Absolute Stereochemistry of Exogonic Acid

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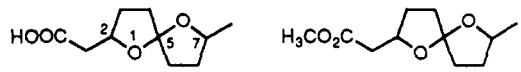
Exogonic acid (2-(carboxymethyl)-7-methyl-1,6-dioxaspiro[4.4]nonane), a resin constituent of the Brazilian tree *Ipomoea operculata* (Martin) is demonstrated to be predominantly the *E,E* and *Z,Z* diastereomers, with the 2*S*,5*S*,7*R* and 2*S*,5*R*,7*R* configurations, respectively. Minor amounts of the 2*R*,5*S*,7*R* *E,Z* and 2*R*,5*R*,7*R* *Z,E* isomers are also present. These conclusions are based on chiral gas chromatographic analyses of suitable derivatives and enantioselective syntheses employing (*S*)-1,2-epoxypropane and (2*S*)-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1,2-epoxybutane as alkylating agents for anions of acetone *N,N*-dimethylhydrazone.

Introduction

Exogonic acid is a significant acidic component (~7%) of the resin of the Brazilian tree *Ipomoea operculata* (Martin),[1,2] and in 1964 Graf and Dahlke[3] assigned structure **1** to this acid, following degradative and some spectroscopic studies. Furthermore, the natural acid was optically active and was considered to be a diastereomeric mixture.[2,3] That **1** is the gross structure of exogonic acid has been confirmed by synthesis[4,5] of the racemate (as the methyl ester **2**), obtained as a mixture of the four possible diastereomers. Our examination of the ^1H and ^{13}C NMR spectra of natural methyl exogonate and of the synthetic diastereomeric mixture led to the suggestion[5] that natural **1** was predominantly the *E,E* and *Z,Z* diastereomers, which differ in configuration at the spiro center only (Scheme I).



1 **2**

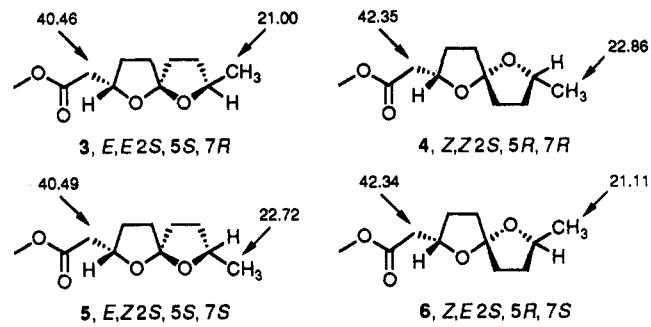
In conjunction with our work on relatively simple insect-derived spiroacetals, we have undertaken studies that demonstrate that natural **1** is indeed predominantly the *E,E* and *Z,Z* diastereomers, with the 2*S*,5*S*,7*R* and 2*S*,5*R*,7*R* configurations, respectively.

Results and Discussion

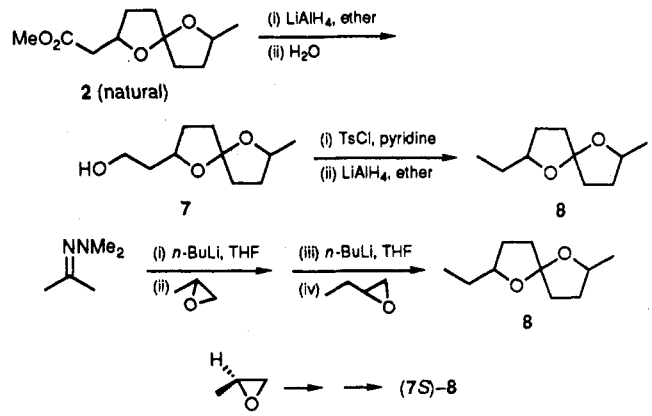
The three chiral centers present in **2** lead to the possibility of the diastereomers **3**–**6**, with one enantiomer of each being indicated in Scheme I.

Exogonic acid was obtained from a sample of the resin in the manner described[2] and a portion of the acid converted to the methyl ester with CH_2N_2. Column or HPLC provided pure ester, as a diastereomeric mixture on the basis of ^1H and ^{13}C NMR analyses[5] and gas chromatography. This material exhibited $[\alpha]^{23}_D$ +7.6° (*c* 5.07, chloroform), whereas Graf and Dahlke[3] report $[\alpha]^{20}_D$ +10.6° (*c*, 7, chloroform).[6] Synthetic[5] racemic **2** is a mixture of the four possible *E,E*, *E,Z*, *Z,E*, and *Z,Z* diastereomers, although the *E,E* ⇄ *Z,Z* and *E,Z* ⇄ *Z,E* interconversions are facile. This fact demonstrates that the free energy differences between these pairs are not large[7] and certainly are much smaller than in the 1,7-dioxaspiro[5.5]undecane system where anomeric effects are so decisive.[8] Thus, in the above synthetic mixture, *E,E* + *Z,Z* should constitute 50% of the diastereomeric mixture. The ^{13}C NMR spectrum of racemic **2** shows readily identifiable signals for H_3CC and CH_2CO_2Me, which are assigned on structures **3**–**6** in Scheme I, on the basis that CH_3 and CH_2CO_2Me in a cis-1,3 relation with oxygen on the tetrahydrofuran ring resonate at lower field than when trans.[9–12] The ^{13}C NMR spectrum of purified natural **2**

Scheme I



Scheme II



(1) Mannich, C.; Schumann, P. *Arch. Pharm. Ber. Dtsch. Pharm. Ges.* **1938**, *276*, 211.
(2) Dahlke, E. Dissertation, Universität Tübingen, 1964.
(3) Graf, E.; Dahlke, E. *Chem. Ber.* **1964**, *97*, 2785.
(4) Jacobsen, R.; Taylor, R. J.; Williams, H. J.; Smith, L. R. *J. Org. Chem.* **1982**, *47*, 3140.
(5) Nishiyama, T.; Woodhall, J. F.; Lawson, E. N.; Kitching, W. *J. Org. Chem.* **1989**, *54*, 2183.
(6) This reported[3] optical rotation pertains to a mixture of Graf and Dahlke's compounds D and E, which they separated from other components, and apparently from at least one other diastereomer, by spinning-band distillation. Thus comparisons of these rotations, in a quantitative sense, are difficult.
(7) Preliminary MM2 calculations by Dr. D. Brecknell on the *E,E* and *Z,Z* diastereomers of 2,7-dimethyl-1,6-dioxaspiro[4.4]nonanes indicate that the free energy difference between them is not likely to exceed 0.5 kcal/mol.
(8) Deslongchamps, P.; Rowan, D. D.; Pothier, N.; Sauve, T.; Saunders, J. K. *Can. J. Chem.* **1981**, *59*, 1106.
(9) Francke, W.; Reith, W.; Sinwell, V. *Chem. Ber.* **1980**, *113*, 2686.
(10) Enders, D.; Dahmen, W.; Dederichs, E.; Gatzweiler, W.; Weuster, P. *Synthesis* **1990**, 1013.
(11) Mori, K.; Ikunaka, M. *Tetrahedron* **1984**, *40*, 3471.
(12) Much of the data in refs 8–10 are summarized in ref 5.

