Stereospecific Dicobalt Octacarbonyl Mediated Enyne Cyclization for the Enantiospecific Synthesis of a 6a-Carbocycline Analogue

Philip Magnus* and Daniel P. Becker

Contribution from the Department of Chemistry, Indiana University, Bloomington, Indiana 47405. *Received May 4, 1987*

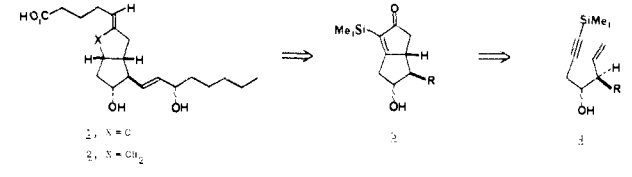
Abstract: D-(+)-Ribonolactone **5** was converted into the butenolide **7** by pyrolysis of the derived ortho ester. Treatment of **7** with trisyl bromide gave the corresponding trisylate **9**, which was converted into **10** by using $Li_2(CH_2{=}CH)_2CuCN$. Exposure of **10** to potassium carbonate in methanol gave epoxide **12**, which underwent ring opening when treated with lithium (trimethylsilyl)acetylide–$BF_3{\cdot}OEt_2$ to give lactone **13**. Reduction of lactone **13** with $LiAlH_4$ gave diol **18**, which was converted into its derived acetonide **19**. When **19** was treated with $Co_2(CO)_8/CO/Ph_3PO$, bicyclo[3.3.0]octenone **21** was formed in a highly stereoselective process. Conversion of **21** into the carbocycline analogue **28** was achieved by standard methods. The absolute configuration of **21** was established by single-crystal X-ray crystallography on the derived bis(*p*-bromobenzylidene) derivative **24**.

The discovery of prostacyclin[1] (PGI_2) (**1**) spurred an enormous amount of synthetic effort to find analogues that exhibited a similar biological response, combined with improved chemical stability.[2] A severe limitation in the use of prostacyclin as a therapeutic agent is its instability to hydrolytic conditions. Under physiological conditions it has a half-life of 3 min. 6a-Carboprostaglandin I_2 (**2**), or carbacyclin, where the oxygen atom of the enol ether function has been replaced by a methylene group, has proven to be the most sought after stable analogue of PGI_2 (**1**).[3,4]

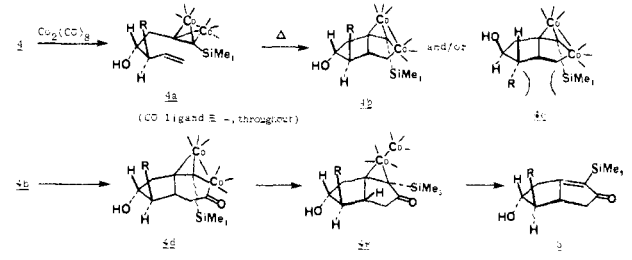
The Pauson–Khand reaction[5] lends itself to an exceptionally concise retrosynthetic representation of the synthesis of 6a-carboprostaglandin, and this is shown in Scheme I. The crucial $Co_2(CO)_8$-mediated cyclization to **4** to give **3** can be predicted to benefit from the Thorpe–Ingold effect.[6] Consequently, the R group should be attached to the secondary hydroxyl group to form a ring. The mechanistic hypothesis[7] we have advanced in order to predict the stereochemical relationship between allylic and propargylic substituents in the substrate (i.e., **4**) and the product **3** predicts that the stereoisomer **3** should be the major product. As a generalization, this hypothesis predicts that allylic and propargylic substituents in the resulting [3.3.0]bicyclooctenone system appear on the exo face, which corresponds to the more stable thermodynamic situation (Scheme II). Complex **4a** can form two cobalt metallocycles, **4b** and/or **4c**, upon alkene insertion into the internal Co–C bond. The newly formed five-membered-ring Co metallocycle is cis fused, since the corresponding trans fusion is unacceptably strained. Co metallocycle **4b** minimizes the steric interactions between the R group and the $SiMe_3$ group, whereas **4c** has a severe interaction between these substituents on the endo face. Subsequent CO insertion into **4b** leads to acylcobalt species **4d**, which undergoes C–Co migration to **4e**, followed by elimination of $[Co_2(CO)_6]$ to give the required bicyclo[3.3.0]octenone **3**.

Since an enantiospecific synthesis of **4** was required, D-(+)-ribonolactone **5** was the most convenient source of chirality.[8] The

Scheme I



Scheme II



(1) Moncada, S.; Gryglewski, R.; Bunting, S.; Vane, J. R. *Nature (London)* **1976**, *263*, 663. Moncada, S.; Vane, J. R. *J. Med. Chem.* **1980**, *23*, 591.

(2) Nelson, N. A.; Kelly, R. C.; Johnson, R. A. *Chem. Eng. News* **1982**, 30.

(3) Whittle, B. J. R.; Moncada, S.; Whiting, T.; Vane, J. R. *Prostaglandins* **1980**, *19*, 605.

(4) For syntheses of carbacyclin, see: Nicolaou, K. C.; Sipio, W. J.; Magolda, R. L.; Seitz, S.; Barnette, W. E. *J. Chem. Soc., Chem. Commun.* **1978**, 1067. Morton, D. R.; Brokaw, F. C. *J. Org. Chem.* **1979**, *44*, 2880. Barco, A.; Benetti, S.; Pollini, P.; Baraldi, P. G.; Gandolfi, C. *Ibid.* **1980**, *45*, 4776. Konishi, Y.; Kawamura, M.; Arai, Y.; Hayashi, M. *Chem. Lett.* **1979**, 1437. Sugie, A.; Shimomura, M.; Katsube, J.; Yamamoto, M. *Tetrahedron Lett.* **1979**, 2607. Shibasaki, M.; Ueda, J.; Ikegami, S. *Ibid.* **1978**, 3743. Yamazaki, M.; Shibasaki, M.; Ikegami, S. *Chem. Lett.* **1981**, 1245. Newton, R. F.; Wadsworth, A. H. *J. Chem. Soc., Perkin Trans. 1* **1982**, 823. Aristoff, P. A. *J. Org. Chem.* **1981**, *46*, 1954. Skuballa, W.; Vorbrüggen, H. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 1046. Shibasaki, M.; Iseka, K.; Ikegami, S. *Tetrahedron Lett.* **1980**, 169. Konishi, Y.; Kawamura, M.; Iguchi, Y.; Arai, Y.; Mayashi, M. *Tetrahedron* **1981**, *37*, 4391. Veno, K.; Suemune, H.; Sakai, K. *Chem. Pharm. Bull.* **1984**, *32*, 3768. Aristoff, P. A.; Johnson, P. D.; Harrison, A. W. *J. Am. Chem. Soc.* **1985**, *107*, 7967.

