Synthesis of the CDE Ring System of the Ginkgolides

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Received September 8, 1986

Several members of the ginkgolide family are known to be platelet activating factor (PAF) platelet receptor antagonists. We report herein a synthesis of an analogue of the ginkgolide CDE ring system, a potential model for ginkgolide PAF platelet receptor binding, from the coupling of dimethyl malonate with the epoxide **2**.

The ginkgolides are a series of highly oxygenated hexacyclic diterpenes first characterized in 1967.[1] Their structures are shown in Figure 1. Recently, this family of compounds has come under pharmacological scrutiny[2] due to the finding that several members express the ability to inhibit the binding of platelet activating factor (PAF) to its platelet receptor.[3]

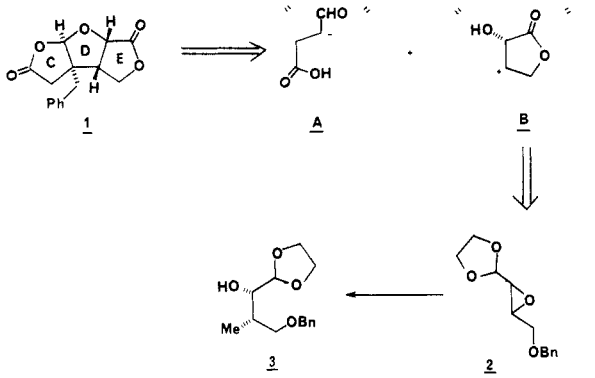
Our interest in PAF receptor antagonists[4] led us to consider the synthesis of fragments of the ginkgolide framework in an effort to determine receptor binding requirements. At this time we report the synthesis of the fragment **1** which corresponds to the CDE ring system of the ginkgolides. The benzyl group at the CD juncture was incorporated to provide a lipophilic site reminiscent of the ginkgolide B ring *tert*-butyl group.

A search of the literature revealed a few reports of syntheses of the bicyclic CD parent ring system within **1**,[5] and some derivatives, but did not uncover the existence of the parent CDE system or its congeners. We therefore set out to synthesize this novel tricycle.

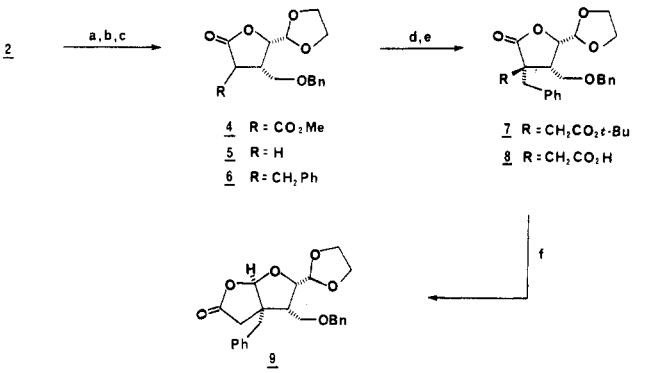
Our initial retrosynthetic analysis split the molecule into the two parts A and B shown in Scheme I. An equivalent of B which we felt would provide the correct regio- and stereochemistry for the DE ring junction is **2**. We had predicted that **2**, due to steric and electronic control, would be regioselectively attacked by a nucleophile.

Indeed, we found that Sharpless et al. had added lithium dimethylcuprate to **2** to give **3** with complete regiocontrol.[6] This left us with controlling the relative stereochemistry

Scheme I

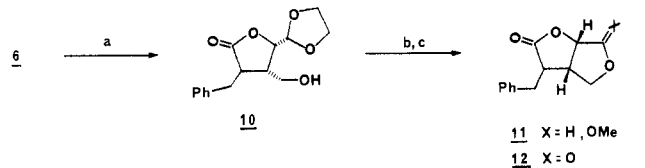


Scheme II[a]



[a] (a) MeOH, $NaCH(CO_2CH_3)_2$, 65 °C, 48 h, 55%; (b) Me_2SO, H_2O, LiCl, 100 °C, 25 h, 84%; (c) THF, LDA, then **5**, -78 °C, 1.25 h then HMPA, BnCl, -78 °C, 3.5 h, 56%; (d) THF, LDA, then **6**, -78 °C, 0.75 h, then HMPA, $BrCH_2CO_2$-*t*-Bu, -78 °C, 3.5 h, 77%; (e) CH_2Cl_2, TFA, room temperature, 3 h, 90%; (f) $PhCH_3$, DIBAL, -78 °C, 4.5 h, then $PhCH_3$, TsOH, 80 °C, 2 min, 50%.

Scheme III[a]



[a] (a) EtOH, 10% Pd/C, H_2 (50 psi), 40 h, 93%; (b) MeOH, BF_3·Et_2O, 50 °C, 20 h, 54%; (c) CH_2Cl_2, MCPBA, BF_3·Et_2O, 60 h, 43%.

(1) (a) Maruyama, M.; Terahara, A.; Itagaki, Y.; Nakanishi, K. *Tetrahedron Lett.* **1967**, 299-302. (b) Maruyama, M.; Terahara, A.; Itagaki, Y.; Nakanishi, K. *Ibid.* **1967**, 303-308. (c) Maruyama, M.; Terahara, A.; Nakadaira, Y.; Woods, M. C.; Nakanishi, K. *Ibid.* **1967**, 309-313. (d) Maruyama, M.; Terahara, A.; Nakadaira, Y.; Woods, M. C.; Takagi, Y.; Nakanishi, K. *Ibid.* **1967**, 315-319. (e) Woods, M. C.; Miura, I.; Nakadaira, Y.; Terahara, A.; Maruyama, M.; Nakanishi, K. *Ibid.* **1967**, 321-326. (f) Sakabe, N.; Takada, S.; Okabe, K. *Chem. Commun.* **1967**, 259-261. (g) Okabe, K.; Yamada, K.; Yamamura, S.; Takada, S. *J. Chem. Soc. C* **1967**, 2201-2206.