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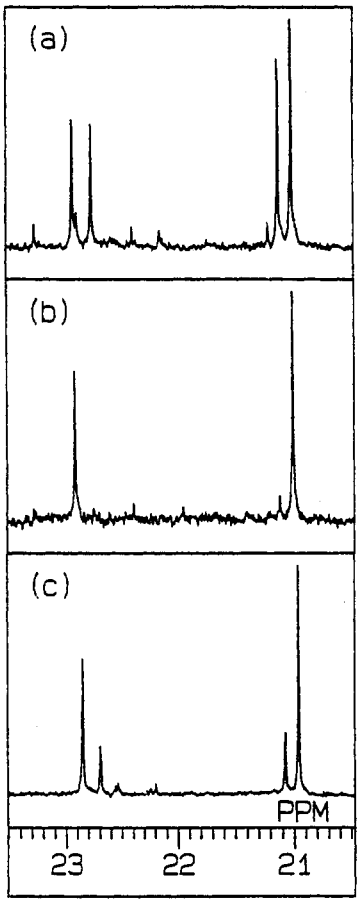
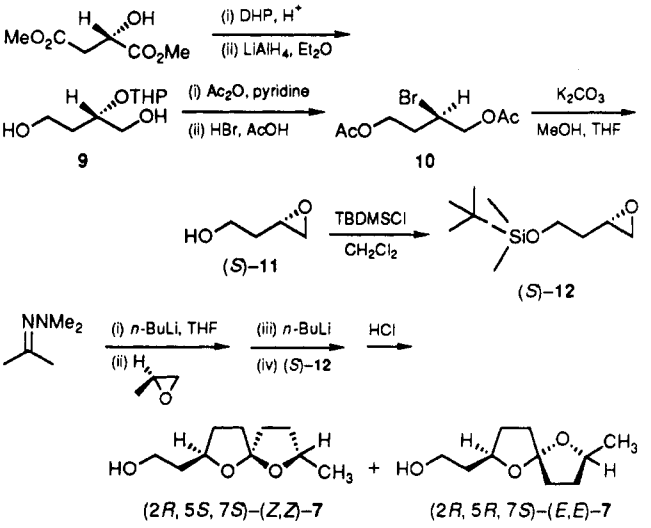


Figure 1. The CCH_3 region of the fully ^1H-decoupled ^{13}C NMR spectrum of (a) racemic methyl exogonate showing four signals corresponding to the *E,E*, *Z,E*, *E,Z*, and *Z,Z* diastereomers, progressing from higher to lower field, (b) the 2*R*,5*R*,7*S* *E,E* and 2*R*,5*S*,7*S* *Z,Z* diastereomers (see Scheme III), and (c) methyl exogonate from natural exogonic acid (treatment with CH_2N_2).

showed again the presence of four diastereomers, but on the basis of the above analysis, the *E,E* and *Z,Z* isomers constitute ca. 80% of the mixture, with *E,Z* and *Z,E* representing the remainder (Figure 1). Other features in the ^{13}C NMR spectrum and the CH_3CH region in the 400-MHz ^1H NMR spectrum are in agreement with this. The predominance of the *E,E* and *Z,Z* diastereomers was confirmed by chiral synthesis (see later) as it is clear (see Scheme I) that these diastereomers have opposite chirality descriptors at $C_{2,7}$ whereas the *E,Z*/*Z,E* pair have like descriptors. Hence enantiocontrolled syntheses (i.e., at C_2 and C_7) may lead to an *E,E*/*Z,Z* mixture or alternatively to an *E,Z*/*Z,E* mixture.

Chiral Gas Chromatographic Examination of 2-Ethyl-7-methyl-1,6-dioxaspiro[4.4]nonane. Schurig has demonstrated[13] that metal chelate phases are efficient for the enantiomeric separation of spiroacetals, particularly those incorporating the 1,6-dioxa[4.4]nonane system.[14] The chiral phase nickel(II) bis(3-heptafluorobutanoyl)-(1*R*)-camphorate, (Ni-*R*-Cam), is particularly useful in this regard,[13,14] but the moderate operating temperature[15] for this phase was not suitable for direct examination of methyl exogonate. Thus our initial examination utilized the more volatile derivative 2-ethyl-7-methyl-1,6-dioxaspiro[4.4]nonane (**8**), derivable from natural **2** via exogonol

Scheme III



(**7**)[3,5] without stereochemical compromise. The standard sequence shown in Scheme II was undertaken to provide **8**, which was separately synthesized as a racemic four-component diastereomeric mixture utilizing the acetone *N,N*-dimethylhydrazone approach of Enders.[10,16] Use of (*S*)-1,2-epoxypropane in this procedure furnished the 7*S* enantiomer of each of the four diastereomers of **8**.

Examination of the racemic mixture of **8**, the 7*S* enantiomers and the naturally derived **8** using the Ni-*R*-Cam column,[15] provided the chromatograms shown in Figure 2. There is a remarkable separation of the eight enantiomers, with the *Z,Z* pair eluting first and the *E,E* pair eluting last, on the basis of results reported by Schurig[13-15] for similar systems, consistent with the anticipated stronger interaction of *E,E* isomers with the metal chelate phase on steric grounds. This order of elution is consistent with our studies[17] of the racemic mixture of 2,7-dimethyl-1,6-dioxaspiro[4.4]nonane, in which the relative proportions are *E,Z* ≡ *Z,E* > *E,E* > *Z,Z*, thus allowing the elution order to be easily established. The assignments shown in Figure 2 were confirmed by the elution orders on a Ni-*S*-Cam column,[18] i.e., using unnatural (*S*)-camphor, and in addition observing column-induced spiro-carbon epimerization which leads to plateaus between the peaks for epimerizing species. Details of this phenomenon are presented elsewhere.[15] Thus, the sample of **8** derived from natural exogonic acid consists predominantly of the 2*R*,5*S*,7*R* *E,E* and 2*R*,5*R*,7*R* *Z,Z* stereoisomers (configurational difference at the spiro carbon), with low levels of the 2*S*,5*S*,7*R* *Z,E* and 2*S*,5*R*,7*R* *E,Z* isomers. Consequently, because of the descriptor change when CH_2CH_3 becomes CH_2COOR, natural exogonic acid is then predominantly **3** (2*S*,5*S*,7*R*) and **4** (2*S*,5*R*,7*R*) with the minor stereoisomers being 2*R*,5*S*,7*R* (mirror image of **6**) and 2*R*,5*R*,7*R* (mirror image of **5**) in Scheme I. It is of interest to note that the minor presence of the *E,Z* and *Z,E* pair is due to some "chiral leakage" at C-2 and not at C-7.

