Synthesis of (*R*)-(4-Methoxy-3,5-dihydroxyphenyl)glycine Derivatives: The Central Amino Acid of Vancomycin and Related Agents

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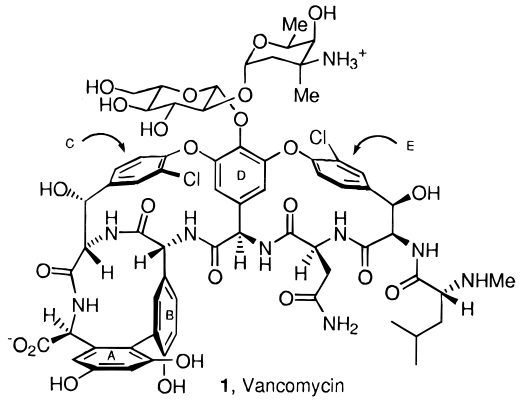
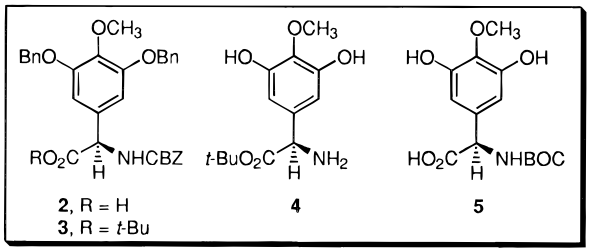
Vancomycin (**1**)[1] was isolated in 1956 from *Streptomyces orientalis* and its structure and stereochemistry were ultimately secured over 25 years later by a combination of chemical degradation,[1b] NMR,[1d,e] and X-ray crystallography studies.[1f] This prototypic member of a large and growing class of clinically effective glycopeptide antibiotics[2−4] which includes teicoplanin,[2a] ristocetin,[2b] β-avoparcin,[2c] actaplanin (A4696),[2d] and A33512B[2e] is characterized by a polycyclic heptapeptide backbone composed of two 16-membered biaryl ether ring systems (CD and DE). Central to the characteristic bicyclic ring system is a (*R*)-(3,4,5-trihydroxyphenyl)glycine in which the meta 3,5-phenols form biaryl ethers to link the CD and DE rings. Herein, we report an asymmetric synthesis of **2**−**5** constituting selectively protected derivatives of (*R*)-(3,4,5-trihydroxyphenyl)glycine[5] which have been utilized in our efforts[6] on the development of synthetic approaches[4] to vancomycin and related agents.

Key to the approach which complements the disclosed routes to the asymmetric synthesis of phenylglycines[7] was the Sharpless asymmetric dihydroxylation[8] of a substituted styrene for introduction of the α-center absolute stereochemistry as well as functionality for subsequent elaboration to the phenylglycine carboxylate. Following selective C4 *O*-methylation of methyl 3,4,5-trihydroxybenzoate as detailed by Pedro,[9] the remaining C3 and C5 phenols were protected as benzyl ethers





(Scheme 1). Two-step conversion of the ester **6** to the aldehyde **8**[10] (95 × 90%) and subsequent Wittig reaction with methylenetriphenylphosphorane provided the substituted styrene **9** (70%) and the key substrate for asymmetric dihydroxylation. Treatment of **9** with AD-mix-α[8] (1:1 *t*-BuOH/H_2O, 0.1 M, 25 °C, 20 h) provided **10** in superb conversions (97%) and high ee's (87% ee). The optical purity of **10** was assessed directly by chiral phase HPLC separation of the enantiomers on an analytical Diacel Chiralpak AD column (0.46 × 25 cm, 10% 2-propanol−hexane, 0.5 mL/min) alongside racemic material. The desired (*S*)-**10** eluted with a retention time of 58.9 min and the enantiomer, (*R*)-**10**, eluted with a retention time of 55.1 min (ratio = 93.5:6.5). Following selective protection of the primary alcohol of **10** as its TBDMS ether **11**, direct azide displacement of the secondary alcohol upon Mitsunobu activation (2.5 equiv of DPPA, 2.5 equiv of DEAD, THF, −20 to 25 °C, 2 h)[11] with clean inversion of stereochemistry and subsequent reduction of the crude azide **12** (2 equiv of Ph_3P, THF−H_2O, 45 °C, 21 h, 65% for two steps) provided the amine **13**. Small amounts of elimination (7%) but no loss of the stereochemical integrity was observed during the displacement. N-CBZ protection of **13** provided **14** (90%), and deprotection of the TBDMS ether provided the key alcohol **15** (92%). The optical purity of **15** obtained directly from **10** without intervening recrystallizations was 84−87% ee indicating a maintenance of the stereochemical integrity throughout the sequence and of the crystalline intermediates, **15** proved to be the most convenient for storage, assessment, and enrichment of the optical purity. One recrystallization from 50% EtOAc−hexane routinely enriched the optical purity of **15** from 87% ee to ≥94% ee. The optical purity of **15** was assessed on a Chiralpak AD HPLC column (0.46 × 25 cm, 30% 2-propanol−hexane, 1.0 mL/min), (*R*)-**15** t_R = 13.0 min and (*S*)-**15** t_R = 7.9 min.

(1) (a) McCormick, M. H.; Stark, W. M.; Pittenger, G. F.; Pittenger, R. C.; McGuire, G. M. *Antibiot. Annu.* **1955**−**1956**, 606. (b) Harris, C. M.; Kopecka, H.; Harris, T. M. *J. Am. Chem. Soc.* **1983**, *105*, 6915. (c) Harris, C. M.; Harris, T. M. *J. Am. Chem. Soc.* **1982**, *104*, 4293. (d) Williams, D. H.; Kalman, J. R. *J. Am. Chem. Soc.* **1977**, *99*, 2768. (e) Williamson, M. P., Williams, D. H. *J. Am. Chem. Soc.* **1981**, *103*, 6580. (f) Sheldrick, G. M.; Jones, P. G.; Kennard, O.; Williams, D. H.; Smith, G. A. *Nature* **1978**, *271*, 223.