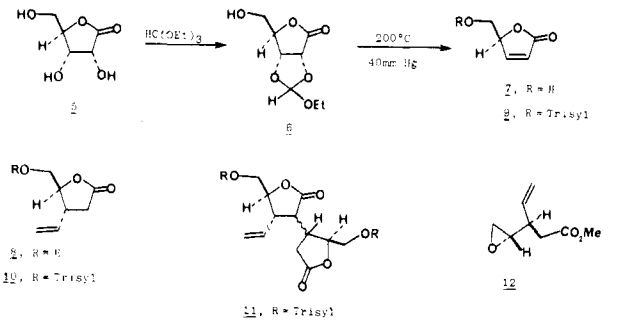
(5) For references to the original discovery of the Pauson–Khand reaction and subsequent applications to the synthesis of a variety of cyclopentenones, see: Khand, I. U.; Knox, G. R.; Pauson, P. L.; Watts, W. E. *J. Chem. Soc., Perkin Trans. 1* **1973**, 975. Khand, I. U.; Knox, G. R.; Pauson, P. L.; Watts, W. E.; Foreman, M. I. *Ibid.* **1973**, 977. Pauson, P. L.; Khand, I. U. *Ann. N.Y. Acad. Sci.* **1977**, *295*, 2. Blandon, P.; Khand, I. U.; Pauson, P. L. *J. Chem. Res., Synop.* **1977**, 8. *J. Chem. Res., Miniprint* **1977**, 153. Khand, I. U.; Pauson, P. L. *J. Chem. Soc., Perkin Trans. 1* **1976**, 30. Billington, D. C.; Pauson, P. L. *Organomet. Chem.* **1982**, *1*, 1560. Pauson, P. L. *Tetrahedron* **1985**, *41*, 5855. Billington, D. C. *Tetrahedron Lett.* **1983**, *24*, 2905. Schore, N. E.; Croudace, M. C. *J. Org. Chem.* **1981**, *46*, 5436. La Belle, B. E.; Knudson, M. J.; Olmstead, M. M.; Hope, H.; Yanuk, M. D.; Schore, N. E. *Ibid.* **1985**, *50*, 5215. Croudace, M. C.; Schore, N. E. *Ibid.* **1981**, *46*, 5357. Knudsen, M. J.; Schore, N. E. *Ibid.* **1984**, *49*, 5025. Smit, W. A.; Caple, R. *Tetrahedron Lett.* **1986**, *27*, 1241, 1245. Montaña, A. M.; Moyano, A.; Pericas, M. A.; Serratosa, F. *Tetrahedron* **1985**, *41*, 5995. Carcellar, E.; Centellas, V.; Moyano, A.; Pericas, M. A.; Serratosa, F. *Tetrahedron Lett.* **1985**, *26*, 2475.

(6) De Tar, D. F.; Luthra, N. P. *J. Am. Chem. Soc.* **1980**, *102*, 4505. Kirby, A. J. *Adv. Phys. Org. Chem.* **1980**, *17*, 208. Eliel, E. L. *Stereochemistry of Carbon Compounds*; McGraw-Hill: New York, 1962; pp 106–202.

(7) For references describing the stereoselectivity of the Pauson–Khand reaction and a working mechanistic hypothesis to rationalize and predict the stereochemical outcome of enyne cyclizations leading to bicyclo[3.3.0]octenones, see: Exon, C.; Magnus, P. *J. Am. Chem. Soc.* **1983**, *105*, 2477. Magnus, P.; Exon, C.; Albaugh-Robertson, P. *Tetrahedron* **1985**, *41*, 5861. Magnus, P.; Principe, L. M. *Tetrahedron Lett.* **1985**, *26*, 4851. Magnus, P.; Principe, L. M.; Slater, M. J. *J. Org. Chem.* **1987**, *52*, 1483.

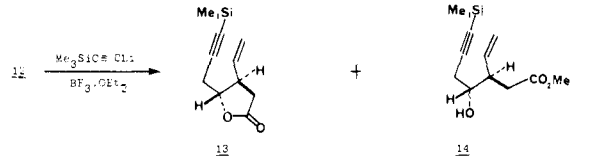
(8) Camps, P.; Cardellach, J.; Font, J.; Ortuno, R. M.; Ponsati, O. *Tetrahedron* **1982**, *38*, 2395. Drew, M. G. B.; Mann, J.; Thomas, A. *J. Chem. Soc., Perkin Trans. 1* **1986**, 2279. Chen, S.-Y.; Joullié, M. *J. Org. Chem.* **1984**, *49*, 2168.

0002-7863/87/1509-7495$01.50/0

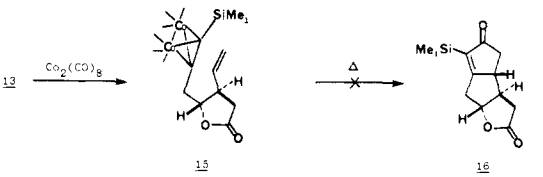


Camps[8] procedure was used to convert ortho ester **6** into butenolide **7** by pyrolysis (Kugelrohr) at 200 °C/40 mmHg (48% yield on a 0.1-mol scale). It should be noted that if **7** is converted into its derived *tert*-butyldimethylsilyl ether with Et_3N/DMAP, substantial amounts of racemization take place. This was revealed when **8** (made from **7** by $Li_2(CH_2{=}CH)_2CuCN$ addition followed by deprotection) was compared with the recent data reported by Kametani[9] and confirmed by ^1H NMR by using (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol in benzene-d_6 (7% optically pure). To avoid this problem and to provide protection of the hydroxyl group of **7** in combination with steric bulk and leaving ability, it was decided to examine the use of the 2,4,6-triisopropylbenzenesulfonyl ("trisyl") group.[10]

