Pseudoguaianolides. 1. Stereospecific Total Synthesis of the Ambrosanolides *dl*-Ambrosin and *dl*-Damsin[†,1]

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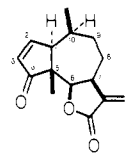
Received December 21, 1981

Abstract: Regio- and stereospecific total syntheses of the sesquiterpene lactones *dl*-ambrosin (**1**) and *dl*-damsin (**2**) are described. Both syntheses start with bromo ketal ester **8** and proceed via the intermediacy of cyclopentenol **4**, the precursor to perhydroazulenone **22**. Elaboration of the α-methylene-γ-butyrolactone functionality and oxidation at C(4) complete the synthesis of *dl*-damsin. Phenylselenenylation of *dl*-damsin and subsequent oxidation and elimination of phenylselenenic acid provide *dl*-ambrosin.

The pseudoguaianolides are a widely distributed class of sesquiterpene lactones[2] first detected in nature before the turn of the century.[3] However, despite their early detection in nature, the existence of the pseudoguaianolide carbon skeleton was only recognized for the first time during the early sixties by Professor Werner Herz and co-workers as a consequence of their work with ambrosin.[4] A combination of chemical studies[4,5] and single-crystal X-ray analysis of 3-bromoambrosin led unambiguously to the relative and absolute configuration of ambrosin depicted in structure **1**.



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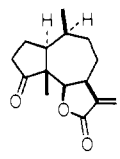

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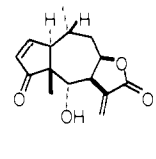

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The pseudoguaianolides can be divided into two groups (ambrosanolides and helenanolides), which differ in stereochemistry at C(10). The ambrosanolides, of which ambrosin (**1**) and damsin (**2**) are representative, have as a characteristic feature at C(10) a β-oriented methyl group, whereas the C(10) methyl group in the helenanolides [cf. helenalin (**3**)] possesses the α orientation. In the latter class, the γ-butyrolactone ring is generally found closed to the oxygen function located at C(8).

The cytotoxic activity found among many of the pseudoguaianolides has been responsible for numerous structure–activity relationship studies during the last decade.[7] It has been shown that the cytotoxic activity of helenalin and ambrosin is primarily due to the presence of the α,β-unsaturated ketone functionality and to a lesser extent the α-methylene-γ-butyrolactone.[8] In contrast to the extensive efforts on the medicinal chemistry front, the array of functional groups located on the perhydroazulene ring system of the pseudoguaianolides coupled with the stereochemical problems associated with elaborating seven-membered rings has been largely responsible for the lack of success at total synthesis prior to 1976.[9]

Our efforts during the past few years have concentrated on developing a route to the pseudoguaianolides that maintained complete stereochemical control during the elaboration of the stereochemistry and the functional groups located on the perhydroazulene ring system. Central to our overall plan was the precondition that our synthetic scheme be general, such that a common synthetic intermediate (cf. **4**) would provide access to both the ambrosanolides and the helenanolides. Cyclopentenol **4** thus became the focal point of our synthetic plan because of its useful structural features. With regard to the ambrosanolides, compound **4** possesses the correct stereochemical assignment at C(1), C(5), and C(10) and has the potential for construction of the seven-membered ring. It was our intention to transform **4** into a suitable keto iodide (cf. **5**), which when submitted to a 7-endo-alkylation would give rise to the perhydroazulene carbon skeleton **6**. The ready availability of **6** would permit completion of the synthesis via generation of the remaining stereochemical centers at C(6) and C(7) for which there was precedent in the literature as a result of early work by Marshall and co-workers on the synthesis of deoxydamsin.[10] With regard to helenanolides,

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† Dedicated to Professor Gilbert Stork on the occassion of his 60th birthday.

(1) Taken from the Ph.D. Thesis of George F. Majetich, University of Pittsburgh, 1979. For a preliminary account of this work, see: Grieco, P. A.; Ohfune, Y.; Majetich, G. *J. Am. Chem. Soc.* **1977**, *99*, 7393.

(2) Devon, T. K.; Scott, A. I. "Handbook of Naturally Occurring Compounds"; Academic Press: New York, 1972; Vol. II, 120–125. Sorm, F.; Dolejš, L. "Guaianolides and Germacroanolides"; Holden-Day: San Francisco, 1965. Yoshioka, H.; Mabry, T. J.; Timmermann, B. W. "Sesquiterpene Lactones"; University of Tokyo Press: Tokyo, 1973. Romo, J.; Romo de Vivar, A. *Fortschr. Chem. Org. Naturst.* **1973**, *25*, 190. Fischer, N. H.; Olivier, E. J.; Fischer, H. D. *Ibid.* **1979**, *38*, 47.

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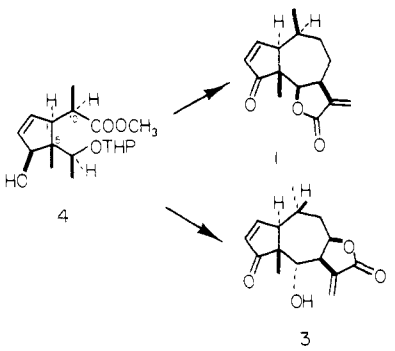

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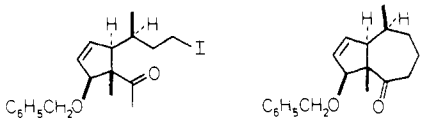
utilization of cyclopentenol **4** as a key intermediate along the pathway to helenalin requires that a clean and efficient mechanism exists for the inversion of configuration at C(10).[11]



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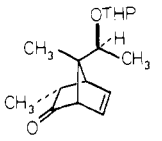
The success of our synthetic program thus became critically dependent upon a direct high-yield synthesis of intermediate **4**. We detail below the synthesis of **4** and its transformation into (±)-damsin and (±)-ambrosin. The problem of preparing **4** was easily reduced to the construction of the functionalized bicyclo[2.2.1]heptane derivative **7**, since oxidative cleavage of **7** and



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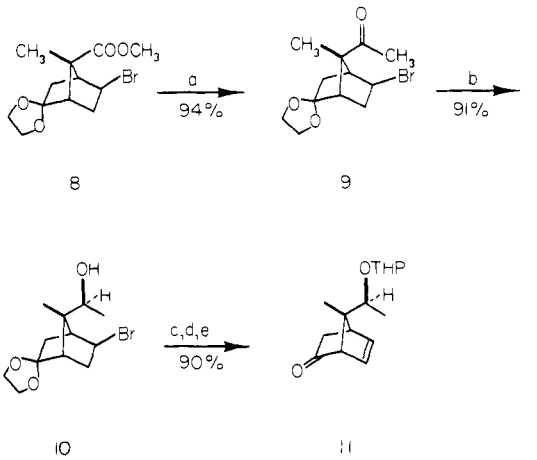
subsequent esterification were anticipated to provide **4** directly. Note that the stereochemistry depicted at C(6) in structure **7** is of no consequence since at some later stage in the synthesis this center will be ultimately destroyed to permit elaboration of the seven-membered ring. The immediate task thus became the stereospecific synthesis of **7**.

Results

Synthesis of Bicyclo[2.2.1]heptenone 7 and Its Conversion into 4. Bromo ketal ester **8**, readily available from norbornadiene in high yield,[12] was treated with excess methyllithium, giving rise exclusively to a 94% yield of crystalline methyl ketone **9** (Chart I). No tertiary alcohol could be detected. This result was not totally unexpected in view of several reports in the literature describing the synthesis of ketones by reaction of organolithium reagents with hindered esters.[13] Attempted reduction of ketone **9** with sodium borohydride led to a complete recovery of starting material. In contrast, the use of lithium aluminum hydride gave rise to a single crystalline alcohol (91%), mp 127.0–127.5 °C, which was shown to possess structure **10** by single-crystal X-ray

Chart I. Synthesis of Bicyclo[2.2.1]heptenone **11**[a]

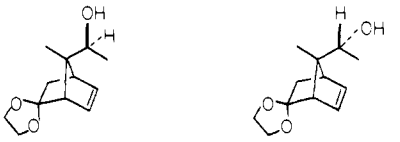


8 9 10 11

[a] (a) MeLi, Et_2O; (b) $LiAlH_4$, THF, reflux; (c) DBU, xylene, reflux; (d) 30% aqueous HOAc, 90 °C; (e) DHP, CH_2Cl_2, TsOH.

analysis.[14] The transformation of **10** into **11** was achieved via a straightforward three-step sequence as outlined in Chart I.

It was of interest to note that when ketone **9** was first subjected to dehydrohalogenation (DBU, xylene, reflux) followed by reduction ($LiAlH_4$, THF) a 1:1 mixture of alcohols **12** (R_f 0.42, hexanes–ether 1:2) and **13** (R_f 0.26) was obtained, which could be readily separated on silica gel.



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With ketone **11** secured, we directed our efforts to incorporating the C(10) methyl group into the bicyclo[2.2.1]heptenone system. The above requirement necessitates incorporation of an endo methyl group adjacent to the carbonyl. Preliminary studies with 7,7-dimethylbicyclo[2.2.1]hept-5-en-2-one (**14**) and methyl iodide led to endo alkylation in high yield. The exclusive formation of **15** is clearly due to the presence of the syn C(7) methyl group,

14 15

which blocks exo attack. Examination of the ^1H NMR spectrum (250 MHz) of product **15** revealed the C(10) proton as a quartet of doublets centered at δ 2.36, with J_{ab} = 4.24 Hz. If any of the exo methylated material were present, the C(10) proton would have appeared as a simple quartet due to the fact that the dihedral angle between the C(10) proton and the bridgehead proton is 90°.[15] Akylation of **11** led exclusively to the endo-alkylated substance **7** in very high yield.

