Mild Reductive Opening of Aryl Pyranosides Promoted by Scandium (III) Triflate

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General Information.

All reactions were carried out in oven or flame-dried glassware under argon atmosphere. Scandium (III) triflate was obtained from Strem. Triethylsilane was obtained from Gelest. All other reagents were purchased from Aldrich. All solvents used for chemical transformations were obtained from a dry solvent system (alumina) and used without further drying. Unless otherwise noted, reactions were magnetically stirred and monitored by thin layer chromatography with Sorbent Technologies 0.20 mm silica gel 60 Å plates. Flash chromatography was performed on Sorbent Technologies 32-63 µm 60 Å silica gel. Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise noted. ¹H and ¹³C NMR spectra were taken in CDCl₃ (one in CD₃OD) at 400 MHz and 75 MHz, respectively. Chemical shifts are reported in parts per million using the solvent internal standard (chloroform, 7.24 and 77.0 ppm; CD₃OD, 3.34 and 49.86 ppm, respectively). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant, integration. Diastereomeric ratios were determined by ¹H NMR (400 MHz) analysis of crude mixtures, operating at signal/noise ratio of 200:1. Infrared resonance spectra were

recorded on a Nexus™ 670 FTIR spectrometer. Optical rotations were recorded on an AUTOPOL III digital polarimeter at 589 nm and reported as follows: concentration (*c* in g/100mL) and solvent. High resolution mass-spectra were obtained on a Finnigan MAT-90 spectrometer at Boston University Mass Spectrometry Laboratory.

General procedure for tetrahydropyran formation from crotylsilanes and aldehyde via [4+2]-annulation:¹

The crotylsilane (either *anti*-(3*S*,*E*)-crotylsilane or *syn*-(3*S*, *E*)-crotylsilane)² (1.1 equiv.) was placed in a round bottom flask equipped with a stir bar and a 0.05M solution of the appropriate aldehyde solution in CH₂Cl₂. The solution was then cooled to –78 °C and triflic acid (1 equiv.) was added in one portion. The reaction was allowed to stir for 24 hours at –78 °C before a saturated solution of NaHCO₃ (equal volume) was added. The solution was allowed to warm to room temperature on its own and extracted three times with CH₂Cl₂. The combined organic extracts were dried over MgSO₄, filtered and concentrated under vacuum to get a crude oil.

The resulting crude dihydropyrans were placed to round bottom flask under an atmosphere of hydrogen with 10% Pd/C (0.1 equiv.) and 10 mL ethyl acetate and stirred for additional 20 hours. After filtering off Pd/C over celite the solutions were concentrated under vacuum to get a crude oil. Product was purified by column chromatography over silica gel with EtOAc/Hexanes(5/95).

(1) For seminal report of [4+2]-annulations involving enantioenriched crotylsilanes see: Huang, H.; Panek, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 9836.

(2) (a) For the preparation of *anti*-(*E*)-crotylsilane see: Yang, M.; Solomon, J. S.; Panek, J. S. *J. Org. Chem.* **1993**, *58*, 1003. (b) For the preparation of *syn*-(*E*)-crotylsilane see: Sparks, M. A.; Panek, J. S. *J. Org. Chem.* **1991**, *56*, 3431.

(2S,5S,6S)-methyl -5-methyl-6-phenyl-tetrahydro-2H-pyran-2-

carboxylate (1a). (Obtained as a colorless oil in 2 step 87% yield from benzaldehyde and *anti*-(2R,3S,*E*)-crotylsilane); $[\alpha]_D^{20} + 0.7$ (*c* 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.33 (m, 5H), 4.61 (d, *J* = 7.8 Hz, 1H), 4.38 (d, *J* = 9.2 Hz, 1H), 3.77 (s, 3H), 2.21 (m, 1H), 2.04 (m, 1H), 1.78 (m, 2H), 1.28 (m, 1H), 0.65 (d, *J* = 6.9 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 173.2, 141.0, 128.5, 128.1, 128.8, 82.7, 73.6, 52.1, 36.2, 29.2, 27.3, 18.2 ppm; IR (film) $\nu_{\max}$ 3030, 2952, 2927, 1745, 1495, 1454 cm⁻¹; HRMS(CI, NH₃) *m/z* calc'd for C₁₄H₁₉O₃ [M+H]⁺ 235.1334, Found 235.1339.

