Robustadials. 3. Total Synthesis of Camphane Analogues[1]

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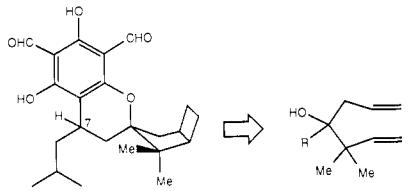
Syntheses from (+)-camphene of all four possible diastereomeric bicyclo[2.2.1]heptane analogues **35** of robustadials were completed. Reaction of [2-(2,4,6-trimethoxyphenyl)ethyl]magnesium bromide with camphenilone produced camphenilol and 2,4,6-trimethoxystyrene by β hydride transfer rather than the desired C–C coupling. This sterically congested skeletal connection was achieved by a Mukaiyama reaction of camphenilone with the enol trimethylsilyl ether of 2,4,6-trimethoxyacetophenone. The extreme proclivity of the resulting β-hydroxy ketone toward retroaldol cleavage is especially noteworthy. The nonidentity of any of the prenylphenol–camphane ethers **35** with robustadial A or B dimethyl ethers provides presumptive evidence that robustadials are bicyclo[3.1.1]heptanes, i.e., pinane derivatives, corresponding to diastereomers of **13**.

Besides their possible utility as new drugs to combat the global resurgence of malaria, our interest in robustadials A and B was piqued by the proposal of bicyclo[3.2.0]-heptane structures **1a** and **1b** for these natural products



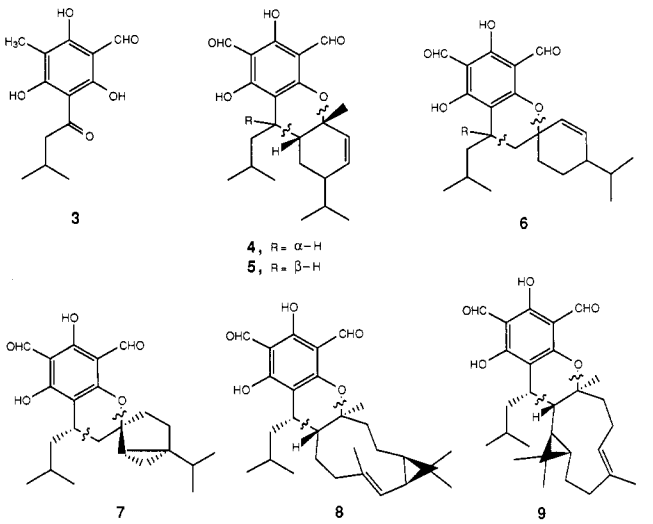
1a, 7α-H
1b, 7β-H

2

which were isolated from Chinese herbal medicinal *Eucalyptus robusta* leaves.[2] While our synthetic strategy using copper(I)-catalyzed photobicyclization[3] of 1,6-heptadienes **2** succeeded admirably, the structure presumed for robustadial A on the basis of NMR, UV, IR, and mass spectral evidence proved incorrect.[4]

The near coincidence of many spectral features suggests that the natural product robustadial A is a close structural analogue of **1a**. The aromatic acetogenin–isopentyl portion proposed for the robustadials is identical with that found in the euglobals, a family of biologically active acetogenin–terpenoids isolated from buds and leaves of *Eucalyptus globulus*.[5] Generally, the remaining terpenoid portion of the euglobals corresponds to known terpenes or sesquiterpenes which apparently add a precursor corresponding to a natural product, grandinol (**3**)[6], across a C=C bond. The remaining terpenoid portion of euglobals Ia_1 (**4**) and Ia_2 (**5**) corresponds to α-phellandrene, while that of euglobal IIb (**6**) corresponds to β-phellandrene. Similarly, sabinene apparently is the biogenetic precursor of euglobal IIa (**7**), while euglobals III (**8**) and IV (**9**) appear to arise from bicyclogermacrene.

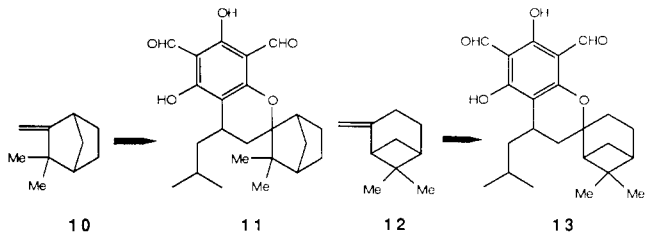
Two general structures, **11** and **13**, are suggested by the hypothesis that robustadials are close structural analogues



3 **4**, R = α-H **5**, R = β-H **6**

7 **8** **9**

of **1** and that their biogenesis is from a terpene. Bicyclo-[2.2.1]heptyl derivatives **11** would be generated by addition of a precursor corresponding to **3** across the C=C bond of camphene (**10**) while bicyclo[3.1.1]heptyl derivatives **13**



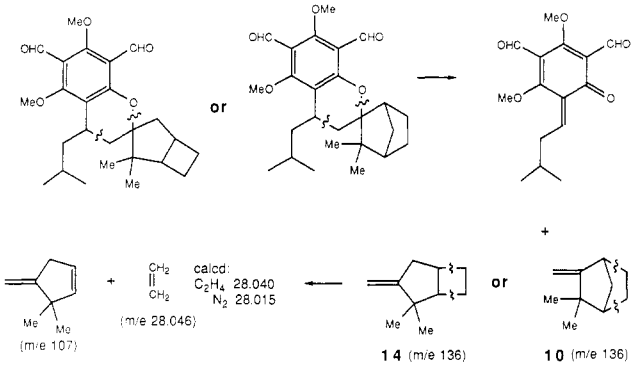
10 **11** **12** **13**

could arise by the analogous addition to β-pinene (**12**). The original choice of a bicyclo[3.2.0] structure for the robustadials was based, at least in part, on the observation of an ion corresponding to C_2H_4 in the mass spectrum of the dimethyl ether of the natural product. This mass spectral fragmentation was rationalized as cleavage of the cyclobutane ring of a bicyclo[3.2.0]heptyl *m/e* 136 fragment **14** to generate ethylene, as in Scheme I.[2] Mass spectral generation of camphene (**10**) and ultimately ethylene from the dimethyl ether of **11** seemed likely. Furthermore, preliminary experiments established that camphene not only undergoes mass spectral fragmentation to produce a fragment at 28.046 corresponding to ethylene but also gives rise to other major fragments at *m/e* 107 and 91 which are found in the mass spectrum of robustadials. The possibility that mass spectral fragmentation of the dimethyl ether of **13** would generate ethylene was less evident. Therefore, syntheses of all four diastereomers of **11** were launched.

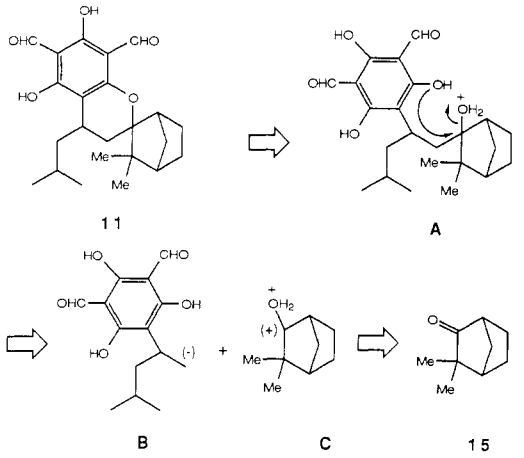
(1) Previous paper in this series: Lal, K.; Zarate, E. A.; Youngs, W. J.; Salomon, R. G. *J. Org. Chem.*, first of three papers in this issue.
(2) Xu, R.; Snyder, J. K.; Nakanishi, K. *J. Am. Chem. Soc.* **1986**, *106*, 734.
(3) For a recent review, see: Salomon, R. G. *Tetrahedron* **1983**, *39*, 485.
(4) Lal, K.; Zarate, E. A.; Youngs, W. J.; Salomon, R. G. *J. Am. Chem. Soc.* **1986**, *108*, 1311.
(5) Sawada, T.; Kozuka, M.; Komiya, T.; Amano, T.; Goto, M. *Chem. Pharm. Bull.* **1980**, *28*, 2546. Amano, T.; Komiya, T.; Hori, M.; Goto, M.; Kozuka, M.; Sawada, T. *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.
(6) Crow, W. D.; Osawa, T.; Paton, D. M.; Willing, R. R. *Tetrahedron Lett.* **1977**, 1073.

0022-3263/88/1953-3681$01.50/0

Scheme I

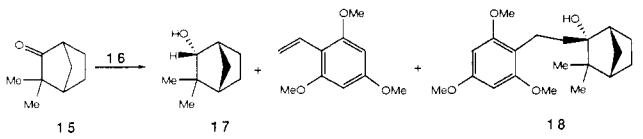


Scheme II



Results and Discussion

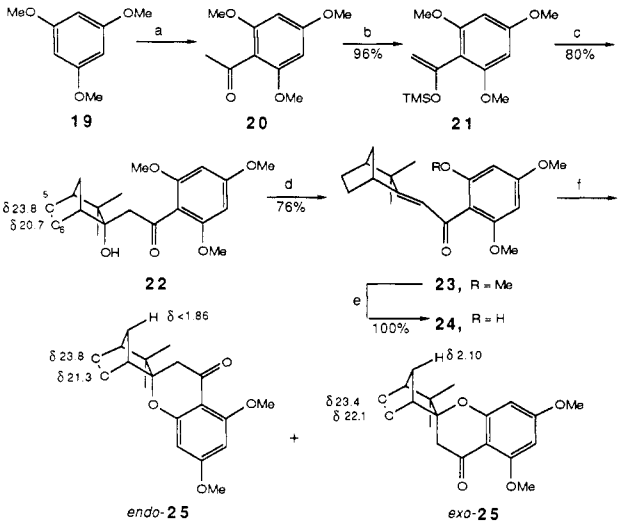
In analogy with our synthesis of **1a**, our strategy (Scheme II) for assembling **11** presumed that the pyran ring could be generated by cyclization of a phenol as in A. A polar synthesis of A from a nucleophilic synthon B plus electrophilic synthon C was especially attractive since camphenilone (**15**), a synthetic equivalent of C, is readily available from camphene (**10**).[7]



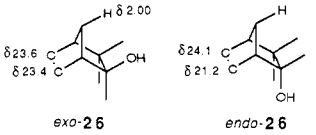
Previously we showed that a sterically congested Grignard reagent, [2-(2,4,6-trimethoxyphenyl)ethyl]magnesium bromide (**16**), abstracts a proton from a sterically hindered ketone rather than undergoing 1,2-addition to its carbonyl group.[1] Since camphenilone has only a bridgehead hydrogen α to the carbonyl group, similar proton abstraction by Grignard reagent **16** was not expected to interfere with 1,2-addition to the carbonyl group. Nevertheless, the requisite 1,2-addition of **16** was again circumvented. Thus, reaction of **16** with **15** produced camphenilol (**17**) and 2,4,6-trimethoxystyrene by β hydride transfer and less than 10% yield of the desired C–C coupling product **18**.