Attention was now focused on the conversion of ketone **7** into intermediate **4**. On the basis of extensive work in our laboratory on the Baeyer–Villiger oxidation of highly functionalized bicyclo[2.2.1]heptenones, it was clear to us that the transformation of **7** into the key compound **4** would necessitate use of basic hydrogen peroxide.[12b,16a,b] While there was some concern that

(11) For a solution to this problem and the application of **4** to the first total synthesis of *dl*-helenalin, see the accompanying paper: Grieco, P. A.; Ohfune, Y.; Majetich, G.; Wang, C.-L. J. *J. Am. Chem. Soc.* following paper in this issue.

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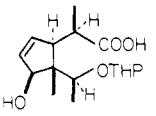
(15) Cf. Marshall, J. L.; Walters, S. R. *J. Am. Chem. Soc.* **1974**, *96*, 6358.

(16) (a) Grieco, P. A.; Ohfune, Y.; Yokoyama, Y.; Owens, W. *J. Am. Chem. Soc.* **1979**, *101*, 4749. (b) Grieco, P. A.; Takigawa, T.; Moore, D. R. *Ibid.* **1979**, *101*, 4380. For an excellent review of the Baeyer–Villiger reaction on bicyclo[2.2.1]heptane systems, see: Krow, G. R. *Tetrahedron* **1981**, *37*, 2697.

the presence of the C(10) secondary endo methyl group might be responsible for the formation of some undesired hydroxy acid, we felt that the presence of the carbon–carbon double bond in **7** would electronically favor the formation of **16**. Of more serious



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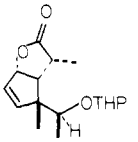

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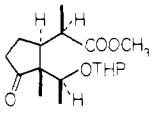
concern was the possibility that under the alkaline conditions required for the Baeyer–Villiger reaction, epimerization at C(10) might occur during the course of the reaction. In the event, oxidation of **7** with hydrogen peroxide and sodium hydroxide in aqueous methanol at 0 °C afforded the sensitive hydroxy carboxylic acid **16** in approximately 75% yield. In the presence of acid or on standing for a few days, acid **16** rearranged to the bicyclic lactone **17**. We[17] and others[18] have observed this facile rearrangement with similar systems on several occasions. We have made extensive use of this type of transformation.[16a,19] The sensitive nature of hydroxy acid **16** was avoided by immediately esterifying **16** upon workup with an ethereal solution of diazomethane. That no equilibration at C(10) had occurred was clearly evident by examination of the ^1H NMR spectrum of **4** as well as subsequent chemical reactions that, as detailed below, culminated in the synthesis of damsin.

Elaboration of Perhydroazulenone 22. With the cyclopentenoid derivative **4** in hand possessing the proper configuration at C(1), C(5), and C(10) for ambrosanolide synthesis, we turned our attention to the transformation of **4** into the perhydroazulenone **22** (Chart II), a potential precursor to damsin. Our plan for the preparation of **22** centered around the intramolecular alkylation of keto iodide **21**. Toward this end, we concentrated on the conversion of **4** into **21**. Reduction (H_2/PtO_2) of the cyclopentene double bond, which was carried out in scrupulously dried ethyl acetate followed by reduction ($LiAlH_4$) of the ester function, provided diol **18** in 96% overall yield. Failure to dry the ethyl acetate during the reduction step resulted in the formation (20–25%) of ketone **23**, which presumably arises by double-bond migration to produce the enol corresponding to **23**.



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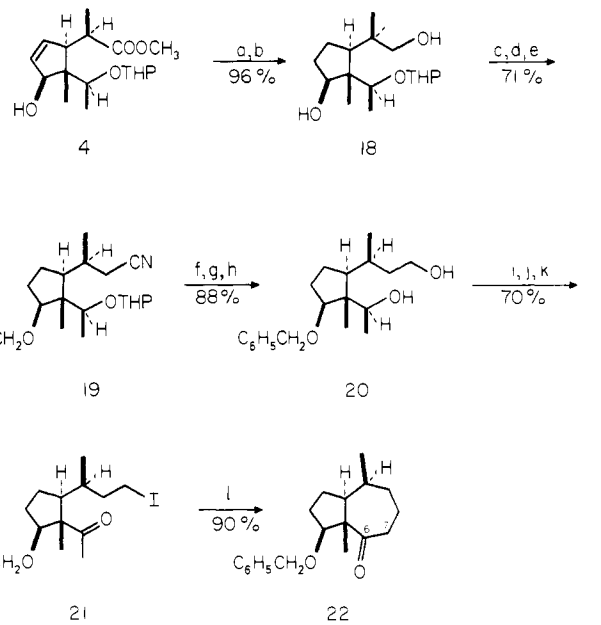
The required one-carbon homologation of primary alcohol **18** was accomplished by using a standard series of transformations (Chart II). Selective tosylation of **18** followed by displacement with sodium cyanide in dimethyl sulfoxide and subsequent benzylation of the C(4) hydroxyl group with sodium hydroxide and benzyl bromide in tetrahydrofuran containing hexamethylphosphoramide and tetrabutylammonium iodide[20] afforded nitrile **19** in 71% overall yield. Attempted benzylation in the absence of tetrabutylammonium iodide proceeded sluggishly and gave at best only a 20% yield of benzyl ether **19**. As illustrated in Chart II, nitrile **19** was efficiently converted into keto iodide **21** via the intermediacy of diol **20**.

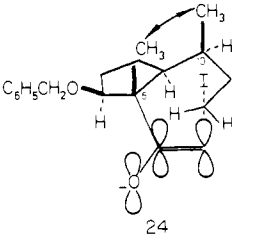
Intramolecular alkylation of **21** would appear, at first glance, to be a straightforward reaction provided O-alkylation could be

Chart II. Synthesis of Perhydroazulenone **22**[a]



[a] (a) H_2, PtO_2, EtOAc; (b) $LiAlH_4$, Et_2O; (c) TsCl, Py; (d) NaCN, Me_2SO; (e) NaH, THF, $PhCH_2Br$, HMPA, Bu_4NI, reflux; (f) *i*-Bu_2AlH, $PhCH_3$, −78 °C; (g) $NaBH_4$, EtOH, 0 °C; (h) MeOH, TsOH; (i) TsCl, Py; (j) Jones reagent; (k) NaI, acetone; (l) $LiN(SiMe_3)_2$, THF, HMPA, −78 °C (30 min) → −20 °C (2 h).

avoided.[21] Close scrutiny reveals, however, that to achieve the necessary collinear arrangement of atoms needed for C-alkylation a very serious 1,3-methyl–methyl interaction between the C(5) methyl and the C(10) methyl develops in the transition state leading to **23** (cf. structure **24**). Initial studies were conducted



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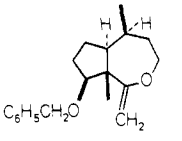
on the corresponding keto tosylate, the direct precursor to iodide **21**; however, only a modest yield of perhydroazulenone **22** could be realized. After numerous attempts examining several bases (e.g., NaH, KO-*t*-Bu, LDA, $LiN(SiMe_3)_2$) in a variety of solvents, the best conditions for the generation of **22** involved use of 1.5 equiv of lithium bis(trimethylsilyl)amide in anhydrous tetrahydrofuran containing 1.0 equiv of HMPA cooled to −20 °C. Under these conditions we were able to realize an 88% yield of **22**. We could not detect any of the seven-membered enol ether **25**.[22]



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(17) Grieco, P. A.; Yokoyama, Y.; Withers, G. P.; Okuniewicz, F. J.; Wang, C.-L. J. *J. Org. Chem.* **1978**, *43*, 4178.

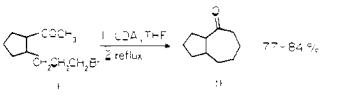
(18) Greene, A. E.; Le Drian, C.; Crabbé, P. *J. Am. Chem. Soc.* **1980**, *102*, 7583.

(19) Grieco, P. A.; Williams, E.; Tanaka, H.; Gilman, S. *J. Org. Chem.* **1980**, *45*, 3537.

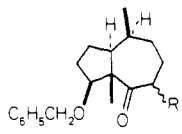
(20) Czernecki, S.; Georgoulis, C.; Provelenghiou, C. *Tetrahedron Lett.* **1976**, 3535.

(21) Cf. Baldwin, J. E.; Kruse, L. I. *J. Chem. Soc., Chem. Commun.* **1977**, 233.

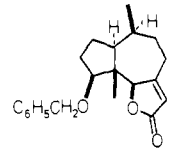
(22) After the completion of our study, a report appeared in the literature detailing the cyclization of bromo ketone i to perhydroazulene ii (House, H. O.; Sayer, T. S. B.; Yau, C.-C. *J. Org. Chem.* **1978**, *43*, 2153).