(2) See for example: (a) Braquet, P. G. B. Patent 8418424, 1984, July 19. (b) Bourgain, R. H.; Maes, L.; Braquet, P.; Andries, R.; Tovqui, L.; Braquet, M. *Prostaglandins* **1985**, *30*, 185-197. (c) Braquet, P. *Ibid.* **1985**, *30*, 687. (d) Bourgain, R. H. Andries, R.; Maes, L.; Sedivy, P.; Braquet, P. *Ibid.* **1985**, *30*, 693. (e) Coeffier, E.; Borrel, M.-C.; Lefort, J.; Chignard, M.; Broquet, C.; Heymans, F.; Vargaftig, B. B. *Ibid.* **1985**, *30*, 699. (f) Baroggi, N.; Cachia, H.; Etienne, A.; Braquet, P. *Ibid.* **1985**, *30*, 700. (g) Chignard, M.; Nunez, D.; Korth, R.; Norel, X.; Braquet, P.; Benveniste, J. *Ibid.* **1985**, *30*, 701. (h) Baranes, J.; LeHagarat, M.; Viossat, I; Hellegouarch, A.; Delaflotte, S.; Clostre, F.; and Braquet, P. *Ibid* **1985**, *30*, 710. (i) Sanchez-Crespo, M.; Fernandez-Gallardo, S.; Nieto M. L.; Baranes, J.; Etienne, A.; Braquet, P. *Ibid.* **1985**, *30*, 714. (j) Etienne, A.; Hecquet, F.; Soulard, C.; Clostre, F.; Braquet, P. *Ibid.* **1985**, *30*, 716. (k) Villamediana, L. M.; Sanz, E.; Caramelo, C.; Fernandez-Gallardo, S.; Sanchez-Crespo, M.; Braquet, P.; Lopez-Novoa, J. M. *Ibid.* **1985**, *30*, 717. (l) Foegh, M. L.; Khirabadi, B. S.; Braquet, P.; Ramwell, P. W. *Ibid.* **1985**, *30*, 718. (m) Touvay, C.; Vilain, B.; Etienne, A.; Braquet, P.; *Ibid.* **1985**, *30*, 719. (n) Braquet, P.; Etienne, A.; Clostre, F. *Ibid.* **1985**, *30*, 722. (o) Doly, M.; Braquet, P.; Bonhomme, B. *Ibid.* **1985**, *30*, 722.

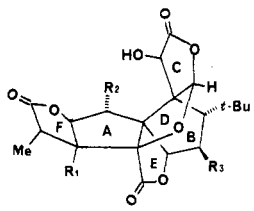
(3) Valone, F. H. *Immunology* **1984**, *52*, 169-174.

(4) (a) Anderson, R. C.; Nabinger, R. C. *Tetrahedron Lett.* **1983**, *24*, 2741-2744. (b) Anderson, R. C.; Reitter, B. E.; Winslow, C. M. *Chem. Phys. Lipids* **1986**, *39*, 73-82. (c) Hsueh, W.; Gonzalez-Crussi, F.; Arroyave, J. L.; Anderson, R. C.; Lee, M. L.; Houlihan, W. J. *Eur. J. Pharm.* **1986**, *123*, 79-83. (d) Winslow, C. M.; Anderson, R. C.; D'Aries, F. J.; Frisch, G. E.; Kowal-DeLillo, A. H.; Lee, M. L.; Saunders, R. N. In *New Horizons in Platelet Activating Factor Research*; Winslow, C. M., Lee, M. L., Eds.; Wiley: London, 1986.

(5) (a) Kraus, G. A.; Landgrebe, K. *Tetrahedron Lett.* **1984**, *25*, 3939-3942. (b) Jalali, M.; Boussac, G.; Lallemand, J. Y. *Ibid.* **1983**, *24*, 4307-4310.

(6) (a) Behrens, C. H.; Sharpless, K. B. *Aldrichimia Acta* **1983**, *16*, 67-80. (b) Danishefsky, S.; Regan, J. *Tetrahedron Lett.* **1981**, *22*, 3919-3922.

0022-3263/87/1952-1186$01.50/0



	R_1	R_2	R_3
GA	OH	H	H
GB	OH	OH	H
GC	OH	OH	OH
GM	H	OH	OH

Figure 1.

between the CD and DE ring junctions and this we felt would be dependent on our choice for an equivalent of A.