(2) (a) Cornell, I. C.; Bardone, M. R.; Deparli, A.; Ferrari, P.; Tuan, G.; Gallo, G. G. *J. Antibiot.* **1984**, *37*, 621. (b) Harris, C. M.; Kibby, J. J.; Fehlner, J. R.; Raabe, A. B.; Barber, T. A.; Harris, T. M. *J. Am. Chem. Soc.* **1979**, *101*, 437. (c) McGahren, W. J.; Martin, J. H.; Morton, G. O.; Hargreaves, R. T.; Leese, R. A.; Lovell, F. M.; Ellestad, G. A.; O'Brien, E.; Holker, J. S. E. *J. Am. Chem. Soc.* **1980**, *102*, 1671. (d) Hunt, A. H.; Debono, M.; Merkel, K. E.; Barnhart, M. *J. Org. Chem.* **1984**, *49*, 635. (e) Debono, M.; Molloy, R. M.; Barnhart, M.; Dorman, D. E. *J. Antibiot.* **1980**, *33*, 1407.

(3) Williams, D. H.; Rajananda, V.; Williamson, M. P.; Bojesen, G. *Top. Antibiot. Chem.* **1980**, *5*, 119. Barna, J. C. J.; Williams, D. H. *Annu. Rev. Microbiol.* **1984**, *38*, 339. Williams, D. H. *Acc. Chem. Res.* **1984**, *17*, 364. Williams, D. H.; Searle, M. S.; Westwell, M. S.; Mackay, J. P.; Groves, P.; Beauregard, D. A. *Chemtracts: Org. Chem.* **1994**, *7*, 133.

(4) Rao, A. V. R.; Gurjar, M. K.; Reddy, K. L.; Rao, A. S. *Chem. Rev.* **1995**, *95*, 2135. Evans, D. A.; DeVries, K. M. *Drugs Pharm. Sci.* **1994**, *63*, 63.

(5) Zhu, J.; Bouillon, J.-P.; Singh, G. P.; Chastanet, J.; Beugelmans, R. *Tetrahedron Lett.* **1995**, *36*, 7081.

(6) Boger, D. L.; Borzilleri, R. M.; Nukui, S. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 3091. Boger, D. L.; Nomoto, Y.; Teegarden, B. R. *J. Org. Chem.* **1993**, *58*, 1425.

(7) Williams, R. M.; Hendrix, J. A. *Chem. Rev.* **1992**, *92*, 889.

(8) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483. Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768.

(9) Cardona, M. L.; Fernandez, M. I.; Garcia, M. B.; Pedro, J. R. *Tetrahedron* **1986**, *42*, 2725.

(10) Sethi, M. L.; Taneja, S. C.; Dhar, K. L.; Atal, C. K. *Indian J. Chem.* **1981**, *20B*, 770.

(11) Bansi, L.; Pramanik, B. N.; Manhas, M. S.; Bose, A. K. *Tetrahedron Lett.* **1977**, *18*, 1977.

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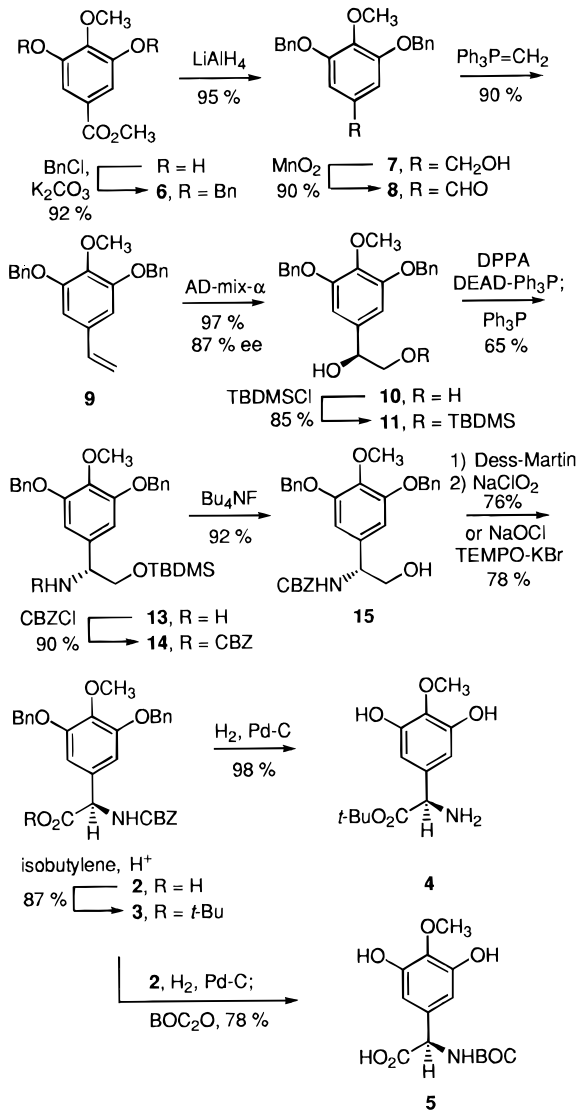
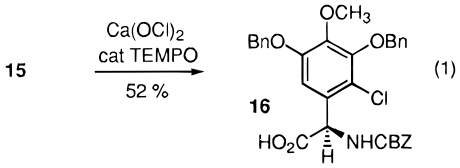
Scheme 1