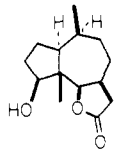
Damsin and Ambrosin. Completion of the damsin synthesis required elaboration of a β-oriented α-methylene-γ-butyrolactone onto the C(6) and C(7) positions of hydroazulene **22**. We thus set out to prepare keto acid **28** with the expectation that enol lactone formation would provide exclusively **29**, which upon simultaneous reduction of the double bond and hydrogenolysis of the benzyl ether would give way to tricyclic lactone **30**. A



26, R = $CH_2CH=C(CH_3)_2$
28, R = CH_2CO_2H



29

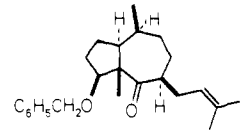


30

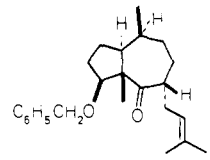
precedent for this type of reaction sequence can be found in the deoxydamsin synthesis of Marshall and Snyder.[10]

Preparation of keto acid **28** was carried out by an indirect three-step reaction sequence in 76% overall yield. Alkylation of ketone **22** with prenyl bromide provided a diastereomeric mixture of ketone **26**, which upon ozonolysis and Jones oxidation of the resultant aldehyde afforded carboxylic acid **28**. Treatment of keto acid **28** with sodium acetate–acetic anhydride at 140 °C for 2 h gave crystalline butenolide **29**, mp 82–83 °C, whose structural assignment was clearly supported by IR (1762, 1634 cm^{-1}) and ^1H NMR data [δ 5.62 (s, 1 H)]. Transformation of butenolide **29** into hydroxy γ-lactone **30** possessing the five contiguous chiral centers of damsin was initially conducted in 89% yield by employing 5% palladium on carbon in ethanol–ethyl acetate (1:2). Whereas complete debenzylation generally was achieved in the first 10 h of reaction under the above conditions, an additional 38 h was required for complete reduction of the butenolide system. Platinum oxide proved to be the catalyst of choice as tricyclic lactone **30** could be realized in 98% yield in less than 14 h.

Observations regarding the prenylation of ketone **22** deserve comment. Chromatography on silicAR CC-7 of the mixture of isomers obtained above during the prenylation reaction provided **27a** (R_f 0.63, hexanes–ether 7:1) and **27b** (R_f 0.61) in a ratio of 35:65. Deprotonation of the diastereomeric mixture **26** with



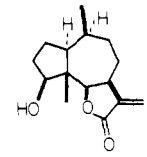
27a



27b

lithium diisopropylamide in tetrahydrofuran followed by kinetic protonation of the resultant enolate with a highly hindered proton source (2,6-di-*tert*-butyl-4-methylphenol) provided an 85:15 ratio respectively of the desired prenylated product **27a** and **27b**. Under equilibrating conditions, **27b** was, as expected, the major product. Confirmation of the above stereochemical assignments was established by conversion of **27a** into tricyclic lactone **30** via (a) reduction with $NaBH_4$, (b) ozonolysis, (c) Jones oxidation of the corresponding γ-lactol, and (d) debenzylation.

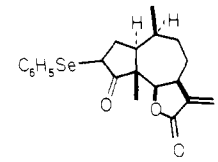
Completion of the synthesis of damsin at this stage required α-methylenation of the γ-butyrolactone ring and oxidation at C(4). Introduction of the α-methylene unit was carried out directly on the unprotected hydroxy lactone **30** in 65% overall yield by the α-hydroxymethylation procedure we introduced some years ago.[23] Mesylation and β elimination of the hydroxymethylated adduct proceeded smoothly, giving rise to the crystalline adduct **31**, mp



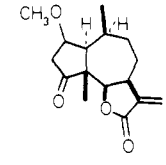
31

114–116 °C. Oxidation of **31** with Jones reagent afforded (±)-damsin, mp 124–125 °C (lit.[9a] mp 124–126 °C). The NMR (250 MHz) and IR spectra of synthetic damsin were identical in all respects with those of natural damsin.

The preparation of (±)-ambrosin was made possible when it was discovered that introduction of an α-phenylselenenyl group into the C(3) position of racemic damsin could be achieved in ethyl acetate containing phenylselenenyl chloride (1.0 equiv) *in the absence of any base.*[24] The high reactivity of the cyclopentenone unit of ambrosin was noted during oxidation of **32** with sodium periodate in aqueous methanol (1:2) by isolation of the 1,4-addition product **33**. Oxidative removal of the phenylselenenyl group with



32



33

aqueous sodium periodate in *tert*-butyl alcohol gave a 41% overall yield from **31** of (±)-ambrosin, mp 188–190 °C, which was identical with an authentic sample of natural ambrosin by comparison with spectral properties (IR, NMR) and thin-layer mobility on several solvent systems.

Experimental Section

Melting points were determined on a Fisher-Johns hot stage melting point apparatus. All melting points and boiling points are uncorrected. Infrared (IR) spectra were determined on a Perkin-Elmer 247 grating infrared spectrometer, and nuclear magnetic resonance (NMR) spectra were recorded either at 60 MHz (Varian T-60A or T-60 spectrometer) or at 250 MHz as indicated. Chemical shifts are reported in parts per million (δ) relative to Me_4Si (δ_{Me_4Si} = 0.0 ppm) as an internal standard. Low-resolution mass spectra were recorded on an LKB-9000 spectrometer. High-resolution spectra were recorded on a Varian MAT CH-5DF instrument. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

Reactions were run under an atmosphere of nitrogen. "Dry" solvents were dried immediately before use. Tetrahydrofuran and dimethoxyethane were distilled from lithium aluminum hydride; dimethylformamide (DMF), hexamethylphosphoramide (HMPA), dimethyl sulfoxide (Me_2SO), and pyridine were distilled from calcium hydride. Diethyl ether and dioxane were distilled from sodium. Methylene chloride was passed through a column of alumina prior to use.

7-Acetyl-5-bromo-7-methylspiro[bicyclo[2.2.1]heptane-2,2′-[1,3]dioxolane] (9). A solution of bromo ester **8**[12] (10.3 g, 33.7 mmol) in 150 mL of anhydrous ether cooled to 0 °C was treated dropwise with 31.6 mL (50.6 mmol) of a 1.6 M solution of methyllithium in ether. After addition was complete, the reaction mixture was warmed to room temperature and stirred for 2 h. The reaction was quenched with a saturated aqueous solution of ammonium chloride, diluted with ether, washed with brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated in vacuo, and the crude ketone was chromatographed on 350 g of silica gel. Elution with 2:1 hexanes–ether provided 9.07 g (93%) of crystalline ketal ketone **9**: mp 69–70 °C; R_f 0.45 (hexanes–ether 2:1); IR (CCl_4) 2980, 2890, 1708, 1475, 1455, 1440, 1420, 1388, 1358, 1330, 1314, 1278, 1246, 1220, 1182, 1163, 1105, 1080, 1060, 1040, 1025, 1010, 950, 900 cm^{-1}; NMR (CCl_4) δ 3.5–4.1 (m, 5 H), 2.1–2.8 (m, 5 H), 2.21 (s, 3 H), 1.55 (d, 1 H, J = 14 Hz), 1.36 (s, 3 H); high-resolution mass

(23) Grieco, P. A.; Hiroi, K. *J. Chem. Soc., Chem. Commun.* **1972**, 1317. Grieco, P. A.; Nishizawa, M.; Burke, S. D.; Marinovic, N. *J. Am. Chem. Soc.* **1976**, *98*, 1612.

(24) Cf.: Sharpless, K. B.; Lauer, R. F.; Teranishi, A. Y. *J. Am. Chem. Soc.* **1973**, *95*, 6137.

spectrum, calcd for $C_{12}H_{17}BrO_3$, *m/e* 288.0361; found, 288.0367. Recrystallization from ether–hexanes gave analytically pure **9**, mp 70–71 °C. Anal. Calcd for $C_{12}H_{17}BrO_3$: C, 49.84; H, 5.93. Found: C, 50.07; H, 6.02.

α,7-Dimethyl-5-bromospiro[bicyclo[2.2.1]hept-5-ene-2,2′-[1,3]dioxolane]-7-methanol (10). To a suspension of 118 mg (3.11 mmol) of lithium aluminum hydride in 4 mL of anhydrous ether at −20 °C was added dropwise a solution of 600 mg (2.07 mmol) of ketone **9** in 3 mL of anhydrous ether. The reaction mixture was stirred at −20 °C for 3 h. The reaction was quenched with reagent grade ("wet") ether and dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure gave crude material, which was chromatographed on 30 g of silica gel. Elution with 2:1 hexanes–ether afforded 550 mg (91%) of a single crystalline alcohol (**10**), mp 127.0–127.5 °C, which was homogeneous by TLC analysis: R_f 0.42 (hexanes–ether 2:1, two developments); IR ($CHCl_3$) 3600, 2990, 2880, 1475, 1460, 1440, 1390, 1375, 1340, 1321, 1300, 1270, 1240, 1205, 1145, 1080, 1055, 1040, 1020, 1000, 965, 945, 925, 904, 888, 871, 850 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 4.80 (br q, 1 H, *J* = 6 Hz, −C*H*OH), 4.15 (dd, 1 H, *J* = 5 Hz, *J* = 9 Hz, C*H*Br), 3.6–3.9 (m, 4 H, $-OCH_2CH_2O-$), 2.61 (dd, 1 H, *J* = 9 Hz, *J* = 16 Hz, C(6) endo proton), 2.41 (m, 2 H), 2.17 (dt, 1 H, *J* = 5 Hz, *J* = 16 Hz, C(6) exo proton), 1.81 (m, 2 H), 1.53 (d, 1 H, *J* = 14 Hz, C(3) endo proton), 1.26 (s, 3 H), 1.18 (d, 3 H, *J* = 6 Hz); high-resolution mass spectrum, calcd for $C_{12}H_{19}BrO_3$, *m/e* 290.0517; found, 290.0523. Anal. Calcd for $C_{12}H_{19}BrO_3$: C, 49.50; H, 6.58. Found: C, 49.41; H, 6.53.