Results and Discussion

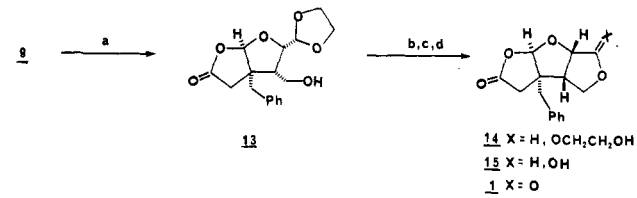
The requisite epoxide **2** was easily prepared from *cis*-butenediol via known procedures[6], and was then reacted with a variety of nucleophiles. Our initial alkylation attempts were with lithiated hydrazones because of the potential to gain stereofacial addition and asymmetric induction using Enders' technology.[7] Unfortunately, the lithiated dimethylhydrazone of hexanal, in the presence and absence of copper,[8] failed to add to the epoxide **2**. Failures also occurred with additions of lithiated butyronitrile[9] and the pyrrolidine enamine of cyclopentanone.[10]

These failures we attributed to the decreased electrophilicity of epoxide **2**, due to inductive electron withdrawal from the C-3 center by the benzyloxy group and from the C-2 center by the acetal, relative to the non-oxygen substituted epoxides utilized previously.[7-9] We postulated that perhaps a softer nucleophile in a more polar solvent would be more appropriate. Therefore, we were quite pleased to find that satisfactory results could be achieved in the addition of dimethyl malonate to **2** to yield the lactone **4** as shown in Scheme II. This provided us with the necessary framework upon which to build. Thus, Krapcho decarbomethoxylation[11] led us to the lactone **5** which was then alkylated with benzyl bromide to give **6**. The C-ring skeleton was appended by further alkylation of **6** with *tert*-butyl bromoacetate to give a single diastereomer which we presumed to be **7**. This diastereoselectivity was expected due to the known propensity for anti addition in similar systems.[12] The stereochemical assignment was confirmed by extensive NOE analysis of the bicycle **9** which was prepared by deesterification, selective lactone reduction, and cyclization of **7**.

At this juncture, the model study shown in Scheme III was initiated for the formation of the remaining E ring. Hydrogenolysis of the benzyl ether in **6** produced **10** which could not be induced to efficiently hydrolyze to the desired hemiacetal with aqueous acids. The product from partial hydrolysis, the 2-hydroxyethoxy acetal, was isolated. The acetal **10** could be effectively converted into the methyl acetals **11** by treatment with boron trifluoride etherate in methanol. Greico oxidation[13] of **11** then led to **12**.

In applying this procedure to the conversion of **9** into **1**, it was found that the benzyl ether could easily be removed to give **13**, but **13** quickly decomposed upon

Scheme IV[a]



[a] (a) EtOH, 10% Pd/C, H_2 (50 psi), 20 h, 73%; (b) $PhCH_3$, TsOH, 60 °C, 0.75 h, 68%; (c) THF, HCl(aq), 0 °C, 10 min, then room temperature, 3.75 h, 58%; (d) CH_2Cl_2, PCC, 4.5 h, 65%.

treatment with either aqueous acids or with methanolic boron trifluoride etherate (Scheme IV).

Partial hydrolysis could, however, be effected by brief treatment of **13** with *p*-toluenesulfonic acid in toluene to yield a separable mixture of the anomers of **14** in a ratio of 1.6:1. Interestingly, while the major anomer of **14** could be converted into the hemiacetal **15** by aqueous acid in less than 4 h, treatment of the minor anomer of **14** under the same conditions for up to 22 h gave decomposition with none of **15** being isolatable. Attempts to equilibrate the minor anomer with the major anomer were unsuccessful as were attempts to affect their ratio by cyclization of **13** with zinc chloride under aprotic conditions.

Nonetheless, the desired target **1** was produced upon oxidation of **15** with pyridinium chlorochromate to complete the synthesis. Thus, with complete stereocontrol at all asymmetric centers, we have synthesized a novel tricyclic ring system corresponding to the ginkgolide CDE fragment.

Unfortunately, compound **1** was not effective at displacing PAF from its platelet receptor.[14] Further studies are therefore in progress in an effort to determine the ginkgolide structural features necessary for binding to the PAF platelet receptor.

Experimental Section

General Methods. Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Proton and carbon NMR spectra were obtained on either a JEOL FX90Q, JOEL FX200, or a Bruker AM500 instrument. The spectra were measured in deuteriochloroform solution, unless otherwise stated, relative to tetramethylsilane (δ 0.00). Each signal is described in terms of chemical shift in parts per million from tetramethylsilane. AB patterns are reported as observed line separations. Infrared spectra were recorded on an Analect Instruments FX-200FTIR spectrometer for thin films unless otherwise noted. Mass spectra were recorded on a Finnigan 4600 GC-MS or VG 7070E mass spectrometer. Exact-mass determinations were obtained on the VG 7070E instrument. Microanalyses were performed by the Physical Chemistry Department, Sandoz Research Institute.

All nonaqueous reactions were run under nitrogen. All organic extracts were dried over anhydrous sodium sulfate. Tetrahydrofuran (THF) was distilled under nitrogen from sodium benzophenone ketyl. Hexamethylphosphoramide (HMPA) and diisopropylamine were distilled from calcium hydride. All other solvents were reagent grade and used as received. Thin-layer chromatography (TLC) was performed on 0.25-mm E. Merck precoated silica gel plates (60F-254). Preparative thin-layer chromatography (PTLC) was performed on 1 mm × 20 cm × 20 cm Analtech precoated silica gel plates (silica gel GF). Silica gel 60 (230–400-mesh) supplied by Merck was used for flash chromatography.

