a mixture of the secondary alcohols (130.0 mg, 0.38 mmol, 81%).

To a solution of Collins reagent (740 mg, 2.87 mmol) in CH_2Cl_2 (5 mL) was added a solution of the alcohols (99.4 mg, 0.29 mmol) in CH_2Cl_2 (2 mL). After 5 min being stirred at room temperature, the mixture was decanted and the black residue was washed with several portions of ether. The organic layer was combined, washed successively with 5% NaOH solution, 5% HCl, saturated $NaHCO_3$ solution, and saturated brine, dried over $MgSO_4$, and concentrated. Chromatography (3 g of silica gel; 5:1 hexane–ethyl acetate) of the residue gave **15** (95.7 mg, 0.28 mmol, 97%).

15: colorless oil; IR 1705 (s) and 1695 (s) cm^{-1}; ^1H NMR δ 4.57 (1 H, m), 2.7–2.45 (2 H, m), 2.2–1.2 (13 H, m), 1.07 (3 H, d, J = 6.5 Hz), 1.05–0.95 (3 H, br), 0.89 (9 H, s), 0.10 (3 H, s), and 0.07 (3 H, s).

***endo*-3- and *exo*-3-Butyl-*exo*-4-methylbicyclo[4.3.0]non-1(9)-en-2-ones (8a and 8b, Respectively).** To a solution of potassium *tert*-butoxide (37.0 mg, 0.33 mmol) in THF (8 mL) was added a solution of **15** (100.0 mg, 0.295 mmol) and *tert*-butyl alcohol (0.05 mL) in THF (2 mL) under argon at room temperature. After being stirred for 30 min, the mixture was treated with saturated NH_4Cl solution and extracted with three portions of ether. The ethereal extracts were combined, washed with saturated brine, and dried over $MgSO_4$. Evaporation of the solvent, followed by chromatography of the residue on silica gel (5 g; 60:1 hexene–ethyl acetate), gave a mixture of **8a** and **8b** (56.7 mg, 0.27 mmol, 92%). Analytical samples of these isomers were obtained by careful fractionation of the eluate.

8a: colorless oil; IR (CCl_4) 2920 (s), 2860 (s), 1680 (s), and 1615 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.57 (1 H, ddd, J = 2.3, 2.3, and 2.3 Hz), 3.08 (1 H, br, $W_{1/2}$ = 5 Hz), 2.5–2.0 (6 H, m), 1.85–1.15 (8 H, m), 1.06 (3 H, d, J = 7.2 Hz), and 0.89 (3 H, m); MS (25 eV), m/z (rel intensity) 206 (M^+, 2.1), 191 (1.5), 151 (13.4), and 150 (100).

8b: colorless oil; IR (CCl_4) 2930 (s), 2860 (s), 1685 (s) and 1620 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.46 (1 H, ddd, J = 2.3, 2.3, and 2.3 Hz), 3.11 (1 H, br, $W_{1/2}$ = 5 Hz), 2.5–2.15 (5 H, m), 2.12–1.8 (3 H, m), 1.8–1.0 (6 H, m), 0.92 (3 H, m), and 0.91 (3 H, d, J = 7.0 Hz); MS (25 eV), m/z (rel intensity) 206 (M^+, 2.0), 191 (4.0), 150 (59.1), and 135 (100); exact mass found m/z 206.1654, calcd for $C_{14}H_{22}O$ M 206.1670.

(±)-Ptilocaulin (1). (a) A solution of guanidine was prepared from the carbonate (22.0 mg, 0.12 mmol) by sonication for 5 min with sodium methoxide (13.0 mg, 0.24 mmol) in methanol under argon. The reaction mixture was carefully filtered and the filtrate was concentrated in vacuo. The reaction flask containing the residue was fitted with a Soxhlet extractor in which were placed 4A molecular sieves and charged with nitrogen and a solution of **8a** (27.6 mg, 0.13 mmol) in benzene (25 mL). The mixture was heated under reflux for 25 h under a nitrogen atmosphere and then allowed to cool to room temperature. The solution was neutralized with 1% HNO_3 (2 mL) and the aqueous layer was extracted with three portions of $CHCl_3$. The extracts were combined, washed with saturated $NaNO_3$ solution,[4b] dried over $MgSO_4$, and concentrated. Chromatography of the residue on silica gel (5 g; $CHCl_3$–MeOH, 85:15) gave (±)-ptilocaulin nitrate (18.8 mg, 0.060 mmol, 50%).

(b) When a mixture of **8a** and **8b** (44.6 mg, 0.216 mmol) was treated by a similar procedure to that described above (±)-**1** was derived in 27% yield (18.1 mg, 0.058 mmol).

(±)-**1**: mp 151–152 °C; ^1H NMR ($CDCl_3$, 270 MHz) δ 8.96 (1 H, br s, $W_{1/2}$ = 5 Hz), 8.30 (1 H, br s, $W_{1/2}$ = 8 Hz), 7.39 (2 H, br s, $W_{1/2}$ = 10 Hz), 3.77 (1 H, m), 2.55–2.3 (4 H, m), 2.2–1.95 (2 H, m), 1.95–1.1 (9 H, m), 1.05 (3 H, d, J = 6.8 Hz), and 0.90 (3 H, t, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ 151.77, 126.99, 121.01, 53.22, 36.52, 33.98, 33.09, 32.22, 29.65, 27.79, 26.95, 24.65, 22.44, 19.53, 14.00; exact mass found m/z 247.2020, calcd for $C_{15}H_{25}N_3$ M 247.2047.

Acknowledgment. We express our sincere appreciation to Professor B. B. Snider of Brandeis University for providing us with ^1H NMR spectra of compounds **8a** and **8b** and natural ptilocaulin. Grateful acknowledgment is also made for support of this investigation by a Grant-in-Aid for Scientific Research No. 60540312 from the Ministry of Education, Science, and Culture, Japan.

Robustadials. 2. Total Synthesis of the Bicyclo[3.2.0]heptane Structure Proposed for Robustadials A and B

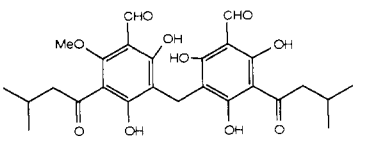
Kasturi Lal, Eugene A. Zarate, Wiley J. Youngs, and Robert G. Salomon*

Department of Chemistry, Case Western Reserve University, Cleveland, Ohio 44106-2699

Received November 29, 1987

Total synthesis of the bicyclo[3.2.0]heptane structure **2a** proposed for robustadial A was achieved. The molecular architecture of the synthetic product was unambiguously established by X-ray crystallographic analysis of an intermediate in the synthesis. However, spectral comparison clearly shows that **2a** is not the correct structure for the natural product robustadial A. Intramolecular copper(I)-catalyzed $2\pi + 2\pi$ photocycloaddition was exploited as the key step for generating the bicyclo[3.2.0]heptane portion of **2a** from the 1,6-heptadiene **16**, which was assembled from 1,3,5-trimethoxybenzene in six steps. Photocyclization of **16** proceeded smoothly, affording **17** in 75–80% yield.

A global resurgence of malaria,[1] the appearance of strains of which are resistant[2] to quinine, its analogues, and many of the relatively small number of known antimalarial drugs, provides an urgent need for the identification and total synthesis of new antimalarial natural products. Several active compounds are contained in an antimalarial ethanol extract of *Eucalyptus robusta* leaves, a plant used in Chinese herbal medicine.[3] Robustaol A (**1**) was the first



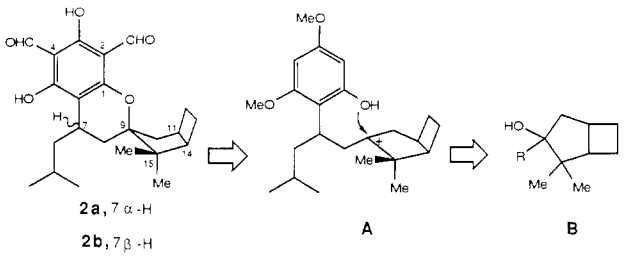
1

component isolated from this extract which showed in vivo antimalarial activity against *Plasmodium berghei* in mice. The structure of **1** was established by total synthesis.[3] A

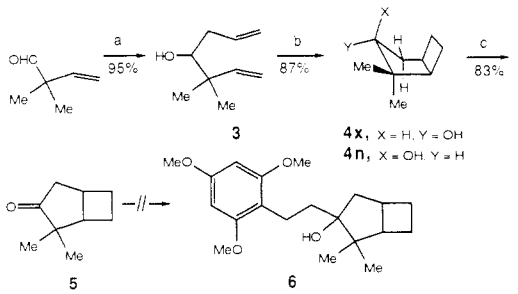
(1) The disease affects about 250 million to 300 million people worldwide each year, causing debilitating illness.
(2) Peter, W. *Br. Med. Bull.* **1982**, *38*, 187.
(3) Qin, G. W.; Chen, H. C.; Wang, H. C.; Qian, M. K. *Huaxue Xuebao* **1981**, *39*, 83.

0022-3263/88/1953-3673$01.50/0

Scheme I



Scheme II[a]



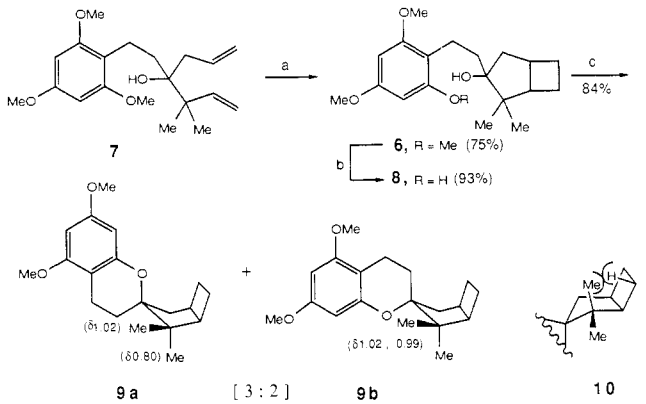
[a] (a) $H_2C{=}CHCH_2MgCl$; (b: $h\nu$/CuOTf; (c) CrO_3/H_2SO_4.

second fraction of the ethanol extract contained several compounds that possessed considerably greater activity than **1**.[4] Two of these compounds, robustadial A and robustadial B, were isolated from this plant and assigned bicyclo[3.2.0]heptane structures **2a** and **2b** respectively on the basis of extensive and sophisticated NMR, UV, IR, and mass spectral studies.[4] Since these epimeric natural products are available only in tiny amounts and are very difficult to separate, biological studies on the individual robustadials A or B have not yet been achieved.[5] To provide a reliable supply for medicinal evaluation, we launched a total synthesis of robustadials. Particularly attractive was the prospect of demonstrating the utility of copper(I)-catalyzed photobicyclization[6] for efficiently assembling the bicyclo[3.2.0]heptane portion of the structures **2a** and **2b**. We now report the successful application of this strategy for synthesis of **2a**. However, spectral comparison clearly shows that **2a** is not the correct structure for the natural product robustadial A.