To provide further insight into these features, an enantioselective synthesis of exogonol (**7**) and methyl exogonate (**2**) was undertaken utilizing (*S*)-1,2-epoxypropane and (2*S*)-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1,2-epoxybutane (**12**) as alkylating agents for the anions generated from acetone *N,N*-dimethylhydrazone (Scheme III).

(13) For example, see: Weber, R.; Schurig, V. *Naturwissenschaften* **1984**, *71*, 408.
(14) Koppenhoefer, B.; Hintzer, K.; Weber, R.; Schurig, V. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 471.
(15) Schurig, V. *J. Chromatogr.* **1988**, *441*, 135.
(16) Enders, D.; Gatzweiler, W.; Dederichs, E. *Tetrahedron* **1990**, *46*, 4757.
(17) Lewis, J. A.; Perkins, M. V. Unpublished results.
(18) Prof. Dr. V. Schurig, private communication.

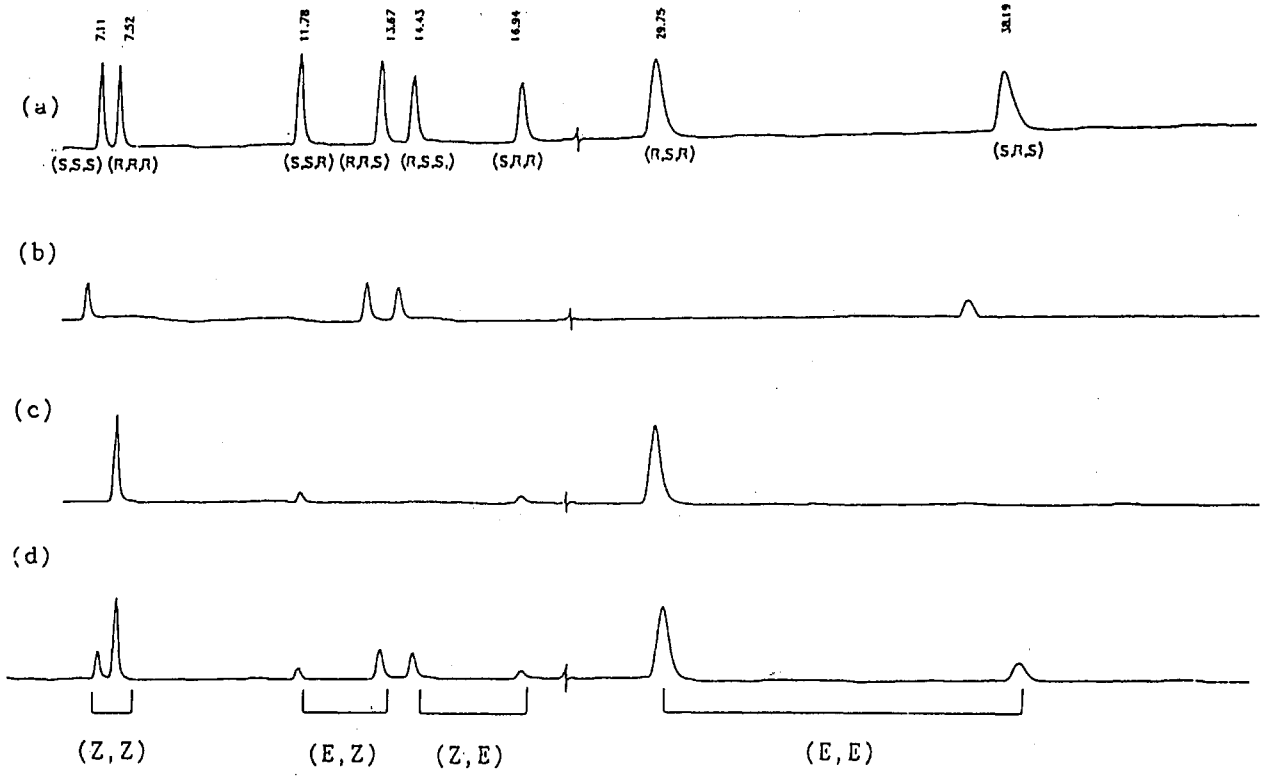


Figure 2. (a) Enantiomer resolution of racemic 2-ethyl-7-methyl-1,6-dioxaspiro[4.4]nonane. The absolute configurations and retention times are indicated. (The enantiomeric sets for the four diastereomers (i.e., *Z,Z*, *E,Z*, *Z,E*, and *E,E*) are indicated below trace (d)). (b) The 7*S* enantiomers of the four diastereomers. (c) Sample derived by reduction of natural exogonic acid (see Scheme II). (d) Mixture of samples b and c. Conditions for traces a–d: 25 M × 0.25 mm fused silica column coated with Ni-*R*-Cam in OV-1, 0.25 μm. Column temperature, 90 °C isothermal. Carrier gas, 0.95 bar He.

(*S*)-1,2-Epoxybutan-4-ol (11) was obtained from (*S*)-dimethyl malate by a slight adaptation of procedures described by Mori[11] and Golding,[19] and exhibited $[\alpha]^{21}_D$ −18.97° (*c* 5, acetone), which may be compared with that reported by Mori[11] ($[\alpha]_D$ −30.6° (*c* 5.10, CH_2Cl_2) and measurements by Boger and Panek[20] for the enantiomer ($[\alpha]^{23}_D$ +16.64° (*c* 5.0, acetone) and +23.42° (*c* 5.0, $CHCl_3$)). The sequence[21] to optically active exogonol (7) is shown in Scheme III. (Note the descriptor change in the formation of (2*R*)-7 from (*S*)-**12**.)