***cis*-(±)-5-(1,3-Dioxolan-2-yl)tetrahydro-2-oxo-4-[(phenylmethoxy)methyl]-3-furancarboxylic Acid Methyl Ester (4).** Epoxide **2**[6] (3.00 g, 12.7 mmol) was dissolved in methanol

(7) Enders, D.; Eichenauer, H. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 549–551.
(8) Corey, E. J.; Enders, D. *Chem. Ber.* **1978**, *111*, 1362–1383.
(9) LeBrogne, J. F.; Cuvigny, T.; Larcheveque, M.; Normant, H. *Synthesis* **1976**, 238–240.
(10) Britten, A. Z.; Owen, W. S.; Went, C. W. *Tetrahedron* **1969**, *25*, 3157–3160.
(11) Krapcho, A. P. *Synthesis* **1982**, 805.
(12) (a) Tomioka, K.; Koga, K. *Tetrahedron Lett.* **1979**, 3315. (b) Prestwick, G. D.; Shieh, H. J. *J. Org. Chem.* **1981**, *46*, 4319. (c) Chen, S. Y.; Jouille, M. M. *J. Org. Chem.* **1984**, *49*, 268.
(13) Grieco, P. A.; Oguri, T.; Yokoyama, Y. *Tetrahedron Lett.* **1978**, 419–420.
(14) Winslow, C. M. *Fed. Proc.* **1984**, *43*, 1941.

(6.00 mL) and added to a 1 M methanolic solution of sodium dimethylmalonate (114 mL). The initially clear, lime-yellow solution was stirred at reflux for 48 h under N_2. The resulting clear, olive-brown solution was then cooled to room temperature and partitioned between 400 mL of EtOAc and 200 mL of H_2O. The aqueous phase was separated and extracted twice with 100 mL of EtOAc. The combined EtOAc layers were washed with 200 mL of brine and dried, and the solvent was removed to give a clear, bright yellow oil. Flash chromatography (petroleum ether–ethyl acetate, 10:1) yielded 2.34 g (54.8%) of ester-lactone **4** as a clear, light yellow oil: ^{1}H NMR δ 7.35–7.15 (m, 5 H), 5.12 (d, J = 2 Hz, 1 H), 4.68 (dd, J = 8, 2 Hz, 1 H), 4.49 (s, 2 H), 4.11–3.40 (m, 8 H), 3.75 (s, 3 H); ^{13}C NMR δ 171.23, 167.99, 137.30, 128.50, 128.43, 127.89, 127.71, 127.62, 101.51, 78.63, 73.30, 67.55, 66.10, 65.53, 53.00, 48.56, 41.25; IR 2957, 2894, 1787, 1742, 1665, 1600, 1446, 1366, 1266, 1153, 1030, 951, 852, 801, 744, 700, 667 cm^{-1}; MS, m/e 337 (MH$^+$). Anal. Calcd for $C_{17}H_{20}O_7$: C, 60.71; H, 5.99. Found: C, 60.77; H, 6.17.

***cis*-(±)-5-(1,3-Dioxolan-2-yl)dihydro-4-[(phenylmethoxy)methyl]-2(3*H*)-furanone (5).** Ester-lactone **4** (3.09 g, 9.20 mmol) and LiCl (2.60 g, 61.3 mmol) were dissolved in Me_2SO (30.0 mL) and H_2O (0.6 mL), and the initially clear colorless solution was stirred and heated in a 110 °C oil bath for 25 h. The black, opaque solution was then cooled and partitioned between 100 mL of CH_2Cl_2 and 100 mL of H_2O. The phases were separated and the aqueous phase was extracted twice with 50 mL of CH_2Cl_2. The combined CH_2Cl_2 solutions were washed with brine (100 mL) and dried, and solvent was removed to give a clear, brown oil. Flash chromatography (petroleum ether–ethyl acetate, 10:1) yielded 2.15 g (84.1%) of lactone **5** as a clear, yellow oil: ^{1}H NMR δ 7.41–7.22 (m, 5 H), 5.18 (d, J = 2 Hz, 1 H), 4.62 (dd, J = 8, 2 Hz, 1 H), 4.51 (s, 2 H), 4.13–3.82 (m, 4 H), 3.66 (d, J = 7 Hz, 2 H), 3.14–2.89 (m, 1 H), 2.47 (d, J = 10 Hz, 2 H); ^{13}C NMR δ 176.04, 137.59, 128.42, 127.84, 127.66, 101.88, 80.10, 73.35, 68.62, 65.99, 65.41, 37.29, 31.07; IR 2894, 1784, 1496, 1474, 1456, 1419, 1376, 1316, 1171, 1114, 1046, 991, 946, 917, 867 cm^{-1}; HRMS (MH$^+$) calcd for $C_{15}H_{18}O_5$ 279.1232, found 279.1211.

***cis*-(±)-5-(1,3-Dioxolan-2-yl)dihydro-4-[(phenylmethoxy)methyl]-3-(phenylmethyl)-2(3*H*)-furanone (6).** A solution of lactone **5** (0.500 g, 1.80 mmol) in 0.500 mL of THF was added, under N_2, to a solution of 0.212 g (1.98 mmol) of lithium diisopropylamide (prepared from 0.219 g of diisopropylamine and 1.24 mL of a 1.6 N hexane solution of *n*-butyllithium) in 3.60 mL of THF at −78 °C. The resultant light yellow mixture was then stirred at −78 °C for 1.25 h. A solution of benzyl chloride (1.04 mL, 9.00 mmol) and HMPA (0.814 mL, 4.68 mmol) in 1.00 mL of THF was then added, and the mixture was stirred at −78 °C, under N_2, for 3.5 h. The clear, light yellow solution was then partitioned between 50 mL of EtOAc and 50 mL of H_2O. The phases were separated, and the aqueous phase was extracted twice with 50 mL of EtOAc. The combined EtOAc layers were washed with brine (50 mL) and dried, and solvent was removed to give a clear, light yellow liquid. Flash chromatography (petroleum ether–ethyl acetate, 12:1) yielded 0.369 g (55.6%) of lactone **6** as a waxy white solid: mp 66.5–69.0 °C; ^{1}H NMR δ 7.39–7.15 (m, 10 H), 5.18 (d, J = 1 Hz, 1 H), 4.52 (dd, J = 8, 1 Hz, 1 H), 4.33 (s, 2 H), 4.18–3.79 (m, 4 H), 3.43 (dd, J = 9, 9 Hz, 1 H), 3.21–3.09 (m, 2 H), 2.93–2.60 (m, 3 H); ^{13}C NMR δ 177.94, 137.85, 137.56, 129.18, 128.65, 128.42, 127.81, 127.63, 126.78, 101.85, 78.61, 73.20, 68.36, 66.14, 65.47, 42.69, 41.99, 35.98; IR 3063, 3032, 2891, 1776, 1602, 1493, 1454, 1366, 1322, 1158, 1114, 1032, 954, 746, 700 cm^{-1}; HRMS (MH$^+$) calcd for $C_{22}H_{24}O_5$ 369.1702, found 369.1728.