7-Methyl-7-[1-[(tetrahydro-2*H*-pyran-2-yl)oxy]ethyl]bicyclo[2.2.1]-hept-5-en-2-one (11). A solution of 462 mg (1.59 mmol) of bromo alcohol **10** and 2.42 g (16.0 mmol) of 1,5-diazabicyclo[5.4.0]undec-5-ene in 20 mL of toluene was refluxed (bath temperature 135 °C) for 23 h. The reaction mixture was cooled to room temperature and chromatographed on silica gel. Elution with 2:1 hexanes–ether afforded 322 mg (97%) of a crystalline olefin: mp 81.0–82.0 °C; R_f 0.42 (hexanes–ether 1:2); IR (CCl_4) 3640, 3525, 3070, 2980, 2890, 1632, 1478, 1460, 1442, 1390, 1378, 1350, 1325, 1301, 1263, 1240, 1210, 1160, 1108, 1082, 1050, 1020, 950, 921, 898 cm^{-1}; NMR (CCl_4) δ 6.3–5.8 (m, 2 H, —C*H*=C*H*—), 4.21 (q, 1 H, *J* = 6 Hz, −C*H*OH), 4.1–3.5 (m, 4 H), 2.66 (br s, 1 H), 2.3–1.9 (m, 2 H), 1.43 (d, 1 H, *J* = 12 Hz, C(3) endo proton), 1.38 (br s, 1 H, O*H*), 1.10 (s, 3 H), 1.08 (d, 3 H, *J* = 6 Hz); high-resolution mass spectrum, calcd for $C_{12}H_{18}O_3$, *m/e* 210.1256; found, 210.1260. Recrystallization from hexanes–ether provided an analytically pure sample, mp 82.5–83.5 °C, which was used directly in the next reaction. Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.46; H, 8.72.

To 10.0 g (47.61 mmol) of the above ketal was added 110 mL of aqueous acetic acid [prepared from glacial acetic acid–water 3:7 (v/v)]. The reaction was heated at 95 °C for 3 h, after which time it was cooled to room temperature and neutralized with a cold solution of sodium hydroxide (100g) in 1 L of water followed by the addition of solid sodium carbonate. The product was isolated by ethyl acetate extraction (4 × 200 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and evaporated in vacuo, leaving 7.74 g (98%) of crystalline ketone: mp 88–89 °C; R_f 0.60 (hexanes–ether 1:1); IR ($CHCl_3$) 3630, 3600–3250, 3080, 3000, 2980, 2950, 1740, 1460, 1430, 1390, 1315, 1240, 1080, 1060, 1005, 990, 935, 920, 870, 810 cm^{-1}; NMR δ (CCl_4) 6.54 (dd, 1 H, *J* = 3.0 and 6.0 Hz, —C*H*=CH—), 5.96 (m, 1 H, —CH=C*H*—), 4.39 (br q, 1 H, *J* = 6.5 Hz, −C*H*OH), 3.10 (br s, 1 H), 2.60 (br s, 1 H), 2.22 (dd, 1 H, *J* = 3.0 and 17.0 Hz, C(3) exo proton), 1.90 (d, 1 H, *J* = 17.0 Hz, C(3) endo proton), 1.59 (br s, 1 H, OH), 1.06 (d, 3 H, *J* = 6.5 Hz), 1.04 (s, 3 H); high-resolution mass spectrum, *m/e* 166.0999; calcd, 166.0994. Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 71.98; H, 8.66.

A solution of the above alcohol (15.2 g, 91.0 mmol) in 500 mL of dry methylene chloride containing *p*-toluenesulfonic acid (300 mg) was cooled to 0 °C and treated with 11.5 g (0.137 mol) of dihydropyran. After 3 h at 0 °C, the reaction was quenched with 10 mL of saturated aqueous sodium bicarbonate solution, diluted with 1 L of ether, and washed with 100-mL portions of saturated aqueous sodium bicarbonate and brine. The organic phase was dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure, providing 24.4 g of crude **11**. Chromatography on 400 g of silica gel (elution with hexanes–ether 2:1) afforded 23.8 g (98%) of the desired keto tetrahydropyranyl ether **11** as a colorless liquid: bp 77–87 °C (bath temperature/0.48 mmHg); IR (CCl_4) 3080, 2990, 2955, 2940, 2910, 2880, 2855, 1755, 1470, 1458, 1445, 1430, 1390, 1375, 1355, 1345, 1325, 1315, 1306, 1290, 1280, 1268, 1209, 1190, 1175, 1135, 1120, 1090, 1080, 1070, 1038, 1030, 995, 938, 875 cm^{-1}; NMR (CCl_4) δ 6.49 (m, 1 H, —C*H*=CH—), 5.97 (m, 1 H, —CH=C*H*—), 4.50 (m, 1 H, −OCHO), 4.20 (q, 1 H, *J* = 7.0 Hz, −CHO), 2.83 (m, 1 H), 2.50 (m, 1 H), 2.11 (dd, 1 H, *J* = 3.0 and 17.0 Hz, C(3) exo proton), 1.78 (d, 1 H, *J* = 17.0 Hz, C(3) endo proton), 1.08 (d, 3 H, *J* = 6.5 Hz), 1.06 (s, 3 H). Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.92; H, 8.69.

3,7-Dimethyl-7-[1-[(tetrahydro-2*H*-pyran-2-yl)oxy]ethyl]bicyclo-[2.2.1]hept-5-en-2-one (7). To a solution of lithium diisopropylamide [prepared from 19.3 g (0.19 mol) of diisopropylamine in 150 mL of freshly distilled tetrahydrofuran and 106.1 mL (0.17 mol) of *n*-butyllithium (1.62 M in hexane)] cooled to 0 °C was added over a 2-h period a solution of 23.9 g (95.5 mmol) of tetrahydropyranyl ether **11** in 150 mL of dry tetrahydrofuran. After an additional 1 h at 0 °C, 142 g (1 mol) of methyl iodide was added. The reaction mixture was warmed to room temperature. After 2 h the reaction was quenched with 10 mL of a saturated aqueous ammonium chloride solution, and the solvent was removed under reduced pressure. The oily residue was taken up with 100 mL of water and was extracted with 3 × 400 mL portions of ether. The combined ether extracts were washed with 50 mL of brine and dried over anhydrous magnesium sulfate. Filtration and concentration in vacuo of the filtrate afforded 25.1 g of crude product. Chromatography on 500 g of silica gel (elution with hexanes–ether 2:1) gave 22.2 g (88%) of the desired methylated bicyclo[2.2.1]heptane derivative **7**: bp 57–65 °C bath temperature/0.85 mmHg); R_f 0.48 (hexanes–ether 2:1); IR (CCl_4) 3070, 2975, 2940, 2860, 2848, 1743, 1470, 1455, 1440, 1390, 1375, 1355, 1345, 1325, 1312, 1286, 1278, 1262, 1205, 1185, 1170, 1135, 1120, 1080, 1038, 1028, 995, 970, 950, 938, 925, 906, 890, 872 cm^{-1}; NMR δ (CCl_4) 6.44 (m, 1 H), 5.90 (m, 1 H), 4.50 (m, 1 H), 0.9–1.1 (m, 9 H); high-resolution mass spectrum, *m/e* 264.1712; calcd, 264.1725. Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.50; H, 9.09.

Methyl α,5-Dimethyl-4-hydroxy-5-[1-[(tetrahydro-2*H*-pyran-2-yl)-oxy]ethyl]-2-cyclopentene-1-acetate (4). A solution of 11.0 g (41.6 mmol) of ketone **7** in methanol (170 mL) containing water (73 mL) was cooled to 0 °C and treated with a solution of 13.3 g (0.33 mol) of sodium hydroxide in 50 mL of water followed by 66.1 mL of 30% hydrogen peroxide (0.58 mol). After ca. 48 h at 0–5 °C, the reaction was extracted twice with 200-mL portions of ether. The excess hydrogen peroxide was destroyed by the addition of solid sodium thiosulfate (134 g, 0.54 mol). The aqueous portion was then adjusted to pH 4.5 and extracted with ethyl acetate. After the pH was readjusted to pH 4.5, the aqueous portion was extracted exhaustively with ethyl acetate. The combined ethyl acetate extracts were dried over anhydrous magnesium sulfate and filtered. The solvent was removed under reduced pressure to afford 10.61 g of the desired hydroxy acid, which was directly esterified with an ethereal solution (1.0 L) of diazomethane prepared from 12.0 g of *N*-nitrosomethylurea. Purification of the condensed residue on 400 g of silica gel using hexanes–ether (1:1) provided 10.9 g (84%) of the desired cyclopentenol methyl ester **4**: bp 130–137 °C (bath temperature/0.80 mmHg) as an oil; R_f 0.55 (hexanes–ether 1:2); IR (CCl_4) 3580, 3525, 3070, 2975, 2950, 2925, 2880, 2850, 1740, 1470, 1455, 1444, 1438, 1420, 1380, 1355, 1344, 1320, 1285, 1275, 1245, 1205, 1175, 1130, 1118, 1079, 1065, 1050, 1035, 1025, 990, 960, 935, 905, 875, 855 cm^{-1}; NMR (CCl_4) δ 5.66 (br s, 2 H), 4.56 (br s, 1 H), 4.33 (br s, 1 H), 3.60 (s, 3 H), 1.4–1.0 (m, 6 H), 0.93 (s, 3 H); high-resolution mass spectrum, *m/e* 294.1819; calcd for $C_{17}H_{28}O_5$–H_2O, 294.1831. Anal. Calcd for $C_{17}H_{28}O_5$: C, 65.36; H, 9.03. Found: C, 65.25; H, 9.09.