Thus use of both *S* epoxides can lead only to the *E,E* and *Z,Z* diastereomers of exogonol (7) with the 2*R*,5*R*,7*S* and 2*R*,5*S*,7*S* configurations, respectively. This material, as the mixture, exhibited ^1H and ^{13}C NMR spectra consisting of two signal sets as expected[5] for two diastereomers of exogonol. This synthetic sample had $[\alpha]^{22}_D$ −19° (*c* 1.6, $CHCl_3$), which is comparable with, but opposite in sign ($[\alpha]^{20}_D$ +16.17° (*c* 1.67, $CHCl_3$)) to, the rotation for a sample obtained from natural exogonic acid, confirming the enantiomeric relationship between the samples. In addition, oxidation of this exogonol and methylation provided methyl exogonate with $[\alpha]^{20}_D$ −4.3° (*c* 5.50, $CHCl_3$), whereas the naturally based methyl exogonate exhibited $[\alpha]^{20}_D$ +7.6° (*c* 5.07, $CHCl_3$). As indicated above, this chiral synthesis can provide the *E,E* and *Z,Z* diastereomers only and the ^{13}C and ^1H NMR spectra of these samples of methyl exogonate and exogonol coincide with those of the predominating isomers of naturally derived methyl exogonate and exogonol, confirming our initial suggestion[5] on the diastereomeric composition of the natural material.

With the availability of the synthetic optically active *E,E* and *Z,Z* exogonols, along with exogonol derived by reduction of natural exogonic acid, chiral gas chromatographic examinations of the trifluoroacetates were conducted. The enantiomers of racemic exogonol (as trifluoroacetate) were not as well separated as those of 2-ethyl-7-methyl-1,6-dioxaspiro[4.4]nonane (the latter shown in Figure 2), and part of the explanation may be associated with coordination to the ester function, somewhat removed from the chiral centers. Comparisons of these chromatograms, along the lines for the data described in Figure 1, demonstrated that the naturally derived exogonols were predominantly the *E,E* 2*S*,5*S*,7*R* and *Z,Z* 2*S*,5*R*,7*R* isomers, and as reduction of naturally derived methyl exogonate would be anticipated to cause no stereochemical compromise at the formal secondary alcohol centers, these descriptors define the stereochemistry of natural exogonic acid. This is in harmony with the analysis (from Figure 2) of the 2-ethyl-7-methyl-1,6-dioxaspiro[4.4]nonanes. We note that our procedure for isolation of exogonic acid from the resin involves an acidification step and this would induce epimerization (*E,E* ⇄ *Z,Z* for example) at the spiro center. However, because of the acidic nature of the resin,[1-3] which contains a number of other alkanoic acids, it is likely that epimeric equilibrium exists in the resin.[22]

(19) Golding, B. T.; Hall, D. R.; Sakrikar, S. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1214.
(20) Boger, D. L.; Panek, J. S. *J. Org. Chem.* **1981**, *40*, 1208.
(21) Consideration of our optical rotation indicates probable exclusive inversion of configuration in the **9** → **10** conversion. In this regard, in addition to refs 10 and 18, see: Wagner, A.; Heitz, M. P.; Mioskonski, C. *Tetrahedron Lett.* **1989**, *30*, 557.
(22) A referee has commented that treatment of the resin with a 2.5 M NaOH solution in the isolation procedure may induce epimerization at C-2 by β-elimination (exogonic acid is a β-alkoxy acid) and reclosure on subsequent acid treatment. Thus chemical epimerization at C-2 could explain the presence of minor levels of 2*R* isomers. However, treatment of natural exogonic acid with 2.5 M NaOD in D_2O for 24 h followed by neutralization with CD_3COOD–CF_3COOD, etc; resulted in no deuterium incorporation at C-10 (i.e., α to COOH). Alternatively, nonstereospecificity in reduction of a (presumed) β-keto acid precursor may be involved.

A number of relatively simple spiroketals have been isolated from plant sources, particularly from *Artemisia* and *Asteracea*,[23] but these compounds generally contain acetylene units in the side chain, often as the enediyne moiety. Compounds closely resembling exogonic acid have not, to our knowledge, been isolated from the plant kingdom and thus comparisons of stereochemistry are not available.

Experimental Section

Isolation of Exogonic Acid (1) and Characterization of Methyl Exogonate (2). The resin (100 g) from *Ipomoea operculata* (Martin) was added to an aqueous sodium hydroxide solution (500 mL of 10% solution) and the suspension was stirred vigorously at room temperature for 24 h. During this time, the resin dissolved to provide a dark brown solution which was acidified with 25% aqueous sulfuric acid, gravity filtered, and extracted with ether (2 × 100 mL; 10 × 50 mL). The combined ether extracts were dried (Na_2SO_4) and evaporated to provide a dark brown viscous oil which was dissolved in aqueous sodium hydroxide (50 mL of 10% solution) and then washed with ether (3 × 20 mL). The separated water layer was acidified to pH 3 (with aqueous H_2SO_4) and the oil was extracted well with ether as before. The combined ether extracts were dried (Na_2SO_4) and evaporated under reduced pressure to provide a brown oil which was fractionally distilled, yielding a very viscous pale yellow oil (5.03 g, bp 110 °C (0.5 mm); lit.[3] bp 172–175 °C (12 mm)). GC analysis indicated that this oil was predominantly (80%) diastereomers of exogonic acid, with the major contaminant (~7%) being of shorter retention time, and subsequently shown to be 4-oxooctanoic acid, as deduced by Graf and Dahlke.[2,3] The IR spectrum closely resembled the published spectrum,[3] with prominent peaks at 3500–3000 (s br, ν_{OH}), 2950 (s, ν_{CH}), 1725 (vs, $\nu_{C=O}$), and bands for the ether linkages between 1050 and 1150 cm^{-1}. The ^{13}C NMR spectrum of this unpurified sample exhibited two sets of signals for two diastereomers of exogonic acid. ^{13}C NMR: ($CDCl_3$) δ 20.94, 22.76 (CH_3); 30.03, 30.47, 31.93, 32.40, 34.93, 35.30, 35.54, 35.94, 40.40, 42.16 (CH_2); 73.86, 74.31, 75.24, 76.30 (C—O); 114.96, 115.11 (spiro C); 176.16, 176.51 (C=O). Signals corresponding to minor isomers were also present, with those at 21.03 and 22.61 (CH_3) being identified. In the 400-MHz ^1H NMR spectrum, the *CH*$_3$CH doublets appeared at δ 1.13 and 1.20, but there was evidence of the minor isomers. There was close agreement in general features with the published[2,3] low-field spectrum of the methyl ester. MS (one diastereomer): *m/z* (rel intensity) (200, M^+, 0), 145 (14.5), 141 (9.8), 127 (16.2), 112 (9.6), 101 (45.9), 100 (11.9), 99 (9.2), 98 (10.2), 97 (11.1), 96 (17.6), 95 (18.9), 85 (49.6), 83 (30.1), 82 (19.5), 81 (25.2), 71 (14.8), 70 (11.1), 60 (23.0), 59 (32.2), 57 (43), 56 (65.2), 55 (100).