Direct oxidation of the primary alcohol to the desired sensitive carboxylic acid **2** was accomplished best using *N*-oxoammonium salts[12] in combination with NaOCl in a buffered solution (2 equiv of 4−6% NaOCl, 1.1 equiv of TEMPO, 0.1 equiv of KBr, acetone−5% aqueous $NaHCO_3$, 0 °C, 2 h, 78%). In the optimization of this reaction it was found that 1.1 equiv of TEMPO was necessary to obtain the desired oxidation product. If a catalytic amount (*ca*. 0.1 equiv) of TEMPO was employed or $Ca(OCl)_2$[13] was substituted for NaOCl, the chlorinated aromatic derivative **16** was isolated as the major product (eq 1). Presumably the TEMPO scavenges any chlorine which is liberated during the reaction. Similarly, propylene oxide could be utilized as the chlorine scavenger; however, the conversions to **15** were lower (40−50%). Using this optimized procedure, **2** could be obtained in good chemical yields (78%) with little or no racemization (94% ee). This could also be accomplished by conducting the oxidation in two separate steps without purification of the sensitive intermediate aldehyde by Dess−Martin oxidation (2 equiv, 30 min, CH_2Cl_2, 25 °C) followed by $NaClO_2$ treatment (9 equiv, 30% 0.7 M aqueous NaH_2PO_4-*t*-BuOH, excess 2-methyl-2-butene, 25 °C, 20 min) which provided **2** in comparable chemical yields (75−77%) but with surprisingly little or no racemization (90−94% ee). Because of the ease of scale up, this latter procedure was used to routinely provide our material.[13] In contrast, alcohol **15** underwent oxidation in the presence of PDC (4.5 equiv, DMF, 25 °C, 21 h) to provide **2** in only modest yields (20−30%) with extensive decomposition. Alternative oxidative conditions examined including $RuCl_3$ (0.2 equiv)−$NaIO_4$ (3 equiv, CCl_4−MeCN−H_2O, 3:1:1, 25 °C, 24 h) or Jones oxidation led to decomposition, and Pt/C (0.1 equiv)−O_2 ($NaHCO_3$, H_2O−acetone, 25 °C, 22 h) led to recovered starting material. Protection of **2** as its *tert*-butyl ester **3** (≥94% ee),[14] which was selected over the methyl ester in order to minimize potential racemization when employed in subsequent synthetic efforts, followed by uneventful CBZ deprotection by hydrogenolysis provided **4**. Similarly, CBZ deprotection of **2** followed by *N*-BOC protection of the free amino acid provided **5**.



Experimental Section

Methyl 3,5-Dihydroxy-4-methoxybenzoate. This compound was prepared by the procedure reported:[9] white needles, mp 147−148 °C (30% EtOAc−hexane), lit.[15] mp 144−145 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.50 (s, 1H), 6.96 (s, 2H), 3.82 (s, 3H), 3.75 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 166.1, 150.7, 139.7, 124.5, 108.5, 59.7, 51.9; IR (neat) ν_{max} 3386, 2996, 1709 cm^{-1}; FABHRMS (NBA−NaI) *m*/*z* 221.0430 (M^+ + Na, $C_9H_{10}O_5$ requires 221.0426).

Methyl 3,5-Bis(benzyloxy)-4-methoxybenzoate (6). A solution of methyl 3,5-dihydroxy-4-methoxybenzoate (4.3 g, 22 mmol) in anhydrous DMF (25 mL) was sequentially treated with K_2CO_3 (11 g, 83 mmol) and $PhCH_2Cl$ (6.5 mL, 57 mmol). The reaction mixture was warmed at 110 °C for 1 h, cooled to 25 °C, and quenched by the addition of H_2O (25 mL). The mixture was stirred for 15 min while the product precipitated. The resulting grey solid was collected by filtration and was washed with H_2O (3 × 15 mL), dried in a vacuum desiccator, and purified by recrystallization from 20% EtOAc−hexane to afford **6** (7.5 g, 92%) as white needles: mp 116.5−118.0 °C (25% EtOAc−hexane), lit. mp 116−118[10] and 118−119 °C;[16] ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.50−7.31 (m, 12H), 5.17 (s, 4H), 3.95 (s, 3H), 3.89 (s, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 166.5, 152.1 (2C), 143.5 (2C), 136.6, 128.5 (4C), 127.9 (2C), 127.3 (4C), 124.9, 109.1 (2C), 71.0 (2C), 60.9, 52.1; IR (neat) ν_{max} 3019, 2933, 1717 cm^{-1}; FABHRMS (NBA−NaI) *m*/*z* 401.1373 (M^+ + Na, $C_{23}H_{22}O_5$ requires 401.1365).

(12) (a) Anelli, P. L.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem.* **1987**, *52*, 2559. (b) Inokuchi, T.; Matsumoto, S.; Nishiyama, T.; Torri, S. *J. Org. Chem.* **1990**, *55*, 462. (c) Miyazawa, T.; Endo, T.; Shiihashi, S.; Okawara, M. *J. Org. Chem.* **1985**, *50*, 1332.

(13) Nwaukwa, S. O.; Keehn, P. M. *Tetrahedron Lett.* **1982**, *23*, 35. Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. Corey, E. J.; Kania, R. S. *J. Am. Chem. Soc.* **1996**, *118*, 1229 and references cited therein. Smith, A. B., III; Leenay, T. L. *J. Am. Chem. Soc.* **1989**, *111*, 5761.

(14) Anderson, G. W.; Callahan, F. M. *J. Am. Chem. Soc.* **1960**, *82*, 3359.

(15) Krauss, A. S.; Taylor, W. C. *Aust. J. Chem.* **1991**, *44*, 1307.

(16) Haslam, E.; Uddin, M. *Tetrahedron* **1968**, *24*, 4015.

(17) Degraw, J. I.; Christensen, J. C.; Brown, V. H.; Cory, M. J. *J. Heterocycl. Chem.* **1974**, *11*, 363.

This reaction has also been conducted on large scale with 115 g of **6** (92%) obtained from 65 g of starting phenol.