(3α,4β,5β)-(±)-5-(1,3-Dioxolan-2-yl)tetrahydro-2-oxo-4-[(phenylmethoxy)methyl]-3-(phenylmethyl)-3-furanacetic Acid 1,1-Dimethylethyl Ester (7). A solution of lactone **6** (0.849 g, 2.31 mmol) in 1.00 mL of THF was added, under N_2, to a solution of 0.272 g (2.54 mmol) of lithium diisopropylamide (prepared from 0.280 g of diisopropylamine and 1.59 mL of a 1.6 N hexane solution of *n*-butyllithium) in 7.70 mL of THF at −78 °C. The resultant dark maroon mixture was then stirred at −78 °C, under N_2, for 0.75 h. A solution of *tert*-butyl bromoacetate (1.12 mL, 6.92 mmol) and HMPA (1.04 mL, 6.01 mmol) in 1.00 mL of THF was then added and the mixture was stirred at −78 °C, under N_2, for 3.5 h. The clear, light orange solution was then partitioned between 50 mL of EtOAc and 50 mL of H_2O. The phases were separated, and the aqueous phase was extracted twice with 50 mL of EtOAc. The combined EtOAc layers were washed with brine (50 mL) and dried, and solvent was removed to give a clear, orange-yellow liquid. Flash chromatography (petroleum ether–ethyl acetate, 8:1) yielded 0.854 g (76.7%) of lactone-ester **7** as a thick, clear, light-yellow oil: ^{1}H NMR δ 7.41–7.05 (m, 10 H), 5.11 (d, J = 2 Hz, 1 H), 4.67 (dd, J = 10, 2 Hz, 1 H), 4.55 (s, 2 H), 4.17–4.08 (m, 2 H), 3.98–3.75 (m, 4 H)8, 3.45–3.27 (m, 1 H), 3.44, 2.71 (AB q, J = 14 Hz, 2 H), 2.72, 2.58 (AB q, J = 17 Hz, 2 H), 1.40 (s, 9 H); ^{13}C NMR δ 177.42, 170.06, 137.62, 135.86, 131.14, 128.51, 127.84, 127.69, 126.87, 101.58, 81.58, 77.85, 73.44, 66.37, 66.02, 65.38, 45.67, 43.16, 41.26, 37.17, 28.03; IR 3024, 2978, 2894, 1776, 1726, 1602, 1491, 1456, 1404, 1366, 1216, 1158, 1087, 1043, 988, 951, 847, 762, 752, 703, 665 cm^{-1}; HRMS (MH$^+$) calcd for $C_{28}H_{34}O_7$ 483.2383, found 483.2377.

(3α,4β,5β)-(±)-5-(1,3-Dioxolan-2-yl)tetrahydro-2-oxo-4-[(phenylmethoxy)methyl]-3-(phenylmethyl)-3-furanacetic Acid (8). Lactone-ester **7** (0.070 g, 0.145 mmol) was dissolved in 2.00 mL of CH_2Cl_2. Trifluoroacetic acid (0.250 mL, 3.24 mmol) was added and the resulting clear, light-olive solution was stirred at room temperature for 3 h, under N_2. Toluene (0.5 mL) was then added, and then the CH_2Cl_2 and trifluoroacetic acid were removed by partial evaporation of the mixture. The resulting clear, light yellow toluene solution was then purified by preparative TLC (chloroform–MeOH, 9:1), yielding 0.056 g (90.3%) of acid **8** as a light-yellow solid: mp 82–85 °C; ^{1}H NMR (CD_3OD) δ 7.42–6.99 (m, 10 H), 5.02 (d, J = 2 Hz, 1 H), 4.65 (dd, J = 10, 2 Hz, 1 H), 4.54 (s, 2 H), 4.15–4.00 (m, 2 H), 4.00–3.78 (m, 4 H), 3.49–3.28 (m, 3 H), 2.83–2.63 (m, 2 H); ^{13}C NMR (CD_3OD) δ 180.31, 174.38, 139.28, 137.44, 132.19, 131.78, 129.76, 129.50, 129.24, 129.06, 128.89, 128.80, 127.92, 127.78, 102.67, 79.28, 74.40, 67.07, 66.99, 66.40, 47.01, 44.27, 40.68, 38.02; IR (KBr) 3456, 3286, 3061, 3032, 2894, 1771, 1689, 1583, 1493, 1419, 1177, 1127, 1087, 990, 948, 785, 744, 703 cm^{-1}; HRMS (MH$^+$) calcd for $C_{24}H_{26}O_7$ 427.1757, found 427.1718.