Treatment of **7** with trisyl chloride/CH_2Cl_2/pyridine under a number of conditions only gave low yields (<30%) of the required derivative **9**, and attempts to improve this situation resulted in elimination and racemization. To circumvent this problem, we treated **7** with trisyl bromide[11]/pyridine/0 °C for 2 h, which gave **9** (77%), $[\alpha]^{22}_D$ −46.5° (*c* 1.26 in $CHCl_3$). Treatment of **9** with the Lipschutz[12] higher order cuprate $Li_2(CH_2{=}CH)_2CuCN$ in Et_2O at −78 °C gave the required 1,4-conjugate addition adduct **10** (64%) and the unusual kinetic Michael product **11** (18%). Apparently, **11** is a single stereoisomer, although we cannot assign the configuration at the α-position. The benefit of having the trisyl group present is clearly demonstrated, in that treatment of **10** with K_2CO_3/MeOH resulted in clean conversion into epoxide **12** (94%). Addition of epoxy methyl ester **12** to a solution of lithium (trimethylsilyl)acetylide and $BF_3{\cdot}OEt_2$[13] in THF at −78 °C gave lactone **13** (73%) and hydroxy ester **14** (11%). Exposure of enyne

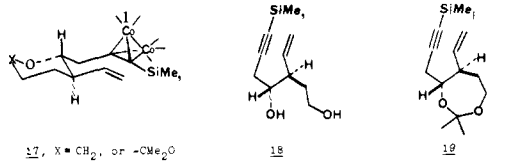


lactone **13** to $Co_2(CO)_8$ in *n*-heptane gave the dicobalt hexacarbonyl complex **15** (92%). The protons α to acetylene move downfield in the ^1H NMR spectrum from 2.8–2.7 ppm for the uncomplexed acetylene to 3.3–3.2 ppm for the cobalt-complexed acetylene. Heating complex **15** in heptane under an atmosphere of CO gave an insoluble polymer. None of the required tricyclic lactone **16** could be detected. Presumably, the strain involved in bringing the alkene appendage close to the complexed acetylene precludes the formation of *trans*-lactone **16**, whereas six- or seven-membered-ring derivatives such as **17** should allow the complexed acetylene and alkene groups to be held in close

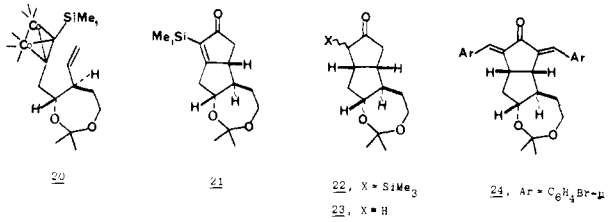


proximity without the excessive strain associated with **15**.

The γ-lactone **13** was reduced with $LiAlH_4$ to give crystalline diol **18** (93%). Similarly, hydroxy ester **14** can be converted into **18**. Treatment of **18** with acetone in benzene containing *p*-toluenesulfonic acid monohydrate (catalyst)/4A molecular sieves gave acetonide **19** (92%), $[\alpha]^{23}_D$ +21.2° (*c* 0.78 in $CHCl_3$). In



general, it is best to preform the $Co_2(CO)_6$–acetylene complex **20** (94%) and purify it by chromatography over silica gel prior to thermolysis. Addition of 1 equiv of tri-*n*-butylphosphine oxide[14] to complex **20** in heptane and heating for 3 days at 85 °C gave **21** (45%) (13% recovered **20** corresponds to a 51% yield of **21**), $[\alpha]^{22}_D$ −116° (*c* 2.47 in $CHCl_3$). The product **21** is a single stereoisomer as judged by ^1H NMR and ^{13}C NMR, and its structure and absolute stereochemistry were confirmed by single-crystal X-ray crystallography of the bis(*p*-bromobenzylidene) derivative **24**.[15]



Hydrogenation of **21** (5% Pd/C) gave α-trimethylsilyl derivative **22** (94%), whereas hydrogenation in a basic solvent such as ethanol gave **23**, albeit in low yield (30%). Protodesilylation of **22** with tetra-*n*-butylammonium fluoride in THF/H_2O gave **23** (94%). To establish the absolute configuration of **23**, it was condensed with 4-bromobenzaldehyde to give the bis(4-bromobenzylidene) derivative **24**. Suitable crystals were grown for X-ray crystallographic structure determination, and the absolute stereochemistry of **24** was confirmed, as shown. This provides unambiguous confirmation that the crucial dicobalt octacarbonyl mediated cyclization proceeded with the stereoselectivity predicted from the mechanistic hypothesis (Scheme II). To establish the optical purity of **23**, it was reduced with $NaBH_4$/EtOH to give **25** as a mixture of epimers (9:1 by HPLC). The major epimer was treated with (±)-(1-naphthyl)ethyl isocyanate to give a mixture of diastereomeric carbamates **26**, whereas treatment of **25** (major epimer, presumably α) with (*S*)-(+)-(1-naphthyl)ethyl isocyanate gave a single carbamate, **26**. HPLC analysis of the carbamates demonstrated that alcohol **25** (α-epimer) and thus ketone **23** were ≥99% enantiomerically pure.

(9) Suzuki, T.; Sato, E.; Kamada, S.; Tada, H.; Unno, K.; Kametani, T. *J. Chem. Soc., Perkin Trans. 1* **1986**, 387.

(10) Itakura, K.; Katagiri, N.; Bahl, C. P.; Wightman, R. H.; Narang, S. A. *J. Am. Chem. Soc.* **1975**, *97*, 7327.

(11) Apparently, trisyl bromide is an unknown compound: it was made from trisyl chloride via the hydrazine and treatment of trisylhydrazine with NaBr/$NaBrO_3$/10% HCl, following a procedure described for tosyl bromide: Poshkus, A. C.; Herweh, J. E.; Magnotta, F. A. *J. Org. Chem.* **1963**, *28*, 2766.

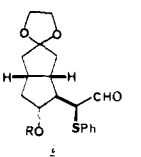
(12) Lipschutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A. *J. Org. Chem.* **1984**, *49*, 3938. Lipschutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A.; Parker, D. *Ibid.* **1984**, *49*, 3928.

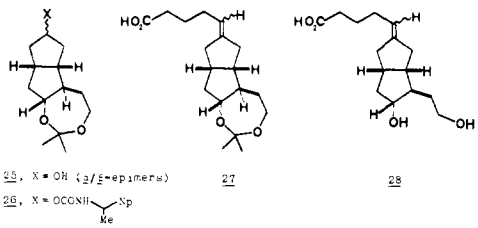
(13) Wada, M.; Sakurai, Y.; Akiba, K. *Tetrahedron Lett.* **1984**, *25*, 1079. Eis, M. J.; Wrobel, J. E.; Ganeni, B. *J. Am. Chem. Soc.* **1984**, *106*, 3693.