3,5-Bis(benzyloxy)-4-methoxybenzyl Alcohol (7). A cooled suspension of $LiAlH_4$ (1.2 g, 32 mmol) in anhydrous THF (30 mL) at 0 °C was treated dropwise with a solution of **6** (6.1 g, 16 mmol) dissolved in THF (25 mL). The resulting mixture was warmed to 25 °C, stirred for 40 min, and recooled to 0 °C before saturated aqueous NH_4Cl (10 mL) was added slowly. The reaction mixture was then filtered, and the remaining solid was washed with EtOAc (4 × 15 mL). The volatiles were removed *in vacuo*, and the remaining residual white solid was purified by recrystallization from 50% EtOAc−hexane to afford **7** (5.4 g, 95%) as white prisms: mp 104.0−104.5 °C (40% EtOAc−hexane), lit. mp 104−105[10] and 105−106 °C;[17] ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.48−7.32 (m, 10H), 6.64 (s, 2H), 5.11 (s, 4H), 4.52 (d, 2H, J = 5.7 Hz), 3.90 (s, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 152.5 (2C), 138.5, 137.0 (2C), 136.5, 128.4 (4C), 127.8 (2C), 127.1 (4C), 106.2 (2C), 70.9 (2C), 65.1, 60.9; IR (neat) ν_{max} 3313, 3065, 3033, 2937 cm^{-1}; FABHRMS (NBA−NaI) m/z 373.1404 (M^+ + Na, $C_{22}H_{22}O_4$ requires 373.1416). Anal. Calcd for $C_{22}H_{22}O_4$: C, 75.46; H, 6.33. Found: C, 75.67; H, 6.16.

This reaction has also been conducted on a large scale with 77 g of **7** (79%) obtained from 115 g of **6**.

3,5-Bis(benzyloxy)-4-methoxybenzaldehyde (8). A solution of **7** (5.2 g, 15 mmol) in anhydrous CH_2Cl_2 (60 mL) was treated with activated MnO_2 (25 g) at 25 °C, and the resulting suspension was stirred for 2 h. The reaction mixture was filtered through a Celite pad (CH_2Cl_2, 5 × 50 mL), and the solvent was removed *in vacuo*. The crude residue was purified by recrystallization from 50% EtOAc−hexane to afford **8** (4.4 g, 90%) as a white powder: mp 85.5−87.5 °C (50% EtOAc−hexane), lit. mp 87−88[10] and 85−88 °C;[15] ^{1}H NMR ($CDCl_3$, 250 MHz) δ 9.79 (s, 1H), 7.49−7.33 (s, 10H), 7.18 (s, 2H), 5.19 (s, 4H), 3.99 (s, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 190.9, 152.9 (2C), 144.9, 136.4 (2C), 131.5, 128.7 (4C), 128.1 (2C), 127.3 (4C), 109.0 (2C), 71.1 (2C), 61.0; IR (neat) ν_{max} 3064, 3032, 2939, 2830, 2731, 1693, 1587 cm^{-1}; FABHRMS (NBA−NaI) m/z 349.1435 (M^+ + H, $C_{22}H_{20}O_4$ requires 349.1440). Anal. Calcd for $C_{22}H_{20}O_4$: C, 75.90; H, 5.79. Found: C, 76.17; H, 5.49.

This reaction has also been conducted on a large scale with PCC (CH_2Cl_2) with 64 g of **8** (85%) obtained from 77 g of **7**.

3,5-Bis(benzyloxy)-4-methoxystyrene (9). A suspension of methyltriphenylphosphonium bromide (12.3 g, 34.5 mmol) in anhydrous THF (70 mL) at −40 °C was treated with *n*-BuLi (1.9 M solution in hexane, 18.1 mL, 34.5 mmol) dropwise over 15 min, and the resulting solution was allowed to warm to −10 °C. After 40 min, the mixture was cooled to −30 °C and a solution of **8** (4.00 g, 11.5 mmol) in THF (7 mL) was added dropwise over 5 min. The resulting orange reaction mixture was warmed to 25 °C, stirred for 1.5 h, quenched by the addition of H_2O (40 mL), and extracted with EtOAc (4 × 20 mL). The combined organic phases were washed with H_2O (2 × 30 mL) and saturated aqueous NaCl (75 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Chromatography (SiO_2, 4 × 24 cm, 10−20% EtOAc−hexane gradient elution) afforded **9** (3.58 g, 90%) as white needles: mp 68.0−68.5 °C (20% EtOAc−hexane); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.50−7.31 (m, 10H), 6.71 (s, 2H), 6.58 (dd, 1H, J = 10.8, 17.5 Hz), 5.58 (d, 1H, J = 17.5 Hz), 5.18 (d, 1H, J = 10.8 Hz), 5.16 (s, 4H), 3.92 (s, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 152.6 (2C), 140.1, 137.1, 136.5 (2C), 133.1, 128.5 (4C), 127.8 (2C), 127.2 (4C), 113.2, 106.1 (2C), 71.1 (2C), 61.0; IR (neat) ν_{max} 3033, 2938, 1580, 1505, 915, 842 cm^{-1}; FABHRMS (NBA−NaI) m/z 347.1662 (M^+ + H, $C_{23}H_{22}O_3$ requires 347.1647). Anal. Calcd for $C_{23}H_{22}O_3$: C, 79.81; H, 6.40. Found: C, 80.10; H, 6.29.

1(*S*)-[3,5-Bis(benzyloxy)-4-methoxyphenyl]-2-hydroxyethanol (10). A stirred suspension of AD-mix-α[8] (Aldrich, 8.1 g, 1.4 g/mmol) in *t*-BuOH-H_2O (1:1, 58 mL) was treated with **9** (2.0 g, 5.8 mmol) at 25 °C, and the resulting two-phase reaction mixture was stirred vigorously at 25 °C for 20 h. Sodium sulfite (Na_2SO_3, 8.7 g, 1.5 g/mmol) was added, and the mixture was stirred for 30 min and diluted with EtOAc (50 mL). After separation of the layers, the aqueous phase was further extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with H_2O (50 mL) and saturated aqueous NaCl (50 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The crude, white solid was purified by recrystallization from 50% EtOAc−hexane to afford **10** (2.1 g, 97%, 87% ee) as white needles: mp 103−104 °C (20% EtOAc−hexane); $[\alpha]^{25}_D$ +21 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.44−7.28 (m, 10H), 6.61 (s, 2H), 5.07 (s, 4H), 4.61 (dd, 1H, J = 3.4, 7.8 Hz), 3.87 (s, 3H), 3.53 (ddd, 2H, J = 3.4, 7.8, 11.3 Hz), 3.05 (br s, 1H, OH), 2.48 (br s, 1H, OH); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 152.4 (2C), 138.6, 136.9 (2C), 136.2, 128.4 (4C), 127.8 (2C), 127.3 (4C), 105.4 (2C), 74.4, 70.9 (2C), 67.9, 60.8; IR (neat) ν_{max} 3386, 3066, 3033, 2933, 2871 cm^{-1}; FABHRMS (NBA−CsI) m/z 513.0661 (M^+ + Cs, $C_{23}H_{24}O_5$ requires 513.0678). Anal. Calcd for $C_{23}H_{24}O_5$: C, 72.67; H, 6.36. Found: C, 72.56; H, 6.37.