(3aα,4α,5α,6α)-(±)-5-(1,3-Dioxolan-2-yl)tetrahydro-4-[(phenylmethoxy)methyl]-3a-(phenylmethyl)furo[3,2-*b*]-furan-2(3*H*)-one (9). Acid **8** (0.368 g, 0.864 mmol) was dissolved in 3.46 mL of toluene (freshly distilled) and cooled to −78 °C. Diisobutylaluminum hydride (1.32 mL of a 1.5 N toluene solution) was then added and the resulting light-yellow solution was stirred at −78 °C for 4.5 h under N_2. The solution was then partitioned between 50 mL of EtOAc and 50 mL of 3 N HCl. The phases were separated and the aqueous phase was extracted twice with 50 mL of EtOAc. The combined EtOAc layers were washed with 50 mL of H_2O and 50 mL of brine and dried, and the solvent was removed to give a clear, gold-yellow oil. This oil and *p*-toluenesulfonic acid (one crystal) were dissolved in toluene (1.00 mL) and heated at 80 °C for 2 min. The cooled solution was then purified by flash chromatography (petroleum ether–ethyl acetate, 8:1), yielding 0.177 g (50%) of lactone **9** as a clear yellow oil: ^{1}H NMR δ 7.43–7.05 (m, 10 H), 5.83 (s, 1 H), 5.07 (d, J = 5 Hz, 1 H), 4.54 (s, 2 H), 4.41 (dd, J = 9, 5 Hz, 1 H), 4.16–3.79 (m, 6 H), 3.20, 2.87 (AB q, J = 14 Hz, 2 H), 2.68 (s, 2 H), 2.76–2.62 (m, 1 H); ^{13}C NMR δ 173.70, 137.68, 136.32, 130.25, 128.84, 128.52, 127.87, 127.60, 127.16, 109.99, 102.30, 81.98, 73.53, 65.73, 65.41, 53.00, 48.12, 39.35, 34.91; IR 3063, 3029, 2926, 2891, 1784, 1604, 1498, 1456, 1419, 1366, 1280, 1216, 1180, 1101, 1030, 983, 954, 915, 883, 756, 703, 667 cm^{-1}; HRMS (MH$^+$) calcd for $C_{24}H_{26}O_6$ 411.1808, found 411.1809.

***cis*-(±)-5-(1,3-Dioxolan-2-yl)dihydro-4-(hydroxymethyl)-3-(phenylmethyl)-2(3*H*)-furanone (10).** Lactone **6** (0.540 g, 1.47 mmol) was dissolved in 2.93 mL of warm ethanol (95%). Palladium (10% on carbon) (0.200 g) was then added, and the resulting mixture was stirred under a positive pressure of H_2 (50 psi) for 40 h at room temperature. The palladium catalyst was then removed from the reaction by filtration through Celite and the filtercake was washed with 40 mL of EtOAc. The combined solutions were concentrated and flash chroamtographed (petroleum ether–ethyl acetate, 5:1) to provide 0.379 g (92.8%) of alcohol **10** as a thick, light yellow oil: ^{1}H NMR δ 7.36–7.10 (m, 5 H), 5.23 (d, J = 2 Hz, 1 H), 4.51 (dd, J = 8, 2 Hz, 1 H), 4.16–3.80 (m, 4 H), 3.65–3.38 (m, 2 H), 3.26–3.09 (m, 1 H), 2.97–2.78 (m, 2 H), 2.70–2.55 (m, 1 H), 2.04 (t, J = 6 Hz, 1 H); ^{13}C NMR δ 177.66, 137.84, 129.17, 128.79, 126.95, 101.97, 78.35, 65.95, 65.46, 60.69, 44.28, 42.55, 35.83; IR 3495, 3029, 2896, 1771, 1604, 1491, 1451, 1324, 1158, 1114, 1022, 956, 785, 756, 703 cm^{-1}; HRMS (MH$^+$)

calcd for $C_{15}H_{18}O_5$ 279.1232, found 279.1215.

***cis*-(±)-Tetrahydro-6-methoxy-3-(phenylmethyl)furo[3,4-*b*]furan-2(3*H*)-one (11).** Alcohol **10** (0.407 g, 1.46 mmol) was dissolved in 2.93 mL of MeOH under N_2. Boron trifluoride etherate (0.118 mL, 0.960 mmol) was then added, and the resultant dark-yellow mixture was stirred at 50 °C for 20 h under N_2. The cooled, clear, dark-orange solution was then partitioned between 50 mL of EtOAc and 50 mL of saturated $NaHCO_3$ solution. The organic phase was separated and the aqueous phase was washed twice with 35 mL of EtOAc. The combined organic solutions were washed with 25 mL of H_2O and 25 mL of brine and dried, and the solvent was removed to give a clear dark yellow oil. Purification by preparative TLC (petroleum ether–ethyl acetate, 8:1) yielded 0.195 g (53.9%) of lactone **11** as a white solid: mp 57–60 °C; ^1H NMR δ 7.40–7.15 (m, 5 H), 4.97 (s, 1 H), 4.53 (d, J = 7 Hz, 1 H), 3.92 (dd, J = 9, 6 Hz, 1 H), 3.57 (dd, J = 9, 1 Hz, 1 H), 3.30 (s, 3 H), 3.35–3.11 (m, 1 H), 2.93–2.79 (m, 3 H); ^{13}C NMR δ 177.82, 137.27, 130.00, 128.94, 128.89, 128.62, 127.10, 106.43, 85.18, 72.15, 54.46, 47.83, 42.22, 37.20; IR 3063, 2933, 2838, 1779, 1607, 1493, 1451, 1374, 1319, 1161, 1106, 1072, 1022, 983, 928, 757, 705, 670 cm^{-1}; HRMS (MH^+) calcd for $C_{14}H_{16}O_4$ 249.1127, found 249.1117.