(2S,5S,6S)-methyl-5-methyl-6-(naphthalen-2-yl)-

tetrahydro-2H-pyran-2-carboxylate (1b). (Obtained as a colorless oil in 2 step 83% yield from 2-naphthaldehyde and *anti*-(2R,3S,*E*)-crotylsilane); $[\alpha]_D^{20} + 7.6$ (*c* 2.30, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.83 (m, 3H), 7.52 (d, *J* = 10 Hz, 1H), 7.45 (m, 2H), 7.26 (d, *J* = 8.0 Hz, 1H), 4.66 (d, *J* = 5.6 Hz, 1H), 4.56 (d, *J* = 10.0 Hz, 1H), 3.78 (s, 3H), 2.29 (m, 1H), 2.13 (m, 1H), 1.87 (m, 2H), 1.32 (m, 1H), 0.68 (d, *J* = 6.8 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 173.1, 138.5, 133.5, 128.3, 128.0, 127.8, 127.1, 127.5, 126.2, 126.0, 125.4, 82.8, 73.7, 52.2, 36.2, 29.2, 27.4, 18.3 ppm; IR (film) $\nu_{\max}$ 3052, 2927, 1744, 1455 cm⁻¹; HRMS(CI, NH₃) *m/z* calc'd for C₁₈H₂₁O₃ [M+H]⁺ 285.1491, Found 285.1489.

(2S,5S,6S)-methyl 6-(4-(dimethylamino)phenyl)-5-methyl-

tetrahydro-2H-pyran-2-carboxylate (1d). (Obtained as a colorless oil in 2 step 81% yield from dimethylaminobenzaldehyde and *anti*-(2R,3S,*E*)-crotylsilane); $[\alpha]_D^{20} + 3.4$ (*c*

2.70, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.19 (d, *J* = 8.8 Hz, 2H), 6.69 (d, *J* = 8.8 Hz, 2H), 4.56 (d, *J* = 4.8 Hz, 1H), 4.25 (d, *J* = 8.8 Hz, 1H), 3.75 (s, 3H), 2.90 (s, 6H), 2.17 (m, 1H), 1.97 (m, 1H), 1.75 (m, 2H), 1.25 (dd, *J* = 12.8, 1.8 Hz, 1H), 0.64 (d, *J* = 6.4 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 173.3, 150.4, 128.5, 120.1, 112.8, 82.4, 73.7, 52.1, 41.02, 35.8, 29.4, 27.4, 18.4 ppm; IR (film) ν_{max} 2950, 2927, 1735, 1524, 1445, 1216, 1149, 1037, 909, 810, 728 cm⁻¹; HRMS(CI, NH₃) *m/z* calc'd for C₁₆H₂₃NNaO₃ [M+Na]⁺ 300.1576, Found 300.1573.

(2*S*,5*S*,6*S*)-methyl 5-methyl-6-(naphthalen-1-yl)-tetrahydro-2H-pyran-2-carboxylate. (Obtained as a colorless oil in 2 step 85% yield from 1-naphthaldehyde and *anti*-(2*R*,3*S*,*E*)-crotylsilane); [α]_D²⁰ + 6.4 (*c* 3.10, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 8.53 (d, *J* = 4.8 Hz, 1H), 7.85 (m, 2H), 7.77 (d, *J* = 9.0 Hz, 1H), 7.42 (m, 2H), 7.24-7.37 (m, 1H), 5.30 (m, 1H), 4.68 (d, *J* = 6.0 Hz, 1H), 3.79 (s, 3H), 2.14-2.30 (m, 3H), 1.94 (dd, *J* = 10.0, 3.2 Hz, 1H), 1.40 (m, 1H), 0.68 (d, *J* = 6.4 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 173.1, 138.4, 133.5, 133.2, 128.3, 128.2, 127.9, 127.1, 126.2, 126.0, 125.3, 82.8, 73.7, 52.8, 36.2, 29.4, 27.4, 18.3 ppm; IR (film) ν_{max} 3032, 2951, 1741, 1458 cm⁻¹; HRMS(CI, NH₃) *m/z* calc'd for C₁₈H₂₁O₃ [M+H]⁺ 285.1491, Found 285.1494.

(2*S*,5*R*,6*R*)-5-Methyl-6-(2,3,5,6-tetramethoxy-4-methylphenyl)-tetrahydro-pyran-2-carboxylic acid methyl ester (1i). (Obtained as a colorless oil in 2 step 86 % yield from 2,3,5,6-tetramethoxy-4-methyl-benzaldehyde³ and

(3) For the preparation of 2,3,5,6-tetramethoxy-4-methyl-benzaldehyde see: Lowe, J. T.; Panek, J. S. *Org. Lett.* **2005**, 7, 1529 and references therein.