Methyl Exogonate (2) from Natural Source. Crude exogonic acid (~2 g) was dissolved in ether and treated with diazomethane. The methyl ester was chromatographed on silica gel (230–400 mesh), eluting with hexane–CH_2Cl_2 (1:1). The recovered, pure methyl exogonate was two components by capillary GC examination, but ^{13}C NMR examination showed the presence of two major and two minor components. $[\alpha]^{20}_D$ +7.6° (*c* 10, $CHCl_3$). IR (neat, cm^{-1}): 2975 (s), 2950 (s), 2870 (m), 1740 (vs), 1440 (m), 1425 (m), 1340 (m), 1325 (m), 1290 (m), 1260 (m), 1175 (s, br), 1060 (s, br), 875 (m). This spectrum matched that reported by Dahlke.[2] ^{13}C NMR ($CDCl_3$): *E,E* diastereomer δ 20.92, 29.99, 31.95, 34.96, 35.28, 40.36, 51.40, 73.90, 74.07, 114.86, 171.34; *Z,Z* diastereomer δ 22.83, 30.49, 32.40, 35.58, 35.94, 42.27, 51.32, 75.33, 75.98, 114.64, 171.84. Other signals associated with the minor *E,Z* and *Z,E* isomer were also present and could be assigned as follows: *Z,E* diastereomer δ 21.03, 30.51, 31.71, 34.50, 35.82, 42.29, 73.68, 75.28, 114.80, with OCH_3 and C=O not resolved. *E,Z* diastereomer: δ 22.67, 29.72, 34.43, 36.50, 40.39, 73.74, 75.86, with OCH_3, spiro C and C=O not resolved. These assignments were facilitated by the spectrum of the racemic synthetic compound[5] which contains all four diastereomers in comparable amounts and by the spectrum of the synthesized optically active sample which is a mixture of the *E,E* and *Z,Z* diastereomers only. (See later in Experimental Section.) ^1H NMR ($CDCl_3$): δ 1.05–1.13 (CC*H*$_3$ doublets), 1.25–2.15 (series of multiplets for ring CH_2), 2.25–2.65 (AB parts of ABX patterns for *CH*$_2$CO$_2$R), 3.55 (3 H, s, OCH_3), 3.92–4.1 (CH_3CH), 4.23–4.35 (RO_2CCH_2CH). The most diagnostic features of the spectrum are the *CH*$_3$CH doublets (J = 6.10 Hz) assigned as follows: δ 1.05 (*Z,E*); 1.06 (*E,E*); 1.125 (*E,Z*); 1.13 (*Z,Z*). ^{13}C–^1H correlated spectroscopy has permitted almost complete assignment of the ^1H and ^{13}C NMR spectra of the *E,E* and *Z,Z* isomers.

Reduction of Natural Exogonic Acid (2) to 2-Ethyl-7-methyl-1,6-dioxaspiro[4.4]nonane (8). To a suspension of lithium aluminum hydride (0.4 g, 10 mmol) in dry ether (10 mL) at 0 °C was added natural exogonic acid (~2 g, 10 mmol) in ether (6 mL). After refluxing for 2 h, the mixture was cooled to 0 °C and water (10 mL) and then cold 10% H_2SO_4 were added dropwise. The organic layer was separated and the aqueous phase was thoroughly extracted with ether. The combined ether layers were washed with H_2O and saturated aqueous Na_2CO_3 and then dried ($MgSO_4$). Removal of solvent under reduced pressure provided a slightly orange oil (0.52 g, 30%) which was predominantly exogonol (7) by GC examination. IR (neat, cm^{-1}): 3400 (s, br), 3000 (s), 2930 (s), 2890 (m), 1450 (m), 1060 (s, br), 850 (m, br). This spectrum matched that reported.[2] The ^1H NMR spectrum was in agreement with that reported for racemic exogonol[5] and along with the ^{13}C NMR spectrum demonstrated the presence of two predominating isomers of exogonol, which were the *E,E* and *Z,Z* diastereomers because of the chemical shift correspondence with authentic *E,E* and *Z,Z* diastereomers. ^{13}C NMR ($CDCl_3$): *E,E* 20.93, 30.46, 31.92, 35.08, 35.58, 37.51, 60.85, 74.22, 77.44, 114.97; *Z,Z* 22.30, 30.34, 32.63, 35.90, 36.40, 37.86, 60.44, 76.24, 78.96, 114.82. Minor signals associated with the *E,Z* and *Z,E* diastereomers were also present. **2-[2′-(Tosyloxy)-ethyl]-7-methyl-1,6-dioxaspiro[4.4]nonane** was prepared from the exogonol and tosyl chloride in pyridine (or triethylamine) in the usual way and was isolated as an oil, part of which was purified by chromatography on silica (TLC eluting with CH_2Cl_2). IR (neat, cm^{-1}): ν_{max} 2968 (s), 2867 (m), 1600 (m), 1489 (w), 1455 (m), 1360 (s), 1189 (s), 1172 (s), 1094 (m). MS: *m/z* (rel intensity) (304, M^+, 0), 141 (100), 123 (20), 113 (50), 112 (38), 111 (23), 99 (50), 98 (52), 95 (30), 91 (75), 85 (97), 83 (24), 81 (24), 71 (23), 68 (80), 67 (34), 65 (31), 57 (45), 56 (47), 55 (70), 43 (42), 41 (34), 39 (23). ^1H NMR ($CDCl_3$): δ 1.16, 1.13 (2 × d, J = 6 Hz, 2 × 3 H, 2 × *CH*$_3$CHO), 1.21–2.14 (m, 10 H, 5 × CH_2), 2.42 (s, 3 H, CH_3), 3.99–4.15 (m, 4 H, 2 × CHO, CH_2O), 7.31 and 7.76 (2 × d, J = 8 Hz, 2 × 2 H, aromatic H). ^{13}C NMR ($CDCl_3$): δ 21.58 (aryl CH_3) 21.04, 21.17, 22.79, 22.84 (*CH*$_3$CHO), 30.25, 30.50, 30.55, 30.87, 31.77, 32.04, 32.50, 32.53 (C-3, C-8), 34.73, 34.86, 34.91, 34.98, 35.16, 35.45, 35.80, 35.98 (C-4, C-9), 36.30, 36.37, 36.46, 36.62 (C-10), 68.00, 68.37 (C-11), 73.83, 74.05, 74.10, 75.34, 75.35, 75.88, 75.98 (C-2, C-7), 114.56, 114.64, 114.72, 114.80 (C-5), 127.89, 127.91, 129.75, 129.76, 133.19, 144.52, 144.60 (aromatic C). (The ^1H and ^{13}C NMR data pertain to the major diastereomers.) This tosylate was then directly reduced.