Results and Discussion

For the total synthesis of **2a** and **2b**, two strategies were explored involving key copper(I)-catalyzed photobicyclizations of 1,6-dienes. For both approaches it was presumed that the pyran ring in **2** could be generated by cyclization of a phenol as in A (Scheme I). Two routes were envisioned for assembling a tertiary alcohol precursor B. In one approach (Scheme II), photobicyclization is performed with a simple diene **3**, and the product **4** is converted to B by oxidation and addition of a trimethoxyphenethyl carbanion to an intermediate ketone **5**. The hydroxy diene **3** is readily available from 2,2-dimethylbut-3-enal[7] by reaction with allylmagnesium bromide. Copper(I)-catalyzed photocyclization of **3** cleanly delivered an epimeric mixture of 2-hydroxybicyclo[3.2.0]heptanes **4x** and **4n**. Oxidation of the mixture produced a single

Scheme III[a]



[a] (a) CuOTf/$h\nu$; (b) EtSNa/DMF; (c) $BF_3{\cdot}OEt_2/CH_2Cl_2$.

ketone **5**. Unfortunately, the Grignard reagent, prepared from 2-(2,4,6-trimethoxyphenyl)ethyl bromide, abstracted a proton from **5**, generating 2-ethyl-1,3,5-trimethoxybenzene rather than providing the desired adduct **6**, which requires 1,2-addition to a sterically congested carbonyl group. Even cyclopentanone underwent proton abstraction (24% yield) by the above-mentioned Grignard reagent in preference to 1,2-addition (14% yield).

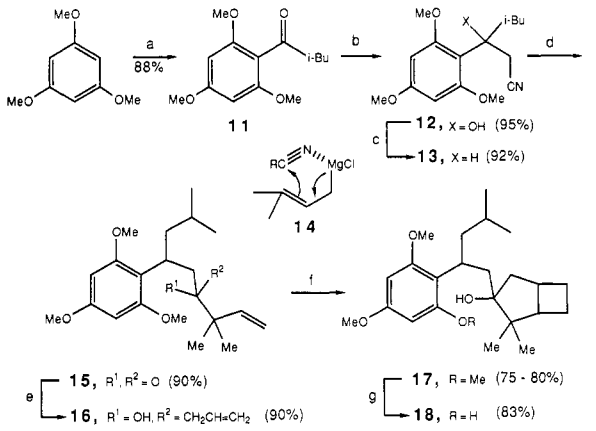
Therefore, we adopted an alternative strategy (Scheme III) in which the sterically congested tertiary alcohol is assembled prior to photocycloaddition. Diene **7** was assembled in 78% overall yield in four steps from 2,4,6-trimethoxybenzaldehyde.[8b]

The synthetic versatility of copper(I)-catalyzed photobicyclizations is demonstrated by the production of **6** in reproducibly good yield upon UV irradiation of **7** in the presence of copper(I) trifluoromethanesulfonate. Monodemethylation of **6** with NaSEt affording **8** set the stage for generation of the pyran ring. The favorable regioselectivity of this demethylation results from a novel remote neighboring group effect of the tertiary alcohol.[8] Heterocyclization of the tertiary alcohol–monophenol **8** by treatment with boron trifluoride diethyl etherate in methylene chloride delivered a 3:2 mixture of epimeric tetrahydrospiro pyrans **9**, which was separated by HPLC on silica gel. ^1H NMR spectral analysis suggests structure **9a** for the less polar major isomer and structure **9b** for the more polar minor isomer. Boat conformations are presumed for these isomers since a chair conformation would incorporate severe steric congestion between an endo hydrogen on the cyclobutyl ring and an endo methyl group as depicted in **10** (Scheme III). The downfield shift to δ 1.02 of the endo methyl group resonance in the ^1H NMR spectrum of **9a** is ascribed to a deshielding effect of the vicinal oxygen. Since the exo methyl group in **9a** is remote from the vicinal oxygen, its resonance occurs at higher field: δ 0.80. In the more polar minor isomer **9b**, both methyl substituents on the cyclopentane ring have deshielding gauche interactions with a vicinal oxygen and consequent downfield ^1H NMR shifts to δ 0.99 and 1.02.

Our successful total synthesis of the bicyclo[3.2.0]heptane **2a**, presumed[4] to be the natural product robustadial A, is outlined in Schemes IV and V. The requisite diene **16** was assembled in 60% overall yield in six steps from 1,3,5-trimethoxybenzene. Friedel–Crafts acylation provided the ketone **11**, in which the carbonyl carbon is

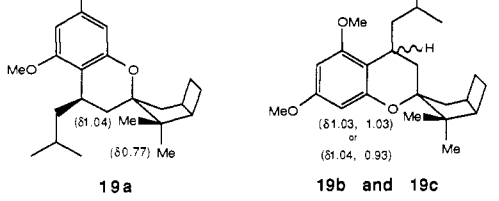
(4) Xu, R.; Synder, J. K.; Nakanishi, K. *J. Am. Chem. Soc.* **1984**, *106*, 734.
(5) Qin, G. W., private communication.
(6) For a recent review, see: Salomon, R. G. *Tetrahedron* **1983**, *39*, 485.
(7) Julia, M.; Baillarge, M. *Bull. Soc. Chim. Fr.* **1966**, 732.
(8) (a) Cannon, J. R.; Feutrill, G. I.; Wong, L. C. *Aust. J. Chem.* **1983**, *36*, 2575. (b) Lal, K.; Ghosh, S.; Salomon, R. G. *J. Org. Chem.* **1987**, *52*, 1072.

Scheme IV[a]



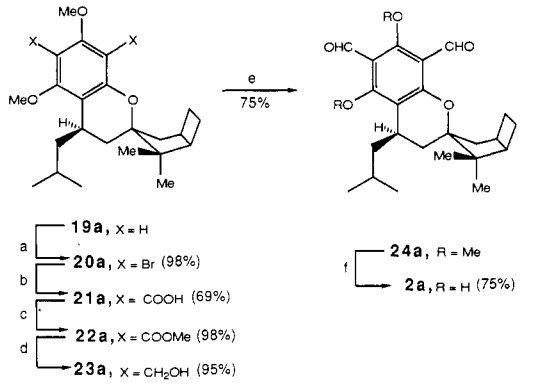
[a] (a) $Me_2CHCH_2COCl/AlCl_3$; (b) $LiCH_2CN$; (c) Et_3SiH/CF_3COOH; (d) $Me_2C{=}CHCH_2MgCl$; (e) $CH_2{=}CHCH_2MgBr$; (f) CuOTf/$h\nu$; (g) EtSNa/DMF.

shielded by two adjacent methoxy groups. Low yields were obtained upon cyanomethylenation of **11** with the anion of dimethyl phosphonoacetonitrile presumably owing to steric congestion. However, lithioacetonitrile,[9] a less bulky nucleophile, added to this carbonyl group to give the benzylic alcohol **12** in excellent yield. After reductive removal of the vestigial hydroxyl group, a ketone **15** was elaborated from nitrile **13** by a regioselective reaction with prenylmagnesium chloride. This appears to be the first example of such a regioselective reaction of this Grignard reagent with a nitrile.[10] The observed preferential electrophilic attack at the more substituted allylic terminus presumably results from pseudointramolecular C–C bond formation as in **14**. Similar pseudointramolecular C–C bond formation probably accounts for the excellent yield of 1,2-adduct **16** produced upon reaction of the sterically congested ketone **15** with allylmagnesium bromide. Since this diene is a mixture of diastereomers, photocyclization produces bicyclo[3.2.0]heptanes **17** as a mixture of diastereomers. Treatment of the derived monophenols **18** with $BF_3{\cdot}OEt_2$ generated an 8:1:1 mixture of diastereomeric pyrans **19a–c** in 77% combined yield. The less polar



major diastereomer **19a** (mp 80–82 °C) was readily isolated by HPLC on a Whatman M-20 μ-Porasil column eluting with 35% toluene in hexane. As for the epimers **9** discussed above, this less polar isomer was assigned the endo phenoxy configuration at the spiro center since only one methyl group on the cyclopentane ring, the endo methyl, shows a downfield-shifted ^1H NMR resonance (at δ 1.04). In contrast, the exo methyl group in **19a**, which has a trans diaxial relationship with the vicinal phenoxy substituent, produces a resonance at δ 0.77. A more polar fraction from the heterocyclization of **17** contained two minor diaste-

Scheme V[a]



[a] (a) Br_2/CH_2Cl_2; (b) *n*-BuLi/THF, then CO_2, then HCl; (c) CH_2N_2; (d) DIBAH/PhMe; (e) PDC; (f) BCl_3.

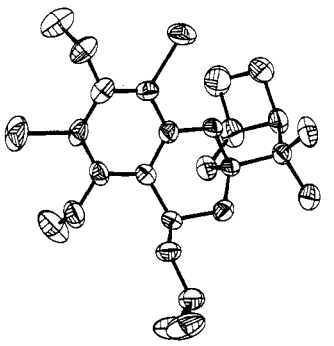
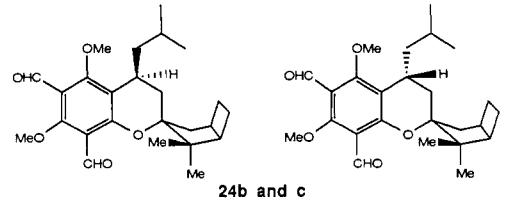


Figure 1. X-ray structure of **20a**.

reomeric pyrans **19b** and **19c**, which were separated by reverse-phase HPLC. As for **9b**, both of these pyrans are presumed to have an exo phenoxy configuration at the spiro center since the methyl groups on the cyclopentane ring all show resonances at relatively low field (δ 0.93–1.04) owing to gauche relationships with a vicinal phenoxy oxygen.