***cis*-(±)-Dihydro-3-(phenylmethyl)furo[3,4-*b*]furan-2(3*H*)-one (12).** Lactone **11** (0.142 g, 0.573 mmol) was dissolved in 2.86 mL of CH_2Cl_2 under N_2. *m*-Chloroperoxybenzoic acid (0.142 g, 0.659 mmol) and boron trifluoride etherate (0.070 mL, 0.573 mmol) were then added, and the clear, yellow solution was stirred at room temperature for 60 h. The resulting cloudy, whitish yellow solution was then partitioned between 25 mL of EtOAc and 20 mL of saturated Na_2SO_3 solution. The organic phase was separated, and the aqueous phase was washed twice with 10 mL of EtOAc. The combined organic solutions were washed with 10 mL of saturated $NaHCO_3$ solution, 20 mL of H_2O, and 20 mL of brine and dried, and the solvent was removed to give a thick, clear, yellow oil. Purification by preparative TLC (petroleum ether–ethyl acetate, 2:1) yielded 0.057 g (42.9%) of dilactone **12** as a white solid: mp 142–144 °C; ^1H NMR δ 7.41–7.12 (m, 5 H), 4.80 (d, J = 8 Hz, 1 H), 4.30 (dd, J = 10, 6 Hz, 1 H), 3.73 (dd, J = 10, 2 Hz, 1 H), 3.42–3.10 (m, 2 H), 2.95–2.80 (m, 2 H); ^{13}C NMR δ 175.14, 170.47, 136.48, 129.24, 128.80, 127.57, 73.79, 69.79, 45.85, 40.47, 35.83; IR 3090, 3029, 2986, 2939, 2872, 1768, 1604, 1586, 1498, 1472, 1459, 1390, 1322, 1308, 1235, 1216, 1182, 1151, 1074, 1053, 1035, 988, 948, 925, 907, 881, 821, 790, 762, 736, 705, 637 cm^{-1}; HRMS (MH^+) calcd for $C_{13}H_{12}O_4$ 233.0814, found 233.0805.

(3a*α*,4*α*,5*α*,6*α*)-(±)-5-(1,3-Dioxolan-2-yl)tetrahydro-4-(hydroxymethyl)-3a-(phenylmethyl)furo[2,3-*b*]furan-2(3*H*)-one (13). Lactone **9** (0.314 g, 0.766 mmol) was dissolved in 7.66 mL of warm ethanol (95%). Palladium (10% on carbon) (0.400 g) was then added and the resulting solution was stirred under a positive pressure of H_2 (50 psi) for 20 h at room temperature. The palladium catalyst was then removed from the reaction by filtration through Celite, and the filtercake was washed with 50 mL of EtOAc. The combined solutions were concentrated, and the resulting hazy, light-yellow taffy-like material was purified by preparative TLC (EtOAc–petroleum ether, 2:1), yielding 0.180 g (73.2%) of alcohol **13** as a white solid: mp 132–135 °C; ^1H NMR δ 7.39–7.10 (m, 5 H), 5.92 (s, 1 H), 5.25 (d, J = 3 Hz, 1 H), 4.52 (dd, J = 6, 3 Hz, 1 H), 4.19–3.90 (m, 6 H), 3.30, 2.99 (AB q, J = 14 Hz, 2 H), 2.86 (t, J = 6 Hz, 1 H), 2.78, 2.58 (AB q, J = 18 Hz, 2 H), 2.47–2.39 (m, 1 H); ^{13}C NMR δ 173.97, 135.95, 129.91, 128.94, 129.28, 110.26, 101.99, 81.61, 65.88, 65.35, 58.40, 52.56, 50.54, 38.75, 36.09; IR 3588, 3485, 3063, 3029, 2896, 1776, 1604, 1496, 1419, 1353, 1274, 1206, 1180, 1145, 1087, 1058, 1030, 980, 839, 801, 762, 705, cm^{-1}; HRMS (MH^+) calcd for $C_{17}H_{20}O_6$ 321.1338, found 321.1329.