Methyl α,5-Dimethyl-4-hydroxy-5-[1-[(tetrahydro-2*H*-pyran-2-yl)-oxy]ethyl]cyclopentane-1-ethanol (18). To cyclopentenol **4** (3.0 g, 9.6 mmol) dissolved in 50 mL of scrupulously dried ethyl acetate was added 50 mg of platinum oxide. The mixture was placed under hydrogen at atmopsheric pressure and vigorously stirred for 2.5 h at room temperature. The reaction was diluted with 50 mL of ethyl acetate and the catalyst removed by filtration through Celite. The filtrate was evaporated in vacuo, leaving 3.0 g of an oily residue, which proved to be extremely sensitive and was used immediately in the next reaction: IR (CCl_4) 3650, 3600–3200, 2950, 2870, 1740, 1460, 1380, 1350, 1320, 1260, 1200, 1160, 1080, 1040, 990 cm^{-1}; NMR δ (CCl_4) 4.60 (br s, 1 H), 3.60 (s, 3 H), 1.3–0.9 (m, 6 H), 0.75 (s, 3 H); high-resolution mass spectrum, *m/e* 296.2000; calcd for $C_{17}H_{30}O_5 - H_2O$, 296.1987.

To a suspension of 726 mg (19.1 mmol) of lithium aluminum hydride in 50 mL of anhydrous ether was added a solution of 3 g (9.55 mmol) of the above ester in 20 mL of anhydrous ether at 0 °C. The reaction mixture was stirred at room temperature for 2 h, after which time it was cooled, quenched with reagent grade ether, and directly dried over anhydrous magnesium sulfate. Filtration and evaporation of the solvent in vacuo afforded 2.77 g of an oily residue, which was chromatographed on 60 g of silica gel (elution with hexanes–ether 1:2), providing 2.64 g (95%) of pure diol **18** [bp 91–102 °C (bath temperature/0.005 mmHg], which was homogeneous on TLC (hexanes–ether 1:3, R_f 0.41): IR ($CHCl_3$) 3640, 3500, 3010, 2975, 2950, 2925, 2880, 2860, 1470, 1380, 1140, 1120, 1080, 1040, 990 cm^{-1}; NMR (CCl_4) δ 4.65 (br s, 1 H), 4.3–3.2 (m, 7 H).

Tetrahydro-2*H*-pyran-2-yl Ether 19 of 2-(2-Cyano-1-methylethyl)-1-methyl-5-(phenylmethoxy)-α,1-dimethylcyclopentane-1-methanol. A solution of 5.36 g (18.0 mmol) of diol **18** in 40 mL of dry pyridine was

treated dropwise at 0 °C with a solution of 3.77 g (19.8 mmol) of recrystallized *p*-toluenesulfonyl chloride in 20 mL of pyridine. After 12 h at 0–5 °C, the reaction mixture was concentrated under high vacuum, and the residue was dissolved in ether and was washed with brine. Filtration and evaporation of the solvent under reduced pressure afforded 8.29 g (100%) of crude tosylate, which was used directly in the next reaction; NMR δ (CCl_4) 7.50 (AB q, 4 H, $\Delta\nu_{AB}$ = 26 Hz, J = 8 Hz), 4.56 (br s, 1 H), 4.3–3.3 (m, 7 H), 2.46 (s, 3 H), 2.0–0.6 (m, 15 H).

To a solution of 8.29 g (18.0 mmol) of the above tosylate in 63 mL of freshly dried Me_2SO at room temperature was added 3.59 g (73.4 mmol) of dry sodium cyanide (dried at 110 °C and stored over phosphorus pentoxide). The reaction was heated to 90 °C and stirred at that temperature for 2 h. The reaction mixture was cooled to room temperature and poured into 60 mL of a solution of aqueous ammonium chloride. The product was isolated by ether extraction (3 × 400 mL portions). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and evaporated in vacuo, leaving 4.86 g of crude nitrile. Purification on 100 g of silica gel (elution with hexanes–ether 1:1) afforded 4.12 g (74%) of pure nitrile: bp 76–87 °C (bath temperature/0.035 mmHg); R_f 0.33 hexanes–ether 1:2; IR (CCl_4) 3650, 3550, 2250. Anal. Calcd for $C_{17}H_{29}NO_3$: C, 69.12; H, 9.89; N, 4.74. Found: C, 68.98; H, 9.89; N, 4.67.

To a stirred suspension of 840 mg (17.4 mmol) of 50% sodium hydride dispersion (washed with dry hexane prior to use) in 30 mL of dry tetrahydrofuran cooled to 0 °C was added dropwise a solution of the above hydroxy nitrile (4.7 g, 15.9 mmol) and 2.85 g (15.9 mmol) of dry hexamethylphosphoramide in 30 mL of tetrahydrofuran over a 30-min period. The reaction mixture was stirred at 0 °C for 30 min and then warmed to room temperature and stirred for 1 h more. Freshly distilled α-bromotoluene (2.99 g, 17.4 mmol) was added, followed by the addition of 2.35 g (6.36 mmol) of tetrabutylammonium iodide. The reaction was heated at 50 °C for 10 h, followed by cooling to room temperature. The reaction was quenched with a saturated aqueous ammonium chloride solution. Removal of the solvent under reduced pressure afforded a residue, which was taken up in 700 mL of ethyl acetate. The organic phase was washed with brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The crude material obtained was chromatographed on 200 g of silica gel. Elution with 2:1 hexanes–ether provided 5.5 g (88%) of pure benzyl ether **19**: bp 91–102 °C (bath temperature/0.1 mmHg); IR (CCl_4) 3100, 3070, 3040, 2950, 2880, 2250, 1500, 1470, 1455, 1440, 1380, 1360, 1280, 1260, 1205, 1135, 1120, 1080, 1040, 990, 945, 905 cm^{-1}; NMR δ (CCl_4) 7.20 (s, 5 H), 4.66–4.33 (m, 3 H), 4.1–3.2 (m, 4 H), 2.3–2.1 (br s, 2 H), 1.3–0.8 (m, 9 H). Anal. Calcd for $C_{24}H_{35}NO_3$: C, 74.77; H, 9.15; N, 3.63. Found: C, 74.91; H, 9.21; N, 3.55.

[1α(S^*),2β(S^*),5β]-1-[2-(3-Hydroxy-1-methylpropyl)-1-methyl-5-(phenylmethoxy)cyclopentyl]ethanol (20). To a solution of nitrile **19** (2.05 g, 5.32 mmol) in 40 mL of freshly distilled toluene cooled to −78 °C was added dropwise over 1 h via syringe 4.16 mL (5.85 mmol) of a 20% solution of diisobutylaluminum hydride in toluene. The reaction was quenched at −78 °C after 1 h by the careful addition of a saturated aqueous solution of ammonium chloride. The reaction mixture was warmed to room temperature and acidified with aqueous hydrochloric acid [prepared from concentrated hydrochloric acid/water 1:9 (v/v)] to pH 5. The mixture was stirred at room temperature for 1 h. The reaction was diluted with 400 mL of ether, washed with 30 mL of a saturated aqueous sodium bicarbonate solution, and dried over anhydrous magnesium sulfate. Filtration and concentration in vacuo of the filtrate provided 2.10 g of crude aldehyde which was used directly in the next reaction: IR (CCl_4) 1720 cm^{-1}; NMR (CCl_4) δ 9.60 (d, 1 H, J = 3 Hz).

The above crude aldehyde (2.10 g, 5.32 mmol) was dissolved in 20 mL of absolute methanol, and sodium borohydride (404 mg, 10.6 mmol) was added portionwise at 0 °C. The mixture was warmed to room temperature and stirred for 2 h. The reaction was quenched by the addition of water. The reaction mixture was evaporated under reduced pressure, leaving a residue, which was taken up with 500 mL of ethyl acetate and 20 mL of brine. The aqueous phase was extracted with ethyl acetate, and the combined ethyl acetate extracts were dried over anhydrous magnesium sulfate. Filtration and concentration in vacuo provided 2.0 g of a crude residue, which was purified on 30 g of silica gel. Elution with hexanes–ether 1:1 provided 491 mg (24%) of recovered nitrile and 1.40 g (70% yield, 94% based on recovered starting material) of the expected alcohol: bp 107–112 °C (bath temperature/0.005 mmHg); R_f 0.31 (hexanes–ether 1:1); IR ($CHCl_3$) 3650, 3450 cm^{-1}. Anal. Calcd for $C_{24}H_{38}O_4$: C, 73.81; H, 9.81. Found: C, 74.10; H, 9.80.

A solution of 2.4 g (6.40 mmol) of the above tetrahydropyranyl ether in 60 mL of absolute methanol was treated with 100 mg of *p*-toluenesulfonic acid. The mixture was stirred at room temperature for 2 h and quenched by the addition of solid sodium bicarbonate. Removal of the solvent under reduced pressure (<0.1 mm) gave an oily residue, which was taken up in ethyl acetate. The organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo leaving 2.14 g of crude diol **20**. Chromatography on 60 g of silica gel (elution with hexanes–ether 1:2) provided 2.09 g (94%) of pure diol **20**: mp 91.0–92.5 °C; IR ($CHCl_3$) 3600, 3450 cm^{-1}; NMR ($CDCl_3$) δ 7.28 (s, 5 H), 4.45 (AB q, 2 H, $\Delta\nu_{AB}$ = 11.8 Hz, J = 12 Hz), 3.9–3.3 (m, 4 H), 1.13 (d, 3 H, J = 6.5 Hz), 0.90 (s, 3 H). An analytical sample was prepared by recrystallization from chloroform–hexanes. Anal. Calcd for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87. Found: C, 74.35; H, 9.83.