A Mukaiyama condensation seemed eminently suited to overcome the steric obstruction encountered during conjunction of the nucleophilic synthon B with the electrophilic synthon C of Scheme II. The implementation of this tactic and subsequent generation of two epimeric spiro pyrans *endo*-**25** and *exo*-**25** are outlined in Scheme III. The trimethylsilyl enol ether **21** of 2,4,6-trimethoxyacetophenone (**20**) condenses smoothly with camphenilone (**15**) in the presence of $TiCl_4$, delivering a single β-hydroxy ketone presumed to be **22**, which would be favored by preferential nucleophilic attack from the less sterically encumbered exo face of the carbonyl group in **15**. The configurational assignment for **22** is supported by ^{13}C NMR comparison with camphene hydrate (*exo*-**26**) and its C-2 epimer *endo*-**26**. The resonance at δ 21.2 ascribed to the carbon at position 6 in *endo*-**26**[9] occurs 2.2 ppm upfield from the resonance for the corresponding carbon in the epimer *exo*-**26** owing to a shielding influence of the endo hydroxyl substituent.[9b] The high-field location of the ^{13}C NMR resonance at δ 20.7 assigned to the carbon at position 6 in **22** attests to the shielding influence of an endo hydroxyl substituent.

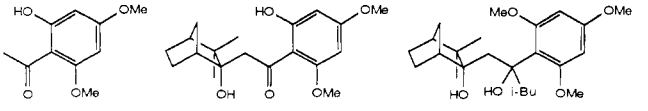
Scheme III[a]



[a] (a) Reference 8; (b) $TMSCl/Et_3N/DMF$; (c) $15/TiCl_4/CH_2Cl_2$; (d) $TsOH/PhH$; (e) BCl_3/CH_2Cl_2; (f) $K_2CO_3/H_2O/EtOH$.



That retroaldol cleavage of **22** is favored at equilibrium under basic conditions is evidenced by the quantitative generation of 2,4-dimethoxy-6-hydroxyacetophenone (**27**) upon attempted demethylation of **22** with sodium ethanethiolate in DMF.[10] Regioselective monodemethylation of **22** to provide **28** was achieved under acidic conditions with BCl_3 albeit in only 60% yield. Since retroaldol cleavage is precluded if the carbonyl group in **22** is consumed by 1,2-addition of an isobutyl nucleophile, the reaction of **22** with isobutylmagnesium bromide was exam-



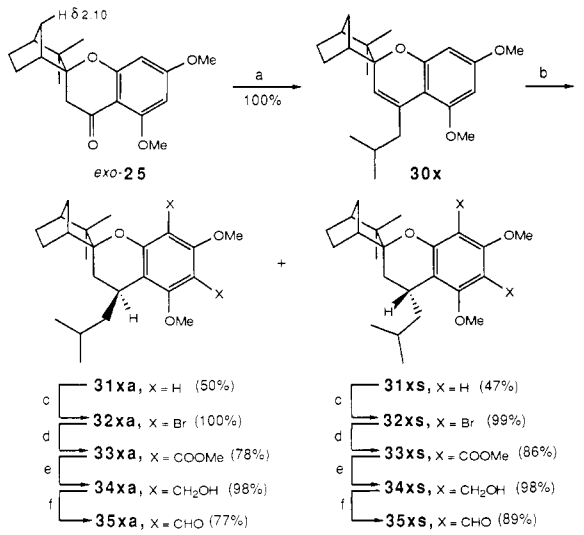
(7) (a) Dalavoy, V. S.; Deodhar, V. B.; Nayak, U. R. *Indian J. Chem., Sect. B* **1982**, *21B*, 396. (b) Monson, R. S. *Advanced Organic Synthesis: Methods and Techniques*; Academic: New York, 1971; pp 6–7. (c) For optically pure **19**, $[\alpha]^{20}_D$ 70.4° (ethanol): *Handbook of Chemistry and Physics*, 56th ed.; Weast, R. C., Ed.; CRC: Cleveland, OH, 1975; p C-229.

(8) Houben, J.; Fischer, W. *J. Prakt. Chem.* **1929**, *123*, 313.

(9) (a) Stothers, J. B.; Teo, K. C. *Org. Magn. Reson.* **1977**, *9*, 712. (b) Schneider, H.-J. *Tetrahedron Lett.* **1970**, 5197. (c) Chemical shift in CCl_4 is δ 2.03: Liu, K.-T. *J. Chin. Chem. Soc. (Taipei)* **1976**, *23*, 1.

(10) Cannon, J. R.; Feutrill, G. I.; Wong, L. C. *Aust. J. Chem.* **u983**, *36*, 2575.

Scheme IV[a]



[a] (a) Me_2CHCH_2MgCl, then aqueous HCl; (b) $H_2/Pd/C$; (c) Py·Br_2/CH_2Cl_2; (d) *n*-BuLi/THF, then CO_2, then HCl, then CH_2N_2/Et_2O; (e) DIBAH/PhMe; (f) PDC.

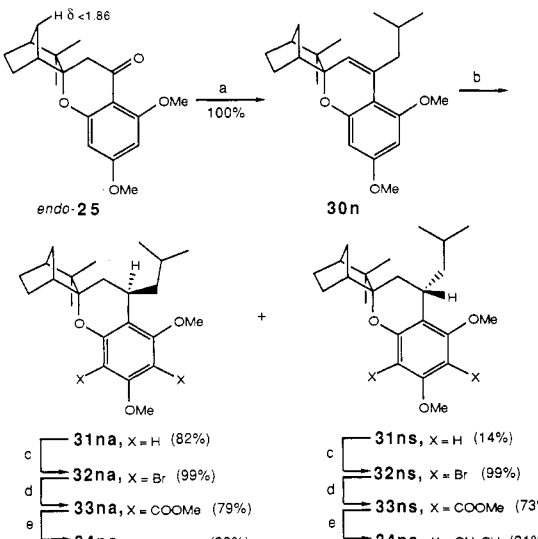
ined. However, rather than the desired adduct **29**, only retroaldol cleavage product **20** was generated.

Alternatively, retroaldol cleavage of **22** could be disfavored by removal of the hydroxyl. This was readily achieved by acid-catalyzed dehydration. Regioselective monodemethylation of the resulting α,β-unsaturated ketone **23** was then induced quantitatively by BCl_3. While the resulting monophenol **24** failed to cyclize under acidic conditions, heating in aqueous ethanol in the presence of potassium carbonate generated the epimeric spiro pyrans *endo*-**25** and *exo*-**25** in high yields. This behavior contrasts with previous observations where similar cyclizations occurred readily under acidic catalysis.[11] Kinetically *exo*-**25** is favored over *endo*-**25** by at least 13:1 since an exo trajectory for addition of a phenolate nucleophile to the β position of enone **25** is less sterically encumbered than an endo trajectory. However, MMP2 calculations[12] suggested that the epimers *endo*-**25** and *exo*-**25** have very similar heats of formation and, therefore, that equilibration should provide mixtures richer in *endo*-**25**. This prediction was borne out by generation of a 1:1 mixture of *endo*-**25** and *exo*-**25** upon prolonged heating of either pure epimer in the presence of K_2CO_3.[12]

The configurational assignments for *endo*-**25** and *exo*-**25** are supported by ^{13}C and ^1H NMR comparisons with *exo*-**26** and *endo*-**26**. Thus, one of the resonances corresponding to the ethano bridge carbons in *endo*-**25** occurs at δ 21.3 owing to the shielding influence of the endo ether oxygen substituent analogous to the upfield shift to δ 21.2 of the resonance for carbon 6 in *endo*-**26** owing to the endo hydroxyl oxygen. Furthermore, the methano bridge hydrogen syn to the spiro pyran shows a downfield shift to δ 2.10 in the ^1H NMR spectrum of *exo*-**25** owing to the deshielding influence of an exo ether oxygen. The resonance for the corresponding hydrogen in *endo*-**25** appears at δ <1.86 while the 7-syn hydrogen resonance for camphene hydrate (*exo*-**26**) appears at δ 2.00 (in $CDCl_3$).[9c]

The four possible diastereomers of the prenylphenol–camphane ethers **35** were assembled from *exo*-**25** and *endo*-**25** as outlined in Schemes IV and V respectively.

Scheme V[a]



[a] (a) Me_2CHCH_2MgCl, then aqueous HCl; (b) $H_2/Pd/C$; (c) Br_2/CH_2Cl_2; (d) *n*-BuLi/THF, then CO_2, then HCl, then CH_2N_2/Et_2O; (e) $LiAlH_4/Et_2O$; (f) PDC.