That **19a** has relative configurations corresponding to **2a** was confirmed by X-ray crystal structural analysis of the derived dibromide **20a** (see Scheme V). These configurations as well as the boat conformation of the bicyclo[3.2.0]heptane ring system are clearly evident from an ORTEP drawing (Figure 1) of the X-ray structure (see Experimental Section).

Lithium–bromine exchange followed by carboxylation, acidification, and O-methylation delivered the diester **22a** (mp 135 °C) from the dibromide **20a**. The dimethyl ether **24a** (mp 40–42 °C) of **2a** was obtained from **22a** by reduction to a diol **23a**, which was then oxidized to the dialdehyde **24a** with pyridinium dichromate (PDC). Analogous sequences were executed to prepare the stereoisomeric dialdehydes **24b** and **24c** from **20b** and **20c**. ^{13}C NMR



comparison of the synthetic dialdehyde methyl ethers **24a–c** with robustadial A dimethyl ether and robustadial B dimethyl ether (Table I) clearly shows that none of the synthetic compounds are identical with either of the naturally derived products. The quaternary carbon at position 2 in **24a** absorbs at δ 47.8 while **24b** and **24c** show

(9) Kaiser, E. M.; Hauser, C. R. *J. Org. Chem.* **1968**, *33*, 3402.

(10) (a) Analogous reactions of allylic zinc reagents are known;[10b] however, crotylmagnesium bromide in diethyl ether undergoes regioselective electrophilic attack by propionitrile at the *less* substituted allylic terminus.[10c] (b) Rousseau, G.; Conia, J. M. *Tetrahedron Lett.* **1981**, *22*, 649. (c) Andrac, M. *Ann. Chim. (Paris)* **1964**, 287.

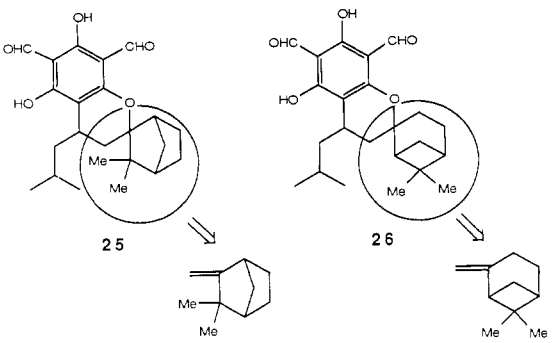
Table I. ^{13}C NMR Spectral Data of Robustadial Dimethyl Ethers and the Synthetic Dialdehyde Dimethyl Ethers 24a–c[a]

robustadial A dimethyl ether	robustadial B dimethyl ether	24a	24b	24c
21.3 q	21.0 q	16.6 q	19.0 t	18.3 t
23.6 q	23.4 q	20.2 t	20.6 q	21.1 q
24.2 q	23.8 q	20.7 q	21.1 q	22.0 q
25.3 t	24.8 t	24.0 t	23.6 q	22.6 q
26.0 d	25.8 d	24.1 q	24.1 q	23.7 q
27.0 t	26.9 d	25.3 d	25.3 d	25.6 d
27.8 d	27.0 t	27.3 q	25.7 t	26.4 d
28.1 q	27.3 q	27.5 d	27.6 d	26.7 t
31.6 t	28.3 t	33.7 t	33.0 t	26.7 t
38.3 s←	38.2 s←	34.2 d	34.4 d	35.8 d
39.9 t	39.1 t	39.6 t	39.8 t	43.6 t
40.9 d	40.5 d	44.9 t	45.6 t	44.6 t
44.2 t	44.5 t	47.8 s←	46.4 s←	47.6 d
49.7 d	51.0 d	50.5 d	48.6 d	48.1 s←
65.0 q	62.5 q	62.2 q	62.2 q	62.9 q
66.0 q	64.8 q	64.8 q	64.7 q	64.9 q
86.0 s⇐	84.8 s⇐	94.8 s⇐	94.2 s⇐	94.7 s⇐
115.9 s	115.6 s	116.0 s	115.7 s	114.8 s
116.5 s	116.4 s	116.2 s	116.4 s	115.4 s
119.0 s	118.8 s	118.7 s	118.9 s	118.1 s
163.3 s	163.4 s	163.5 s	164.1 s	163.0 s
165.0 s	165.5 s	165.4 s	165.1 s	165.0 s
165.2 s	165.7 s	165.9 s	165.8 s	166.0 s
187.4 d	187.6 d	187.6 d	187.5 d	187.5 d
187.4 d	187.6 d	187.6 d	187.8 d	187.6 d

[a] All spectra were recorded in $CDCl_3$ solutions. The designations s, d, t, and q refer to proton-coupled multiplicities singlet, doublet, triplet, and quartet respectively. The designations ← and ⇐ highlight high-field and low-field resonances respectively owing to quaternary carbons.

absorptions at δ 46.4 and 48.1. In contrast, the corresponding quaternary carbons in robustadials A and B absorb about 10 ppm upfield at δ 38.2–38.3. Likewise, the quaternary carbons at position 3 in **24a–c** absorb at δ 94.5 ± 0.3, but the corresponding quaternary carbons in robustadials A and B absorb at least 10 ppm upfield at δ 86.0 and 84.8 respectively. Furthermore, ^1H NMR comparison of the dialdehyde **24a** with robustadial A dimethyl ether clearly showed their nonidentity. Especially noteworthy are two resonances at δ 2.50 and 2.71, which correspond to the bridgehead methine hydrogens in **24a**. The corresponding methine hydrogen resonances for robustadial A occur at higher field.

Demethylation of **24a** with BCl_3 completed our total synthesis of **2a**.[11] Evidently, the structures of robustadial A and, presumably, robustadial B are isomeric with those proposed previously.[4] Biogenetic considerations suggest a terpenoid origin for the non-prenylphenol portion of robustadials.[12] Rather than the bicyclo[3.2.0]heptyl structures suggested originally, we propose that the terpenoid portion of the robustadials might reasonably be a bicyclo[2.2.1]heptane ring system **25** derived from camphene or a bicyclo[3.1.1]heptyl ring system **26** derived from pinene. Further synthetic studies described in the accompanying paper[13] rule out prenylphenol–camphane



structures **25**, and it now seems likely that the robustadials are prenylphenol derivatives **26** of pinane.

Experimental Section

All reactions were run under a positive pressure of dry nitrogen or argon. Reactions requiring anhydrous conditions were performed in flame-dried glassware cooled under nitrogen. Anhydrous solvents were transferred with an oven-dried syringe. Solvents were distilled before use: benzene and toluene from potassium, dimethylformamide (DMF) and acetonitrile from calcium hydride, dichloromethane and carbon tetrachloride from phosphorus pentoxide, diethyl ether and pentane from sodium hydride (mineral oil dispersion), tetrahydrofuran (THF) from potassium benzophenone ketyl. All chromatography solvents were distilled prior to use. Triply distilled water and methanol used for reverse-phase HPLC were degassed under water-aspirator vacuum for 15–20 min prior to use. 1-Chloro-3-methyl-2-butene was either purchased from Eastman Kodak or prepared as described previously.[14] Thin-layer chromatography (TLC) was performed on glass plates coated with 0.25 mm of silica gel (Kieselgel 60 F_{254}, E. Merck, Darmstadt, Germany) and preparative TLC on glass plates coated with 0.5 mm of silica gel. Analytical TLC plates were developed by spraying of the plates with vanillin indicator (6% w/v vanillin in 10% v/v ethanolic H_2SO_4) and heating with hot air. Flash chromatography[15] was performed on 230–400-mesh silica gel 60 supplied by E. Merck. Column eluates in preparative HPLC were monitored with a variable wavelength UV absorbance detector or a differential refractometer. Gas chromatography (GC) was performed on a gas chromatograph equipped with a thermal conductivity detector using 11 ft × $^1/_4$ in. columns containing the specified column packing, and flow rates of helium were on the order of 20–30 mL/min. Melting points are uncorrected.

^1H and ^{13}C NMR spectra were recorded at 200 and 50.31 MHz, respectively, in $CDCl_3$ unless stated otherwise. Hydrogen substitution on C atoms was determined with fully H coupled spectra, assisted by fully decoupled and attached proton test (APT) ^{13}C NMR experiments. The signs + and – refer to the peaks above the base line (s and t) and peaks below the base line (d and q), respectively, in APT experiments. Mass spectra (MS) were obtained on an AEI MS30 double-beam mass spectrometer at an ionizing current of 3 A and ionizing voltage of 30–45 eV.

2-(2,4,6-Trimethoxyphenyl)ethyl Bromide. A solution of 2-(2,4,6-trimethoxyphenyl)ethan-1-ol[8b] (0.55 g, 2.59 mmol), triphenylphosphine (0.85 g, 3.24 mmol), and carbon tetrabromide (1.08 g, 3.26 mmol) in anhydrous CH_3CN (25 mL) was stirred at room temperature for 2 h. Solvent was removed under reduced pressure, and the residue thus obtained was purified by flash chromatography (10% CH_2Cl_2 in hexanes) to give the title bromide (0.63 g, 88%), which crystallized from *n*-pentane: mp 88–90 °C; ^1H NMR δ 3.10 (m, 2 H), 3.39 (m, 2 H), 3.77 (s, 6 H), 3.78 (s, 3 H), 6.08 (s, 2 H).

Anal. Calcd for $C_{11}H_{15}BrO_3$: C, 48.01; H, 5.49. Found: C, 48.12; H, 5.49.

3,3-Dimethylhepta-1,6-dien-4-ol (3). Allylmagnesium bromide (22.5 mL, 0.9 M in ether, 20.3 mmol), was added with stirring to a solution of 2,2-dimethylbut-3-enal[7] (1.70 g, 17.3 mmol) in

(11) Lal, K.; Zarate, E. A.; Youngs, W. J.; Salomon, R. G. *J. Am. Chem. Soc.* **1986**, *108*, 1311.

(12) Sawada, T.; Kozuka, M.; Komiya, T.; Amano, T.; Goto, M. *Chem. Pharm. Bull.* **1980**, *8*, 2546. Amano, T.; Komiya, T.; Hori, M.; Goto, M.; Kozuka, M.; Sawada, T. *Chromatographia* **1981**, *13*, 545 (*J. Chromatogr.* **1981**, *208*, 347). Kozuka, M.; Sawada, T.; Kasahara, F.; Mizuta, E.; Amano, T.; Komiya, T.; Goto, M. *Chem. Pharm. Bull.* **1982**, *30*, 1952. Kozuka, M.; Sawada, T.; Mizuta, E.; Kasahara, F.; Amano, T.; Komiya, T.; Goto, M. *Chem. Pharm. Bull.* **1982**, *30*, 1964.