(14) Pauson, P. L. *Tetrahedron* **1985**, *41*, 5855.

(15) For details of the X-ray crystallographic structural determination of **24**, request report no. 86164 from the Department of Chemistry, Molecular Structure Center, Indiana University, Bloomington, IN 47405.

(16) Similar structures to **23** and **28**, such as i have been converted into carbocycline derivatives: Mori, K.; Tsuji, M. *Tetrahedron* **1986**, *42*, 435. Kojima, K.; Koyama, K.; Amemiya, S. *Ibid.* **1985**, *41*, 4449.





25, X = OH (α/β-epimers) 27 28

26, X = OCONH(Np)(Me)

Treatment of ketone **23** with the ylide derived from 4-(carboxybutyl)triphenylphosphonium bromide and potassium hydride gave acid **27** (58%) as an inseparable mixture of *E*/*Z* isomers. Mild hydrolysis of **27** gave diol **28**, thus completing the stereospecific synthesis of a 6a-carbocycline analogue. The synthesis of **28** proceeds in ten steps, with an overall yield of 7.5%.

Experimental Section

(−)-(4*S*)-4-(((2,4,6-Triisopropylbenzenesulfonyl)oxy)methyl)-2-butenolide (9). To hydroxy butenolide **7** (148 mg, 1.30 mmol) in CH_2Cl_2 (1.3 mL) at 0 °C was added pyridine (113 mg, 1.43 mmol) followed by solid trisyl bromide (677 mg, 1.95 mmol; dried for 12 h over P_2O_5 prior to use). After 2 h at 0 °C and 16 h of storage at −20 °C, 1 N HCl (20 mL) was added, plus additional CH_2Cl_2 (10 mL). Separation and extraction of the aqueous phase with CH_2Cl_2 were followed by washing of the combined organic phases in 1 N HCl, H_2O (2×), and brine. Drying and removal of the solvent in vacuo gave a white solid, which was chromatographed, eluting with CH_2Cl_2/petroleum ether (60/40 and 80/20), followed by EtOAc/CH_2Cl_2/petroleum ether (5/80/15) to give **9** (381 mg, 77%) as white needles: mp 121.5–122.5 °C (CH_2Cl_2/hexane); $[\alpha]^{22}_D$ −46.5° (*c* 1.26 in $CHCl_3$); IR ($CHCl_3$) 3030, 1771, 1603, 1351, 1180 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.52 (1 H, dd, *J* = 5.8, 1.5 Hz), 7.19 (2 H, s), 6.23 (1 H, dd, *J* = 5.7, 2.0 Hz), 5.28–5.24 (1 H, m), 4.32–4.21 (2 H, m), 4.08 (2 H, quint, *J* = 6.7 Hz), 2.91 (1 H, quint, *J* = 6.9 Hz), 1.25 (18 H, d, *J* = 6.8 Hz). Anal. Calcd for $C_{20}H_{28}O_5S$: C, 63.13; H, 7.42. Found: C, 63.26; H, 7.38.

(+)-(2*S*,3*R*)-2-(((2,4,6-Triisopropylbenzenesulfonyl)oxy)methyl)-3-vinyl-γ-butyrolactone (10) and Adduct 11. To CuCN (140 mg, 1.56 mmol) in Et_2O (3 mL) at −78 °C was added vinyllithium (1.39 mL of a 2.25 M solution in THF, 3.12 mmol). After warming to 0 °C for 12 min and then recooling to −78 °C, a solution of trisyl butenolide **9** (540 mg, 1.42 mmol) in Et_2O/THF (8 mL of a 1:1 solution) was added dropwise. After 1 h at −78 °C the reaction mixture was poured into a saturated aqueous solution of NH_4Cl (20 mL, buffered to pH 8 with aqueous NH_3). The aqueous phase was extracted with CH_2Cl_2 (3×), and the combined organic phases were washed with H_2O and dried (Na_2SO_4). Removal of the solvent in vacuo gave a yellow oil (598 mg), which was chromatographed on silica gel, eluting with EtOAc/CH_2Cl_2/petroleum ether (5/55/40), giving **10** (369 mg, 64%) as colorless needles: mp 87–88.5 °C (CH_2Cl_2/hexane); $[\alpha]^{21}_D$ +46.1° (*c* 1.33 in $CHCl_3$); IR ($CHCl_3$) 3021, 1791, 1600, 1178 cm^{-1}; ^1H NMR (360 MHz, $CdCl_3$) δ 7.19 (2 H, s), 5.73 (1 H, ddd, *J* = 18, 10, 8.2 Hz), 5.23 (1 H, d, *J* = 8.2 Hz), 5.22 (1 H, d, *J* = 18 Hz), 4.37 (1 H, ddd, *J* = 7.9, 4.5, 2.7 Hz), 4.28 (1 H, dd, *J* = 11, 2.7 Hz), 4.19 (1 H, dd, *J* = 11, 4.5 Hz), 4.09 (2 H, sept, *J* = 6.8 Hz), 3.10 (1 H, quint, *J* = 8.7 Hz), 2.91 (1 H, sept, *J* = 6.9 Hz), 2.76 (1 H, dd, *J* = 18, 8.9 Hz), 2.47 (1 H, dd, *J* = 19, 9.9 Hz), 1.26 (12 H, d, *J* = 6.8 Hz), 1.26 (6 H, d *J* = 6.9 Hz); MS *m*/*e* 408 (M^+, 5), 367 (8), 283 (15), 267 (21), 218 (20), 203 (100), 187 (86), 159 (38), 125 (32); MS *m*/*e* calcd for $C_{22}H_{32}O_5S$ 408.1970, found 408.1962. Anal. Calcd for $C_{22}H_{32}O_5S$: C, 64.68; H, 7.89. Found: C, 64.68; H, 7.91.