(3a*α*,3b*β*,6a*β*,7a*α*)-(±)-Hexahydro-6-(2-hydroxyethoxy)-3a-(phenylmethyl)difuro[2,3-*b*:3′,4′-*d*]furan-2(3*H*)-one (14). Alcohol **13** (0.0997 g, 0.312 mmol) was added to toluene (2.08 mL) and heated to 60 °C. *p*-Toluenesulfonic acid (two crystals) was then added to the cloudy, white solution and the resulting clear and colorless solution was allowed to stir at 60 °C for 0.75 h under N_2. The cooled, clear, and colorless solution was then purified by preparative TLC (EtOAc–petroleum ether, 4:1), yielding the major isomer of **14** (0.0415 g, 41.5%) as a white solid and the minor isomer of **14** (0.0262 g, 26.2%) as a clear, thick oil. Major isomer: mp 133–134 °C; ^1H NMR δ 7.38–7.05 (m, 5 H), 5.96 (s, 1 H), 5.12 (d, J = 4 Hz, 1 H), 4.89 (dd, J = 7, 4 Hz, 1 H), 4.10 (t, J = 8 Hz, 1 H), 3.99 (t, J = 8 Hz, 1 H), 3.90–3.65 (m, 6 H), 3.00–2.86 (m, 2 H), 2.81, 2.50 (AB q, J = 18 Hz, 2 H); ^{13}C NMR δ 174.07, 135.24, 129.58, 129.07, 127.51, 111.47, 103.26, 83.97, 72.00, 65.30, 61.81, 52.11, 51.75, 39.39, 37.41; IR 3448, 3063, 3029, 2931, 2880, 1787, 1609, 1493, 1456, 1416, 1364, 1277, 1227, 1182, 1145, 1061, 1014, 980, 891, 850, 803, 759, 705, 639 cm^{-1}; MS, m/e 321 (MH^+). Minor isomer: ^1H NMR δ 7.39–7.00 (m, 5 H), 5.81 (s, 1 H), 5.19 (s, 1 H), 4.81 (d, J = 6 Hz, 1 H), 4.29–4.02 (m, 2 H), 3.82–3.58 (m, 4 H), 3.06–2.90 (m, 3 H), 2.80, 2.50 (AB q, J = 18 Hz, 2 H), 2.20 (br s, 1 H); ^{13}C NMR δ 173.65, 135.46, 129.76, 129.09, 127.48, 110.96, 106.37, 88.56, 69.85, 66.84, 61.99, 53.64, 50.98, 39.57, 37.55; IR 3485, 2936, 1787, 1652, 1496, 1454, 1419, 1350, 1180, 1106, 1051, 983, 756, 705 cm^{-1}; MS, m/e 321 (MH^+).

(3a*α*,3b*β*,6a*β*,7a*α*)-(±)-Hexahydro-6-hydroxy-3a-(phenylmethyl)difuro[2,3-*b*:3′,4′-*d*]furan-2(3*H*)-one (15). The major isomer of **14** (0.0201 g, 0.0628 mmol) was dissolved in 1.57 mL of THF and cooled in an ice–water bath. Aqueous HCl (37%) (1.57 mL) was then added and the mixture was stirred at 0 °C for 10 min. The cold bath was then removed and the reaction was allowed to warm to and remain at room temperature for a total of 3.5 h. The clear and colorless solution was then partitioned between 50 mL of CH_2Cl_2 and 50 mL of brine. The phases were separated and the aqueous phase was extracted twice with 25 mL of CH_2Cl_2. The combined CH_2Cl_2 layers were then dried and the solvent was removed at room temperature to give a clear, colorless oil. Purification by preparative TLC (EtOAc–petroleum ether, 4:1) yielded 0.010 g (57.6%) of lactol **15** as a thick, clear, colorless oil: ^1H NMR δ 7.38–7.05 (m, 5 H), 5.81 (s, 1 H), 5.54 (d, J = 3 Hz, 1 H), 4.80 (d, J = 6 Hz, 1 H), 4.26–4.22 (m, 2 H), 3.08–2.99 (m, 1 H)8 2.98, 2.95 (AB q, J = 12 Hz, 2 H), 2.80, 2.50 (AB q, J = 18 Hz, 2 H), 2.42 (d, J = 3 Hz, 1 H); ^{13}C NMR δ 173.75, 135.35, 129.68, 129.00, 127.43, 110.86, 100.57,88.99, 66.99, 53.52, 50.69, 39.38, 37.52; IR 3464, 3421, 3381, 3331, 2941, 1787, 1498, 1454, 1419, 1374, 1346, 1277, 1180, 1135, 1098, 1058, 1019, 980, 956, 923, 847, 762, 705 cm^{-1}; MS, m/e 277 (MH^+).

(3a*α*,3b*β*,6a*β*,7a*α*)-(±)-Tetrahydro-3a-(phenylmethyl)difuro[2,3-*b*:3′,4′-*d*]furan-2,6(3*H*,6a*H*)-dione (1). Lactol **15** (0.0065 g, 0.024 mmol) was dissolved in 0.24 mL of CH_2Cl_2. Pyridinium chlorochromate (0.016 g, 0.072 mmol) was then added and the solution was stirred at room temperature for 4.5 h under N_2. Purification of the resulting opaque, brown solution by preparative TLC (EtOAc–petroleum ether, 4:1) yielded 0.0042 g (65.1%) of dilactone **1** as a white solid: mp 208–210 °C dec; ^1H NMR (CD_3OD/Me_2SO-d_6, 1/1) δ 7.34–7.24 (m, 5 H), 6.14 (s, 1 H), 4.93 (d, J = 5.5 Hz, 1 H), 4.61, 4.50 (AB octet, J = 9.0, 8.3 Hz, 2 H), 3.37–3.33 (m, 1 H), 3.00 (s, 2 H), 2.82, 2.68 (AB q, J = 18.6 Hz, 2 H); ^{13}C NMR (CD_3OD/Me_2SO-d_6, 1/1) δ 174.19, 172.04, 135.88, 129.86, 128.50, 126.93, 109.89, 78.82, 67.54, 53.56, 48.87, 37.37, 36.09; IR (KBr) 3418, 2931, 1782, 1496, 1454, 1424, 1385, 1335, 1280, 1206, 1187, 1119, 1101, 1058, 1014, 962, 915, 876, 772, 723, 705 cm^{-1}; HRMS (MH^+) calcd for $C_{15}H_{14}O_5$ 275.0919, found 275.0912.

Acknowledgment. We thank Prof. R. K. Boeckman, Jr. for helpful discussions, Dr. M. J. Shapiro for NMR analyses, Dr. E. W. Fu for mass spectral services, and Dr. C. M. Winslow for pharmacological studies.