(13) Mazza, S. M.; Lal, K.; Salomon, R. G. *J. Org. Chem.*, second of three papers in this issue.

(14) Jones, W. J.; Chorley, H. W. T. *J. Chem. Soc.* **1946**, 832.

(15) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

anhydrous ether (20 mL) at 0 °C. The resulting solution was stirred at room temperature for 30 min, then hydrolyzed with a saturated aqueous NH_4Cl solution (10 mL), and finally extracted with ether (3 × 20 mL). The combined ether extracts were washed with water (3 × 10 mL), dried ($MgSO_4$), and filtered, and the solvent was rotary evaporated below 20 °C to give **3** (2.3 g, 95%) as an oil: ^1H NMR δ 1.04 (s, 6 H), 1.65 (d, J = 5.8 Hz, H), 2.08 (m, 2 H), 3.37 (m, H), 5.07 (m, 4 H), 5.85 (m, 2 H).

2,2-Dimethylbicyclo[3.2.0]heptan-3-ols 4. A solution of **3** (2.30 g, 16.4 mmol) and CuOTf (0.17 g) in anhydrous ether (240 mL) was illuminated with a medium-pressure Hanovia mercury vapor UV lamp under an atmosphere of argon through an internal water-cooled quartz immersion well for 3 h. The reaction mixture was then washed with aqueous NH_4OH solution (3 × 10 mL) and then water (3 × 10 mL), dried ($MgSO_4$), and filtered, and the solvent was removed by careful distillation. The residue thus obtained was purified by GC to give **4n** and **4x**. ***endo*-2,2-Dimethylbicyclo[3.2.0]heptan-3-ol (4n)**: ^1H NMR δ 0.68 (s, 3 H), 1.02 (s, 3 H), 1.65 (m, 3 H), 1.88 (m, H), 2.23 (m, 4 H), 2.73 (m, H), 3.82 (d, J = 5.4 Hz, H). Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 77.10; H, 11.36. ***exo*-2,2-Dimethylbicyclo[3.2.0]heptan-3-ol (4x)**: ^1H NMR δ 0.68 (s, 3 H), 0.91 (s, 3 H), 1.35 (m, H), 1.76 (m, 5 H), 2.14 (m, H), 2.32 (m, H), 2.57 (m, H), 4.22 (dd, J = 7.2, 10.4 Hz, H). Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 77.12; H, 11.57. The total yield of photocyclization products **4n** plus **4x** was 2 g (87%).

2,2-Dimethylbicyclo[3.2.0]heptan-3-one (5). Jones reagent (6.3 mL, 2.70 M, 17.0 mmol) was added portionwise with stirring to a solution of the alcohols **4** (2.2 g, 15.7 mmol) in acetone (12.5 mL) at 0 °C over 15 min. The reaction mixture was stirred at 5–10 °C for 2 h, followed by addition of an aqueous NaCl solution (25 mL) and extraction with ether (3 × 30 mL). The combined extracts were washed successively with saturated aqueous NaCl (3 × 5 mL), saturated aqueous $NaHCO_3$ (3 × 5 mL), and water (3 × 5 mL), then dried ($MgSO_4$), and filtered, and the solvent was removed by rotary evaporation at <20 °C. The residue thus obtained was distilled under reduced pressure to give **5** (1.80 g, 83%), bp 58–59 °C (10 mm). An analytical sample was obtained by GC: ^1H NMR δ 0.88 (s, 3 H), 0.92 (s, 3 H), 1.43 (m, H), 1.67 (m, H), 2.10 (m, 3 H), 2.73 (m, 3 H).

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.44; H, 10.32.

Benzopyrans 9. $BF_3{\cdot}OEt_2$ (0.81 mL, 0.93 g, 6.5 mmol) was added with stirring to a solution of **8**[8b] (2.0 g, 6.24 mmol) in CH_2Cl_2 (50 mL) at room temperature. The resulting yellow solution was stirred for 30 min, then quenched by addition of saturated aqueous $NaHCO_3$ solution (5 mL), and extracted with ether (100 mL). The extract was washed with water (3 × 5 mL), dried ($MgSO_4$), and filtered, and the solvent was removed under reduced pressure. The residue thus obtained contained two isomers which showed HPLC retention times (Whatman M-20 partisil column, 35% toluene in hexanes) of 54 and 75 min at 14 mL/min. A less polar isomer **9a** (0.97 g, 51%) was obtained as an oil: ^1H NMR δ 0.80 (s, 3 H), 1.02 (s, 3 H), 1.5–2.3 (7 H), 2.3–2.6 (m, 3 H), 2.73 (m, 2 H), 3.75 (s, 3 H), 3.77 (s, 3 H), 5.99 (d, J = 2.4 Hz, H), 6.02 (d, J = 2.4 Hz, H); ^{13}C NMR δ 16.35 (–, q), 17.34 (+, t), 20.58 (+, t), 24.22 (+, t), 25.15 (+, t), 26.70 (–, q), 34.31 (–, d), 40.03 (+, t), 47.04 (+, s), 51.21 (–, d), 55.05 (–, q, 2 C), 90.29 (–, d), 90.95 (+, s), 93.62 (–, d), 103.01 (+, s), 155.41 (+, s), 158.24 (+, s), 159.35 (+, s). Anal. Calcd for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.51; H, 8.65. A more polar isomer **9b** (0.63 g, 33%) was also obtained as an oil: ^1H NMR δ 0.99 (s, 3 H), 1.02 (s, 3 H), 1.4–2.3 (9 H), 2.3–2.5 (m, H), 2.6–2.8 (2 H), 3.72 (s, 3 H), 3.75 (s, 3 H), 5.93 (d, J = 2.4 Hz, H), 5.98 (d, J = 2.4 Hz, H); ^{13}C NMR δ 17.49 (+, t), 19.06 (+, t), 21.08 (–, q), 23.47 (–, q), 24.97 (+, t), 25.99 (+, t), 34.56 (–, d), 40.26 (+, t), 45.91 (+, s), 49.11 (–, d), 55.04 (–, q), 55.09 (–, q), 90.31 (–, d), 90.76 (+, s), 93.50 (–, d), 102.87 (+, s), 155.46 (+, s), 158.16 (+, s), 159.14 (+, s).

Anal. Calcd for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.56; H, 8.43.

2-Isovaleryl-1,3,5-trimethoxybenzene (11). $AlCl_3$ (11.34 g, 0.085 mol) was added in small portions (0.5 g each) with stirring to a solution of 1,3,5-trimethoxybenzene (16.82 g, 0.10 mol) and isovaleryl chloride (12.8 mL, 12.7 g, 0.015 mol) in anhydrous CH_2Cl_2 (200 mL) at –10 to –5 °C over 2 h. The resulting yellow solution was stirred at 0 °C for 30 min and then treated carefully with water (20 mL). The organic layer was diluted with ether (200 mL) and then washed with aqueous $NaHCO_3$ solution (4 × 25 mL) and water (3 × 10 mL). After drying ($MgSO_4$), filtration, and solvent removal under reduced pressure, the residue was purified by flash chromatography (10% ethyl acetate in hexanes) to give 1,3,5-trimethoxybenzene (2 g) and (20% ethyl acetate in hexanes) to furnish **11** (19.56 g, 88% based on trimethoxybenzene consumed) as an oil: ^1H NMR δ 0.90 (d, J = 6.8 Hz, 6 H), 2.16 (m, J = 6.8 Hz, H), 2.57 (d, J = 6.8 Hz, 2 H), 3.72 (s, 6 H), 3.77 (s, 3 H), 6.05 (s, 2 H).

Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.64; H, 7.99. Found: C, 66.76; H, 7.85.

3-Hydroxy-5-methyl-3-(2,4,6-trimethoxyphenyl)hexanenitrile (12). To a solution of *n*-butyllithium (30.4 mL, 2.6 M in hexanes, 79.1 mmol) in anhydrous THF (175 mL) at –78 °C under argon was added anhydrous CH_3CN (4.25 mL, 3.34 g, 81.3 mmol) over 5 min with stirring. After the mixture was stirred at –78 °C for $^1/_2$ h, the resulting white suspension was treated with a solution of **11** (19 g, 75.30 mmol) in anhydrous THF (75 mL) during 15–20 min. The cold bath was removed, and the pale yellow solution was stirred for 10 min before it was poured into ice/water/HCl (500 g) and extracted with ether (3 × 75 mL). The organic extracts were washed with water (3 × 20 mL), dried ($MgSO_4$), and filtered, and the solvent was removed under reduced pressure. The residue thus obtained was crystallized from *n*-hexanes to afford **12** (21.0 g, 95%): mp 60–63 °C; ^1H NMR δ 0.72 (d, J = 6.4 Hz, 3 H), 0.84 (d, J = 6.4 Hz, 3 H), 1.57 (m, 2 H), 2.00 (m, H), 2.73 (d, J = 16 Hz, H), 3.25 (d, J = 16 Hz, H), 3.79 (s, 3 H), 3.84 (s, 6 H), 6.17 (s, 2 H), 6.50 (s, H).

Anal. Calcd for $C_{16}H_{23}NO_4$: C, 65.51; H, 7.90. Found: C, 65.57; H, 7.89.

5-Methyl-3-(2,4,6-trimethoxyphenyl)hex-2-enenitrile. A solution of **12** (2.86 g, 9.75 mmol) and *p*-toluenesulfonic acid (0.01 g, 0.05 mmol) in anhydrous benzene (100 mL) was boiled under reflux with stirring for $^1/_2$ h by using a Dean–Stark trap, cooled to room temperature, diluted with ether (150 mL), extracted with aqueous $NaHCO_3$ solution (3 × 5 mL) and water (3 × 5 mL), dried ($MgSO_4$), and filtered, and the solvent was removed under reduced pressure. The residue thus obtained was purified by flash chromatography (10% ethyl acetate in hexanes) to give the title alkene (2.55 g, 95%), which crystallized from *n*-hexanes: mp 76–78 °C; ^1H NMR δ 0.88 (d, J = 6.8 Hz, 6 H), 1.52 (m, H), 2.62 (d, J = 7.2 Hz, 2 H), 3.73 (s, 6 H), 3.80 (s, 3 H), 5.22 (s, H), 6.09 (s, 2 H).

Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69. Found: C, 69.81; H, 7.75.

5-Methyl-3-(2,4,6-trimethoxyphenyl)hexanenitrile (13). Method A. A solution of the above alkene (2.50 g, 9.08 mmol), triethylsilane (4.0 mL, 2.91 g, 25.0 mmol), and trifluoroacetic acid (5.50 mL, 8.14 g, 71.4 mmol) was gently boiled under reflux at 80 °C for 2 h. The contents of the flask were cooled to room temperature, poured carefully into saturated aqeuous $NaHCO_3$ solution (250 mL), and extracted with ether (3 × 40 mL). The combined organic extracts were washed with water (3 × 5 mL), dried ($MgSO_4$), and filtered, and the solvent was removed under reduced pressure. Excess triethylsilane was removed under high vacuum (0.2 mm) at 80 °C (oil-bath temperature). The residue thus obtained was purified by flash chromatography (10% ethyl acetate in hexanes) to give **13** (2.32 g, 92%) as an oil: ^1H NMR δ 0.78 (d, J = 7 Hz, 3 H), 0.82 (d, J = 7 Hz, 3 H), 1.37 (m, 3 H), 1.86 (m, H), 2.66 (d, J = 7 Hz, 2 H), 3.76 (s, 9 H), 6.09 (s, 2 H).

Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.28: H, 8.36; N, 5.05. Found: C, 69.25; H, 8.29; N, 5.16.

Method B. Trifluoroacetic acid (18.5 mL, 27.4 g, 0.24 mol) was added with stirring to a solution of **12** (11.7 g, 0.04 mol) and triethylsilane (16.0 mL, 11.7 g, 0.10 mol) in CH_2Cl_2 (100 mL) at –78 °C. The cold bath was removed, and the reaction mixture was allowed to come to room temperature over 1 h, during which time trifluoroacetic acid melted and reaction occurred. The contents of the flask were then poured cautiously into saturated aqueous $NaHCO_3$ solution (250 mL), with careful avoidance of excess effervescence. The resulting mixture was extracted with ether (3 × 75 mL). The combined organic extracts were washed with water (3 × 20 mL), dried ($MgSO_4$), and filtered, and the solvent was removed under reduced pressure. Excess triethylsilane was removed under high vacuum (0.2 mm) at 80 °C (oil-bath

temperature). The residue thus obtained was purified by flash chromatography (10% ethyl acetate in hexanes) to give **13** (11.2 g, 95%) as an oil identical with the same product prepared by method A as described above.

6-(2,4,6-Trimethoxyphenyl)-3,3,8-trimethylnon-1-en-4-one (15). Isopentenylmagnesium chloride (135 mL, 0.45 M in THF, 60.8 mmol, prepared from 4-chloro-2-methyl-2-butene and Mg turnings in THF; N.B. attempts to make this reagent in concentrations more than 0.45–0.50 M led to extensive decomposition with formation of a white precipitate) was added dropwise with stirring to a solution of **13** (11.1 g, 40 mmol) in anhydrous THF (75 mL) at −20 °C under argon over 30 min. The reaction mixture was stirred for an additional 15 min and then hydrolyzed with 10% HCl. The yellow solution thus formed was boiled under reflux for 30 min, then cooled to room temperature, and extracted with ether (3 × 75 mL). The combined organic extracts were washed with water (3 × 10 mL), dried ($MgSO_4$), and filtered, and the solvent was removed under reduced pressure. The residue thus obtained was purified by flash chromatography (10% ethyl acetate in hexanes) to give ketone **15** (12.5 g, 90%) as an oil: ^1H NMR δ 0.74 (d, J = 6 Hz, 3 H), 0.84 (d, J = 6 Hz, 3 H), 1.02–1.28 (9 H), 1.70 (t, J = 9.8 Hz, H), 2.82 (d, J = 2.4 Hz, H), 2.85 (d, J = 2 Hz, H), 3.75 (s, 9 H), 5.03 (m, 2 H), 5.84 (m, H), 6.06 (s, 2 H).

Anal. Calcd for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.45; H, 9.26.

4-Allyl-6-(2,4,6-trimethoxyphenyl)-3,3,8-trimethylnon-1-en-4-ol (16). Allylmagnesium bromide (45 mL, 0.8 M in ether, 36 mmol) was added dropwise with stirring to a solution of **15** (10.5 g, 30 mmol) in anhydrous ether (100 mL) at −20 °C over 30 min. The reaction mixture was stirred for an additional 30 min, then hydrolyzed with a saturated aqueous NH_4Cl solution (20 mL), and extracted with ether (3 × 40 mL). The combined organic extracts were washed with water (3 × 10 mL), dried ($MgSO_4$), and filtered, and the solvent was removed under reduced pressure. The residue thus obtained was purified by flash chromatography (10% ethyl acetate in hexanes) to give **16** (10.5 g, 90%) as an oil: ^1H NMR δ 0.75 (d, J = 6.4 Hz, 3 H), 0.78 (d, J = 6.8 Hz, 3 H), 0.95 (s, 6 H), 1.11 (m, 2 H), 1.38 (m, H), 1.85 (m, 2 H), 2.42 (m, 3 H), 3.49 (m, H), 3.76 (s, 6 H), 3.78 (s, 3 H), 4.99 (m, 4 H), 5.97 (m, 2 H), 6.10 (s, 2 H).

Anal. Calcd for $C_{24}H_{38}O_4$: C, 73.80; H, 9.81. Found: C, 73.62; H, 9.67.

2,2-Dimethyl-3-[4-methyl-2-(2,4,6-trimethoxyphenyl)-pentyl]bicyclo[3.2.0]heptan-3-ol (17). A solution of **16** (2.75 g, 7.04 mmol) and CuOTf (0.5 g) in anhydrous ether (240 mL) was illuminated through a water-cooled quartz immersion well with a Hanovia medium-pressure UV lamp under argon for 3 h. The reaction mixture was then washed with an aqueous NH_4OH solution (3 × 10 mL) and water (3 × 10 mL), then dried ($MgSO_4$), and filtered, and the solvent was removed under reduced pressure. The residue thus obtained was purified by flash chromatography (6% ethyl acetate in hexanes) to give one diastereomer of **4,4-dimethyl-3-[4-methyl-2-(2,4,6-trimethoxyphenyl)pentyl]bicyclo[3.2.0]hept-3-ene** (0.4 g, 15%): ^1H NMR δ 0.74 (d, J = 4.8 Hz, 3 H), 0.79 (s, 6 H), 0.83 (d, J = 6.2 Hz, 3 H), 1.04–1.45 (3 H), 1.45–2.16 (5 H), 2.20–2.61 (2 H), 2.93 (m, H), 3.53 (m, H), 3.74 (s, 6 H), 3.76 (s, 3 H), 4.93 and 5.26 (2 s, H), 6.07 (s, 2 H). Anal. Calcd for $C_{24}H_{36}O_3$: C, 77.37; H, 9.74. Found: C, 77.39; H, 9.58. The reaction also provided **17** (2.06 g, 75%) as an oil which solidified on standing: ^1H NMR δ 0.70 (s, 3 H), 0.78 (d, J = 6.4 Hz, 3 H), 0.82 (d, J = 6.4 Hz, 3 H), 0.85 (s, 3 H), 1.06–1.42 (2 H), 1.45–1.95 (6 H), 1.96–2.50 (5 H), 2.68 (m, H), 3.48 (m, H), 3.77 (s, 3 H), 3.78 (s, 3 H), 3.82 (s, 3 H), 6.12 (s, 2 H); MS, m/e (relative intensity) 390 (11, M^+), 333 (6), 238 (10.6), 237 (65). Anal. Calcd For $C_{24}H_{38}O_4$: C, 73.80; H, 9.81. Found: C, 73.92; H, 9.80.

3-[2-(4,6-Dimethoxy-2-hydroxyphenyl)-4-methylpentyl]-2,2-dimethylbicyclo[3.2.0]heptan-3-ol (18). Ethanethiol (0.94 mL, 0.79 g, 12.7 mmol) was added to a suspension of sodium hydride (0.31 g, 12.9 mmol, 0.52 g, of a 60% oil dispersion) in anhydrous DMF (18 mL) under an atmosphere of argon. The mixture was stirred for 5 min before a solution of **17** (2 g, 5.12 mmol) in anhydrous DMF (12 mL) was added; the resulting mixture was then boiled under reflux for 2 h (150 °C oil-bath temperature). The cooled mixture was acidified with 10% HCl and extracted with ether (3 × 30 mL). The combined ether extracts were washed with water (3 × 5 mL), dried ($MgSO_4$), and filtered, and the solvent was removed under reduced pressure. The residue thus obtained was purified by flash chromatography (6% ethyl acetate in hexanes) to give **18** (1.60 g, 83%), which crystallized from n-pentane: mp 125–127 °C; ^1H NMR δ 0.72 (s, 3 H), 0.78 (d, J = 4.6 Hz, 3 H), 0.80 (s, 3 H), 0.80 (d, J = 4.4 Hz, 3 H), 1.10–1.50 (2 H), 1.52–2.38 (11 H), 2.48 (m, H), 2.81 (m, H), 3.19 (m, H), 3.73 (s, 3 H), 3.75 (s, 3 H), 6.08 (s, 2 H); MS, m/e (relative intensity) 376 (0.3, M^+), 301 (6.5), 223 (36), 167 (39).

Anal. Calcd for $C_{23}H_{36}O_4$: C, 73.36; H, 9.64. Found: C, 73.44; H, 9.69.