The carbonyl group of **25** was replaced by isobutyl by reaction with isobutylmagnesium chloride followed by dehydration of an intermediate tertiary benzylic alcohol. Catalytic hydrogenation of the resulting alkenes **30x** and **30n** provided the epimers **31xs** plus **31xa** and **31ns** plus **31na**, respectively. A molecular mechanics conformational analysis and ^1H NMR studies confirming the configurational assignments for all four diastereomers of **31** are presented elsewhere.[12]

Introduction of formyl groups into **31** was then achieved by bromination, lithium–bromine exchange, carboxylation, O-methylation, reduction, and finally partial oxidation to afford four diastereomeric dialdehydes **35**. ^{13}C NMR comparison of the synthetic dialdehyde methyl ethers **35** (Table I) with robustadial A dimethyl ether and robustadial B dimethyl ether (Table I in previous paper) shows many similarities. However, none of the synthetic compounds are identical with either of the naturally derived products. The quaternary carbons at position 3 in the diastereomers of **35** absorb at δ 43.7–46.3. In contrast, the corresponding quaternary carbons in robustadials A and B absorb at least 5 ppm upfield at δ 38.2–38.3. Likewise, the quaternary carbons at position 2 in the diastereomers of **35** absorb at δ 89.9 ± 0.8, but the corresponding quaternary carbons in robustadials A and B absorb at slightly higher field, δ 86.0 and 84.8 respectively.

Although the prenylphenol–camphanes **35** are not robustadials, it seems quite likely that these biogenetic hybrids will be found in *Eucalyptus* plants. Thus, camphene has been identified in *E. globulus*,[13] and the natural occurrence of a variety of acetogenin–terpenoids in *Eucalyptus* plants demonstrates their ability to assemble complex structures by the union of acetogenins, e.g., grandinol (**3**), with various terpenoids.[6] Our syntheses also establish the absolute configurations of the prenylphenol–camphanes **35** by correlation with (+)-camphenilone.[7]

Apparently the observation of ethylene as a major fragment in the mass spectrum of robustadials was a red herring which misdirected attention toward a readily

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(12) Jirousek, M. R.; Mazza, S. M.; Salomon, R. G. *J. Org. Chem.*, third of three papers in this issue.

(13) Guenther, E.; Atthausen, D. *The Essential Oils: Volume 2 the Constitutents of Essential Oils*; D. Van Nostrand: New York, 1949; p 66.

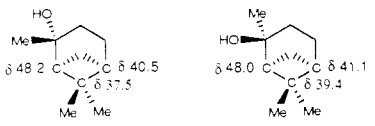
Table I. ^{13}C NMR Spectral Data of Dialdehyde Dimethyl Ethers 35[a]

35xa	35xs	35na	35ns
20.8 q	20.8 q	20.9 q	20.7 q
22.5 t	22.7 q	21.3 t	21.8 q
23.2 q	22.7 t	22.3 q	22.2 t
23.8 q	23.8 t	23.5 t	23.7 t
24.0 t	24.1 q	23.8 q	24.2 q
24.8 t	25.1 q	25.6 d	25.3 d
25.4 q	25.3 d	27.1 q	25.9 q
25.5 d	28.1 d	27.4 d	27.7 d
26.9 d	30.9 t	33.8 t	34.4 t
26.9 d	30.9 t	33.8 t	34.4 t
35.2 t	34.5 t	34.5 t	34.6 t
42.8 t	43.7 d	44.9 s ←	43.7 s ←
46.3s ←	44.2 t	45.3 t	44.0 d
47.5 d	44.9 s ←	49.6 d	45.2 t
48.6 d	49.0 d	50.4 d	49.1 d
62.7 q	62.1 q	62.6 q	62.2 q
65.0 q	64.7 q	65.1 q	64.8 q
89.1 s ⇐	89.8 s ⇐	88.1 s ⇐	88.3 s ⇐
115.0 s	115.7 s	115.0 s	115.4 s
115.4 s	116.2 s	115.8 s	116.6 s
117.8 s	118.6 s	118.8 s	119.3 s
163.0 s	164.0 s	163.6 s	164.4 s
165.5 s	165.2 s	165.6 s	165.4 s
166.1 s	166.0 s	166.1 s	165.9 s
187.5 d	187.6 d	187.5 d	187.5 d
187.5 d	187.7 d	187.5 d	187.5 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 ⇐ refer to quaternary carbons at positions 3 and 5 respectively.

cleavable ethano moiety in these natural products. The Columbia group presumed a cyclobutane ring in **1** as the progenitor of this fragment[2] while we postulated the ethano bridge of a camphane structure **11** as the source of this mass spectral fragment. It now seems likely that this fragment is generated from the pinane segment of **13**. In retrospect, generation of ethylene from **13** is virtually inevitable since cationic rearrangement in the mass spectrometer of the pinane segment of **13** to produce a camphane structure finds analogy in solvolytic rearrangements of pinanes,[14] and we have already shown that ethylene is a major fragment in the mass spectrum of camphene (see Scheme I).

Abundant evidence supports our conclusion that robustadials are pinane derivatives **13**. As noted at the outset, natural products of mixed acetogenin–terpenoid biosynthetic origin occur widely in *Eucalyptus* plants. The requisite terpenoid precursors, i.e., pinanes, have been found in *E. robusta* leaves which yield an oil consisting "largely of pinene".[15] NMR chemical shift comparisons of robustadials with *cis*- and *trans*-nopinol[16] show strong similarities. The C-1 bridgehead methine carbon in the



nopinols shows resonances at δ 48.1 ± 0.1. Corresponding resonances in robustadials A and B appear at δ 49.7 and 51.0 respectively. The fit is even closer for the C-5 bridgehead methine carbons which would experience less influence of the prenylphenol portion in the robustadials. These carbons show resonances at δ 40.8 ± 0.3 in the nopinols while the robustadials show corresponding resonances at δ 40.7 ± 0.2. Even the resonances of the quaternary carbons at C-6 in *cis*- and *trans*-nopinol at δ 39.4 and 37.5 correspond closely to quaternary carbon resonances at δ 38.3 and 38.4 found in the spectra of robustadials A and B respectively.

Experimental Section

General.[17] The purity of all titled compounds was estimated to be ≥95% by TLC and NMR spectral analyses. Circular dichroism (CD) measurements were done on a JASCO J-40 automatic continuous spectropolarimeter. Optical rotations were recorded on a Perkin-Elmer 141 polarimeter. Mass spectra (MS) were done by Midwest Center for Mass Spectrometry, University of Nebraska, Lincoln, NE.

Reaction of Grignard Reagent 16 with Camphenilone (15). Camphenilone (**15**) (250 mg, 1.81 mmol) in anhydrous THF (2 mL) was added at room temperature to the Grignard reagent **16** prepared from 2-(2,4,6-trimethoxyphenyl)ethyl bromide (498 mg, 1.80 mmol) and magnesium (89 mg, 3.71 mmol) in anhydrous THF (4 mL). The mixture was refluxed for 2 h. The cooled mixture was hydrolyzed with saturated aqueous NH_4Cl solution (10 mL) and extracted with chloroform (3 × 10 mL). The combined extracts were dried ($MgSO_4$) and stripped of volatiles under reduced pressure. The residue was flash chromatographed on a 40-mm-diameter silica gel column (5% and 10% ethyl acetate in hexanes) to give in turn (2,4,6-trimethoxyphenyl)ethane (1.03 g, 29.0%), 2,4,6-trimethoxystyrene (180 mg, 51.2%), camphenilol (**17**) (103 mg, 40.6%), and 1,2-addition product **18** (51 mg, 8.9%). **2,4,6-Trimethoxystyrene**: ^1H NMR δ 3.80 (3 H, s), 3.81 (6 H, s), 5.28 (H, dd, J = 12.2 and 2.9 Hz), 5.93 (H, dd, J = 18.1 and 2.9 Hz), 6.11 (2 H, s), 6.88 (H, dd, J = 18.1 and 12.2 Hz). Grignard 1,2-addition product **18**: ^1H NMR δ 0.91 (6 H, s), 0.99–1.38 (4 H), 1.55–2.02 (7 H), 2.18 (H), 2.62 (H, m), 3.78 (9 H, s), 6.11 (2 H, s); mass spectrum, m/z obsd 334.2141 (M^+, calcd for $C_{20}H_{30}O_4$ 334.2144).

1-[1-(Trimethylsiloxy)vinyl]-2,4,6-trimethoxybenzene (21). 2,4,6-Trimethoxyacetophenone (11.2 g, 53.3 mmol) in anhydrous DMF (12 mL) was added to triethylamine (22.51 g, 222 mmol) and trimethylsilyl chloride (12.15 g, 112 mmol) in anhydrous DMF (40 mL) at room temperature with stirring under nitrogen. This was heated at reflux for 90 h. After cooling, ether (50 mL) was added and the whole poured into saturated aqueous $NaHCO_3$ (100 mL). The aqueous phase was extracted with ether (3 × 30 mL). The extracts and the organic phase were combined and dried ($MgSO_4$). The volatiles were removed under reduced pressure, and the residue was flash chromatographed (20% ethyl acetate in hexanes) to give **21** as a colorless oil (11.88 g, 100% yield based on starting material consumed, 79.0% conversion). The product oil solidified on extended standing at −20 °C: mp 47–48 °C; ^1H NMR δ 0.08 (9 H, s), 3.77 (6 H, s), 3.79 (3 H, s), 4.25 (H, s), 4.69 (H, s), 6.08 (2 H, s); mass spectrum, m/z obsd 282.1281 (M^+, calcd for $C_{14}H_{22}O_4Si$ 282.1281).