1(*S*)-2-[(*tert*-Butyldimethylsilyl)oxy]-1-[3,5-bis(benzyloxy)-4-methoxyphenyl]ethanol (11). A solution of **10** (1.8 g, 4.7 mmol) in anhydrous DMF (20 mL) was treated with *t*-BuMe_2SiCl (0.86 g, 5.7 mmol) and imidazole (0.45 g, 6.6 mmol) at 0 °C under Ar. The resulting reaction mixture was warmed to 25 °C and stirred for 5 h before H_2O (40 mL) was added. The aqueous phase was extracted with EtOAc (3 × 30 mL), and the combined extracts were washed with H_2O (75 mL), saturated aqueous NaCl (75 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Flash chromatography (SiO_2, 5 × 25 cm, 10−20% EtOAc−hexane gradient elution) afforded **11** (2.0 g, 85%) as a colorless oil: $[\alpha]^{25}_D$ +12 (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.48−7.28 (m, 10H), 6.66 (s, 2H), 5.14 (s, 4H), 4.60 (ddd, 1H, J = 2.0, 3.6, 8.1 Hz), 3.89 (s, 3H), 3.66 (dd, 1H, J = 3.6, 10.1 Hz), 3.44 (dd, 1H, J = 8.1, 10.1 Hz), 2.99 (d, 1H, J = 2.0 Hz), 0.94 (s, 9H), 0.08 (s, 6H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 152.4 (2C), 138.9, 137.1 (2C), 135.7, 128.4 (4C), 127.7 (2C), 127.3 (4C), 105.9 (2C), 74.1, 71.0 (2C), 68.8, 60.8, 25.8 (3C), 18.2, −5.4 (2C); IR (film) ν_{max} 3475, 3064, 3032, 2952, 2927, 2856 cm^{-1}; FABHRMS (NBA−CsI) m/z 627.1570 (M^+ + Cs, $C_{29}H_{38}O_5Si$ requires 627.1543).

1(*R*)-2-[(*tert*-Butyldimethylsilyl)oxy]-1-[3,5-bis(benzyloxy)-4-methoxyphenyl]ethylamine (13). A solution of **11** (0.94 g, 1.9 mmol) in anhydrous THF (14 mL) at −20 °C was treated sequentially with Et_3N (1.3 g, 4.8 mmol) diphenyl phosphorazidate (DPPA, 1.0 mL, 4.8 mmol), and diethyl azodicarboxylate (DEAD, 0.75 mL, 4.8 mmol). The reaction mixture was warmed to 25 °C, stirred for 2 h, and concentrated *in vacuo*. Chromatography (SiO_2, 4 × 24 cm, 5−10% EtOAc−hexane gradient elution) afforded 0.9 g of an inseparable 9:1 mixture of azide **12** and the corresponding elimination product, respectively, as a colorless oil which was carried on

together into the subsequent step. For **12**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.46−7.31 (m, 10H), 6.55 (s, 2H), 5.12 (s, 4H), 4.42 (dd, 1H, J = 4.2, 8.3 Hz), 3.87 (s, 3H), 3.67 (dd, 1H, J = 4.2, 10.6 Hz), 3.61 (dd, 1H, J = 8.3, 10.6 Hz), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.6 (2C), 139.4, 137.0 (2C), 132.3, 128.5 (4C), 127.9 (2C), 127.4 (4C), 106.8 (2C), 71.2 (2C), 68.3, 67.3, 60.9, 26.0 (3C), 18.3, −5.4 (2C); IR (film) ν_{max} 3065, 3032, 2928, 2857, 2099 cm^{-1}; MS (electrospray) m/z 542 (M^+ + Na).

The mixture of azide **12** and the elimination product from the previous reaction (0.9 g) in THF (17 mL) was treated with Ph_3P (0.91 g, 3.5 mmol) and H_2O (0.31 mL, 0.017 mol) at 25 °C. The resulting reaction mixture was warmed at 45 °C for 21 h. The volatiles were removed *in vacuo*, and the residue was purified by flash chromatography (SiO_2, 4 × 24 cm, 5−20% EtOAc−hexane gradient elution) to afford **13** (0.61 g, 65% based on starting alcohol **11**) and the elimination product (68 mg, 7%) as colorless oils. For **13**: $[\alpha]^{25}_D$ −9.7 (*c* 2.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.45−7.30 (m, 10H), 6.66 (s, 2H), 5.18 (s, 4H), 3.93 (dd, 1H, J = 3.9, 8.6 Hz), 3.87 (s, 3H), 3.57 (dd, 1H, J = 3.9, 9.8 Hz), 3.37 (dd, 1H, J = 8.6, 9.8 Hz), 0.88 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 152.3 (2C), 138.5, 138.0, 137.1 (2C), 128.3 (4C), 127.7 (2C), 127.2 (4C), 106.4 (2C), 70.9 (2C), 69.4, 60.7, 57.5, 25.8 (3C), 18.2, −5.5 (2C); IR (film) ν_{max} 3383, 3064, 3032, 2953, 2928, 2856 cm^{-1}; FABHRMS (NBA−CsI) m/z 626.1723 (M^+ + Cs, $C_{29}H_{39}NO_4Si$ requires 626.1703).