(±)-[1′α,3′β,3′(*R),5′α]-3,4-Dihydro-5,7-dimethoxy-2′,2′-dimethyl-4-(2-methylpropyl)spiro[2*H*-1-benzopyran-2,3′-bicyclo[3.2.0]heptane] (19a).** $BF_3{\cdot}OEt_2$ (0.58 mL, 0.67 g, 4.72 mmol) was added with stirring to a solution of **18** (1.7 g, 4.51 mmol) in CH_2Cl_2 (40 mL) at room temperature. The resulting yellow solution was stirred for 30 min and then quenched with saturated aqueous $NaHCO_3$ solution (5 mL). The mixture was diluted with ether (100 mL), washed with water (3 × 6 mL), dried ($MgSO_4$), and filtered, and the solvent was removed under reduced pressure. The residue thus obtained was purified by HPLC (Whatman M-20 Partisil column, 35% toluene in hexanes). A less polar fraction, which emerged from the column after 31 min at a flow of 14 mL/min, contained one pure major isomer **19a** (1 g, 62%), which crystallized from hexanes: mp 80–82 °C; ^1H NMR δ 0.77 (s, 3 H), 0.86 (d, J = 6.6 Hz, 3 H), 0.93 (d, J = 6.4 Hz, 3 H), 1.04 (s, 3 H), 1.38–2.19 (10 H), 2.34–2.56 (2 H), 2.64 (m, H), 2.81 (m, H), 3.72 (s, 3 H), 3.75 (s, 3 H), 5.98 (d, J = 2.4 Hz, H), 6.02 (d, J = 2.6 Hz, H); ^{13}C NMR δ 16.36 (−, q), 20.59 (+, t), 21.22 (−, q), 23.84 (+, t), 24.37 (−, q), 25.58 (−, d), 26.84 (−, q), 27.28 (−, d), 34.41 (−, d), 34.68 (+, t), 38.81 (+, t), 45.05 (+, t), 47.15 (+, s), 50.86 (−, d), 54.92 (−, q), 55.10 (−, q), 91.37 (+, s), 91.41 (−, d), 94.61 (−, d), 109.04 (+, s), 156.15 (+, s), 159.07 (+, s), 159.15 (+, s); MS, m/e (relative intensity) 358 (12.4, M^+), 301 (49.7), 223 (3.0), 167 (10). Anal. Calcd for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 77.03; H, 9.66.

A more polar fraction, which emerged from the column after 49 min at a flow of 14 mL/min, contained a mixture of two isomers (0.25 g, 15%). These isomers were separated by reverse-phase HPLC (Waters Bondapak C-18 column, 20% H_2O in methanol) to give **19b** (125 mg, 7.7%) and **19c** (105 mg, 6.6%). Compound **19b** showed the following spectral data: ^1H NMR δ 0.90 (d, J = 6.6 Hz, 3 H), 0.97 (d, J = 6.4 Hz, 3 H), 1.03 (s, 6 H), 2.62 (m, 2 H), 1.36–2.36 (11 H), 2.88 (m, H), 3.72 (s, 3 H), 3.75 (s, 3 H), 5.93 (d, J = 2.4 Hz, H), 6.01 (d, J = 6.4 Hz, H); ^{13}H NMR δ 19.40 (+, t), 20.93 (−, q), 21.25 (−, q), 23.80 (−, q), 24.36 (−, q), 25.58 (+, t), 25.65 (−, d), 27.66 (−, d), 34.47 (−, d), 34.65 (+, t), 39.42 (+, t), 45.02 (+, t), 45.89 (+, s), 48.96 (−, d), 55.02 (−, q), 55.12 (−, q), 90.72 (+, s), 91.72 (−, d), 94.48 (−, d), 109.20 (+, s), 156.30 (+, s), 158.86 (+, s), 158.99 (+, s); HRMS calcd for $C_{23}H_{34}O_3$ 358.2508, found 358.2512; MS, m/e (relative intensity) 358 (5.9, M^+), 301 (26.6.6), 233 (2.9), 181 (2.3), 167 (6.8), 81 (1.2). Compound **19c** showed the following spectral data: ^1H NMR δ 0.92 (d, J = 6.4 Hz, 3 H), 0.93 (s, 3 H), 0.97 (d, J = 6.4 Hz, 3 H), 1.04 (s, 3 H), 1.18–1.94 (8 H), 1.95–2.38 (3 H), 2.72 (m, 2 H), 2.96 (m, H), 3.72 (s, 3 H), 3.74 (s, 3 H), 5.91 (d, J = 2.4 Hz, H), 5.98 (d, J = 2.4 Hz, H); ^{13}C NMR δ 18.52 (+, t), 21.45 (−, q), 22.06 (−, q), 22.67 (−, q), 23.89 (−, q), 26.02 (−, d), 26.47 (−, d), 26.79 (+, t), 28.14 (+, t), 35.96 (−, d), 43.38 (+, t), 43.96 (+, t), 47.44 (+, s), 47.97 (−, d), 55.10 (−, q), 55.13 (−, q), 90.81 (−, d), 91.00 (+, s), 93.63 (−, d), 108.22 (+, s), 154.83 (+, s), 158.48 (+, s), 159.08 (+, s); HRMS calcd for $C_{23}H_{34}O_3$ 358.2508, found 358.2501; MS, m/e (relative intensity) 358 (4.3, M^+), 301 (17.2), 233 (2), 231 (2), 191 (2.8), 167 (6), 91 (1.1), 81 (1.7).

(±)-[1′α,3′β,3′(*R),5′α]-6,8-Dibromo-3,4-dihydro-5,7-dimethoxy-2′,2′-dimethyl-4-(2-methylpropyl)spiro[2*H*-1-benzopyran-2,3′-bicyclo[3.2.0]heptane] (20a).** Bromine (0.30 mL, 0.94 g, 5.88 mmol) was added with stirring to a solution of **19a** (1.05 g, 2.93 mmol) in CH_2Cl_2 (20 mL) over 2 min. The mixture was stirred for an additional 2 min before saturated aqueous $NaHCO_3$ (5 mL) was added. The resulting mixture was extracted with ether (60 mL), the extract was washed with water (3 × 5 mL), dried ($MgSO_4$), and filtered, and the solvent was evaporated under reduced pressure to give **20a** (1.48 g, 98%), which was crystallized from hexanes: mp 131–133 °C; ^1H NMR δ 0.81 (s, 3 H), 0.88 (d, J = 6.6 Hz, 3 H), 0.95 (d, J = 6.6 Hz, 3

Table II. Crystal and Data Collection Details for $C_{23}H_{32}Br_2O_3$

formula	$C_{23}H_{32}Br_2O_3$
formula wt	516.324 amu
space group	$P\bar{1}$
a	9.148 (2) Å
b	10.052 (2) Å
c	13.736 (4) Å
α	93.38 (2)°
β	107.13 (2)°
γ	104.25 (2)°
vol	1158.0 (5) Å^3
Z	2
ρ(obsd)	1.48 g/cm^3
ρ(calcd)	1.48 g/cm^3
cryst dimens	0.33 × 0.26 × 0.14 mm
cryst faces	$(0\bar{1}3)$, $(00\bar{3})$, $(0\bar{2}0)$, $(02\bar{2})$, $(\bar{2}02)$, $(20\bar{2})$, $(\bar{2}12)$, (020)
cryst vol	0.0126 mm^3
diffractometer	Syntex $P2_1$
radiation	Mo Kα (0.710 73 Å)
monochromator	graphite crystal
linear abs coeff	34.842 cm^{-1}
transmission factors	0.4122–0.6406
temp	23 °C
scan type	2θ–θ
scan speed	3.91 deg min^{-1}
scan range	1.1° below Kα_1 to 1.1° above Kα_2
2θ scan limits	3.0–45.0°
std reflections	3 per 100 reflections
indices	$(4\bar{5}\bar{3})$, $(\bar{2}\bar{5}3)$, $(3\bar{1}5)$
cryst stability	no indication of std reflection decay during data collection
total reflections scanned	3373
unique data $F_o^2 > 3\sigma(F_o^2)$	1976
av abs corr	0.7454
final no. of variables	253
$R(F)$ $(F_o^2 > 3\sigma F_o^2)$	0.037
$R_w(F)$ $(F_o^2 > 3\sigma F_o^2)$	0.040

H), 1.10 (s, 3 H), 1.24–2.27 (10 H), 2.52 (m, H), 2.72 (m, 2 H), 2.90 (m, H), 3.75 (s, 3 H), 3.82 (s, 3 H); MS, m/e (relative intensity) 518 (7), 516 (3.7, M$^+$), 461 (13.7), 382 (7.5), 328 (8), 326 (16).

Anal. Calcd for $C_{23}H_{32}Br_2O_3$: C, 53.50; H, 6.25. Found: C, 53.63, H, 6.25.

Collection of X-ray Diffraction Data for 20a. Colorless single crystals suitable for examination by X-ray diffraction procedures were obtained upon recrystallization of **20a** from hexane. A crystal (dimensions 0.33 × 0.26 × 0.14 mm) was selected for data collection on a Syntex $P2_1$ automated four-circle diffractometer. The crystal was found to be triclinic, and no systematic absences were observed, suggesting the space group $P\bar{1}$. Unit cell parameters and the orientation matrix were obtained and data collection was carried out by using a 2θ–θ scan. Details appear in Table II.

The positions of the non-hydrogen atoms were found by direct methods.[16] All hydrogen atoms whose approximate positions could be obtained from the electron density map were placed in idealized positions, and those remaining were included by calculation (all were based upon C–H = 0.95 Å, tetrahedral or trigonal angles, and idealized thermal parameters with B = 1.0 Å^2 greater than the equivalent B of the atom to which it is attached). Refinement was based on F and involved only those reflections having $F_o^2 > 3\sigma(F_o^2)$. Full-matrix least-squares refinement of positional and anisotropic thermal parameters for all non-hydrogen atoms led to final convergence with $R(F)$ = 0.037, $R_w(F)$ = 0.040, and GOF = 1.3151 for 253 variables and 1976 reflections.

(±)-[1′α,3′β,3′(*R),5′α]-3,4-Dihydro-5,7-dimethoxy-2′,2′-dimethyl-4-(2-methylpropyl)spiro[2*H*-1-benzopyran-2,3′-bicyclo[3.2.0]heptane]-6,8-dicarboxylic Acid (21a).** Compound **20a** (1.36 g, 2.63 mmol) in anhydrous THF (10 mL) was added dropwise with stirring to a solution of *n*-butyllithium (6.74 mL, 2.35 M in hexanes, 15.9 mmol) in anhydrous THF (35 mL) at −78 °C under an atmosphere of argon over 5 min. The reaction mixture was stirred for an additional 2 min before anhydrous CO_2 gas was bubbled through it. The resulting mixture was poured into an ice/water/HCl mixture (100 g) and then extracted with ether (3 × 40 mL). The combined organic phases were extracted with saturated aqueous $NaHCO_3$ solution (3 × 10 mL) and then water (2 × 5 mL). The $NaHCO_3$ extract was acidified with 10% HCl and then extracted with ether (3 × 30 mL). The combined extracts were washed with water (3 × 5 mL), dried ($MgSO_4$), and filtered, and the solvent was removed under reduced pressure to give **21a** (0.82 g, 69%), which was crystallized from ethyl acetate/hexanes: mp 118–121 °C; ^{1}H NMR δ 0.81 (s, 3 H), 0.90 (d, J = 6.6 Hz, 3 H), 0.96 (d, J = 6.4 Hz, 3 H), 1.06 (s, 3 H), 1.11–2.42 (11 H), 2.50 (m, H), 2.70 (m, H), 2.90 (m, H), 3.84 (s, 3 H), 3.90 (s, 3 H).