Mukaiyama Adduct 22. Silyl enol ether **21** (8.76 g, 31.0 mmol) in anhydrous methylene chloride (40 mL) was added dropwise over a 1-h period to a solution of camphenilone[7] (4.76 g, 34.5 mmol) with $[\alpha]^{20}_D$ +6.1° (*c* 3.6, ethanol) and $TiCl_4$ (6.49 g, 34.2 mmol) in anhydrous methylene chloride (160 mL) with stirring at 0 °C under nitrogen. The reaction mixture color went to yellow to black to brown to orange during the course of the addition. The mixture was then stirred at room temperature for 6.5 h. The mixture was hydrolyzed by addition of water (100 mL). The aqueous phase was extracted with methylene chloride (3 × 30 mL), and the extracts were combined with the organic phase. This solution was dried ($MgSO_4$) and stripped of volatiles under reduced pressure. The residue was taken up in ether and treated with activated charcoal to remove colored impurities. The residue from stripping the filtered solution was crystallized from hexanes

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(17) See ref 1 for description of solvent purification, chromatographic methods, and spectroscopic information.

containing a little ethyl acetate to yield hydroxy ketone **22** (6.87 g), mp 135–137 °C. The residue from the mother liquor was flash chromatographed (10% ethyl acetate in hexanes) to yield, in order of elution, camphenilone (0.74 g), **22** (1.73 g), and 2,4,6-trimethoxyacetophenone (0.80 g). The total yield of **22** was 8.60 g (79.8%): ^{1}H NMR δ 0.93 (3 H, s), 1.00 (3 H, s), 1.05–1.36 (3 H), 1.52–1.78 (3 H), 1.95–2.17 (2 H), 3.06 (2 H, s), 3.74 (6 H, s), 3.79 (3 H, s), 4.36 (H, s), 6.06 (2 H, s); ^{13}C NMR δ 20.65 (+, t), 21.58 (–, q), 23.78 (+, t), 27.00 (–, q), 34.38 (+, t), 43.01 (+, s), 49.40 (–, d), 50.07 (–, d), 51.80 (+, t), 55.32 (–, q), 55.64 (–, q, 2 C), 80.03 (+, s), 90.43 (–, d, 2 C), 113.14 (+, s), 158.15 (+, s, 2 C), 162.46 (+, s), 207.26 (+, s); mass spectrum, m/z obsd 348.1924 (M^+, calcd for $C_{20}H_{28}O_5$ 348.1937).

Demethylation of 22 with BCl_3. To **22** (29 mg, 0.083 mmol) in dry methylene chloride (1 mL) was added 1 M boron trichloride in methylene chloride solution (0.50 mL, 0.5 mmol), and the mixture was stirred at room temperature for 8 h. Water (10 mL) was then added and the mixture extracted with methylene chloride (3 × 10 mL). The combined extracts were dried ($MgSO_4$) and stripped of volatiles under reduced pressure. The residue was flash chromatographed on a 10-mm-diameter silica gel column (5% ethyl acetate in hexanes) to give monophenol **28** (12 mg, 59.5% based on starting material consumed): ^{1}H NMR δ 0.89 (3 H, s), 1.02 (3 H, s), 1.06–1.38 (3 H), 1.43–1.81 (5 H), 1.92–2.17 (2 H), 3.08 (H, d, J = 18.6 Hz), 3.49 (H, d, J = 18.7 Hz), 3.80 (3 H, s), 3.85 (3 H, s), 4.28 (H), 5.91 (H, d, J = 2.3 Hz), 6.04 (H, d, J = 2.2 Hz); mass spectrum, m/z obsd 334.1782 (M^+ calcd for $C_{19}H_{26}O_5$ 334.1780).

Enone 23. Hydroxy ketone **22** (2.50 g, 7.18 mmol) and *p*-toluenesulfonic acid (100 mg, 0.58 mmol) in dry benzene (60 mL) were heated at reflux for 1.5 h, after which TLC showed the absence of hydroxy ketone **22**. On cooling, the solution was stripped of volatiles under reduced pressure. The residue was flash chromatographed on a 100-mm-diameter silica gel column (15% ethyl acetate in hexanes and then 20% ethyl acetate in hexanes) to give enone **23** (1.80 g, 75.9%): ^{1}H NMR δ 1.04 (3 H, s), 1.05 (3 H, s), 1.09–1.98 (7 H), 3.54–3.63 (H), 3.73 (6 H, s), 3.80 (3 H, s), 5.98 (H, s), 6.08 (2 H, s); mass spectrum, m/z obsd 330.1843 (M^+, calcd for $C_{20}H_{26}O_4$ 330.1831).

Phenol 24. To enone **23** (0.10 g, 0.30 mmol) in dry methylene chloride (3 mL) was added 1 M boron trichloride in methylene chloride solution (1 mL) at 0 °C under nitrogen. After the mixture was stirred for 2 h at room temperature, water (10 mL) was added and the mixture was well stirred for 5 min. The phases were separated, and the aqueous phase was extracted with methylene chloride (3 × 5 mL). The combined extracts and methylene chloride phase were washed with saturated aqueous $NaHCO_3$ solution and dried ($MgSO_4$). Removal of volatiles under reduced pressure gave **24** as a yellow oil (98 mg, 100%): ^{1}H NMR δ 1.09 (3 H, s), 1.11 (3 H, s), 1.22–2.12 (8 H), 3.72–3.88 (H), 3.79 (3 H, s), 3.80 (3 H, s), 5.89 (H, d, J = 2.4 Hz), 6.05 (H, d, J = 2.4 Hz), 6.66 (H, s); mass spectrum, m/z obsd 316.1684 (M^+, calcd for $C_{19}H_{24}O_4$ 316.1668).

***exo*- and *endo*-25.** Compound **24** (727 mg) and anhydrous K_2CO_3 (7.5 g) in 95% ethanol (150 mL) were heated at reflux for 7.5 h under nitrogen. After cooling, the mixture was filtered and stripped of volatiles under reduced pressure. The residue was taken up in methylene chloride and this solution filtered and stripped of solvent under reduced pressure. The material thus obtained was washed with 10% ethyl acetate in hexanes, leaving *exo*- and *endo*-**25** (411 mg). The wash was stripped of solvent under reduced pressure and the residue flash chromatographed to give starting enone (180 mg) (20% ethyl acetate in hexanes) and then a mixture of *exo*- and *endo*-**25** (130 mg) (ethyl acetate). The total yield of cyclized product was 541 mg (98.9% based on **24** consumed, 74.4% conversion).

Crystallization of such a mixture of *exo*- and *endo*-**25** (1.011 g) from 10% ethyl acetate in hexanes yielded *exo*-**25** (778 mg, mp 147–149 °C). The residue from stripping the solvents from the mother liquor under reduced pressure was chromatographed by HPLC using a Whatman Partisil M20 column (70% methyl *tert*-butyl ether in hexanes at 12 mL/min) to give *exo*-**25** after 73 min (68 mg) and after 81 min *endo*-**25** (128 mg, mp 148.5–150.5 °C). *exo*-**25**: ^{1}H NMR δ 0.93 (3 H, s), 1.06 (3 H, s), 1.06–1.17 (H), 1.17–1.69 (4 H), 1.79 (H, m), 2.04–2.15 (H), 2.39 (H, m), 2.70 (H, d, J = 16 Hz), 2.72 (H, d, J = 16 Hz), 3.79 (3 H, s), 3.83 (3 H, s), 5.96 (H, d, J = 2.3 Hz), 5.99 (H, d, J = 2.2); ^{13}C NMR δ 22.09 (+, t), 22.94 (–, q), 23.37 (+, t), 25.20 (–, q), 34.36 (+, t), 41.86 (+, t), 44.87 (+, s), 46.02 (–, d), 49.31 (–, d), 55.25 (–, q), 55.76 (–, q), 90.15 (+, s), 91.71 (–, d), 93.35 (–, d), 105.46 (+, s), 161.47 (+, s), 164.28 (+, s), 165.71 (+, s), 189.87 (+, s); mass spectrum, m/z obsd 316.1668 (M^+, calcd for $C_{19}H_{24}O_4$ 316.1668). *endo*-**25**: ^{1}H NMR δ 0.99 (3 H, s), 1.03 (3 H, s), 1.09–1.44 (3 H), 1.60–1.86 (4 H), 2.39 (H, m), 2.53 (H, d, J = 16.2 Hz), 2.83 (H, d, J = 16.2 Hz), 3.81 (3 H, s), 3.84 (3 H, s), 5.98 (H, d, J = 2.3 Hz), 6.04 (H, d, J = 2.2 Hz); ^{13}C NMR δ 21.30 (+, t), 21.81 (–, q), 23.85 (+, t), 26.50 (–, q), 34.25 (+, t), 43.46 (+, s), 45.58 (+, t), 45.99 (–, d), 49.29 (–, d), 55.52 (–, q), 56.04 (–, q), 88.36 (+, s), 92.28 (–, d), 93.62 (–, d), 105.79 (+, s), 161.89 (+, s), 164.41 (+, s), 165.92 (+, s), 190.84 (+, s); mass spectrum, m/z obsd 316.1667 (M^+, calcd for $C_{19}H_{24}O_4$ 316.1668).

Alkene 30x. To *exo*-**25** (921 mg, 6.1 mmol) in anhydrous ethyl ether (25 mL) was added a 2 M isobutylmagnesium chloride/ether solution (12.0 mL, 24 mmol) at room temperature under nitrogen. After 1.5 h of stirring, saturated aqueous NH_4Cl solution was added followed by 4% aqueous HCl (50 mL). This mixture was stirred vigorously for 15 min. The separated aqueous phase was extracted with methylene chloride (3 × 25 mL), and the extracts were added to the separated ether phase. This was dried ($MgSO_4$), and the volatiles were removed under reduced pressure. The resulting residue was heated in ethyl acetate (3 mL), and after cooling, alkene **30x** (1.80 g) was filtered off. The residue from the stripped filtrate was flash chromatographed on a 45-mm-diameter silica gel column (2% ethyl acetate in hexanes) to give additional product (0.332 g). The total yield of **30x** was thus 98.5%: ^{1}H NMR δ 0.79 (3 H, d, J = 6.7 Hz), 0.84 (3 H, d, J = 6.6 Hz), 0.95 (3 H, s), 1.03 (3 H, s), 0.90–1.16 (H), 1.16–1.82 (6 H), 2.04–2.36 (3 H), 2.47–2.62 (H), 3.74 (3 H, s), 3.74 (3 H, s), 5.37 (H, s), 5.97 (H, d, J = 2.4 Hz), 6.04 (H, d, J = 2.4 Hz); ^{13}C NMR δ 21.61 (+, t), 22.15 (–, q), 22.64 (–, q), 24.20 (+, t), 24.72 (–, q), 26.18 (–,q), 26.93 (–, d), 34.53 (+, t), 45.30 (+, t), 46.49 (+, s), 47.31 (–, d), 49.15 (–, d), 55.12 (–, q, 2 C), 86.32 (+, s), 91.73 (–, d), 94.30 (–, d), 106.04 (+, s), 119.89 (–, d), 132.76 (+, s), 156.54 (+, s), 157.49 (+, s), 160.31 (+, s); mass spectrum, m/z obsd 356.2338 (M^+, calcd for $C_{23}H_{32}O_3$ 356.2351).