For the elimination product: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.54−7.32 (m, 10H), 6.77 (d, 1H, J = 12.1 Hz), 6.49 (s, 2H), 5.90 (d, 1H, J = 12.1 Hz), 5.15 (s, 4H), 3.90 (s, 3H), 0.96 (s, 9H), 0.20 (s, 6H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 152.6 (2C), 141.9, 137.3 (2C), 133.8, 132.0, 128.5 (4C), 127.8 (2C), 127.2 (4C), 112.6, 105.2 (2C), 71.2 (2C), 61.0, 25.6 (3C), 18.3, −5.2 (2C); IR (film) ν_{max} 3032, 2953, 2928, 2857, 1758, 1645 cm^{-1}.

1(*R*)-*N*-[(Benzyloxy)carbonyl]-2-[(*tert*-butyldimethylsilyl)oxy]-1-[3,5-bis(benzyloxy)-4-methoxyphenyl]ethylamine (14). A solution of **13** (0.20 g, 0.41 mmol) in THF−H_2O (1:1, 4.0 mL) was treated with Na_2CO_3 (86 mg, 0.81 mmol) and benzyl chloroformate (64 μL, 0.46 mmol) at 25 °C under Ar. After 2.5 h, the reaction mixture was poured into H_2O (10 mL) and extracted with EtOAc (4 × 10 mL). The combined organic layers were washed with H_2O (3 × 10 mL) and saturated aqueous NaCl (3 × 10 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Chromatography (SiO_2, 3.5 × 10 cm, 10−25% EtOAc−hexane gradient elution) afforded **14** (0.22 g, 90%) as a white solid: mp 84.5−85.0 °C (20% EtOAc−hexane); $[\alpha]^{25}_D$ −15.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.44−7.29 (m, 15H), 6.58 (s, 2H), 5.40 (d, 1H, NH, J = 7.4 Hz), 5.08 (s, 6H), 4.65−4.60 (m, 1H), 3.87 (s, 3H), 3.80 (dd, 1H, J = 4.0, 10.2 Hz), 3.65−3.58 (m, 1H), 0.88 (s, 9H), −0.08 (s, 3H), −0.10 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ 156.4, 152.5 (2C), 138.6, 136.7 (2C), 134.0, 132.4, 128.4 (6 C), 128.0, 127.9 (2C), 127.4 (6C), 106.3 (2C), 71.0 (2C), 66.1, 66.7, 60.8, 56.6, 26.1 (3C), 18.5, −5.5 (2C); IR (neat) ν_{max} 3358, 3064, 3032, 2928, 2856, 1688, 1593, 1532 cm^{-1}; FABHRMS (NBA−CsI) m/z 760.2042 (M^+ + Cs, $C_{37}H_{45}NO_6Si$ requires 760.2070). Anal. Calcd for $C_{37}H_{45}NO_6Si$: C, 70.84; H, 7.22; N, 2.23. Found: C, 70.66; H, 7.28; N, 2.21.

1(*R*)-*N*-[(Benzyloxy)carbonyl]-1-[3,5-bis(benzyloxy)-4-methoxyphenyl]-2-hydroxyethylamine (15). A solution of **14** (0.22 g, 0.36 mmol) in THF (5 mL) at 0 °C was treated dropwise with a 1.0 M solution of Bu_4NF in THF (0.43 mL, 0.43 mmol) under Ar. The resulting reaction mixture was warmed to 25 °C, stirred for 2 h, poured into H_2O (10 mL), and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with H_2O (20 mL), saturated aqueous NaCl (25 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography (SiO_2, 3.5 × 10 cm, 20−50% EtOAc−hexane gradient elution) afforded **15** (0.17 g, 92%) as a white powder. Recrystallization (50% EtOAc−hexane) provided **15** (0.16 g, 88%, ≥94% ee): mp 118−119 °C (50% EtOAc−hexane); $[\alpha]^{23}_D$ −21 (*c* 0.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42−7.29 (m, 15H), 6.52 (s, 2H), 5.40−5.36 (br s, 1H, NH), 5.09 (s, 6H), 4.69−4.64 (m, 1H), 3.89 (s, 3H), 3.78−3.74 (m, 2H), 1.78 (br s, 1H, OH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.3, 152.6 (2C), 138.6, 136.8 (2C), 136.1, 134.7, 128.4 (6C), 128.2, 127.9 (2C), 127.3 (6C), 106.1 (2C), 71.0 (2C), 66.8, 66.1, 60.8, 56.9; IR (neat) ν_{max} 3332, 3041, 2950, 1685, 1595, 1535, 1509 cm^{-1}; FABHRMS (NBA−CsI) m/z 646.1229 (M^+ + Cs, $C_{31}H_{31}NO_6$ requires 646.1206). Anal. Calcd for $C_{31}H_{31}NO_6$: C, 72.55; H, 6.08; N, 2.73. Found: C, 72.55; H, 6.11; N, 2.71.

