and 50 mg of *p*-toluenesulfonic acid in 15 mL of benzene was heated under reflux with continuous removal of water for 2.5 h. The reaction mixture was diluted with 100 mL of ether, washed with two 100-mL portions of sodium bicarbonate and two 100-mL portions of brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed over 30 g of silica gel (eluted with ethyl acetate–hexane, 1:5) to give 1.3 g (89%) of **42**: IR (CH_2Cl_2) 1725 cm^{-1}; ^1H NMR (CCl_4) δ 1.35 (t, J = 7 Hz, 3 H, CH_3), 1.7–2.2 (m, 2 H, CH_2), 2.5–3.0 (m, 2 H, CH_2), 3.5–4.1 (m, 4 H, CO_2), 4.23 (q, J = 7 Hz, 2 H, CO_2CH_2), 4.72 (t, J = 4 Hz, 1 H, OCHO), 7.1–7.4 and 7.5–7.9 (m, 4 H, Ar H); mass spectrum, m/e (relative intensity) 250 (11), 205 (14), 119 (16), 100 (60), 87 (15), 73 (100); exact mass calcd for $C_{14}H_{18}O_4$ m/e 250.1205, found m/e 250.1210.

3-[2-(1,3-Dioxolan-2-yl)ethyl]benzoic Acid (43). A mixture of 1.29 g (5.2 mmol) of ester **42** in 20 mL of 5% aqueous sodium hydroxide and 20 mL of methanol was heated under reflux for 1 h. The methanol was removed in vacuo. The residue was diluted with 100 mL of water, acidified with 3 N aqueous hydrochloric acid, extracted with three 100-mL portions of dichloromethane, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed over 30 g of silica gel (eluted with ethyl acetate–hexane, 1:2) to give 992 mg (87%) of acid **43** as a white solid: mp 94–95 °C; IR (CH_2Cl_2) 3300–2500 (br), 1705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.75–2.25 (m, 2 H, CH_2), 2.6–3.1 (m, 2 H, CH_2Ar), 3.7–4.2 (m, 4 H, CH_2O), 4.87 (t, J = 4 Hz, 1 H, OCHO), 7.2–7.6 and 7.7–8.2 (m, 4 H, Ar H), 11.88 (s, 1 H, CO_2H); mass spectrum, m/e (relative intensity) 222 (5), 135 (7), 100 (21), 77 (7), 73 (100); exact mass calcd for $C_{12}H_{14}O_4$ m/e 222.0892, found m/e 222.0876.

3-[2-(1,3-Dioxolan-2-yl)ethyl]-1-methyl-2,5-cyclohexadiene-1-carboxylic Acid (44). To a solution of 493 mg (2.2 mmol) of acid **43** in 10 mL of tetrahydrofuran and 50 mL of ammonia was added 95 mg (13.6 mmol) of lithium metal in small portions. The reaction mixture was stirred for 10 min followed by the addition of 1.37 g (96.4 mmol) of methyl iodide in one portion. The reaction mixture was stirred for 30 min and then quenched with 513 mg (9.7 mmol) of ammonium chloride. The ammonia was allowed to evaporate and traces were removed in vacuo. The residue was dissolved in 150 mL of water and acidified with 3 N aqueous hydrochloric acid. The oil was extracted with three 100-mL portions of dichloromethane. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed over 20 g of silica gel (eluted with ethyl acetate–hexane, 1:1) to give 504 mg of **44**: IR (CH_2Cl_2) 3300–2500 (br), 1715 cm^{-1}; ^1H NMR (CCl_4) δ 1.28 (s, 3 H, CH_3), 1.5–2.33 (m, 4 H, CH_2CH_2), 2.48–2.8 (m, 2 H, $=CCH_2$), 3.6–4.05 (m, 4 H, CH_2O), 4.73 (t, J = 4 Hz, 1 H, OCHO), 5.45 and 5.68 (s, 3 H, =CH), 10.97 (s, 1 H, CO_2H); mass spectrum, m/e (relative intensity) 131 (69), 105 (100), 86 (15), 73 (54).

***rel*-(1*S*,5*S*,8*S*)-5-[2-(1,3-Dioxolan-2-yl)ethyl]-8-iodo-1-methyl-6-oxabicyclo[3.2.1]oct-2-en-7-one (45).** To a solution of 454 mg (1.9 mmol) of acid **44** in 10 mL of saturated aqueous sodium bicarbonate and 16 mL of ether cooled in an ice–water bath was added 510 mg (2.0 mmol) of iodine in one portion. The reaction mixture was stirred at 0 °C for 5 h, diluted with 150 mL of ether, washed with two 75-mL portions of saturated aqueous sodium bisulfite, two 75-mL portions of brine, and two 75-mL portions of saturated aqueous sodium bicarbonate, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed over 20 g of silica gel (eluted with ethyl acetate–hexane, 1:5) to give 548 mg (78%) of **45**: IR (CH_2Cl_2) 1780 cm^{-1}; ^1H NMR (CCl_4) δ 1.28 (s, 3 H, CH_3), 1.5–1.9 (m, 4 H, CH_2CH_2), 2.3–2.6 (m, 2 H, $=CH_2C=$), 3.6–3.95 (m, 4 H, CH_2O), 4.13 (d, J = 1 Hz, 1 H, CHI), 4.6–4.85 (m, 1 H, OCHO), 5.31 (dm, J = 9 Hz, 1 H, =CH), 5.83 (dt, J = 9, 3 Hz, 1 H, =CH); exact mass calcd for $C_{13}H_{17}O_4I$ m/e 364.0172, found m/e 364.0149.