$LiAlH_4$ (30 mg, 0.76 mmol) was added to the crude tosylate (0.26 g) in dry ether (5 mL) and after 12 h an additional 10 mg of $LiAlH_4$ was added. After 24 h, the mixture was cooled (ice bath) and the excess hydride destroyed by the addition of water (0.5 mL), 15% KOH (0.5 mL), and water (1 mL). After stirring for 1 h, the mixture was filtered and the filter cake washed with additional ether. The ether layer was separated and then combined with further ether extracts of the aqueous layer. The ether fraction was washed with saturated NaCl solution, dried ($MgSO_4$), and evaporated to provide an oil which (by VPC) contained small amounts of unreacted tosylate and exogonol, together with (at least) two isomers of a more volatile compound. This oil was chromatographed on silica gel (230–400 mesh), eluting with pentane–CH_2Cl_2 (2:1) to give a yellowish oil containing at least two isomers of the desired **2-ethyl-7-methyl-1,6-dioxaspiro-[4.4]nonane (8).** This material was purified by preparative gas chromatography and exhibited GC-MS and IR behavior on the Ni-*R*-Cam column (see Figure 2) identical with that of authentic synthetic racemic 8 described below. Thus 8 as derived from natural exogonic acid (2) was predominantly the 2*R*,5*S*,7*R* *E,E* and 2*R*,5*R*,7*R* *Z,Z* stereoisomers, with low levels of the 2*S*,5*S*,7*R*

(23) (a) See, for example: Bohlmann, F.; Burkhardt, T.; Zdero, C. *Naturally Occurring Acetylenes*; Academic Press: London, 1973; p 430. (b) For a brief survey of naturally occurring spiroketals, see: Perron, F.; Albizati, K. F. *Chem. Rev.* **1989**, *89*, 1617.

Z,E and 2*S*,5*R*,7*R E,Z* isomers.

Synthesis of Racemic 2-Ethyl-7-methyl-1,6-dioxaspiro-[4.4]nonane and the 7*S* Enantiomers as the *E,E*, *Z,Z*, *E,Z*, and *Z,E* Diastereomers. In the manner described in detail by Enders and Dederichs[10] the anion from acetone *N,N*-dimethylhydrazone was alkylated with 1,2-epoxybutane. Re-formation of the anion at the methyl group was followed by alkylation with 1,2-epoxypropane and subsequent treatment with acetic acid. Cyclization to the spiroketal[24] was effected by refluxing the THF solution to which had been added Amberlite IR-120 resin and anhydrous $MgSO_4$.[16] Evaporation of the filtered solution provided an oil which was dissolved in CH_2Cl_2 and washed with saturated Na_2CO_3 and H_2O. The organic phase was separated, dried ($MgSO_4$), and concentrated under reduced pressure to provide an oil in about 50% yield. This oil was shown by GC-MS to consist mainly of diastereomers of the title spiroketal and final purification was effected by preparative gas chromatography. MS: *m/z* (rel intensity) (170, M^+, 1.2), 153 (5.3), 142 (6.8), 141 (86.5), 123 (11.9), 115 (25.4), 112 (21.2), 101 (54.4), 97 (38.8), 95 (14.8), 85 (100), 83 (25.8), 81 (13.9), 70 (14.5), 69 (30.8), 57 (53.3), 56 (48.4), 55 (61.6). The low-resolution spectra of other isomers were very similar. Exact mass: 170.1305 (calcd for $C_{10}H_{18}O_2$, 170.1307); 171.1392 (calcd for (M + 1), $C_{10}H_{19}O_2$, 171.1384). IR (neat, cm^{-1}): 2966 (s), 2876 (s) 1744 (w), 1461 (m), 1379 (w), 1341 (w), 1074 (m), 1013 (m), 895 (m), 861 (m). ^1H NMR ($CDCl_3$): δ 0.88, 0.87 (2 × t, *J* = 7.4 Hz, 2 × 6 H, 2 × CH_2CH_3), 1.17, 1.186, 1.260, 1.264 (4 × d, *J* = 6.1 Hz, 4 × 3 H, 4 × $CHCH_3$), 1.39–2.09 (m, 5 × 10 H, 5 × $-CH_2-$), 3.52–3.55, 3.86–3.88, 3.96–4.09, 4.10–4.24 (m, 4 × 2 H), $-CHO$). ^{13}C NMR ($CDCl_3$): δ 9.84, 9.90, 10.15 (CH_3CH_2), 21.14, 21.29, 22.79, 22.95 (CH_3CH), 28.40, 28.47, 29.44, 29.68, 30.10, 30.29, 30.33, 31.89, 32.23, 32.63, 32.64, 35.17, 35.18, 35.63, 35.66, 36.15, 36.39, 36.50, 36.67, (C-3, C-4, C-8, C-9, C-10), 73.72, 74.02, 75.72, 75.78, 79.20, 79.37, 81.24, 81.29 (C-2, C-7), 114.29, 114.48, 114.54, 114.78 (C-5). Use of (*S*)-1,2-epoxypropane in the above sequence provided the 7*S* enantiomers of the four diastereomers of this system, and their analysis on the Ni-*R*-Cam column is shown in Figure 2.