(*R*)-*N*-[(Benzyloxy)carbonyl]-[3,5-bis(benzyloxy)-4-methoxyphenyl]glycine (2). Method A: A solution of **15** (84 mg, 0.16 mmol) in acetone (0.4 mL) at 0 °C was added to an aqueous 5% $NaHCO_3$ solution (0.4 mL), and additional acetone (*ca*. 0.4 mL), was added until stirring became possible. This heterogeneous mixture was treated sequentially with KBr (1.9 mg, 0.016 mmol) and TEMPO (28 mg, 0.18 mmol). Sodium hypochlorite (NaOCl, Aldrich 4−6% or *ca*. 0.5 M solution, 0.40 mL, 0.21 mmol) was added dropwise over 10 min, and the mixture was stirred at 0 °C. After 1 h, additional NaOCl (0.20 mL, 0.10 mmol) was added. The reaction mixture was stirred for 1 h before the addition of H_2O (10 mL), and EtOAc (10 mL). The aqueous phase was extracted with EtOAc (3 × 10 mL), and the combined organic layers were washed with H_2O (20 mL) and saturated aqueous NaCl (20 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Chromatography (SiO_2, 3.5 × 10 cm, 2−10% CH_3OH−$CHCl_3$ gradient elution) afforded **2** (67 mg, 78%, ≥94% ee)[18] as a white solid: mp 128.5−130.0 °C (EtOH−hexane); $[\alpha]^{25}_D$ −72 (*c* 1.0, CH_3OH); ^{1}H NMR (CD_3OD, 400 MHz) δ 7.45−7.16 (m, 15H), 6.75 (s, 2H), 5.05 (s, 1H), 4.99 (s, 2H), 4.96 (s, 4H), 3.67 (s, 3H); ^{13}C NMR (CD_3OD, 100 MHz) δ 173.8, 158.0, 153.9 (2C), 140.0, 138.4 (2C), 138.1, 134.2, 129.5 (6C), 129.0, 128.9 (2C), 128.8 (6C), 108.1 (2C), 72.0 (2C), 67.8, 61.3, 59.3; IR (neat) ν_{max} 3316, 3016, 2937, 1717, 1592 cm^{-1}; FABHRMS (NBA−CsI) m/z 660.1023 (M^+ + Cs, $C_{31}H_{29}NO_7$ requires 660.0998). Method B: A solution of **15** (56 mg, 0.11 mmol) in CH_2Cl_2 (1.1 mL) at 0 °C was treated with Dess−Martin 12-I-5 periodinane reagent[13] (92 mg, 0.22 mmol), and the resulting heterogeneous mixture was gradually warmed to 25 °C. After 30 min of stirring, the suspension was diluted with Et_2O (2 mL), poured into a saturated aqueous solution of $NaHCO_3$ (5 mL) containing $Na_2S_2O_3$−

(18) The optical purity of **3** (94% ee) derived from **10** (87% ee) was assessed by chiral phase HPLC separation of the enantiomers on a Chiralpak AD HPLC column (0.46 × 25 cm, 30% 2-propanol−hexane, 1.0 mL/min) alongside racemic material, t_R = 13.0 min for (*R*)-**3** and t_R = 21.0 min for (*S*)-**3** (97:3), in which the enrichment of the optical purity (≥94% ee) was accomplished by recrystallization of intermediate **15**. Consequently, the optical purity of **2**, the precursor to **3**, following oxidation of **15** must be ≥94% ee. The optical purity of **4** (94% ee) was established upon conversion to the Mosher amide upon treatment with (−)-(*R*)-MTPCl and ^{19}F and ^{1}H NMR analysis alongside racemic material: ^{19}F NMR ($CDCl_3$) δ −70.0 (3.0), −70.2 (97.0); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.52 (s, 1.94), 6.39 (s, 0.06 H). Due to its chromatographic polarity, the optical purity of **5** was not assessed by chiral phase HPLC, but its use in subsequent efforts[6] indicated that little or no racemization occurred in its preparation.

H_2O (0.19 g, 0.76 mmol), and stirred until two distinct layers were observed. The two layers were separated, and the aqueous phase was extracted with Et_2O (3 × 7 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (2 × 7 mL) and saturated aqueous NaCl (7 mL), dried (Na_2SO_4), and concentrated *in vacuo* to afford crude aldehyde (54 mg, 99%) which was sufficiently pure to use in the subsequent step. A buffered solution of $NaClO_2$ (Aldrich, 80%, 0.11 g, 0.99 mmol) and NaH_2PO_4 (0.10 g, 0.74 mmol) in H_2O (1 mL) was added dropwise to a solution of the aldehyde (54 mg, 0.11 mmol) in 2-methyl-2-butene (0.65 mL) and *t*-BuOH (2.6 mL, 1:4) at 25 °C. After stirring the reaction mixture for 20 min at 25 °C, the volatiles were removed *in vacuo*, and the residue was diluted with H_2O (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (SiO_2, 2.5 × 10 cm, 5−10% CH_3OH−$CHCl_3$ gradient elution) afforded **2** (43 mg, 75% over two steps) as a white solid: $[\alpha]^{25}_D$ −72 (*c* 0.9, CH_3OH), ≥94% ee).[18]

(*R*)-*N*-[(Benzyloxy)carbonyl]-[3,5-bis(benzyloxy)-2-chloro-4-methoxyphenyl]glycine (16). A solution of **15** (25 mg, 0.049 mmol) in acetone (0.2 mL) at 0 °C was added to an aqueous 5% $NaHCO_3$ solution (0.2 mL), and additional acetone was added (0.3 mL) until stirring became possible. This heterogeneous mixture was treated with TEMPO (0.08 mg, 0.005 mmol) followed by $Ca(OCl)_2$ (17 mg, 0.12 mmol). The resulting reaction mixture was stirred at 0 °C for 2 h, poured into H_2O (5 mL), and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with H_2O (10 mL) and saturated aqueous NaCl (20 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Chromatography (SiO_2, 2.5 × 10 cm, 2−10% CH_3OH−$CHCl_3$ gradient elution) afforded **16** (14 mg, 52%) as a colorless oil: $[\alpha]^{25}_D$ −56 (*c* 0.025, CH_3OH); ^1H NMR (CD_3OD, 400 MHz) δ 7.38−7.14 (m, 15H), 6.89 (s, 1H), 5.60 (s, 1H), 4.98 (s, 2H), 4.95 (s, 2H), 4.90 (s, 2H), 3.72 (s, 3H); ^{13}C NMR (CD_3OD, 100 MHz) δ 174.0, 158.1, 152.8 (2C), 150.3, 146.0, 138.5, 138.0 (2C), 132.5, 129.6 (2C), 129.5 (4C), 129.4 (2C), 129.2, 129.1 (2C), 129.0, 128.9 (2C), 111.0 (2C), 76.6 (2C), 72.2, 67.8, 61.7; IR (neat) ν_{max} 3393, 1701, 1485, 1414, 1369, 1338, 1218, 1097 cm^{-1}; FABHRMS (NBA−CsI) *m*/*z* 694.0621 (M^+ + Cs, $C_{31}H_{28}ClNO_7$ requires 694.0609).