Continued elution with EtOAc/CH_2Cl_2/petroleum ether (10/50/40) gave adduct **11** (102 mg, 18%) as a white foam: mp 54–68 °C; $[\alpha]^{28}_D$ +24.8° (*c* 2.47 in $CHCl_3$); IR ($CHCl_3$) 3025, 1792, 1785, 1608, 1571, 1180 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.20 (2 H, s), 7.19 (2 H, s), 5.72 (1 H, ddd, *J* = 17, 9.9, 8.9 Hz), 5.40 (1 H, d, *J* = 17 Hz), 5.37 (1 H, d, *J* = 9.8 Hz), 4.86 (1 H, m), 4.34–4.27 (3 H, m), 4.21–4.15 (2 H, m), 4.06 (2 H, sept, *J* = 6.7 Hz), 4.04 (2 H, sept, *J* = 6.7 Hz), 2.98–2.87 (4 H, m), 2.85–2.77 (1 H, m), 2.78 (1 H, dd, *J* = 18, 9.9 Hz), 2.57 (1 H, dd, *J* = 18, 9.9 Hz), 2.57 (1 H, dd, *J* = 18, 5.3 Hz), 1.26 (12 H, d, *J* = 6.9 Hz), 1.25 (12 H, d, *J* = 6.9 Hz), 1.24 (12 H, d, *J* = 6.2 Hz); ^{13}C NMR (90 MHz, $CDCl_3$, off-resonance decoupled) δ 174.3, 174.2, 154.1, 150.9, 150.8, 133.4, 128.6, 128.3, 123.8, 122.4, 79.2, 78.9, 69.0, 65.7, 47.5, 46.4, 36.3, 34.1, 31.6, 29.6, 24.6, 24.5, 23.4. Anal. Calcd for $C_{42}H_{60}S_2O_{10}$: C, 63.93; H, 7.66. Found: C, 63.98; H, 7.79.

Methyl (3*R*,4*S*)-3-Vinyl-4,5-epoxypentanoate (12). To trisyl γ-lactone **10** (203 mg, 0.498 mmol) in dry MeOH (5 mL) at 0 °C was added K_2CO_3 (76 mg, 0.55 mmol). After 1 h at 0 °C and 1 h at 22 °C, an additional quantity (40 mg, 0.29 mmol) of K_2CO_3 was added. After 1 h more at 22 °C, the reaction was diluted with ether (10 mL), washed with water (2×), and then back-extracted with ether. Removal of most of the solvent via careful distillation through a Vigreux column gave an oil plus a white solid (potassium trisylate). The oil was dissolved in CH_2Cl_2 (leaving the white solid) and applied to a bed of silica gel. Elution with $CHCl_3$/petroleum ether (80/20) gave epoxide **12** (73 mg, 94%) as a colorless oil: bp 106–108 °C (14 mmHg); IR ($CHCl_3$) 3086, 1738, 1645, 1261 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 5.78 (1 H, ddd, *J* = 17, 11, 7.0 Hz), 5.16 (1 H, dd, *J* = 17, 1.0 Hz), 5.14 (1 H, dd, *J* = 11, 1.0 Hz), 3.68 (3 H, s), 2.93 (1 H, ddd, *J* = 6.7, 4, 2.7 Hz), 2.80 (1 H, t, *J* = 4 Hz), 2.63 (1 H, dd, *J* = 15, 5.3 Hz), 2.58 (1 H, dd, *J* = 4.8, 2.7 Hz), 2.50 (1 H, dd, *J* = 15, 8.2 Hz), 2.5–2.4 (1 H, m). Anal. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found: C, 61.30; H, 7.60.

(+)-(3*R*,4*R*)-3-Vinyl-4-(3-(trimethylsilyl)-2-propynyl)-γ-butyrolactone (13). To BF_3·OEt_2 (4.8 g, 34 mmol; freshly distilled) in THF (17 mL) was added lithium (trimethylsilyl)acetylide (34 mmol; prepared from *n*-BuLi (34 mmol) and (trimethylsilyl)acetylene (3.3 g, 34 mmol) in THF, −78 to −30 to −78 °C). After 4 min at −78 °C epoxide **12** (1.76 g, 11.2 mmol) in THF (10 mL) was added slowly. After the addition was complete, the reaction was stirred for an additional 15 min at −78 °C and then quenched with the addition of H_2O (15 mL). After warming to 20 °C over 0.5 h, the solution was extracted with ether (3×). The combined organic phases were washed with H_2O (2×) and brine and dried (Na_2SO_4). Removal of the solvent in vacuo gave an oil, which was chromatographed on silica gel, eluting with EtOAc/petroleum ether (2/98, then 5/95) to give γ-lactone **13** (1.83 g, 73%) as a colorless oil: $[\alpha]_D$ +46.1° (*c* 1.78 in $CHCl_3$); IR ($CHCl_3$) 2180, 1781, 1645, 1253, 844 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 5.80 (1 H, ddd, *J* = 17, 10, 7.9 Hz), 5.21 (1 H, d, *J* = 17 Hz), 5.18 (1 H, d, *J* = 10 Hz), 4.30 (1 H, dt, *J* = 7.2, 5.1 Hz), 3.08 (1 H, quint, *J* = 8.2 Hz), 2.80 (1 H, dd, *J* = 18, 8.8 Hz), 2.73 (1 H, dd, *J* = 17, 5.4 Hz), 2.63 (1 H, dd, *J* = 17, 4.8 Hz), 2.60 (1 H, dd, *J* = 18, 9.3 Hz), 0.17 (9 H, s); MS *m*/*e* 223 (M^+, 6), 207 (43), 163 (19), 147 (15), 135 (38), 111 (100), 109 (24), 83 (24), 73 (93); MS *m*/*e* calcd for $C_{12}H_{19}O_2Si$ (MH^+) 223.1154, found 223.1152.