[1α,2β(R^*),5β]-1-[2-(3-Iodo-1-methylpropyl)-1-methyl-5-(phenylmethoxy)cyclopentyl]ethanone (21). Diol **20** (2.92 g, 9.55 mmol) was dissolved in 4 mL of dry pyridine, cooled to 0 °C, and treated dropwise with a solution of 2.28 g (11.5 mmol) of freshly recrystallized *p*-toluenesulfonyl chloride in 2 mL of pyridine. After 18 h at 0–5 °C the reaction mixture was concentrated under high vacuum, and the residue was dissolved in ether and washed with brine. Concentration of the combined ether extracts in vacuo provided 4.28 g of monotosylate, which was used directly in the next reaction: R_f 0.78 (hexanes–ether 1:3); IR (CCl_4) 3500, 1600, 1360, 1180, 1160 cm^{-1}; NMR (CCl_4) δ 7.46 (AB q, 4 H, $\Delta\nu_{AB}$ = 27 Hz, J = 8 Hz), 2.40 (s, 3 H).

A solution of the above crude monotosylate (4.28 g, 9.1 mmol) in 30 mL of acetone (reagent grade) cooled to 0 °C was treated with 10 mL of 0.7 M Jones reagent. After 15 min, the reaction was quenched with 2-propanol to consume the excess oxidizing reagent. The reaction was diluted with 100 mL of acetone, and the acetone solution was decanted. Evaporation of the solvent in vacuo left an oily residue that was dissolved in ether. The chromium salts were dissolved in 50% brine solution and extracted with ether twice. The combined ether extracts were washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure leaving 4.04 g of residue. Purification on 100 g of silica gel (elution with hexanes–ether 2:1) provided 3.81 g (87% overall from **20**) of the desired keto tosylate, which was used directly in the next reaction: R_f 0.57 (hexanes–ether 1:1); IR ($CHCl_3$) 1710, 1600, 1460, 1370, 1350, 1180, 1170 cm^{-1}; NMR (CCl_4) δ 7.48 (AB q, 4 H, $\Delta\nu_{AB}$ = 27 Hz, J = 8 Hz), 4.33 (br s, 2 H), 4.2–3.6 (m, 3 H), 2.43 (s, 3 H), 2.06 (s, 3 H), 1.10 (s, 3 H), 0.56 (d, 3 H, J = 7 Hz).

A mixture of the above tosylate (3.8 g, 8.29 mmol) and dry sodium iodide (3.70 g, 24.8 mmol) in 120 mL of reagent grade acetone was stirred at room temperature for 16 h. After heating at 55 °C to complete the reaction, the solvent was removed under reduced pressure, and the residue dissolved in ether and washed with water. The ether solution of the product was dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo, giving 3.74 g of essentially pure iodide **21**. Chromatography on 100 g of silica gel (elution with hexanes–ether 2:1) provided 3.26 g (95%) of pure iodide 21: R_f 0.77 (hexanes–ether, 2:1); IR (CCl_4) 2900, 2800, 1685, 1480, 1455, 1435, 1405, 1380, 1370, 1340, 1260, 1230, 1195, 1175, 1145, 1110, 1060, 1035, 1025 cm^{-1}; NMR (CCl_4) δ 7.20 (s, 5 H), 4.32 (s, 2 H), 3.76 (br t, 1 H, J = 7 Hz), 2.8–3.4 (m, 2 H), 2.06 (s, 3 H), 1.15 (s, 3 H), 0.60 (s, 3 H, J = 7 Hz); high-resolution mass spectrum, m/e 414.1050; calcd for $C_{19}H_{27}IO_2$, 414.1056.

(3α,3aα,8α,8aβ)-Octahydro-3a,8-dimethyl-3-(phenylmethoxy)-4-(1*H*)-azulenone (22). To a solution of lithium hexamethyldisilylamide, prepared at 0 °C from 769 mg (4.78 mmol) of hexamethyldisilazane in 15 mL of anhydrous tetrahydrofuran and 2.95 mL (4.34 mmol) of *n*-butyllithium (1.47 M in hexane) and cooled to −78 °C, was added dropwise over a 45-min period a solution of 915 mg (2.10 mmol) of keto iodide **21** in 15 mL of tetrahydrofuran containing 427 mg (7.96 mmol) of dry HMPA. The reaction mixture was stirred at −78 °C for 1 h and warmed to −20 °C, where stirring was continued for 3 h. After 2 h at 0 °C, the reaction was quenched with 5 mL of water. The reaction mixture was diluted with 50 mL of ether, washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The crude residue was chromatographed on 30 g of silica gel (elution with benzene–ethyl acetate 100:1), providing 12 mg (1%) of unreacted keto iodide **21** (R_f 0.57, benzene–ethyl acetate 20:1) and 533 mg (88%) of the desired bicyclic ketone **22**, which crystallized upon standing: mp 31.5–33.0 °C; R_f 0.50; IR (CCl_4) 3060, 3030, 2960, 2930, 2875, 1691, 1500, 1455, 1385, 1355, 1345, 1305, 1286, 1260, 1215, 1205, 1138, 1120, 1092, 1064, 1028, 982, 965, 910 cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 1.03 (d, 3 H, J = 6.8 Hz), 1.18 (s, 3 H), 1.3–2.1 (m, 10 H), 1.52 (dd, 1 H, J = 8 Hz, 4 Hz), 2.4–2.6 (m, 2 H), 4.03 (t, 1 H, J = 7 Hz), 4.37 (AB q, 2 H, $\Delta\nu_{AB}$ = 25 Hz, J = 12 Hz), 7.20 (s, 5 H). Anal. Calcd for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.67; H, 9.40.

(3α,3aα,8a,8aβ)-Octahydro-3a,8-dimethyl-5-(3-methyl-2-butenyl)-3-(phenylmethoxy)-4(1*H*)-azulenone (26). To a solution of 780 mg (7.72 mmol) of diisopropylamine in 10 mL of dry tetrahydrofuran at −78 °C was added dropwise 4.89 mL (7.13 mmol) of a 1.46 M solution of *n*-butyllithium in hexane. After stirring for 15 min, 1.06 g (5.94 mmol) of dry hexamethylphosphoramide was added followed by dropwise addition of 1.60 g (5.94 mmol) of ketone **22** in 10 mL of tetrahydrofuran.

Stirring was continued at −78 °C for 30 min. After the solution was warmed to −20 °C, 2.66 g (17.8 mmol) of 1-bromo-3-methyl-2-butene was added in one portion. Stirring was continued at −20 °C for 3 h. The reaction was quenched at −20 °C with 1.5 mL of water. The tetrahydrofuran was removed under reduced pressure, and the residue was taken up in ether and brine. After several ether extractions of the aqueous phase, the combined ether layers were dried over anhydrous magnesium sulfate and condensed, leaving 2.31 g of crude product. Purification on 120 g of silica gel (elution with hexanes–ether 5:1) provided 1.83 g (87%) of ketone **26** as a mixture of isomers at C(7), which was used directly in the next reaction. Continued elution provided 68 mg (4%) of the starting ketone **22**.

For the purpose of characterizing the two isomers, 50 mg of ketone **26** was chromatographed on 20 g of silicAR CC-7. Elution with 20:1 hexanes–ether provided 17.5 mg (35%) of **27a** [R_f 0.63 (hexanes–ether 7:1); IR (CCl_4) 3080, 3060, 3030, 2960, 2920, 2875, 2850, 1691, 1500, 1470, 1435, 1425, 1390, 1365, 1355, 1230, 1210, 1130, 1110, 1090, 1070, 1030, 983, 970, 940 cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 1.05 (d, 3 H, J = 7.2 Hz), 1.26 (s, 3 H), 1.62 (s, 3 H), 1.68 (s, 3 H), 2.3–2.5 (m, 2 H), 2.70 (m, 1 H), 4.31 (AB q, 2 H, $\Delta\nu_{AB}$ = 17 Hz, J = 8 Hz), 4.51 (t, 1 H, J = 8.2 Hz), 5.01 (m, 1 H), 7.20 (s, 5 H); high-resolution mass spectrum, m/e 354.2557; calcd for $C_{24}H_{34}O_2$, 354.2559 and 32.5 mg (65%) of crystalline **27b** [mp 69–70 °C; R_f 0.61; IR (CCl_4) 3070, 3030, 2970, 2920, 2880, 2960, 1700, 1500, 1455, 1440, 1385, 1360, 1140, 1120, 1095, 1030, 985 cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 0.94 (d, 3 H, J = 7.18 Hz), 1.10 (s, 3 H), 1.60 (s, 3 H), 1.64 (s, 3 H), 2.24–2.52 (m, 2 H), 2.92 (quintet, 1 H, J = 7.6 Hz), 3.66 (t, 1 H, J = 8.7 Hz), 4.26 (AB q, 2 H, $\Delta\nu_{AB}$ = 72 Hz, J = 12.3 Hz), 7.13–7.28 (m, 5 H)]. An analytical sample was prepared by recrystallization from carbon tetrachloride. Anal. Calcd for $C_{24}H_{34}O_2$: C, 81.31; H, 9.67. Found: C, 81.23; H, 9.78.