Anal. Calcd for $C_{25}H_{34}O_7$: C, 67.24; H, 7.67. Found: C, 67.21, H, 7.63.

Dimethyl (±)-[1′α,3′β,3′(*R),5′α]-3,4-Dihydro-5,7-dimethoxy-2′,2′-dimethyl-4-(2-methylpropyl)spiro[2*H*-1-benzopyran-2,3′-bicyclo[3.2.0]heptane]-6,8-dicarboxylate (22a).** A solution of **21a** (0.80 g, 1.79 mmol) in ether (20 mL) was treated dropwise with an ethereal solution of CH_2N_2 until a yellow color persisted. Solvent was removed under reduced pressure, and the product thus obtained was purified by flash chromatography (12% ethyl acetate in hexanes) to give **22a** (0.83 g, 98%), which was crystallized from ethyl acetate/hexanes: mp 135 °C; ^{1}H NMR δ 0.79 (s, 3 H), 0.88 (d, J = 6.6 Hz, 3 H), 0.94 (d, J = 6.4 Hz, 3 H), 1.02 (s, 3 H), 1.02–2.25 (11 H), 2.48 (m, H), 2.66 (m, H), 2.84 (m, H), 3.76 (s, 3 H), 3.77 (s, 3 H), 3.79 (s, 3 H), 3.88 (s, 3 H).

Anal. Calcd for $C_{27}H_{38}O_7$: C, 68.33; H, 8.07. Found: C, 68.42; H, 7.99.

(±)-[1′α,3′β,3′(*R),5′α]-3,4-Dihydro-6,8-bis(hydroxymethyl)-5,7-dimethoxy-2′,2′-dimethyl-4-(2-methylpropyl)spiro[2*H*-1-benzopyran-2,3′-bicyclo[3.2.0]heptane] (23a).** Diisobutylaluminum hydride (DIBAH) (2.25 M, 2 M in toluene, 4.50 mmol) was added with stirring to a solution of **22a** (0.43 g, 0.91 mmol) in anhydrous toluene (8 mL) at −78 °C under an atmosphere of argon over 15 min. The resulting mixture was stirred for 1 h followed by the addition of saturated aqueous NH_4Cl. After being warmed to room temperature, the mixture was acidified with citric acid monohydrate and then extracted with ether (3 × 20 mL). The combined organic extracts were washed with water (3 × 5 mL), dried ($MgSO_4$), and filtered, and the solvent was removed under reduced pressure. The residue thus obtained was purified by flash chromatography (40% ethyl acetate in hexanes) to give **23a** (0.36 g, 95%) as an oil, which solidified upon standing: ^{1}H NMR δ 0.84 (s, 3 H), 0.90 (d, J = 6.4 Hz, 3 H), 0.97 (d, J = 6.4 Hz, 3 H), 1.07 (s, 3 H), 1.08–2.44 (13 H), 2.56 (m, H), 2.72 (m, H), 2.89 (m, H), 3.76 (s, 3 H), 3.85 (s, 3 H), 4.67 (br s, 4 H).

Anal. Calcd for $C_{25}H_{38}O_5$: C, 71.73; H, 9.15. Found: C, 71.89; H, 9.15.

(±)-[1′α,3′β,3′(*R),5′α]-6,8-Diformyl-3,4-dihydro-5,7-dimethoxy-2′,2′-dimethyl-4-(2-methylpropyl)spiro[2*H*-1-benzopyran-2,3′-bicyclo[3.2.0]heptane] (24a).** A mixture of **23a** (0.35 g, 0.84 mmol) and pyridinium dichromate (PDC) (3.0 g, 7.97 mmol) in CH_2Cl_2 (20 mL) was stirred at room temperature for 10 h and then diluted with ether (50 mL). The supernatant was decanted from a brown solid. The insoluble residue was washed thoroughly with anhydrous ether (3 × 5 mL). The combined organic solutions were passed through a short column of Florisil, and the solvent was removed under reduced pressure. The residue thus obtained was purified by flash chromatography (10% ethyl acetate in hexanes) to give **24a** (0.26 g, 75%) as an amorphous powder: mp 40–42 °C; ^{1}H NMR δ 0.83 (s, 3 H), 0.88 (d, J = 6.6 Hz, 3 H), 0.95 (d, J = 6.4 Hz, 3 H), 1.10 (s, 3 H), 1.13–2.33 (11 H), 2.50 (m, H), 2.71 (m, H), 2.87 (m, H), 3.84 (s, 3 H), 3.90 (s, 3 H), 10.26 (s, H), 10.35 (s, H); ^{13}C NMR (see Table I); ^{1}H NMR (pyridine-d_5) δ 0.80 (s, 3 H), 0.88 (d, J = 6.6 Hz, 3 H), 0.98 (d, J = 6.4 Hz, 3 H), 1.03–1.40 (4 H), 1.43–2.24 (9 H), 2.45 (m, 3 H), 3.00 (m, H), 3.90 (s, 3 H), 3.97 (s, 3 H), 10.51 (s, H), 10.64 (s, H); HRMS calcd for $C_{25}H_{34}O_5$ 414.2406, found 414.2410; MS, m/e (relative intensity) 414 (1.5, M$^+$), 357 (5.2),

(16) (a) Main, P.; Fiske, S. J.; Hulls, S. E.; Lessinger, L.; Germain, G.; Declercq, J. P.; Woolfson, M. M. *Multan 80. A System of Computer Programmes for the Automatic Solution of Crystal Structures from X-ray Diffraction Data*; University of York, England, University of Louvain, Belgium. (b) The UCLA Crystallographic Computing Package, Jan 5, 1982.

279 (2.2), 223 (9.1), 135 (0.7), 107 (1.2), 91 (2.1), 81 (3.5).

(±)-[1′α,3′β,3′(R*),5′α]-6,8-Diformyl-3,4-dihydro-5,7-dihydroxy-2′,2′-dimethyl-4-(2-methylpropyl)spiro[2H-1-benzopyran-2,3′-bicyclo[3.2.0]heptane] (2a). Boron trichloride (1.5 mL, 1.0 M in CH_2Cl_2, 1.5 mmol) was added with stirring to a solution of **24a** (0.12 g, 0.29 mmol) in CH_2Cl_2 (2.5 mL) under argon at 0 °C. The resulting solution was allowed to come to room temperature and then stirred for 10 h. Water (2 mL) was carefully added, and the resulting mixture was diluted with ether (20 mL). The organic solution was washed with water (3 × 5 mL), dried ($MgSO_4$), and filtered, and the solvent was removed under reduced pressure. The residue thus obtained was purified by flash chromatography (2% ethyl acetate in hexanes) to give **2a** (0.084 g, 75%), which crystallized from hexanes: mp 129–30 °C; ^1H NMR δ 0.86 (s, 3 H), 0.90 (d, J = 6.6 Hz, 3 H), 0.95 (d, J = 6.4 Hz, 3 H), 1.08 (s, 3 H), 1.17–2.33 (11 H), 2.55 (m, H), 2.79 (m, 2 H), 10.01 (s, H), 10.15 (s, H), 13.52 (s, H), 13.56 (s, H); HRMS calcd for $C_{23}H_{30}O_5$ 386.2093, found 386.2089; MS, m/e (relative intensity) 386 (2.4, M^+), 329 (12.2), 251 (4.8), 195 (8.3), 91 (1.0), 81 (3.8).

Dibromide 20b. Arene **19b** (150 mg, 0.42 mmol) was brominated with bromine (43 μL, 134 mg, 0.84 mmol) in CH_2Cl_2 (4 mL) by following the procedure described for **20a**. The dibromide **20b** (213 mg, 98.6%) was crystallized from n-hexanes: mp 80–84 °C; ^1H NMR δ 0.90 (d, J = 6.4 Hz, 3 H), 0.98 (d, J = 6.4 Hz, 3 H), 1.04 (s, 3 H), 1.09 (s, 3 H), 1.13–1.31 (11 H), 2.69 (m, 2 H), 2.95 (m, H), 3.74 (s, 3 H), 3.81 (s, 3 H); HRMS calcd for $C_{23}H_{32}{}^{79}Br^{81}BrO_3$ 516.0700, found 516.0714; MS, m/e (relative intensity) 518 (2.2), 516 (5.3, M^+), 514 (2.2), 461 (4.2), 459 (6.8), 147 (1.1), 107 (1.5), 93 (1.6), 81 (6.9).

Dicarboxylic Ester 22b. Dibromide **20b** (175 mg, 0.34 mmol) was lithiated with n-butyllithium (0.87 mL, 2.35 M in hexanes, 2.03 mmol) in THF (6 mL) and then carboxylated with CO_2 according to the procedure described for **21a**. The resulting dicarboxylic acid **21b** was treated with an ethereal solution of CH_2N_2 until a yellow color persisted. Solvent was removed under reduced pressure. The residue thus obtained was purified by flash chromatography (12% ethyl acetate in hexanes) to give **22b** (120 mg, 75% based on dibromide **20b**) as an oil: ^1H NMR δ 0.89 (d, J = 6.6 Hz, 3 H), 0.95 (s, 3 H), 0.95 (d, J = 6.6 Hz, 3 H), 1.00 (s, 3 H), 1.06–1.38 (11 H), 2.58 (m, 2 H), 2.91 (m, H), 3.74 (s, 3 H), 3.77 (s, 3 H), 3.83 (s, 3 H), 3.87 (s, 3 H); HRMS calcd for $C_{27}H_{38}O_7$ 474.2617, found 474.2610; MS, m/e (relative intensity) 474 (1.2, M^+), 417 (5.6), 385 (2.5), 307 (2), 251 (1.5), 105 (1.4), 81 (1.4), 69 (4), 57 (3.1), 43 (3.1), 41 (5.4).