***tert*-Butyl (*R*)-*N*-[(Benzyloxy)carbonyl]-[3,5-bis(benzyloxy)-4-methoxyphenyl]glycine (3).** A sealed tube reaction vessel was charged with **2** (0.14 g, 0.27 mmol), anhydrous CH_2Cl_2 (2.7 mL), and concentrated H_2SO_4 (2.8 μL, 0.053 mmol) at −15 °C. Before the tube was sealed, excess isobutylene gas was bubbled through the suspension until the volume tripled (9 mL, *ca*. 5 min). The reaction vessel was sealed, and the mixture was warmed to 25 °C and stirred for 24 h. The tube was then cooled to −78 °C, opened to the atmosphere, and allowed to slowly warm to 25 °C. N_2 was bubbled through the solution to remove the residual isobutylene. A 5% aqueous $NaHCO_3$ solution (10 mL) and EtOAc (10 mL) were added and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with 5% aqueous $NaHCO_3$ (20 mL) and saturated aqueous NaCl (20 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Chromatography (SiO_2, 3.5 × 10 cm, 10−40% EtOAc−hexane gradient elution) afforded **3** (0.13 g, 87%, 94% ee[18]) as a white film: $[\alpha]^{25}_D$ −60 (*c* 1.3, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.44−7.25 (m, 15H), 6.64 (s, 2H), 5.78 (d, 1H, NH, J = 7.2 Hz), 5.12 (s, 1H), 5.10 (s, 4H), 5.09 (s, 2H), 3.90 (s, 3H), 1.32 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.6, 155.3, 152.7 (2C), 139.3, 136.9 (2C), 136.2, 132.7 (2C), 128.5 (6C), 128.2 (2C), 127.9 (4C), 127.3 (2C), 106.5 (2C), 82.7, 71.0 (2C), 67.0, 60.9, 58.3, 27.8 (3C); IR (film) ν_{max} 3346, 3056, 2978, 2929, 1721, 1529 cm^{-1}; FABHRMS (NBA−CsI) *m*/*z* 716.1604 (M^+ + Cs, $C_{35}H_{37}NO_7$ requires 716.1624).

***tert*-Butyl (*R*)-(3,5-Dihydroxy-4-methoxyphenyl)-glycine (4).** A solution of **3** (0.13 g, 0.22 mmol) in CH_3OH (2.5 mL) at 25 °C was treated with 10% Pd−C (13 mg) and was stirred under 1 atm of H_2 for 5 h. The reaction mixture was filtered through a pad of Celite (10% CH_3OH−$CHCl_3$, 3 × 10 mL), and the solvent was removed *in vacuo*. Chromatography (SiO_2, 3.5 × 10 cm, 5−10% CH_3OH−$CHCl_3$ gradient elution) afforded **4** (59 mg, 98%) as a white film: $[\alpha]^{25}_D$ −53 (*c* 0.27, CH_3OH);[18] ^1H NMR (CD_3OD, 400 MHz) δ 6.24 (s, 2H), 4.07 (s, 1H), 3.64 (s, 3H), 1.30 (s, 9H); ^{13}C NMR (CD_3OD, 100 MHz) δ 172.2, 149.9 (2C), 135.3, 134.5, 105.2 (2C), 80.6, 58.8, 57.8, 26.1 (3C); IR (neat) ν_{max} 3349, 3269, 2958, 2912, 1712, 1560, 1523 cm^{-1}; FABHRMS (NBA−NaI) *m*/*z* 292.1156 (M^+ + Na, $C_{13}H_{19}NO_5$ requires 292.1161).

(*R*)-*N*-[(*tert*-Butyloxy)carbonyl]-(3,5-dihydroxy-4-methoxyphenyl)glycine (5). A solution of **2** (45 mg, 0.085 mmol) in CH_3OH (0.9 mL) at 25 °C was treated with 10% Pd−C (4.5 mg, 0.10 wt equiv), and the mixture was stirred under 1 atm of H_2 for 8 h. The reaction mixture was filtered through a pad of Celite (CH_3OH, 50 mL), the solvent was removed *in vacuo*, and the product was dried under vacuum to afford the deprotected amino acid (18 mg, 0.085 mmol) which was used directly in the following reaction.

A solution of the amino acid (18 mg, 0.085 mmol) in THF−H_2O (1:1, 1.7 mL) was treated with $NaHCO_3$ (22 mg, 0.26 mmol) and di-*tert*-butyl dicarbonate (41 mg, 0.19 mmol) at 25 °C under Ar. After 10 h, aqueous citric acid (pH = 3−4, 1.7 mL) was added to the reaction mixture, and the mixture was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with saturated aqueous NaCl (1 × 2 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Chromatography (SiO_2, 3 × 14 cm, CH_2Cl_2−CH_3OH−HOAc 88:10:6) afforded **5** (22 mg, 78%) as a white film: $[\alpha]^{25}_D$ −89 (*c* 0.8, CH_3OH);[18] ^1H NMR (CD_3OD, 400 MHz) δ 6.41 (s, 2H), 4.92 (s, 1H), 3.76 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (CD_3OD, 100 MHz) δ 175.3, 157.3, 151.8, 136.5, 135.1, 107.8, 80.6, 60.7, 28.7, 28.5; IR (neat) ν_{max} 3345, 2976, 2932, 1694, 1600, 1504, 1455, 1161 cm^{-1}; FABHRMS (NBA−NaI) *m*/*z* 336.1069 (M^+ + Na, $C_{14}H_{19}NO_7$ requires 336.1059).

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Supporting Information Available: ^1H NMR spectra of **6**, **11**, **13**, **16**, and **2**−**5** are provided (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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