31xa and 31xs. Alkene **30x** (1.80 g, 5.1 mmol) and 5% palladium on charcoal (0.20 g), in ethyl acetate (25 mL) were stirred under hydrogen at room temperature and atmospheric pressure for 4 h. The mixture was filtered and stripped of volatiles under reduced pressure. The residue was crystallized from ethyl acetate (10 mL) to give **31xa** (786 mg), mp 139–141 °C. The residue after removal of solvents under reduced pressure from the mother liquor was chromatographed by reverse-phase HPLC using a Whatman Partisil 10 ODS-3 column (20% water in acetonitrile at 12 mL/min) to give after 122 min **31xs** (854 mg) and after 130 min **31xa** (128 mg). The total yield of reduced product was 97.7%. **31xa**: ^{1}H NMR δ 0.89 (3 H, d, J = 6.4 Hz), 0.92 (3 H, s), 0.98 (3 H, d, J = 6.1 Hz), 0.99 (3 H, s), 1.03–1.14 (H), 1.17–1.83 (9 H), 1.90–2.05 (H), 2.11–2.24 (H), 2.30 (H, m), 2.86 (H, m), 3.73 (6 H, s), 5.95 (H, d, J = 2.2), 5.97 (H, d, J = 2.3 Hz); ^{13}C NMR δ 21.25 (–, q), 22.66 (+, t), 23.30 (–), 24.11 (–), 24.26 (+, t), 25.32 (–), 25.84 (–), 26.20 (+, t), 26.90 (–), 34.97 (+, t), 42.56 (+, t), 45.58 (+, s), 46.97 (–, d), 49.04 (–, d), 55.11 (–, q), 55.20 (–, q), 85.23 (+, s), 90.91 (–, d), 93.72 (–, d), 108.03 (+, s), 155.42 (+, s), 158.78 (+, s), 159.10 (+, s); mass spectrum, m/z obsd 358.2502 (M^+, calcd for $C_{23}H_{34}O_3$ 358.2508. **31xs**: ^{1}H NMR δ 0.87 (3 H, d, J = 6.5 Hz), 0.94 (3 H, d, J = 6.3 Hz), 0.95 (3 H, s), 1.11 (3 H, s), 0.91–1.83 (9 H), 1.91–2.37 (4 H), 2.73 (H, m), 3.73 (3 H, s), 3.74 (3 H, s), 5.96 (H, d, J = 2.5 Hz), 5.99 (H, d, J = 2.5 Hz); ^{13}C NMR δ 21.41 (–, q), 22.76 (–, q), 22.86 (+, t), 24.12 (+, t), 24.32 (–, q), 25.04 (–, q), 25.76 (–, d), 28.11 (–, d), 32.20 (+, t), 34.31 (+, t), 43.17 (–, d), 44.12 (+, s), 44.46 (+, t), 49.41 (–, d), 55.02 (–, q), 55.17 (–, q), 86.19 (+, s), 91.54 (–, d), 94.58 (–, d), 109.08 (+, s), 156.45 (+, s), 158.92 (+, s), 159.18 (+, s); mass spectrum, m/z obsd 358.2502 (M^+, calcd for $C_{23}H_{34}O_3$ 358.2508).

Alkene 30n. To *endo*-**25** (1.713 g, 5.42 mmol) in anhydrous ethyl ether (40 mL) was added a 2 M isobutylmagnesium chloride/ether solution (10.0 mL, 20 mmol) at room temperature under nitrogen. After 4 h of stirring, 4% aqueous HCl (50 mL) was added and the mixture stirred vigorously for 15 min. The aqueous phase was extracted with methylene chloride (3 × 25 mL), and the extracts were added to the ether phase. The solution was dried

($MgSO_4$) and stripped of volatiles under reduced pressure. The residue was flash chromatographed on an 80-mm-diameter silica gel column (10% ethyl acetate in hexanes) to give alkene **30n** (1.817 g, 100% based on *endo*-**25** consumed, 94.2% conversion): ^{1}H NMR δ 0.78 (3 H, d, J = 6.6 Hz), 0.85 (3 H, d, J = 6.6 Hz), 0.92 (6 H, s), 0.96–1.86 (7 H), 1.98–2.32 (3 H), 2.62 (H, m), 3.73 (3 H, s), 3.74 (3 H, s), 5.15 (H, s), 5.97 (H, d, J = 2.4 Hz), 6.07 (H, d, J = 2.4 Hz); ^{13}C NMR δ 20.34 (+, t), 22.02 (–, q), 22.87 (–, q), 23.48 (–, q), 24.57 (+, t), 27.09 (–, d), 28.87 (–, q), 34.07 (+, t), 44.77 (+, t), 45.28 (+, s), 49.09 (–, d), 50.18 (–, d), 55.23 (–, q, 2 C), 84.99 (+, s), 91.98 (–, d), 94.52 (–, d), 106.44 (+, s), 124.10 (–, d), 130.60 (+, s), 157.30 (+, s), 157.56 (+, s), 160.22 (+, s); mass spectrum, m/z obsd 356.2354 (M^+, calcd for $C_{23}H_{32}O_3$ 356.2351).

31na and 31ns. Alkene **30n** (1.65 g, 4.6 mmol) and 5% palladium on charcoal (165 mg) in ethyl acetate (30 mL) were stirred under hydrogen at room temperature and at atmospheric pressure for 4 h, after which time the mixture was filtered and the solvents were removed under reduced pressure. The residue obtained crystallized on standing overnight with hexanes (5 mL) to give **31na** (442 mg), mp 89–91 °C. The mother liquor was stripped of solvent and the residue chromatographed by reverse-phase HPLC using a Whatman Partisil 10 ODS-3 column (21% water in acetonitrile at 12 mL/min) to give after 117 min **31ns** (240 mg) and after 127 min **31na** (915 mg). The total yield of reduced product is 96.2%. **31na**: ^{1}H NMR δ 0.79 (3 H, s), 0.88 (3 H, d, J = 6.2 Hz), 0.93 (3 H, d, J = 6.1 Hz), 1.00 (3 H, s), 1.09–1.43 (4 H), 1.51–1.88 (6 H), 1.95–2.25 (2 H), 2.32 (H, m), 2.90 (H, m), 3.73 (6 H, s), 6.00 (2 H, s); ^{13}C NMR δ 21.01 (+, t), 21.53 (–, q), 22.19 (–, q), 23.85 (+, t), 23.92 (–, q), 26.16 (–, d), 27.06 (–, q), 27.59 (–, d), 34.43 (+, t), 35.14 (+, t), 44.23 (+, s), 45.31 (+, t), 49.01 (–, d), 50.64 (–, d), 55.11 (–, q), 55.22 (–, q), 84.29 (+, s), 91.28 (–, d), 94.18 (–, d), 109.21 (+, s), 156.30 (+, s), 158.79 (+, s), 158.97 (+, s); mass spectrum, m/z obsd 358.2518 (M^+, calcd for $C_{23}H_{34}O_3$ 358.2508). **31ns**: ^{1}H NMR δ 0.85 (3 H, d, J = 6.5 Hz), 0.94 (3 H, d, J = 6.4 Hz), 1.00 (3 H, s), 1.04 (3 H, s), 0.97–1.39 (4 H), 1.39–1.84 (6 H), 1.84–2.16 (2 H), 2.24 (H, m), 2.84 (H, m), 3.73 (6 H, s), 5.99 (2 H, s); ^{13}C NMR δ 21.22 (–, q), 21.64 (+, t), 21.74 (–, q), 23.93 (+, t), 24.43 (–, q), 25.59 (–, q), 25.98 (–, d), 27.64 (–, d), 34.41 (+, t), 35.49 (+, t), 42.97 (+, s), 43.86 (–, d), 45.05 (+, t), 49.42 (–, d), 54.98 (–, q), 55.19 (–, q), 84.72 (+, s), 91.77 (–, d), 94.49 (–, d), 109.65 (+, s), 156.83 (+, s), 158.82 (+, s), 158.97 (+, s); mass spectrum, m/z obsd 358.2513 (M^+, calcd for $C_{23}H_{24}O_3$ 358.2508).

Dibromide 32xa. Freshly prepared pyridine perbromide[18] (1.07 g, 4.48 mmol) was added in small portions (~50 mg each) with stirring to a solution of **31xa** (0.80 g, 2.23 mmol) in CH_2Cl_2 (30 mL) over 10 min. The resulting pale yellow solution was stirred for 5 min, diluted with ether (100 mL), then washed with water (3 × 6 mL), dried ($MgSO_4$), and filtered, and the solvent was removed under reduced pressure. The residue thus obtained was extracted with hot hexanes and filtered, and the solvent was removed under reduced pressure to give **32xa**, which was crystallized from hexanes to yield pure dibromide **32xa** (1.15 g, 100%): mp 127–128 °C dec; ^{1}H NMR δ 0.89 (d, J = 6.2 Hz, 3 H), 0.93 (s, 3 H), 1.01 (d, J = 6.0 Hz, 3 H), 1.06 (s, 3 H), 1.14–1.89 (10 H), 2.01 (m, H), 2.28 (m, 2 H), 2.92 (m, H), 3.78 (s, 3 H), 3.83 (s, 3 H); HRMS calcd for $C_{23}H_{32}{}^{79}Br^{81}BrO_3$ 516.0700, found 516.0689; mass spectrum, m/z (relative intensity) 518 (2.0), 516 (4.6, M^+), 514 (2.3) 459 (98.9), 379 (5.2), 365 (6.6), 325 (17.5), 137 (8.8), 121 (18.2), 107 (12.0), 93 (26.2), 81 (44.1), 69 (100), 55 (40.8).