(*S*)-1,2-Epoxy-4-butanol ((*S*)-11). Dimethyl (*S*)-(−)malate was prepared as described[20] and had $[\alpha]^{25}_D$ −8.0° (neat) (lit.[20] $[\alpha]^{25}_D$ −7.57°). (*S*)-Dimethyl 2-*O*-(2-tetrahydropyranyl)malate (as a diastereomeric mixture) was acquired from the above ester by treatment with dihydropyran and pyridinium *p*-toluenesulfonate in CH_2Cl_2 in the normal way. IR (neat, cm^{-1}): ν_{max} 2942 (s), 2856 (m), 1744 (s), 1434 (s), 1279 (s), 1194 (s), 1169 (s), 1125 (s), 1071 (s), 1034 (s), 975 (s). ^1H NMR ($CDCl_3$): δ 4.65 (m, 1 H), 4.45 (m, 1 H), 3.65 (s, 3 H), 3.55 (s, 3 H), 2.75 (m, 2 H), 1.55 (br m, 8 H). ^{13}C NMR ($CDCl_3$): δ 171.49, 170.10, 99.22, 96.96, 72.90, 70.11, 61.95, 61.57, 51.74, 51.44, 37.50, 37.10, 29.93, 29.74, 24.97, 24.88, 18.62, 18.31. These data compare favorably with those reported.[20] **(*S*)-2-(2′-Tetrahydropyranyloxy)-1,4-butanediol (9).** Reduction of the above THP-protected ester with $LiAlH_4$ in ether was conducted as reported[20,25] to provide the diol **9** in 55% yield after water-base quenching and extraction with ether. IR (neat, cm^{-1}): 3391 (br s), 2942 (s), 2867 (m), 1440 (w), 1381 (w), 1349 (w), 1109 (w), 1071 (s), 1023 (s), 980 (m), 804 (w). ^1H NMR ($CDCl_3$): δ 4.61 (m, 1 H), 3.27–4.25 (m, 9 H), 1.3–1.9 (m, 8 H). ^{13}C NMR ($CDCl_3$): δ 100.90, 99.74, 79.98, 75.29, 65.68, 64.51, 64.43, 58.68, 34.32, 34.06, 31.14, 31.01, 24.95, 24.81, 20.69. These spectral data are in excellent agreement with those reported.[25] The diol **9** (15 g, 79 mmol) was dissolved in dry pyridine (20 mL) and dry CH_2Cl_2 (50 mL), and to this stirred cooled solution (0 °C) were added acetic anhydridfe (17 mL) and DMAP (20 mg). After 12 h the reaction mixture was poured onto crushed ice (20 g) and concentrated HCl (5 mL). The organic layer was separated and the aqueous phase was extracted well with CH_2Cl_2. The combined organic fractions were washed with saturated aqueous $CuSO_4$ (until the organic layer was clear) and then with H_2O, saturated $NaHCO_3$, and brine. The dried ($MgSO_4$) organic phase was concentrated in vacuo to provide the diacetate of **9** (16.6 g, 77%) which was not purified. A solution of HBr in HOAc (45%, 70 mL) was added dropwise over 10 min to the cooled and stirred diacetate (16.6 g, 60 mmol). After addition was complete, stirring was continued for 1 h at room temperature and then the mixture was poured into ice–H_2O, neutralized with Na_2CO_3, and extracted with ether. The ether extract was dried ($MgSO_4$), concentrated in vacuo, and distilled (118–120 °C, 1 mm) to provide **(*R*)-2-bromo-1,4-butanediol 1,4-diacetate (10)** (13.45 g, 88%), $[\alpha]^{20}_D$ −25.9° (*c* 3.43, $CHCl_3$). IR (neat, cm^{-1}): 2966 (w), 1739 (s), 1422 (m), 1366 (s), 1233 (s), 1044 (s). ^1H NMR ($CDCl_3$): δ 1.96–2.02 (m, 8 H, $-CH_2-$, 2 × CH_3), 3.36–3.50 (m, 2 H, OCH_2CH), 4.02–4.06 (m, 2 H, OCH_2), 4.99–5.04 (m, 1 H, CHBr). ^{13}C NMR ($CDCl_3$): δ 20.66, 20.69, 31.52, 33.69, 60.01, 69.25, 170.00, 170.62. This bromo diacetate **10** was then converted to the title compound **(*S*)-1,2-epoxy-4-butanol (11)** by a reported procedure[11] except that (*S*)-1-bromo-2,4-butanediol 2,4-diacetate was employed previously.[11] Thus **10** (13.4 g, 53 mmol) was added to a suspension of K_2CO_3 (10 g) in methanol (30 mL) and THF (20 mL) and the mixture was stirred vigorously overnight. After filtration and concentration in vacuo the residue was chromatographed over SiO_2, eluting with hexane/ether (1:4). Epoxide **11** was obtained as a pale yellow oil (4 g, 85%) (24% from (*S*)-malic acid), $[\alpha]^{25}_D$ −18.97° (*c* 5.1, acetone) (lit.[20] $[\alpha]^{23}_D$ +16.64° (*c* 5.0, acetone) and +23.42° (*c* 5.0, $CHCl_3$) for enantiomer; lit.[11] $[\alpha]^{24}_D$ −30.6° (*c* 5.10, CH_2Cl_2)). ^1H NMR ($CDCl_3$): δ 1.47–1.55 (m, 1 H), 1.69–1.77 (m, 1 H), 2.41 (dd, *J* = 2.7, 4.9 Hz, 1 H), 2.63 (t, *J* = 4.5 Hz, 1 H), 2.89–2.93 (m, 1 H), 3.58 (t, *J* = 6 Hz, 2 H). ^{13}C NMR: δ 34.74, 46.61, 50.26, 59.38.

(2*S*)-4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-1,2-epoxybutane (12) was obtained from epoxy alcohol (*S*)-**11** by the procedure of Mori,[11] and distillation (64–67 °C, 5 mm) provided (*S*)-**12** in 81% yield. ^1H NMR ($CDCl_3$): δ 0.02 (s, 6 H), 0.86 (s, 9 H), 1.60–1.82 (m, 2 H), 2.44–2.50 (m, 1 H), 2.71–2.77 (m, 1 H), 2.95–3.04 (m, 1 H), 3.69–3.79 (m, 2 H). ^{13}C NMR ($CDCl_3$): δ 5.43, 18.23, 25.85, 35.86, 47.14, 50.03, 59.98.

(2*R*,5*R*,7*S*)- and (2*R*,5*S*,7*S*)-2-(2′-Hydroxyethyl)-7-methyl-1,6-dioxaspiro[4.4]nonane ((*E,E*)-7 and (*Z,Z*)-7) (Exogonols). Alkylations of anions derived from acetone *N,N*-dimethylhydrazone with (*S*)-1,2-epoxypropane and (*S*)-**12** were conducted in the prescribed manner[10,24] to produce the *tert*-butyldimethylsilyl ethers of the above exogonols. A solution of the crude ethers (3.2 g) in acetic acid (20 mL), water (20 mL), and THF (20 mL)[26] was stirred overnight at 20 °C and then poured into ice–H_2O and extracted with ether. The ether solution was washed with saturated $NaHCO_3$, H_2O, and saturated NaCl solution and dried ($MgSO_4$). After concentration in vacuo, the oil was purified by HPLC (ether acetate/hexane, 1:1) to provide the 2*R*,5*R*,7*S* and 2*R*,5*S*,7*S* stereoisomers of exogonol (**7**) (2.1 g, 47%). The ^1H and ^{13}C NMR and low resolution mass spectra were concordant with those previously reported.[5] This synthesis provides only one enantiomer of the *E,E* and *Z,Z* diastereomers, and "chiral" analysis of the trifluoroacetates showed an ee of 95%, $[\alpha]^{20}_D$ −19° (*c* 11.6, $CHCl_3$). Exogonol obtained by reduction of the methyl ester of natural exogonic acid (**2**) exhibited $[\alpha]^{20}_D$ +16.17° (*c* 1.67, $CHCl_3$). ^{13}C NMR ($CDCl_3$): 2*R*,5*R*,7*S* δ 20.89, 30.39, 31.86, 35.04, 35.52, 37.41, 60.68, 74.19, 77.25, 114.97; 2*R*,5*S*,7*S* δ 22.20, 30.28, 32.54, 35.83, 36.29, 37.81, 60.49, 76.20, 78.76, 114.83.