(+)-(4*R*,5*R*)-1-(Trimethylsilyl)-4,7-dihydroxy-5-vinyl-1-heptyne (18). To a slurry of $LiAlH_4$ (625 mg, 16.4 mmol) in Et_2O (17 mL) at 0 °C was added a solution of γ-lactone **13** (1.83 g, 8.23 mmol) in Et_2O (10 mL). After 1 h at 0 °C the reaction solution was poured into a saturated aqueous solution of NH_4Cl (50 mL). Extraction with Et_2O (12×; product detected in the first 11 extractions by TLC), drying (Na_2SO_4), and removal of solvent in vacuo gave a colorless oil (IR recorded), which was redissolved in CH_2Cl_2/hexane (5/95). Removal of this solvent mixture gave diol **18** (1.72 g, 92.5%) as flocculent white needles: mp 61.5–63 °C (hexanes); $[\alpha]^{23}_D$ +17.3° (*c* 1.01 in $CHCl_3$); IR (thin film) 3340, 3072, 2163, 1635, 840 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 5.63 (1 H, dt, *J* = 18, 10 Hz), 5.13 (1 H, dd, *J* = 18, 1.7 Hz), 5.12 (1 H, dd, *J* = 10, 1.7 Hz), 3.74 (1 H, quint, *J* = 5.6 Hz), 3.63 (2 H, m), 2.53 (1 H, dd, *J* = 17, 3.9 Hz), 2.35 (1 H, dd, *J* = 17, 7.6 Hz), 2.32 (1 H, m), 2.04 (1 H, s), 1.96 (1 H, dddd, *J* = 14, 8.0, 5.7, 4.7 Hz), 1.72 (1 H, s), 1.62 (1 H, ddt, *J* = 14, 8.6, 5.6 Hz), 0.16 (9 H, s). Anal. Calcd for $C_{12}H_{22}O_2Si$: C, 63.66; H, 9.80. Found: C, 63.37; H, 9.65.

(+)-(4*R*,5*R*)-1-(Trimethylsilyl)-4,7-(isopropylidenedioxy)-5-vinyl-1-heptyne (19). To a solution of diol **18** (2.20 g, 9.72 mmol) in benzene (90 mL) and acetone (7 mL, 97 mmol) was added 4-Å molecular seives (15 g) followed by TsOH·H_2O (92 mg, 0.48 mmol). The reaction was stirred for 72 h at 22 °C and then filtered, rinsing with dry Et_2O. The resulting solution was washed with saturated aqueous $NaHCO_3$, H_2O, and brine and dried ($MgSO_4$). Removal of the solvent in vacuo gave a slightly yellow crystalline solid (2.48 g), which was chromatographed on silica gel, eluting with EtOAc/petroleum ether (5/95) to give acetonide **19** (1.91 g, 74%) as white needles: mp 46–47.5 °C (CH_2Cl_2/hexane); $[\alpha]^{23}_D$ +21.2° (*c* 0.78 in $CHCl_3$); IR ($CHCl_3$) 3070, 2168, 1640, 1591, 1250, 1073, 843 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 5.51 (1 H, dt, *J* = 17, 10 Hz), 5.04 (1 H, dd, *J* = 17, 1.7 Hz), 4.99 (1 H, dd, *J* = 10, 1.7 Hz), 3.81 (2 H, m), 3.58 (1 H, dt, *J* = 12, 3.2 Hz), 2.50 (1 H, dd, *J* = 17, 2.8 Hz), 2.21 (1 H, dd, *J* = 17, 9.9 Hz), 2.09 (1 H, ddd, *J* = 15, 9.6, 5.8 Hz), 1.40 (3 H, s), 1.35 (3 H, s), 0.21 (9 H, s). Anal. Calcd for $C_{15}H_{26}O_2Si$: C, 67.62; H, 9.84. Found: C, 67.52; H, 9.60. On a larger scale **19** was obtained in 92% yield.

[(4*R*,5*R*)-1-(Trimethylsilyl)-4,7-(isopropylidenedioxy)-1-heptyne]-hexacarbonyldicobalt (20). To a solution of acetonide **19** (165 mg, 0.62 mmol) in *n*-heptane (1 mL, purged with CO for 1.5 h prior to use) was added $Co_2(CO)_8$ (222 mg, 0.65 mmol). After 3 h at 22 °C the dark brown solution was applied directly to a bed of silica gel and eluted with EtOAc/petroleum ether (1/99) to give **20** (320 mg, 94%) as a dark red-brown oil: IR (hexanes) 2081, 2042, 2013, 1595, 1250, 1218, 1081, 838 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 5.79 (1 H, ddd, *J* = 17, 10, 7.9 Hz), 5.16 (1 H, d, *J* = 17 Hz), 5.12 (1 H, d, *J* = 10 Hz), 3.94 (1 H, ddd, *J* = 9.8, 4.4, 2.6 Hz), 3.81 (1 H, t, *J* = 11 Hz), 3.59 (1 H, dt, *J* = 12, 3.3 Hz), 3.37 (1 H, dd, *J* = 16, 2.4 Hz), 3.29 (1 H, dd, *J* = 16, 4.6 Hz), 2.51 (1 H, m), 1.76 (1 H, m), 1.62 (1 H, m), 1.36 (3 H, s), 1.35

(3 H, s), 0.33 (9 H, s).

(−)-(5*R*,6*R*,7*R*)-2-(Trimethylsilyl)-6,7-((isopropylidenedioxy)ethylene)bicyclo[3.3.0]oct-2-en-3-one (21). To complex **20** (1.28 g, 2.32 mmol) in *n*-heptane (23 mL, purged with CO for 3 h prior to use) was added tri-*n*-butylphosphine oxide (506 mg, 2.32 mmol). The solution was sealed in a screwcap resealable tube under an atmosphere of CO and heated to 85 °C (over glyme heated at reflux) for 71 h. After cooling, the solution was applied directly to a bed of Florisil and eluted with EtOAc/petroleum ether (5/95–50/50), giving tricyclic enone **21** (304 mg, 45%) as a colorless oil: $[\alpha]^{22}_D$ 116° (*c* 2.47 in $CHCl_3$); UV λ_{max} = 239 nm (ϵ = 11 000 in MeOH); IR (thin film) 1697, 1613, 1215, 833 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 4.32 (1 H, q, *J* = 8.7 Hz), 3.76 (2 H, dd, *J* = 7.7, 1.4 Hz), 3.07 (1 H, dd, *J* = 20, 9.3 Hz), 2.50 (3 H, m), 2.04 (1 H, m), 1.83 (1 H, ddd, *J* = 13.8, 4.4, 1.4 Hz), 1.48 (1 H, m), 1.38 (3 H, s), 1.36 (3 H, s), 1.32 (1 H, m), 0.17 (9 H, s); ^{13}C NMR (75 MHz, $CDCl_3$, gated decoupled) δ 213.1 (s), 193.1 (s), 136.4 (s), 101.5 (s), 76.5 (d), 61.5 (t), 52.2 (d), 51.4 (d), 41.3 (t), 34.9 (t), 32.8 (t), 25.5 (q), 24.5 (q), 1.38 (q); MS *m/e* calcd for $C_{16}H_{26}O_3Si$ 294.1651, found 294.1642.