Diester 33xa. Dibromide **32xa** (595 mg, 1.15 mmol) was added with stirring to a solution of *n*-butyllithium (3.70 mL, 2.50 M in hexanes, 9.25 mmol) in anhydrous THF (25 mL) at −78 °C over 10 min under an atmosphere of argon. The resulting suspension was stirred for 30–40 min whereupon it became a clear solution. Dry carbon dioxide was bubbled for 2 min through the reaction mixture, which was then allowed to come to room temperature. It was poured into an ice/water/HCl mixture (20 g) and extracted with ether (3 × 12 mL). The combined ether extracts were washed with saturated aqueous $NaHCO_3$ solution (3 × 4 mL) and then water (3 × 2 mL). The aqueous layer was acidified with 10% HCl and then extracted with ether (3 × 10 mL). The extract was washed with water (3 × 2 mL), dried ($MgSO_4$), and filtered, and the solvent was removed on a Rotavapor. The residue thus obtained was dissolved in ether (5 mL) and treated with ethereal CH_2N_2 solution until the yellow color persisted. Solvent was removed under reduced pressure. The residue thus obtained was purified by flash chromatography (10% ethyl acetate in hexanes) to give **33xa**, which upon crystallization from ethyl acetate afforded **33xa** (425 mg, 78% based on dibromide), mp 131–133 °C; ^{1}H NMR δ 0.88 (d, J = 6.0 Hz, 3 H), 0.90 (s, 3 H), 0.93 (s, 3 H), 0.98 (d, J = 6.0 Hz, 3 H), 1.06–1.84 (10 H), 2.03 (m, 2 H), 2.28 (d, J = 4.2 Hz, H), 2.88 (m, H), 3.74 (s, 3 H), 3.78 (s, 3 H), 3.85 (s, 3 H), 3.87 (s, 3 H); HRMS calcd for $C_{27}H_{38}O_7$ 474.2617, found 474.2609; mass spectrum, m/z (relative intensity) 474 (0.5, M^+), 417 (100), 385 (28.3), 335 (4.0), 251 (10.7), 121 (6.6), 93 (10.1), 79 (6.5), 69 (8.4), 55 (9.4).

Diol 34xa. A solution of diisobutylaluminum hydride (DIBAH) (3.16 mL, 1.5 M in toluene, 4.74 mmol) was added with stirring to a solution of diester **33xa** (375 mg, 0.79 mmol) in anhydrous toluene (15 mL) at −78 °C under argon during 15 min. The resulting mixture was stirred for 1 h followed by addition of saturated aqueous NH_4Cl solution (2 mL). The mixture was allowed to come to room temperature, diluted with water (10 mL), made acidic with saturated aqueous citric acid, and then extracted with ether (3 × 10 mL). The combined organic extracts were washed with water (3 × 2 mL), dried ($MgSO_4$), and filtered, and the solvent was removed under reduced pressure. The residue thus obtained was purified by flash chromatography (30% ethyl acetate in hexanes) to give **34xa** (325 mg, 98%), which solidified upon standing: mp 59–61 °C; ^{1}H NMR δ 0.90 (d, J = 6.0 Hz, 3 H), 0.95 (s, 3 H), 1.02 (d, J = 6.0 Hz, 3 H), 1.04 (s, 3 H), 1.09–1.90 (10 H), 2.06 (m, 2 H), 2.19–2.33 (3 H), 2.90 (m, H), 3.76 (s, 3 H), 3.83 (s, 3 H), 4.65 (br s, 4 H); HRMS calcd for $C_{25}H_{38}O_5$ 418.2719, found 418.2719; mass spectrum, m/z (relative intensity) 418 (3.8, M^+), 361 (100), 343 (50.1), 275 (2.7), 209 (4.8), 121 (17.2), 93 (22.9), 81 (15.9), 69 (32.3), 55 (29.3).

Dialdehyde 35xa. A mixture of diol **34xa** (280 mg, 0.67 mmol) and pyridinium dichromate (PDC) (4.60 g, 2.23 mmol) in CH_2Cl_2 (15 mL) was stirred at room temperature for 24 h and then diluted with ether (25 mL). The supernatant was decanted from the brown solid. The insoluble residue was washed thoroughly with anhydrous ether (3 × 5 mL). The combined organic extracts 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 (15% ethyl acetate in hexanes) to give **35xa** (215 mg, 77%): UV λ_{max} (methanol) 261 (ϵ 25 900), 283 (15 250), 328 nm (3500); CD (methanol) 220 ($\Delta\epsilon$ −1.35), 260 (−1.04), 290 (+0.72), 321 (+0.41), 350 nm (−0.22); $[\alpha]^{20}_D$ −0.45° (c 2.64, $CHCl_3$); ^{1}H NMR δ 0.89 (d, J = 6.2 Hz, 3 H), 0.94 (s, 3 H), 1.01 (d, J = 6.2 Hz, 3 H), 1.03 (s, 3 H), 1.13–1.93 (10 H), 2.13 (m, 2 H), 2.31 (d, J = 4.0 Hz, H), 2.94 (m, H), 3.83 (s, 3 H), 3.91 (s, 3 H), 10.24 (s, H), 10.36 (s, H); ^{13}C NMR (see Table I); HRMS calcd for $C_{25}H_{34}O_5$ 414.2406, found 414.2406; mass spectrum, m/z (relative intensity) 414 (10.3, M^+), 357 (100), 305 (2.1), 275 (8.6), 223 (19.3), 135 (2.3), 91 (2.7), 67 (4.1), 55 (3.6).

Dibromide 32xs. This dibromide was prepared from **31xs** (390 mg, 1.09 mmol) and pyridine perbromide (550 mg, 2.30 mmol) in CH_2Cl_2 (15 mL) by following the procedure described for **32xa**: yield, 556 mg (99%); crystallized from hexanes; mp 119–121 °C; ^{1}H NMR δ 0.89 (d, J = 6.6 Hz, 3 H), 0.96 (d, J = 6.6 Hz, 3 H), 0.96 (s, 3 H), 1.01–1.48 (5 H), 1.21 (s, 3 H), 1.49–1.89 (4 H), 1.98–2.35 (4 H), 2.83 (m, H), 3.73 (s, 3 H), 3.82 (s, 3 H); HRMS calcd for $C_{23}H_{32}{}^{79}Br^{81}BrO_3$ 516.0700, found 516.0670; mass spectrum, m/z (relative intensity) 518 (3.5), 516 (7.0, M^+), 514 (4.1), 459 (100), 365 (11.2), 325 (20.6), 121 (8.9), 93 (8.6), 69 (21.8), 55 (15.1).

Diester 33xs. Reaction of dibromide **32xs** (505 mg, 0.98 mmol) with *n*-butyllithium (3.15 mL, 2.5 M in hexanes, 7.87 mmol) and THF (25 mL) followed by ethereal CH_2N_2 afforded diester **33xs** (400 mg, 86%), by the procedure described for the preparation of **33xa** from **32xa**. Diester **33xs** solidified upon standing: mp 89–91 °C; ^{1}H NMR δ 0.87 (d, J = 6.4 Hz, 3 H), 0.92 (s, 3 H), 0.94 (d, J = 6.4 Hz, 3 H), 1.00 (s, 3 H), 1.08–1.49 (6 H), 1.50–1.86 (3 H), 1.95 (m, H), 2.06–2.38 (3 H), 2.76 (m, H), 3.72 (s, 3 H), 3.77 (s, 3 H), 3.84 (s, 3 H), 3.86 (s, 3 H); HRMS calcd for $C_{27}H_{38}O_7$ 474.2617, found 474.2602; mass spectrum, m/z (relative intensity) 474 (2.4, M^+), 417 (84.2), 385 (62.6), 251 (13.5), 121 (14.2), 97 (30.7), 83 (44.6), 69 (75.7), 57 (100).

(18) McElvain, S. M.; Morris, L. R. *J. Am. Chem. Soc.* **1951**, *73*, 206.

Diol 34xs. This diol (278 mg, 98%) was prepared from **33xs** (320 mg, 0.67 mmol), DIBAH (2.70 mL, 1.5 M in toluene, 4.05 mmol), and toluene (12 mL) by following the procedure described for the preparation of **34xa**: ^{1}H NMR δ 0.90 (d, J = 6.6 Hz, 3 H), 0.97 (d, J = 6.6 Hz, 3 H), 0.98 (s, 3 H), 1.08 (m, 2 H), 1.16 (s, 3 H), 1.21–1.51 (3 H), 1.52–2.03 (5 H), 2.11–2.48 (5 H), 2.80 (m, H), 3.71 (s, 3 H), 3.82 (s, 3 H), 4.64 (m, 4 H); HRMS calcd for $C_{25}H_{38}O_5$ 418.2719, found 418.2734; mass spectrum, m/z (relative intensity) 418 (2.8, M$^+$), 361 (58.2), 343 (100), 209 (15.3), 161 (10.1), 121 (35.2), 93 (53.5), 69 (48.9), 55 (53.6).