Diol 23b. Diester **22b** (90 mg, 0.19 mmol) was reduced with DIBAH (0.57 mL, 2 M in toluene, 1.14 mmol) in toluene (2 mL), affording diol **23b** as an oil (78 mg, 98%), by following the procedure described for **23a**: ^1H NMR δ 0.90 (d, J = 6.4 Hz, 3 H), 0.98 (d, J = 6.6 Hz, 3 H), 1.04 (s, 3 H), 1.05 (s, 3 H), 1.06–2.37 (13 H), 2.63 (m, 2 H), 2.92 (m, H), 3.73 (s, 3 H), 3.77 (s, 3 H), 4.57 and 4.59 (2 s, 2 H), 4.63 (s, 2 H); HRMS calcd for $C_{25}H_{38}O_5$ 418.2719, found 418.2707; MS, m/e (relative intensity) 418 (4.4, M^+), 361 (7.8), 343 (12.1), 265 (5.9), 209 (3), 91 (1.7), 81 (2.6).

Dialdehyde 24b. A mixture of diol **23b** (39 mg, 0.093 mol) and pyridinium dichromate (400 mg, 1.06 mmol) in CH_2Cl_2 (5 mL) was stirred at room temperature for 10 h and worked up as described for **24a**. The residue thus obtained was purified by preparative TLC (30% ethyl acetate in hexanes) to give dialdehyde **24b** (27 mg, 70%): ^1H NMR δ 0.89 (d, J = 6.6 Hz, 3 H), 0.97 (d, J = 6.6 Hz, 3 H), 1.05 (s, 6 H), 1.06–1.35 (11 H), 2.62 (m, 2 H), 2.93 (m, H), 3.82 (s, 3 H), 3.89 (s, 3 H), 10.23 (s, H), 10.25 (s, H); ^{13}C NMR (see Table I); ^1H NMR (pyridine-d_5) δ 0.90 (d, J = 6.4 Hz, 3 H), 1.01 (s, 3 H), 1.02 (d, J = 6.4 Hz, 3 H), 1.11 (s, 3 H), 1.11–2.36 (11 H), 2.59 (m, 2 H), 3.09 (m, H), 3.91 (s, 3 H), 3.99 (s, 3 H), 10.52 (s, H), 10.53 (s, H); HRMS calcd for $C_{25}H_{34}O_5$ 414.2406, found 414.2402; MS, m/e (relative intensity) 414 (0.2, M^+), 357 (2.9), 344 (0.4), 121 (1.1), 107 (1.1), 91 (3.2), 81 (4.9), 79 (3.9).

Dibromide 20c. Bromination of **19c** (210 mg, 0.59 mmol) with bromine (60 μL, 187 mg, 0.117 mmol) in CH_2Cl_2 (5 mL), following the procedure described for **20a**, provided dibromide **20c** (296 mg, 98%), which crystallized from n-hexanes: mp 90–93 °C; ^1H NMR δ 0.92 (d, J = 6.4 Hz, 3 H), 0.93 (s, 3 H), 0.98 (d, J = 6.4 Hz, 3 H), 1.04 (s, 3 H), 1.39–1.98 (8 H), 1.99–2.38 (3 H), 2.82 (m, 2 H), 3.05 (m, H), 3.80 (s, 3 H), 3.82 (s, 3 H); HRMS calcd for $C_{23}H_{32}{}^{79}Br^{81}BrO_3$ 516.0700, found 516.0719; MS, m/e (relative intensity) 518 (1.8), 516 (4.5, M^+), 514 (2.4), 461 (6.0), 459 (11.6), 458 (1.3), 457 (6.4), 93 (0.5), 81 (0.8).

Dicarboxylic Ester 22c. Dibromide **20c** (290 mg, 0.56 mmol) was lithiated with n-butyllithium (1.43 mL, 2.35 M in hexanes, 3.36 mmol) in THF (7.5 mL) and then carboxylated with CO_2 according to the procedure described for **21a**. The resulting dicarboxylic acid **21c** was treated with an ethereal solution of CH_2N_2 until a yellow color persisted. Solvent was removed under reduced pressure. The residue thus obtained was purified by flash chromatography (12% ethyl acetate in hexanes) to give **22c** (180 mg, 67% based on dibromide) as an oil: ^1H NMR δ 0.89 (s, 3 H), 0.90 (d, J = 6.2 Hz, 3 H), 0.96 (d, J = 6.2 Hz, 3 H), 1.02 (s, 3 H), 1.34–1.90 (8 H), 1.91–2.36 (3 H), 2.48 (m, H), 2.73 (m, H), 2.95 (m, H), 3.75 (s, 3 H), 3.78 (s, 3 H), 3.84 (s, 3 H), 3.87 (s, 3 H); HRMS calcd for $C_{27}H_{38}O_7$ 474.2617, found 474.2636; MS, m/e (relative intensity) 474 (2.6, M^+), 417 (10.3), 385 (3), 307 (2.3), 251 (2), 82 (2.1), 69 (2.3), 43 (2.3), 41 (5.5).

Diol 23c. According to the procedure described for **23a**, diester **22c** (150 mg, 0.32 mmol) was reduced with DIBAH (0.79 mL, 2 M in toluene, 1.58 mmol) in toluene (2.5 mL). The crude product was purified by flash chromatography (35% ethyl acetate in hexanes) to give **23c** (130 mg, 98%) as an oil: ^1H NMR δ 0.92 (d, J = 6.4 Hz, 3 H), 0.95 (s, 3 H), 0.99 (d, J = 6.2 Hz, 3 H), 1.08 (s, 3 H), 1.35–1.94 (8 H), 1.95–2.56 (5 H), 2.71 (m, 2 H), 2.95 (m, H), 3.78 (s, 3 H), 3.82 (s, 3 H), 4.59 (s, 2 H), 4.65 (s, 2 H); HRMS calcd for $C_{25}H_{38}O_5$ 418.2719, found 418.2722; MS, m/e (relative intensity) 418 (3.4, M^+), 361 (6.8), 343 (4.6), 265 (4.5), 209 (2.3), 119 (1.1), 91 (1.1), 85 (1.6), 83 (1.9).

Dialdehyde 24c. A mixture of diol **23c** (65 mg, 0.15 mmol) and pyridinium dichromate (584 mg, 1.55 mmol) in CH_2Cl_2 (5 mL) was stirred at room temperature for 10 h and worked up as described for **24a**. The residue thus obtained was purified by preparative TLC (30% ethyl acetate in hexanes) to give dialdehyde **24c** (45 mg, 70%): ^1H NMR δ 0.91 (d, J = 6.4 Hz, 3 H), 0.91 (s, 3 H), 0.97 (d, J = 6.4 Hz, 3 H), 1.05 (s, 3 H), 1.39–2.40 (11 H), 2.72 (m, 2 H), 3.03 (m, H), 3.84 (s, 3 H), 3.90 (s, 3 H), 10.23 (s, 2 H); ^{13}C NMR (see Table I); ^1H NMR (pyridine-d_5) δ 0.94 (d, J = 6.4 Hz, 3 H), 0.96 (s, 3 H), 1.00 (s, 3 H), 1.01 (d, J = 6.4 Hz, 3 H), 1.43–2.40 (11 H), 2.74 (m, 2 H), 3.09 (m, H), 3.95 (s, 3 H), 3.98 (s, 3 H), 10.51 (s, H), 10.52 (s, H); HRMS calcd for $C_{25}H_{34}O_5$ 414.2406, found 414.2405; MS, m/e (relative intensity) 414 (1.9, M^+), 357 (4.2), 345 (1.0), 279 (1.6), 275 (1.1), 247 (0.8), 223 (7.2), 81 (1.0).

Acknowledgment. This work was supported by grants from the National Science Foundation (to R.G.S.) and the donors of the Petroleum Research Fund, administered by the American Chemical Society (to W.J.Y.). We thank Profs. Xu, Synder, and Nakanishi for copies of spectra of the robustadials.

Registry No. (±)-**2a**, 114862-22-5; (±)-**3**, 114862-23-6; (±)-**4x**, 114925-65-4; (±)-**4n**, 114862-24-7; (±)-**5**, 114862-25-8; (±)-**8**, 114925-66-5; (±)-**9a**, 114862-26-9; (±)-**9b**, 114925-67-6; **11**, 101032-04-6; (±)-**12**, 114862-27-0; (±)-**13**, 114862-28-1; (±)-**15**, 114862-29-2; (±)-(R*,R*)-**16**, 114862-30-5; (±)-(R*,S*)-**16**, 114862-35-0; **17**, 101032-09-1; **18**, 101054-45-9; (±)-**19a**, 114925-68-7; (±)-**19b**, 114925-69-8; (±)-**19c**, 114925-70-1; (±)-**20a**, 114925-71-2; (±)-**20b**, 114925-72-3; (±)-**20c**, 114925-73-4; (±)-**21a**, 114862-31-6; (±)-**21b**, 114925-74-5; (±)-**21c**, 114925-75-6; (±)-**22a**, 114925-76-7; (±)-**22b**, 114925-77-8; (±)-**22c**, 114925-78-9; (±)-**23a**, 114862-32-7; (±)-**23b**, 114925-79-0; (±)-**23c**, 114925-80-3; (±)-**24a**, 114925-81-4; (±)-**24b**, 114925-82-5; (±)-**24c**, 114925-83-6; 2,4,6-$(MeO)_3C_6H_2(CH_2)_2OH$, 832-87-1; 2,4,6-$(MeO)_3C_6H_2(CH_2)_2Br$, 106800-22-0; 1,3,5-$(MeO)_2C_6H_3$, 621-23-8; i-BuCOCl, 108-12-3; $OHCCMe_2CH{=}CH_2$, 5820-05-3; 2,4,6-$(MeO)_3C_6H_2C(i\text{-}Bu){=}CHCN$, 114862-33-8; $Me_2C{=}CHCH_2Cl$, 503-60-6; Robustadial A, 88130-99-8; 4,4-dimethyl-3-[4-methyl-2-(2,4,6-trimethoxyphenyl)pentyl]bicyclo[3.2.0]hept-3-ene, 114862-34-9.

Supplementary Material Available: Tables of bond lengths and angles, fractional atomic coordinates, and anisotropic thermal parameters for non-hydrogen atoms of **20a** (5 pages). Ordering information is given on any current masthead page.