(+)-(1*S*,2*S*,5*S*,6*R*,7*R*)-2-(Trimethylsilyl)-6,7-((isopropylidenedioxy)ethylene)bicyclo[3.3.0]octan-3-one (22). A suspension of 5% Pd/C (88 mg, 0.04 mmol) in EtOAc (2 mL, passed through basic alumina and distilled prior to use) was stirred under an atmosphere of H_2 for 1 h, after which time a solution of trimethylsilyl enone **21** (255 mg, 0.864 mmol) in EtOAc (6 mL; purified as above) was added. The suspension was stirred under an atmosphere of H_2 for 21 h at 22 °C and then filtered through Celite. Removal of the solvent in vacuo gave trimethylsilyl ketone **22** (240 mg, 94%) as a colorless oil, which solidified on standing: $[\alpha]^{19}_D$ +125° (*c* 0.64 in $CHCl_3$); IR ($CHCl_3$) 1712, 1251, 1159, 1080, 845 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 3.97–3.90 (1 H, m), 3.80–3.67 (2 H, m), 3.00–2.86 (1 H, m), 2.58 (1 H, ddd, *J* = 19, 10, 2 Hz), 2.15 (1 H, dd, *J* = 11, 1.8 Hz), 2.11–2.02 (2 H, m), 1.88–1.77 (1 H, m), 1.48–1.20 (4 H, m), 1.36 (3 H, s), 1.35 (3 H, s), 0.16 (9 H, s); MS *m/e* calcd for $C_{16}H_{28}O_3Si$ 296.1808, found 296.1795.

(−)-(1*R*,5*S*,6*R*,7*R*)-6,7-((Isopropylidenedioxy)ethylene)bicyclo[3.3.0]octan-3-one (23). To a solution of trimethylsilyl ketone **22** (28 mg, 0.094 mmol) in THF (1 mL) at 0 °C, buffered with NH_4Cl (7 mg, 0.13 mmol) and H_2O (1 drop), was added tetra-*n*-butylammonium fluoride (0.13 mL of a 1 M solution in THF). After 15 min at 0 °C a saturated aqueous solution of NH_4Cl (1 mL) was added. Extraction with ether (2×), washing with H_2O and brine, drying (Na_2SO_4), and removal of the solvent in vacuo gave **23** (21.4 mg, 100%) as a colorless oil, which solidified to a colorless, waxy solid (microscopic rods): mp 45–50 °C; $[\alpha]^{26}_D$ −1.9° (*c* 0.94 in $CHCl_3$); IR ($CHCl_3$) 1732, 1382, 1222, 1154, 1088, 908 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 4.00 (1 H, td, *J* = 9.6, 7.8 Hz), 3.73 (2 H, m), 2.69 (1 H, quint d, *J* = 8.6, 1.6 Hz), 2.60 (1 H, ddd, *J* = 19, 10, 1.5 Hz), 2.43 (1 H, ddd, *J* = 19, 9.4, 1.4 Hz), 2.34 (1 H, dt, *J* = 13, 8.1 Hz), 2.21 (1 H, ddd, *J* = 20, 11, 2.2 Hz), 2.06 (1 H, ddd, *J* = 20, 12, 1.3 Hz), 1.72 (1 H, dd, *J* = 11, 2.3 Hz), 1.44–1.25 (4 H, m), 1.35 (3 H, s), 1.33 (3 H, s); ^{13}C NMR (75 MHz, $CDCl_3$, gated decoupled) δ 220.0 (s), 101.2 (s), 76.6 (d), 61.3 (t), 52.4 (d), 45.9 (t), 42.5 (t), 42.2 (d), 39.1 (t), 34.7 (d), 33.0 (t), 25.3 (q), 24.7 (q); MS *m/e* 224 (M^+, 12), 209 (27), 166 (38), 122 (25), 109 (30), 96 (43), 79 (55), 68 (100); MS *m/e* calcd for $C_{13}H_{20}O_3$ 224.1412, found 224.1413.

(1*S*,5*S*,6*R*,7*R*)-2,4-Bis(4-bromobenzylidene)-6,7-((isopropylidenedioxy)ethylene)bicyclo[3.3.0]octan-3-one (24). To a solution of ketone **23** (5.4 mg, 0.024 mmol) and 4-bromobenzaldehyde (9 mg, 0.048 mmol) in absolute ethanol (0.5 mL) was added benzyltrimethylammonium hydroxide (0.005 mL of a 40% solution in methanol, 0.01 mmol) with stirring under argon at 21 °C. After 22 h the thick yellow suspension was filtered and the light yellow filter cake was rinsed 3 times with absolute ethanol. Drying under vacuum gave bisbenzylidine **24** as a yellow solid (5.5 mg, 42%), which was recrystallized to give yellow needles suitable for X-ray crystallographic analysis: mp 177–181 °C (CH_2Cl_2/hexane); IR ($CHCl_3$) 3005, 1694, 1624, 1587, 1208, 1074, 1010 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.57–7.46 (8 H, m), 7.43 (1 H, s), 7.41 (1 H, s), 4.20 (1 H, q, *J* = 9 Hz), 3.83 (1 H, qd, *J* = 8, 3 Hz), 3.65 (1 H, td, *J* = 14, 7 Hz), 1.56–1.20 (4 H, m), 1.32 (3 H, s), 1.22 (3 H, s); MS *m/e* calcd for $C_{27}H_{26}{}^{80}Br_2O_3$ (MH^+) 561.0286, found 561.0269.