Dialdehyde 35xs. A mixture of **34xs** (250 mg, 0.60 mmol) and pyridinium dichromate (4.0 g, 10.63 mmol) in CH_2Cl_2 (15 mL) was stirred at room temperature for 24 h and worked up as described for the preparation of dialdehyde **35xa**. The residue thus obtained was purified by flash chromatography (15% ethyl acetate in hexanes) to give **35xs** (220 mg, 89%): UV λ_{max} (methanol) 261 (ϵ 25150), 283 (16100), 328 nm (3800); CD (methanol) 212 ($\Delta\epsilon$ −2.06), 252 (+1.12), 319 (+0.34), 346 nm (−0.31); $[\alpha]^{20}_D$ +6.03° (c 3.68, $CHCl_3$); ^{1}H NMR δ 0.89 (d, J = 6.6 Hz, 3 H), 0.96 (d, J = 6.6 Hz, 3 H), 0.98 (s, 3 H), 1.13 (m, 2 H), 1.16 (s, 3 H), 1.22–2.00 (8 H), 2.11 (m, 2 H), 2.33 (m, H), 2.82 (m, H), 3.82 (s, 3 H), 3.90 (s, 3 H), 10.25 (s, H), 10.33 (s, H); ^{13}C NMR (see Table I); HRMS calcd for $C_{25}H_{34}O_5$ 414.2406, found 414.2416; mass spectrum, m/z (relative intensity) 414 (1.6, M$^+$), 357 (100), 275 (12.5), 263 (19.3), 223 (42.6), 121 (12.7), 93 (15.7), 69 (20.0), 55 (19.7).

Dibromide 32na. Bromine (123 μL, 384 mg, 2.40 mmol) was added with stirring to solution of **31na** (430 mg, 1.20 mmol) in CH_2Cl_2 (20 mL) over a period of 2 min. The mixture was stirred for another 2 min before saturated aqueous $NaHCO_3$ solution (5 mL) was added, diluted with ether (30 mL). The organic layer was washed with water (3 × 3 mL), dried ($MgSO_4$), and filtered, and the solvent was removed under reduced pressure to give **32na**: yield, 614 mg (99%); ^{1}H NMR δ 0.73 (s, 3 H), 0.89 (d, J = 6.4 Hz, 3 H), 0.97 (d, J = 6.2 Hz, 3 H), 1.02 (s, 3 H), 1.16–1.43 (4 H), 1.60–2.03 (6 H), 2.22–2.40 (3 H), 3.03 (m, H), 3.76 (s, 3 H), 3.83 (s, 3 H); HRMS calcd for $C_{23}H_{32}{}^{79}Br^{81}BrO_3$ 516.0700, found 516.0695; mass spectrum, m/z (relative intensity) 518 (3.2), 516 (6.7, M$^+$), 514 (3.6), 462 (11.2), 461 (50.1), 460 (22.0), 459 (100), 457 (52.7), 417 (16.6), 385 (7.0), 325 (20.7), 182 (7.0), 93 (8.6), 81 (8.2), 69 (14.7), 67 (17.9).

Diester 33na. This diester was prepared from the dibromide **32na** (595 mg, 1.15 mmol), n-butyllithium (3.0 mL, 2.5 M in hexanes, 7.50 mmol), THF (20 mL), and ethereal CH_2N_2 by following the procedure as described for the preparation of diester **33xa**: yield, 430 mg (79% based on dibromide **32na**); ^{1}H NMR δ 0.75 (s, 3 H), 0.88 (d, J = 6.4 Hz, 3 H), 0.95 (d, J = 6.2 Hz, 3 H), 1.02 (s, 3 H), 1.14–1.44 (4 H), 1.55–2.11 (7 H), 2.25 (m, 2 H), 2.99 (m, H), 3.75 (s, 3 H), 3.78 (s, 3 H), 3.87 (s, 3 H), 3.88 (s, 3 H); HRMS calcd for $C_{27}H_{38}O_7$ 474.2617, found 474.2617; mass spectrum, m/z (relative intensity) 474 (2.4, M$^+$), 443 (6.1), 418 (23.6), 417 (100), 385 (40.4), 307 (8.9), 251 (12.8), 132 (5.9), 93 (3.5), 81 (6.2), 69 (13.3), 67 (4.7).

Diol 34na. A solution of lithium aluminum hydride (2.10 mL, 1.0 M in ether, 2.10 mmol) was added with stirring to a solution of diester **33na** (400 mg, 0.84 mmol) in anhydrous ether (20 mL) at 0 °C under argon during 10 min. The reaction mixture was allowed to come to room temperature over 30 min, carefully hydrolyzed with water, and filtered. The inorganic residue was washed with ether (3 × 5 mL). The combined organic extracts were washed with water (2 × 2 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 diol **34na** as a syrup: yield, 345 mg (99%); ^{1}H NMR δ 0.75 (s, 3 H), 0.90 (d, J = 6.6 Hz, 3 H), 0.98 (d, J = 6.6 Hz, 3 H), 1.06 (s, 3 H), 1.12–1.45 (4 H), 1.51–2.11 (8, H), 2.18–2.47 (3 H), 3.01 (m, H), 3.76 (s, 3 H), 3.84 (s, 3 H), 4.71 (m, 4 H); HRMS calcd for $C_{25}H_{38}O_5$ 418.2719, found 418.2717; mass spectrum, m/z (relative intensity) 418 (4.3, M$^+$), 362 (22.1), 361 (100), 344 (14.8), 343 (65.3), 327 (3.8), 265 (3.9), 251 (2.30), 209 (8.2), 107 (3.6), 93 (6.8), 91 (6.7), 81 (5.7), 79 (61), 69 (13.3), 55 (11.1).

Dialdehyde 35na. A mixture of diol **34na** (180 mg, 0.43 mmol) and pyridinium dichromate (1.80 g, 4.78 mmol) in CH_2Cl_2 (25 mL) was stirred at room temperature for 16 h and worked up as described for the preparation of dialdehyde **35xa**. The residue thus obtained was purified by preparative TLC (30% ethyl acetate in hexanes) to give **35na** (120 mg, 67%): UV λ_{max} (methanol) 261 (ϵ 25250), 282 (15900), 328 nm (4000); CD (methanol) 213 ($\Delta\epsilon$ −1.94), 222 (−1.94), 246 (−0.28), 366 nm (−0.17); $[\alpha]^{20}_D$ −0.21° (c 4.85, $CHCl_3$); ^{1}H NMR δ 0.78 (s, 3 H), 0.91 (d, J = 6.2 Hz, 3 H), 0.98 (d, J = 6.0 Hz, 3 H), 1.06 (s, 3 H), 1.15–1.50 (4 H), 1.54–1.91 (6 H), 1.99–2.46 (3 H), 3.04 (m, H), 3.85 (s, 3 H), 3.92 (s, 3 H), 10.25 (s, H), 10.41 (s, H); ^{13}C NMR (see Table I); HRMS calcd for $C_{25}H_{34}O_5$ 414.2406, found 414.2412; mass spectrum, m/z (relative intensity) 414 (2.4, M$^+$), 373 (10.1), 358 (25.2), 357 (100), 345 (14.0), 331 (3.2), 281 (9.8), 275 (28.9), 263 (11.4), 223 (39.3), 209 (5.2), 109 (4.1), 95 (4.2), 91 (7.8), 84 (6.2), 81 (6.3), 69 (10.3), 67 (11.8), 55 (11.5).

Dibromide 32ns. Reaction of **31ns** (195 mg, 0.54 mmol) and bromine (56 μL, 174 mg, 1.08 mmol) in CH_2Cl_2 (5 mL) following the procedure described for **38na** provided **32ns** (278 mg, 99%), which crystallized from ethyl acetate in hexanes: mp 144–145 °C; ^{1}H NMR δ 0.87 (d, J = 6.4 Hz, 3 H), 0.97 (d, J = 6.4 Hz, 3 H), 1.02 (s, 3 H), 1.14 (s, 3 H), 1.11–1.46 (3 H), 1.47–1.94 (7 H), 1.98–2.22 (3 H), 3.00 (m, H), 3.74 (s, 3 H), 3.82 (s, 3 H); HRMS calcd for $C_{23}H_{32}{}^{79}Br^{81}BrO_3$ 516.0700, found 516.0689; mass spectrum, m/z (relative intensity) 518 (3.1), 516 (6.6, M$^+$), 514 (3.4), 459 (100), 374 (4.0), 365 (95), 363 (5.6), 325 (19.3), 323 (10.3), 137 (3.9), 121 (8.5), 109 (7.0), 95 (8.4), 81 (19.6), 69 (42.5), 67 (16.6), 55 (16.3).

Diester 33ns. This diester was prepared from dibromide **32ns** (260 mg, 0.50 mmol), n-butyllithium (1.4 mL, 2.5 M in hexanes, 3.50 mmol), THF (8 mL), and ethereal CH_2N_2 by following the procedure described for the preparation of diester **33xa**: yield, 175 mg (73% based on dibromide), which was crystallized from ethyl acetate in hexanes; mp 152–153 °C; ^{1}H NMR δ 0.86 (d, J = 6.4 Hz, 3 H), 0.94 (d, J = 6.2 Hz, 3 H), 0.95 (s, 3 H), 0.98 (s, 3 H), 1.04–1.39 (3 H), 1.41–1.82 (7 H), 2.10 (m, 2 H), 2.22 (d, J = 3.6 Hz, H), 2.94 (m, H), 3.74 (s, 3 H), 3.77 (s, 3 H), 3.86 (s, 3 H), 3.87 (s, 3 H); HRMS calcd for $C_{27}H_{38}O_7$ 474.2617, found 474.2613; mass spectrum, m/z (relative intensity) 474 (2.6), 443 (6.4), 418 (25.0), 417 (100), 385 (50.4), 359 (3.0), 335 (5.6), 307 (10.3), 251 (16.3), 137 (3.3), 121 (4.6), 95 (6.1), 81 (14.0), 69 (30.8), 55 (12.6).