Trifluoroacetate of Exogonol. Racemic exogonol was treated with trifluoroacetic anhydride in CH_2Cl_2 for 1 h, after which the volatiles were evaporated to provide the ester, which was characterized by its mass spectrum, IR, and NMR spectra. MS: *m/z* (rel intensity) (282, M^+, 1), (267, 10.9), 238 (19), 227 (19.6), 182 (13.1), 141 (64.6), 113 (33.2), 112 (30.3), 111 (15.1), 101 (48.9), 99 (12.9), 97 (16.6), 95 (18.2), 93 (11.9), 85 (100), 83 (41.9). IR (neat, cm^{-1}): 2976 (m), 1787 (s), 1570 (w), 1458 (w), 1381 (w), 1356 (m), 1221 (s), 1166 (s). ^1H NMR ($CDCl_3$): δ 1.168, 1.193, 1.248, 1.259 (3 H, d, *J* = 6.1 Hz, 4 CH_3), 1.3–2.25 (m, 5 × CH_2), 4.05–4.55 (m, 5 H, CHO). ^{13}C NMR ($CDCl_3$): δ 158.48 (q, *J* = 41.5 Hz, *C*-(O)CF_3), 114.59 (q, *J* = 285 Hz, CF_3), 115.70, 115.63, 115.54, 115.48 (spiro C), 76.88, 76.78, 76.42, 76.33, 75.10, 75.00, 74.87, 74.78, 65.68, 65.48 (C–O), 36.50, 36.11, 35.97, 35.65, 35.45, 35.27, 35.24, 35.21, 34.75, 34.56, 34.00, 33.55, 32.29, 32.23, 31.80, 31.51, 30.53, 30.46, 30.19, 29.93, 22.39, 22.14, 20.91, 20.81.

Oxidation of the (2*R*,5*R*,7*S*)- and (2*R*,5*S*,7*S*)-exogonols (7) to exogonic acid was conducted as previously reported[5] for

(24) For a detailed description of this route to 2,7-dimethyl-1,6-dioxaspiro[4.4]-nonane, see: Perkins, M. V.; Fletcher, M. T.; Kitching, W.; Drew, R. A. I.; Moore, C. J. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1111.

(25) Seuring, B.; Seebach, D. *Helv. Chim. Acta* **1977**, *60*, 1175.

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the racemic material, except that the intermediate aldehyde in the sequence (exogonal) was oxidized to the acid by a different procedure.[27] Methylation (CH_2N_2) then provided methyl exogonate as the 2*R*,5*R*,7*S* *E*,*E* and 2*R*,5*S*,7*S* *Z*,*Z* stereoisomers, $[\alpha]^{20}_D$ −4.3° (*c* 5.05, $CHCl_3$). The methyl ester of purified natural exogonic acid exhibited $[\alpha]^{20}_D$ +7.6°. The ^1H and ^{13}C NMR spectra and GC-MS data of this synthesized methyl exogonate were identical with those previously reported.[5] ^{13}C NMR ($CDCl_3$): 2*R*,5*R*,7*S* *E*,*E* δ 21.01, 30.10, 32.04, 35.39, 35.07, 40.47, 51.52, 74.01, 74.19, 114.97, 171.46; 2*R*,5*S*,7*S* *Z*,*Z* 22.91, 30.58, 32.48, 35.68, 36.05, 42.56, 51.44, 75.43, 76.10, 114.74, 171.97.

(27) Shamma, M.; Rodriguez, H. R. *Tetrahedron* **1968**, *24*, 6583.

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Supplementary Material Available: ^{13}C and ^1H NMR spectra of the synthetic (2*R*,5*R*,7*S*)-(*E*,*E*)- and (2*R*,5*S*,7*S*)-(*Z*,*Z*)-methyl exogonates (i.e., mirror images of **3** and **4**) and the ^{13}C NMR spectrum of natural **2** (4 pages). Ordering information is given on any current masthead page.

Cascade Polymers:[1] Synthesis and Characterization of Four-Directional Spherical Dendritic Macromolecules Based on Adamantane

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The syntheses and spectral characteristics of four-directional spherical dendritic macromolecules utilizing an adamantane core have been described. The dendrimer syntheses utilized 4-amino-4-(3-acetoxypropyl)-1,7-diacetoxyheptane or di-*tert*-butyl 4-amino-2-[(*tert*-butoxycarbonyl)ethyl]heptanedioate as the key building block. An improved synthetic procedure to 1,3,5,7-adamantanetetracarboxylic acid is reported.

Introduction

The design and construction of polyfunctionalized dendritic macromolecules based on a four-directional *C*-core[4-7] have afforded a microenvironment which affords entrance to the field of unimolecular micelles.[8] Work on related dendritic macromolecules has been reviewed[9] and recently reported.[10] Cascade molecules, particularly silvanols[11] and arborols,[12] possessing other orders of directionality, have unique molecular shapes and have been shown to aggregate in a specific manner dependent directly on complementary interactions. For example, two-directional cascade molecules possessing a dumbbell shape organize in an orthogonal array to form aqueous gels,[13,14] or when possessing an unsaturated core organize in a nonorthogonal manner giving rise to supramolecular helical ropes.[15] Combined with our continued interest in dendritic polymers and micellar mimics, convenient preparation of a bridgehead-functionalized adamantane to provide a core topology approximating a tetrahedral nucleus facilitates the synthesis of a spherical, four-directional cascade infrastructure. We herein describe the divergent syntheses and characterization of four-directional spherical dendritic macromolecules, which utilize the bridgehead positions of adamantane as the molecular core.

Results and Discussion

The directionality inherent in the admantane nucleus provides the desired tetrahedral motif; however, functionalization of the unactivated bridgehead CH bonds has been limited.[16] Direct, selective oxyfunctionalization of adamantane with methyl(trifluoromethyl)dioxirane has recently been shown[17] to afford the adamantane-1,3,5,7-tetrol in good yields. Treatment of this tetrol with chloroacetic acid or an acrylic ester would afford the homolo-

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