(+)-(1*S*,5*S*,6*R*,7*R*)-3-Hydroxy-6,7-((isopropylidenedioxy)ethylene)bicyclo[3.3.0]octane (25). To a solution of ketone **23** (21.7 mg, 0.0967 mmol) in absolute ethanol (0.5 mL) was added sodium borohydride (4 mg, 0.11 mmol) with stirring at 21 °C. After 12 h at 21 °C, brine was added (1 mL) and the solution was extracted with diethyl ether (5×). Drying with sodium sulfate and removal of the solvent in vacuo gave alcohol **25** (20.2 mg, 92%) as a mixture of epimers about the C-3 hydroxyl (shown to be in a 9:1 ratio by HPLC). Chromatography of Florisil of a 5.9-mg portion of the alcohols accomplished separation of the two epimers, giving the major diastereomer (2.8 mg, 48%) as a colorless oil, which solidified on standing to microscopic needles: mp 80–82 °C; $[\alpha]^{21}_D$ +53° (*c* 0.29 in $CHCl_3$); IR ($CHCl_3$) 3618, 3570–3280, 1383, 1210, 1089 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 4.31 (1 H, quint, *J* = 5.7 Hz), 3.89 (1 H, ddd, *J* = 11, 9.7, 6.6 Hz), 3.77 (1 H, td, *J* = 12, 1.0 Hz), 3.67 (1 H, ddd, *J* = 12, 3.5, 2.7 Hz), 2.44–2.31 (1 H, m), 2.14–1.97 (3 H, m), 1.90 (1 H, qd, *J* = 10, 4.7 Hz), 1.81–1.74 (1 H, m), 1.70–1.20 (6 H, m), 1.34 (3 H, s), 1.33 (3 H, s); MS *m/e* calcd for $C_{13}H_{22}O_3$ 226.1569, found 226.1567.

Preparation of Diastereomeric Carbamates 26 from 25 and (+)-1-(1-Naphthyl)ethyl Isocyanate. To a solution of alcohol **25** (1.2 mg, 0.0053 mmol) in dry toluene (0.3 mL) was added (±)-1-(1-naphthyl)ethyl isocyanate (1.0 mg, 0.0053 mmol), and the resulting solution was heated under reflux for 47 h. This crude reaction mixture was concentrated in vacuo and redissolved in 20/80 ethyl acetate/hexane for analysis for HPLC (see the following experimental entry).

Preparation of Carbamate 26 from 25 and (*S*)-(+)-1-(1-Naphthyl)ethyl Isocyanate: Determination of Optical Purity by HPLC. To a solution of alcohol **25** (5.2 mg, 0.023 mmol) in dry toluene (0.3 mL) was added (*S*)-(+)-1-(1-naphthyl)ethyl isocyanate (4.5 mg, 0.023 mmol), and the resulting solution was heated under reflux for 47 h. This crude reaction mixture was concentrated in vacuo and redissolved in 20/80 ethyl acetate/hexane for analysis by HPLC on silica gel. Injections of 20 μL of a solution of ca. 5 mg/mL were eluted at a rate of 2.5 mL/min under a pressure of 1600 psi. Detection was accomplished by UV monitoring at 254 nm, revealing the presence of two diastereomers in a ratio of 98.5:1.5, with retention times of 6.4 and 7.4 min, respectively. Thus, ignoring kinetic resolution, the optical purity of carbamate **26** (and of related carbacyclin precursors) is 98.5%. Analysis of the diastereomeric carbamates **26** (prepared from (±)-1-(1-naphthyl)ethyl isocyanate as described in the preceding experimental entry) with the identical HPLC system revealed the two diastereomers (retention times 6.4 and 7.4 min, respectively) in a ratio of 25:75. Thus, considering kinetic resolution, the optical purity of carbamate **26**, and corresponding ketone **23**, is ≥99%.

Wittig Procedure: Preparation of Acid 27. To the dry powder potassium hydride (19 mg, 0.47 mmol; from 54 mg of a 35% oil dispersion washed 4 times with dry pentane and dried under a stream of argon) was added dry dimethyl sulfoxide (0.1 mL; distilled 3 times from calcium hydride) at 21 °C. The effervescence proceeded for 10 min at 21 °C, and after 0.5 h, a solution of (4-carboxybutyl)triphenylphosphonium bromide (105 mg, 0.24 mmol; dried for 7 days in the presence of phosphorus pentoxide under high vacuum over ethanol at reflux) in dimethyl sulfoxide (0.4 mL) was added dropwise. The resulting red ylide was stirred for 20 min at 21 °C, after which time a solution of ketone **23** (17.7 mg, 0.0789 mmol) in dimethyl sulfoxide (0.4 mL) was added. When the addition was complete, the solution was heated to 40 °C. A high vacuum was applied for several hours in order to reduce the volume to ca. 0.2 mL, and then the concentrated solution was stirred for 3 days at 40 °C. The reaction solution was then transferred via pipet directly into pH 3 buffer (1 mL; HCl/potassium biphthalate) and extracted with diethyl ether (3×). The organic phase was washed with water (2×) and brine and dried over $MgSO_4$. Removal of the solvent gave a colorless solid (35 mg), which was chromatographed on Florisil, eluting with ethyl acetate/petroleum ether/acetic acid (2/97/1), giving acid **27** (13.9 mg, 58%) as a colorless oil: IR ($CHCl_3$) 3602, 3001, 1710, 1222, 1085, 1042 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 5.28–2.50 (1 H, m), 3.90–3.80 (1 H, m), 3.80–3.65 (2 H, m), 2.65–2.25 (5 H, m), 2.25–1.83 (5 H, m), 1.80–1.65 (2 H, m), 1.50–1.15 (6 H, m), 1.34 (3 H, s), 1.32 (3 H, s); MS *m/e* calcd for $C_{18}H_{28}O_4$ 308.1988, found 308.1995.

Hydrolysis of Acid Acetonide 27 to Diol 28. To a solution of acetonide **27** (3.1 mg, 0.010 mmol) in THF (0.2 mL) at 0 °C was added 35% aqueous acetic acid (0.2 mL). The solution was warmed to 21 °C and stirred for 2 h, after which time toluene (20 mL) was added and the mixture was stripped in vacuo. The toluene addition/evaporation sequence was repeated twice, leaving diol acid **28** (2.4 mg, 89%) as a colorless oil: IR ($CHCl_3$) 3600, 3660–2800, 1708, 1223, 1075 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 5.30–5.20 (1 H, m), 3.98–3.87 (1 H, m), 3.80–3.66 (2 H, m), 2.91 (3 H, s, br), 2.52–1.91 (10 H, m), 1.85–1.15 (7 H, m).

The TLC of this material showed only one spot (phosphomolybdic acid visualization) after elution in a wide variety of solvent systems. A multiple (3×) elution in ethyl acetate/hexane/acetic acid (80/19/1) resolved the material into two spots for the two olefin isomers (R_f 0.40 and 0.37 after three elutions).

Acknowledgment. The National Science Foundation is thanked for their financial support of this work. Dr. John Huffman (Molecular Structure Center, Indiana University, Bloomington, IN 47405) is gratefully thanked for the X-ray crystallographic structure determination of **24**.