(3aα,3aα,8α,8aβ)-Octahydro-3a,8-dimethyl-3-(phenylmethoxy)-4-(1*H*)-oxoazulene-5-acetic Acid (28). The prenylated ketone **26** (1.76 g, 4.98 mmol) was dissolved in 60 mL of dry methylene chloride, cooled to −78 °C, and treated with 187 mL of a cool (−78 °C) saturated solution of ozone (7.40 mmol) in methylene chloride. After stirring at −78 °C for 30 min, 25 mL of freshly distilled dimethyl sulfide was added at −78 °C. The reaction mixture was allowed to warm to room temperature and was stirred at that temperature for 12 h. The solvent was then removed under reduced pressure, and the resulting 1.61 g of crude aldehyde was chromatographed directly on 100 g of silica gel. Elution with 3:1 hexanes–ether provided 1.55 g (95%) of the desired keto aldehyde, which was used directly in the next reaction: R_f 0.54 (hexanes–ether 1:1); IR (CCl_4) 3085, 3070, 3040, 2970, 2930, 2880, 2855, 2720, 1725, 1695, 1605, 1500, 1460, 1440, 1380, 1350, 1300, 1230, 1135, 1095, 1060, 1030, 995, 970, 910 cm^{-1}; NMR δ (CCl_4) 9.7 (s, 1 H), 7.20 (s, 5 H), 4.3 (AB q, 2 H, $\Delta\nu_{AB}$ = 14 Hz, J = 12 Hz), 1.08 (s, 3 H), 0.90 (d, 3 H, J = 7 Hz).

A solution of 768 mg (2.34 mmol) of the above keto aldehyde dissolved in 60 mL of reagent grade acetone cooled to 0 °C was treated dropwise with 2.0 mL of standard Jones reagent. After 1 h at 0 °C and 30 min at room temperature, the excess Jones reagent was quenched by the addition of 2-propanol. The solvent was removed in vacuo. The residue was taken up in ether and brine. The aqueous phase was extracted repeatedly with ether, and the combined ether extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure, leaving 807 mg of essentially pure keto acid **28**. Purification on 20 g of silica gel (elution with hexanes–ether–acetic acid 1:2:1 drop per 100 mL of volume) provided 792 mg (98%) of crystalline material, which was recrystallized from ether: mp 125–127 °C; IR ($CHCl_3$) 3600–2800, 2970, 2930, 1705, 1450, 1385, 1290, 1130, 1100, 1030, 995, 910 cm^{-1}; NMR $CDCl_3$ δ 9.5 (br s, 1 H), 7.25 (s, 5 H), 4.35 (AB q, 2 H, $\Delta\nu_{AB}$ = 14 Hz, J = 12 Hz), 1.15 (s, 3 H), 0.93 (d, 3 H, J = 7 Hz). Anal. Calcd for $C_{21}H_{28}O_4$: C, 73.23; H, 8.19. Found: C, 73.01; H, 8.11.

(6aα,6aβ,9aα,9aα,9bβ)-5,6,6a,7,8,9a,9b-Octahydro-6,9a-dimethyl-9-(phenylmethoxy)azuleno[4,5-*b*]furan-2(4*H*)-one (29). A mixture of 792 mg (2.3 mmol) of keto acid **28** and 943 mg (11.9 mmol) of sodium acetate in 30 mL of acetic anhydride was heated at reflux for 2 h. The mixture was cooled to 0 °C, and 60 mL of ether was added followed by filtration. The filtrate was then evaporated under reduced pressure (<0.1 mm), providing 922 mg of crude product. Purification by column chromatography on 40 g of silica gel (elution with 1:1 hexanes–ether) provided 521 mg (69%) of butenolide **29** as a white crystalline material: mp 82–83 °C; R_f 0.60 (hexanes–ether 1:2); IR (CCl_4) 3070, 3025, 2980, 2960, 2940, 2870, 1765, 1640, 1630, 1500, 1471, 1455, 1424, 1405, 1390, 1355, 1345, 1315, 1290, 1272, 1241, 1220, 1201, 1170, 1160, 1144, 1114, 1085, 1075, 1060, 1025, 985, 965, 905 cm^{-1}; NMR (250 MHz, CCl_4) δ 0.78 (s, 3 H), 1.00 (d, 3 H, J = 7.3 Hz), 2.57 (dd, 1 H, J = 17, 8 Hz), 2.82 (dd, 1 H, J = 17, 10 Hz), 3.76 (t, 1 H, J = 5 Hz), 4.53 (s, 1 H), 4.57 (AB q, 2 H, $\Delta\nu_{AB}$ = 27 Hz, J = 11.8 Hz), 5.72 (s, 1 H), 7.16–7.34 (m, 5 H). An analytical sample was prepared by recrystallization from ether. Anal. Calcd for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03. Found: C, 77.49; H, 8.01.

(3aα,6β,6aα,9β,9aβ,9bα)-Decahydro-9-hydroxy-6,9a-dimethylazuleno[4,5-*b*]furan-2(3*H*)-one (30). A suspension of 113 mg (0.47 mmol) of butenolide **29** was dissolved in 10 mL of ethyl acetate, and 25 mg of platinum oxide was added. The reaction mixture was placed under hydrogen at atmospheric pressure and stirred at room temperature for 12 h. The reaction mixture was then diluted with 50 mL of ethyl acetate, dried directly over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure, providing 120 mg of essentially pure hydroxy lactone **30**. Chromatography on 10 g of silica gel (elution with hexanes–ether 1:2) provided 111 mg (98%) of pure lactone **30**: mp 40.5–41.5 °C; R_f 0.23 (hexanes–ether 1:2); IR (CCl_4) 3600, 2970, 2930, 2875, 1789, 1475, 1456, 1420, 1390, 1375, 1365, 1350, 1335, 1325, 1315, 1293, 1265, 1240, 1220, 1175, 1152, 1125, 1110, 1090, 1070, 1060, 1040, 995, 973, 950, 897 cm^{-1}; NMR (250 MHz, CCl_4) δ 0.96 (s, 3 H), 1.05 (d, 3 H, J = 7.3 Hz), 1.4–2.12 (m, 11 H), 2.18 (dd, 1 H, J = 17.4, 12.2 Hz), 2.48 (dd, 1 H, J = 17.4 and 10.1 Hz), 2.79–2.92 (m, 1 H), 3.88 (t, 1 H, J = 9.2 Hz), 4.27 (d, 1 H, J = 9.5 Hz). Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.36; H, 9.28.

(3aα,6β,6aα,9β,9aβ,9bα)-Decahydro-9-hydroxy-6,9a-dimethyl-3-methyleneazuleno[4,5-*b*]furan-2(3*H*)-one (31). To a solution of diisopropylamine (90 mg, 0.90 mmol) in 4 mL of dry tetrahydrofuran cooled to −78 °C was added 578 μL of a 1.46 M solution of *n*-butyllithium in hexane. After 15 min, a solution of 86 mg (0.36 mmol) of hydroxy lactone **30** and 64 mg (0.36 mmol) of hexamethylphosphoramide in 4 mL of dry tetrahydrofuran was added dropwise over a period of 30 min. After 30 min at −78 °C, the reaction mixture was warmed to −25 °C and formaldehyde, generated from 150 mg of paraformaldehyde at 150 °C, was passed into the reaction mixture with the aid of a stream of dry nitrogen. After complete depolymerization, the reaction mixture was stirred for an additional 30 min at −25 °C. The reaction was quenched by the addition of a saturated aqueous solution of ammonium chloride. The reaction mixture was diluted with 30 mL of ether and 30 mL of ethyl acetate and directly dried over anhydrous magnesium sulfate. Evaporation under reduced pressure of the filtrate provided 254 mg of residue, which was purified on 12 g of silica gel. Elution with 3:1 ether–ethyl acetate gave 18 mg (20%) of recovered hydroxy lactone **30** and 68 mg (70%, 90% based on the recovered starting material) of white crystalline hydroxymethylated lactone, which was used directly in the next reaction: mp 115–117 °C; R_f 0.52 (ether–ethyl acetate 3:1); IR ($CHCl_3$) 3600, 1760 cm^{-1}; NMR ($CDCl_3$) δ 1.00 (s, 3 H), 1.06 (d, 3 H, J = 7 Hz), 3.6–4.2 (m, 3 H), 4.38 (d, 1 H, J = 10 Hz).

A solution of the above diol (65 mg, 0.24 mmol) in 2 mL of dry pyridine containing 33 mg (0.29 mmol) of methanesulfonyl chloride was allowed to stir for 2 h at 0 °C. The reaction mixture was quenched by the addition of 2 mL of saturated aqueous sodium bicarbonate solution and extracted repeatedly with ethyl acetate. The combined ethyl acetate extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo, leaving 97 mg of essentially pure monomesylate, which was homogeneous by TLC analysis and used directly in the next reaction: R_f 0.63 (ether); IR (CCl_4) 3600, 1782, 1440, 1370, 1180 cm^{-1}; NMR (CCl_4) δ 0.93 (s, 3 H), 1.01 (d, 3 H, J = 7 Hz), 2.96 (s, 3 H), 3.86 (m, 1 H), 4.30 (m, 3 H).