***rel*-(1*S*,5*S*,8*S*)-8-Iodo-1-methyl-5-(3-oxopropyl)-6-oxabicyclo[3.2.1]oct-2-en-7-one (46).** A solution of 495 mg (1.35 mmol) of acetal **45** in 10 mL of 80% aqueous formic acid was stirred at 0 °C for 6 h. The reaction mixture was diluted with 150 mL of ether, washed with three 75-mL portions of brine, three 75-mL portions of saturated sodium bicarbonate, and two 75-mL portions of brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed over 20 g of silica gel (eluted with dichloromethane) to give 380 mg (87%) of **46**: IR (CH_2Cl_2) 1770, 1720 cm^{-1}; ^1H NMR (CCl_4) δ 1.27 (s, 3 H, CH_3), 1.65–2.8 (m, 6 H, CH_2CH_2, and $=CCH_2C=$), 4.19 (d, J = 1 Hz, 1 H, CHI), 5.67 (dm, J = 9 Hz, 1 H, =CH), 5.86 (dt, J = 9, 3 Hz, 1 H, =CH), 9.73 (s, 1 H, CHO); mass spectrum, m/e (relative intensity) 131 (18), 105 (100), 91 (13), 77 (10).

***rel*-(1*S*,5*S*,8*S*)-1,1-Dimethylethyl 5-[8-Iodo-7-oxo-1-methyl-6-oxabicyclo[3.2.1]oct-2-en-5-yl]-2(*E*)-pentenoate (47).** A solution of 302 mg (0.94 mmol) of aldehyde **46** and 483 g (1.29 mmol) of [(*tert*-butoxycarbonyl)methylene]triphenylphosphorane in 6 mL of dry benzene was heated at 60 °C for 4.5 h. The solvent was removed in vacuo. The residue was chromatographed over 20 g of silica gel (eluted with dichloromethane) to give 371 mg (94%) of iodo ester **47**: IR (CH_2Cl_2) 1790, 1715, 1665 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (s, 3 H, CH_3), 1.41 (s, 9 H, *t*-Bu), 1.6–2.6 (m, 6 H CH_2CH_2 and $=CH_2$), 4.15 (d, J = 1 Hz, 1 H, CHI), 5.2–6.0 (m, 3 H, =CH and $=CHCO_2$), 6.75 (dt, J = 16, 6 Hz, 1 H, $CH=CCO_2$); mass spectrum, m/e (relative intensity) 191 (20, M – CO_2I – C_4H_8), 173 (31), 131 (25), 105 (100), 57 (54).

***rel*-(1*R*,3a*S*,7*R*,7a*R*)-1,1-Dimethylethyl 1,2,3,4,7,7a-Hexahydro-7-methyl-8-oxo-3a,7-(epoxymethano)-3a*H*-indene-1-acetate (47) and *rel*-(1*S*,3a*S*,7*R*,7a*R*)-1,1-Dimethylethyl 1,2,3,4,7,7a-Hexahydro-7-methyl-8-oxo-3a,7-(epoxymethano)-3a*H*-indene-1-acetate (48).** To a solution of 310 mg (0.74 mmol) of iodo ester **47** and 5 mg of AIBN in 11 mL of dry benzene under reflux was added a solution of 418 mg (1.43

(30) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.

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).

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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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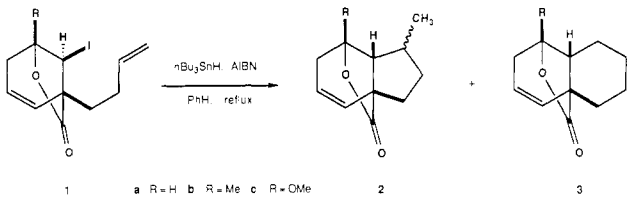
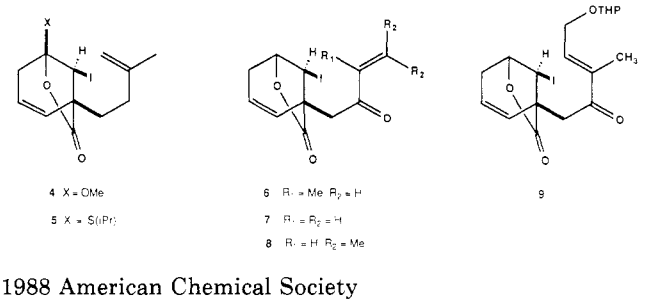
Iodo lactones **4** and **5** were prepared from *m*-anisic acid (**10**) and *m*-(isopropylthio)benzoic acid (**15**), respectively, by using a reductive alkylation–halolactonization–free radical cyclization sequence. Enones **6–9** were prepared from benzoic acid by way of acid chloride **30** by using 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]



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