Diol 34ns. This diol was prepared from diester **33ns** (152 mg, 0.32 mmol), lithium aluminum hydride (0.79 mL, 1.0 M in ether, 0.79 mmol), and ether (10 mL), by following the procedure as described for the preparation of diol **34na**. It was purified by preparative TLC (50% ethyl acetate in hexanes): yield, 120 mg (91%); ^{1}H NMR δ 0.88 (d, J = 6.6 Hz, 3 H), 0.97 (d, J = 6.4 Hz, 3 H), 1.03 (s, 3 H), 1.09 (s, 3 H), 1.13–1.92 (10 H), 2.01–2.30 (5 H), 2.98 (m, H), 3.74 (s, 3 H), 3.83 (s, 3 H), 4.64 and 4.67 (2 br s, 4 H); HRMS calcd for $C_{25}H_{38}O_5$ 418.2719, found 418.2708; mass spectrum, m/z (relative intensity) 418 (4.5, M$^+$), 362 (21.1), 361 (100), 344 (13.8), 343 (60), 209 (7.9), 121 (8.3), 109 (8.2), 97 (12.7), 95 (15.2), 93 (11.4), 85 (10.8), 83 (20.6), 81 (36.5), 69 (75.2), 55 (37.4).

Dialdehyde 35ns. A mixture of diol **34ns** (96 mg, 0.23 mmol) and pyridinium dichromate (854 mg, 2.27 mmol) in CH_2Cl_2 (6 mL) was stirred at room temperature for 24 h and worked up as described for the preparation of dialdehyde **35xa**. The residue thus obtained was purified by preparative TLC (30% ethyl acetate in hexanes) to give **35ns**: yield, 74 mg (78%); UV λ_{max} (methanol) 261 (ϵ 24350), 283 (15100), 328 nm (3350); CD (methanol) 210 ($\Delta\epsilon$ −0.83), 218 (−0.74), 229 (−1.07), 259 (−1.53), 320 (−0.34), 350 nm (+0.12); $[\alpha]^{20}_D$ −10.47° (c 3.40, $CHCl_3$); ^{1}H NMR δ 0.88 (d, J = 6.6 Hz, 3 H), 0.97 (d, J = 6.4 Hz, 3 H), 1.05 (s, 3 H), 1.11 (s, 3 H), 1.12–1.43 (3 H), 1.48–2.33 (10 H), 2.95 (m, H), 3.84 (s, 3 H), 3.91 (s, 3 H), 10.28 (s, H), 10.37 (s, H); ^{13}C NMR (see Table I); HRMS calcd for $C_{25}H_{34}O_5$ 414.2406, found 414.2415; mass spectrum, m/z (relative intensity) 414 (1.3, M$^+$), 358 (22.3), 357 (100), 327 (3.0), 289 (4.4), 275 (14.3), 263 (10.2), 223 (33.5), 135 (4.4), 121 (6.7), 109 (5.0), 95 (6.4), 93 (7.4), 91 (6.5), 83 (5.4), 81 (11.8), 71 (10.2), 69 (29.5), 67 (15.5), 57 (14.4), 55 (17.9).

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Registry No. **15**, 50896-19-0; **16** (bromide), 106800-22-0; **17**, 79896-06-3; **18**, 114942-85-7; **19**, 621-23-8; **20**, 832-58-6; **21**, 114942-86-8; **22**, 114942-87-9; **23**, 114942-89-1; **24**, 114906-87-5;

exo-**25**, 114906-86-4; *endo*-**25**, 114976-80-6; **28**, 114942-88-0; **30x**, 114942-90-4; **30n**, 115014-28-3; **31xa**, 114906-84-2; **31xs**, 114976-78-2; **31na**, 114976-79-3; **31ns**, 115014-29-4; **32xa**, 114942-91-5; **32xs**, 115014-30-7; **32na**, 115014-34-1; **32ns**, 115014-38-5; **33xa**, 114942-92-6; **33xa** (acid), 114942-95-9; **33xs**, 115014-31-8; **33xs** (acid), 115014-42-1; **33na**, 115014-35-2; **33na** (acid), 115014-43-2; **33ns**, 115014-39-6; **33ns** (acid), 115014-44-3; **34xa**, 114942-93-7; **34xs**, 115014-32-9; **34na**, 115014-36-3; **34ns**, 115014-40-9; **35xa**, 114942-94-8; **35xs**, 115014-33-0; **35na**, 115014-37-4; **35ns**, 115014-41-0; 2,4,6-$(MeO)_3C_6H_2Et$, 67827-55-8; 2,4,6-$(MeO)_3C_6H_2CH{=}CH_2$, 40243-91-2; robustadial A, 88130-99-8; robustadial B, 88197-30-2.

Robustadials. 4. Molecular Mechanics and Nuclear Magnetic Resonance Studies of Conformational and Configurational Equilibria: 3,4-Dihydrospiro[2*H*-1-benzopyran-2,2′-bicyclo[2.2.1]heptanes][1]

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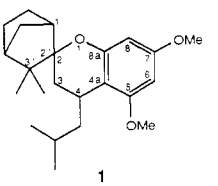
Conformational information obtained by molecular mechanics calculations aided in the interpretation of ^1H NMR experiments employed in the structural characterization of all four possible diastereomeric 3,4-dihydro-4-(2-methylpropyl)spiro[2*H*-1-benzopyran-2,2′-bicyclo[2.2.1]heptanes] **1**. The facile interconversion of energetically similar conformers of endo–trans (NT) and exo–trans (XT) diastereomers of **1** predicted by molecular mechanics calculations was verified by the observation of temperature-dependent changes of chemical shifts in the ^1H NMR spectra of these diastereomers. Molecular mechanics calculations also provided a good prediction of the configurational equilibrium which could be established under basic catalysis between two epimeric 3,4-dihydrospiro[2*H*-1-benzopyran-4-one-2,2′-bicyclo[2.2.1]heptanes] *endo*-**2** and *exo*-**2**.

Modern FT-NMR techniques have been employed to characterize remarkably complex organic structures without the need for X-ray crystal structural analysis. These methods are especially important for noncrystalline substances. Quaternary carbons complicate NMR analysis, especially of stereostructure, by precluding vicinal coupling of hydrogen atoms between regions of the molecule that are separated by the quaternary atom. Nuclear Overhauser effects (NOE) can bridge the gap. Nevertheless, the frequency of erroneous structural conclusions[2] makes it evident that additional approaches are needed for the accurate determination of molecular structures without the use of X-ray analysis. While NMR experiments are useful for unravelling questions of molecular conformation in solution, we considered the possibility that the reverse might also be true. That is, conformational information, available by molecular mechanics calculations, might be useful for interpreting NMR experiments to answer questions about molecular architecture. We now report a molecular mechanics conformational analysis and ^1H NMR studies that led to complete stereostructural characterization of all four possible diastereomeric 3,4-dihydro-4-(2-methylpropyl)spiro[2*H*-1-benzopyran-2,2′-bicyclo[2.2.1]heptanes] **1**, intermediates prepared in conjunction with our studies on the structures of robustadials.[1,3]



1

Results and Discussion

Conformation and Conformational Equilibria of Four Diastereomers. The possible conformational flexibility of the pyran ring in the four diastereomers of **1** complicates quantitative analysis of their ^1H NMR spectra. Thus, interactions between remote portions of such molecules depend on precise spatial relationships. We modeled the conformations of the diastereomers by using molecular mechanics calculations to aid in interpretation of NOE experiments and in analysis of temperature-dependent effects on the chemical shifts of the camphane methyl groups. The MMP2 program[4] was used to model the conformational dynamics of the diastereomers. The stabilities of conformers can be compared by calculation of their steric energies, the direct sum of the force-field increments.[4] These steric energies represent the thermally averaged energies relative to the same molecule but with all bond lengths, bond angles, and torsional angles set to their strainless values and the atoms having van der Waals and electrostatic interactions corresponding to infinite

(1) For previous paper in this series, see: Mazza, S. M.; Lal, K.; Salomon, R. G. *J. Org. Chem.*, second of three papers in this issue.

(2) For examples, see the following. (a) Robustadials. Xu, R.; Snyder, J. K.; Nakanishi, K. *J. Am. Chem. Soc.* **1984**, *106*, 734. Refuted in: Lal, K.; Zarate, E. A.; Youngs, W. J.; Salomon, R. G. *J. Am. Chem. Soc.* **1986**, *108*, 1311. (b) Azadirachtin. Zanno, P. R.; Miura, I.; Nakanishi, K. *J. Am. Chem. Soc.* **1975**, *97*, 1975. Revised by: Kraus, W.; Bokel, M.; Klenk, A.; Pöhnl, H. *Tetrahedron Lett.* **1985**, *26*, 6435 and Broughton, H. B.; Ley, S. V.; Slawin, A. M. Z.; Williams, D. J.; Morgan, E. D. *J. Chem. Soc., Chem. Commun.* **1986**, 46. (c) Stoechospermol. Solimabi, L. F.; Kamat, S. Y.; Paknikar, S. K. *Tetrahedron Lett.* **1980**, *21*, 2249. Revised by: Gerwick, W. H.; Fenical, W.; Sultanbawa, M. U. S. *J. Org. Chem.* **1981**, *46*, 2233. (d) Xylomollin. Kubo, I.; Miura, I.; Nakanishi, K. *J. Am. Chem. Soc.* **1976**, *98*, 6704. Revised by: Nakane, M.; Hutchinson, C. R.; VanEngen, D.; Clardy, J. *J. Am. Chem. Soc.* **1978**, *100*, 7079. (e) Specionin. Conway, C.; Nakanishi, K. *J. Chem. Soc., Chem. Commun.* **1983**, 605. Revised by Van der Eycken, E.; Van der Eycken, J.; Vandewalle, M. *J. Chem. Soc., Chem. Commun.* **1985**, 1719 and Van der Eycken, E.; De Bruyn, A.; Van der Eycken, J.; Callant, P.; Vandewalle, M. *Tetrahedron* **1986**, *42*, 5385.

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