The above mesylate (97 mg, 0.24 mmol) was dissolved in 4 mL of dry benzene containing 55 mg (0.36 mmol) of 1,5-diazabicyclo[5.4.0]undec-5-ene. After 1 h at room temperature, the solvent was removed in vacuo, and the residue was chromatographed on 15 g of silica gel. Elution with ether gave 56 mg (64% overall from **30**) of crystalline α-methylene lactone **31**: mp 114–116 °C; R_f 0.65 (ether); IR (CCl_4) 3600, 3010, 2975, 2925, 2875, 1780, 1478, 1405, 1394, 1338, 1318, 1295, 1275, 1260, 1150, 1136, 1110, 1090, 1050, 1035, 995, 978, 945 cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 0.84 (s, 3 H), 1.04 (d, 3 H, J = 7.2 Hz), 1.5–2.2 (m, 10 H), 2.44 (br s, 1 H, OH), 3.35 (m, 1 H), 4.01 (t, 1 H, J = 9.2 Hz), 4.49 (d, 1 H, J = 9.5 Hz), 5.50 (d, 1 H, J = 3.5 Hz), 6.21 (d, 1 H, J = 3.5 Hz); high-resolution mass spectrum, m/e 232.1454; calcd for $C_{15}H_{22}O_3$–H_2O, 232.1463. Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.05; H, 8.79.

***dl*-Damsin (2).** To a solution of 32 mg (0.13 mmol) of alcohol **31** in 7 mL of acetone cooled to −15 °C was added dropwise 0.7 M Jones reagent until the red color persisted. After 15 min, the mixture was quenched with 2-propanol. The reaction was diluted with 30 mL of acetone and the acetone solution decanted and evaporated, leaving an oily residue, which was dissolved in ether. The chromium salts were dissolved in 50% brine and extracted with ether. The combined ether extracts were washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure, leaving 39 mg of residue. Purification on 10 g of silica gel (elution with ether) provided 28.5 mg (90%) of pure crystalline damsin: mp 124–125 °C (recrystallized from 2-propanol) (lit.[9a] mp 124–126 °C); IR ($CHCl_3$) 3020, 2970, 2930, 2875, 1765, 1740, 1660, 1475, 1450, 1410, 1386, 1338, 1315, 1275, 1220, 1165, 1150, 1122, 1058, 1020, 1009, 980, 950, 935 cm^{-1}; NMR (250 MHz, CCl_4) δ 1.00 (s, 3 H), 1.08 (d, 3 H, J = 7.5 Hz), 1.7–2.4 (m, 10 H), 3.30 (m, 1 H),

4.53 (d, 1 H, J = 8.5 Hz), 5.53 (d, 1 H, J = 3.0 Hz), 6.27 (d, 1 H, J = 3.0 Hz).

***dl*-Ambrosin (1).** To 15 mg of synthetic damsin (0.072 mmol) in 3 mL of freshly distilled ethyl acetate was added 16 mg (0.079 mmol) of phenylselenenyl chloride at room temperature. Over a 4-h period, the reddish reaction mixture turned pale yellow, whereupon the reaction was quenched with solid sodium bicarbonate. The reaction was diluted with 50 mL of ethyl acetate, washed with brine, dried over anhydrous magnesium sulfate, and filtered. The filtrate was evaporated under reduced pressure, leaving 47 mg of a residue. Purification on 10 g of silica gel (elution with ether–ethyl acetate 3:1) provided 24 mg (100%) of selenide **32**: R_f 0.92 (ether–ethyl acetate 3:1); IR ($CHCl_3$) 1765, 1732, 1660, 1580 cm^{-1}; NMR (CCl_4) δ 7.0–7.7 (m, 5 H), 6.15 (d, 1 H, J = 3 Hz), 5.35 (d, 1 H, J = 3 Hz), 3.45 (d, 1 H, J = 9 Hz).

To a solution of 24 mg (0.060 mmol) of the above monoselenide **32** in 1.5 mL of dry *tert*-butyl alcohol was added 35 mg (0.16 mmol) of sodium periodate at room temperature. The reaction mixture was warmed to 60 °C. After 2 h at 60 °C, the reaction was cooled to room temperature and diluted with 50 mL of ethyl acetate and 5 mL of brine. The aqueous layer was extracted with 2 × 15 mL portions of ethyl acetate, and the combined organic extracts were dried over anhydrous magnesium sulfate. The oily residue obtained upon evaporation of the solvent in vacuo was purified on 5 g of silica gel. Elution with ethyl acetate–benzene (1:1) afforded 7 mg (41%) of white crystalline *dl*-ambrosin (**1**): mp 188–190 °C (recrystallized from chloroform–hexane); IR ($CHCl_3$) 3025, 2985, 2960, 2940, 2880, 1770, 1710, 1665, 1595, 1478, 1458, 1410, 1386, 1370, 1345, 1330, 1315, 1305, 1285, 1275, 1245, 1214, 1160, 1115, 1105, 1085, 1068, 1024, 1010, 988, 970, 950, 835 cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 1.06 (d, 3 H, J = 7 Hz), 1.18 (s, 3 H), 2.28 (m, 1 H), 2.55 (m, 1 H), 3.03 (m, 1 H), 3.47 (m, 1 H), 4.67 (d, 1 H, J = 9 Hz), 5.51 (d, 1 H, J = 3 Hz), 6.14 (dd, 1 H, J = 6 Hz and 3 Hz), 6.29 (d, 1 H, J = 3 Hz), 7.50 (dd, 1 H, J = 6 Hz and 2 Hz).

Acknowledgment. This investigation was supported by Public Health Service research grants (CA 13689 and CA 28865) from the National Cancer Institute and the National Institutes of Health NMR Facility for Biomedical Studies at Mellon Institute (RR-00292). We thank Drs. Mugio Nishizawa and Narihiko Fukamiya for many helpful discussions. We are indebted to Professor James A. Marshall for a sample gift of natural damsin and Professor Eloy Rodriguez for samples of natural ambrosin and damsin.

Registry No. (±)-**1**, 64813-79-2; (±)-**2**, 60133-11-1; (±)-**4**, 82041-93-8; dihydro-(±)-**4**, 82041-94-9; (±)-**7**, 82041-95-0; (±)-**9**, 64798-67-0; (±)-**10**, 82041-96-1; (±)-**11**, 82041-97-2; (±)-**11** alcohol, 81987-60-2; (±)-**16**, 81987-61-3; (±)-**18**, 82041-98-3; (±)-**18** monotosylate, 81987-62-4; (±)-**18** nitrile, 82041-99-4; (±)-**19**, 82042-00-0; (±)-**19** aldehyde, 81987-63-5; (±)-**19** alcohol, 81987-64-6; (±)-**20**, 82042-01-1; (±)-**20** monotosylate, 81987-65-7; (±)-**20** keto tosylate, 81987-66-8; (±)-**21**, 64798-77-2; (±)-**22**, 64798-78-3; (±)-**23**, 81987-67-9; (±)-**26**, 64798-79-4; (±)-**26** keto aldehyde, 81987-68-0; (±)-**27**a, 82042-02-2; (±)-**27**b, 82042-03-3; (±)-**28**, 64798-80-7; (±)-**29**, 64798-81-8; (±)-**30**, 64798-82-9; hydroxymethyl-**30**, 81987-69-1; **30** monomesylate, 81987-71-5; (±)-**31**, 64798-83-0; (±)-**32**, 81987-70-4; (±)-**8**, 54701-92-7; (±)-**12**, 82042-04-4; (±)-**13**, 82042-05-5; (±)-**14**, 81987-72-6; (±)-**15**, 81987-73-7; i, 81987-74-8; ii, 56029-64-2; 1-bromo-3-methyl-2-butene, 870-63-3.

Pseudoguaianolides. 2. Stereocontrolled Total Synthesis of the Helenanolide *dl*-Helenalin[†,1]

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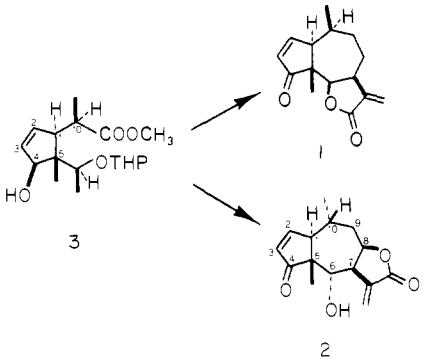
Received December 21, 1981

Abstract: A stereocontrolled total synthesis of the sesquiterpene lactone *dl*-helenalin (**2**) is described. The synthesis starts with cyclopentenol **3** and proceeds via the intermediacy of perhydroazulenone **20**. Elaboration of **20** into epoxy alcohol **28** sets the stage for introduction of the C(7)–C(8) cis-fused α-methylene-γ-butyrolactone. Oxidation at C(4) completes the synthesis of *dl*-helenalin.

Several years ago we embarked on a program that had as its ultimate goal the development of a general synthetic route for the construction of ambrosanolides (cf. ambrosin (**1**)) and helenanolides (cf. helenalin (**2**)) from a common synthetic intermediate. Our initial strategy centered around the key cyclopentenol **3**. The elaboration of **3** into ambrosin has been reported in the preceding paper.[2] We detail below the transformation of **3** into *dl*-helenalin, which constitutes the successful realization of our initial goal, i.e., the ability of cyclopentenol **3** to function as a *common synthetic* intermediate for both helenanolide and ambrosanolide synthesis.



Helenalin (**2**), which possesses six chiral centers about a flexible seven-membered ring, is representative of a group of pseudoguaianolides[3] known as helenanolides, which have as a characteristic feature a C(10) α-oriented methyl group. Helenalin was first isolated from *Helenium autumnale* over 65 years ago.[4] Its

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† Dedicated to Professor Gilbert Stork on the occassion of his 60th birthday.

(1) Taken in part from the Ph.D. Thesis of George F. Majetich, University of Pittsburgh, 1979. For a preliminary account of this work, see: Ohfune, Y.; Grieco, P. A.; Wang, C.-L. J.; Majetich, G. *J. Am. Chem. Soc.* **1978**, *100*, 5946.

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