syn-(2*R*,3*S*,*E*)-crotylsilane). $[\alpha]_D^{20}$ - 8.7 (*c* 0.70, CHCl₃); ¹H NMR (CDCl₃, 400 MHz): δ 4.46 (d, *J* = 13.6 Hz, 1H), 4.11 (d, *J* = 15.6 Hz, 1H), 3.91 (s, 3H), 3.78 (s, 3H), 3.77 (s, 3H), 3.73 (s, 3H), 3.68 (s, 3H), 2.46 (m, 1H), 2.14 (s, 3H), 1.99 (m, 1H), 1.96 (m, 1H), 1.74 (q, *J* = 16.4 Hz, 1H), 1.31 (q, *J* = 16.4 Hz, 1H), 0.65 (d, *J* = 9.2 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 172.1, 148.8, 148.6, 147.6 147.2, 125.8, 124.9, 79.4, 77.2, 61.4, 61.0, 60.1, 60.0, 51.8, 32.8, 32.0, 29.6, 18.0, 9.2; IR (film) $\nu_{\max}$ 2941, 1756, 1463 cm⁻¹; HRMS(CI, NH₃) *m/z* calc'd for C₁₉H₂₈O₇ [M]⁺ 368.1835, found: 368.1832.

General procedure for reduction of methyl ester to primary alcohol

To a solution of ester (0.1 mmol) in Et₂O (5.0 mL) at 0 °C was added LiBH₄ (0.3 mmol). To the cool solution MeOH (0.2 mmol) was added dropwise under an atmosphere of argon. The reaction mixture was allowed to warm up to room temperature over 2 hours and stirred at room temperature for an additional 4-6 hours. The mixture was then cooled to 0 °C and MeOH (2.0 mL) was added followed by H₂O (2.0 mL) and 1.0M aqueous solution of HCl. The mixture was stirred at 0 °C for 20 minutes, extracted three times with Et₂O. The combined organic extracts were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel to yield the desired alcohol.

yl]methanol (1f). (Obtained in 99% yield from ester **1a**); $[\alpha]_D^{20}$ + 13.2 (*c* 1.62, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.34 (m, 5H), 4.21 (d, *J* = 8.8 Hz, 1H), 4.03 (d, *J* = 7.2 Hz, 1H), 3.46 (d, *J* = 6.8 Hz, 2H), 1.89 (m, 2H), 1.65 (m, 1H), 1.58 (m, 1H), 1.40 (m, 1H), 0.75 (d, *J* = 7.2 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 141.3, 128.6, 128.1, 127.6, 79.3,

73.2, 61.6, 35.4, 27.7, 25.1, 18.4 ppm; IR (film) $\nu_{\max}$ 3392, 2927, 1493, 1454 cm^{-1} ; HRMS(CI, NH_3) m/z calc'd for $\text{C}_{13}\text{H}_{18}\text{NaO}_2$ $[\text{M}+\text{Na}]^+$ 229.1204, Found 229.1206.

[(2S,5S,6S)-5-Methyl-6-(naphthalen-1-yl)-tetrahydro-2H-pyran-

2-yl]methanol (1g). (Obtained in 96% yield from ester (see SI-4)); $[\alpha]_{\text{D}}^{20} + 50.3$ (c 2.90, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 8.36 (d, $J = 8.4$ Hz, 1H), 7.86 (d, $J = 8.0$ Hz, 1H), 7.80 (d, $J = 8.0$ Hz, 1H), 7.51 (m, 3H), 7.32 (m, 1H), 4.98 (d, $J = 8.8$ Hz, 1H), 4.18 (d, $J = 4.8$ Hz, 1H), 3.51 (d, $J = 6.6$ Hz, 2H), 2.26 (m, 1H), 2.06 (br m, 1H), 1.81 (m, 1H), 1.68 (m, 1H), 1.54 (m, 1H), 1.31 (m, 1H), 0.77 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 136.7, 134.3, 132.1, 129.1, 128.7, 128.6, 126.2, 125.7, 125.4, 124.8, 76.5, 73.6, 61.4, 35.1, 28.4, 25.4, 18.9 ppm; IR (film) $\nu_{\max}$ 3401, 3048, 2926, 1638, 1597, 1456 cm^{-1} ; HRMS(CI, NH_3) m/z calc'd for $\text{C}_{17}\text{H}_{20}\text{NaO}_2$ $[\text{M}+\text{Na}]^+$ 279.1362, Found 279.1366.

[(2S,3S,4R,5S,6R)-4-(tert-Butyl-dimethyl-silanyloxy)-3,5-

dimethyl-6-(2,3,5,6-tetramethoxy-4-methyl-phenyl)-tetrahydro-pyran-2-yl]-

methanol (1j). (Obtained in 95% yield from known ester.³) $[\alpha]_{\text{D}}^{20} + 30.1$ (c 0.83, CHCl_3); ^1H NMR (CDCl_3 , 400 MHz): δ 4.45 (d, $J = 10.8$ Hz, 1H), 3.84 (s, 3H), 3.74 (s, 3H), 3.72 (s, 3H), 3.76 (s, 3H), 3.73 (obsc. m, 1H), 3.65 (dt, $J = 8.8, 2.8$ Hz, 1H), 3.47 (td, $J = 10.4, 2.8$ Hz, 2H), 2.54 (m, 1H), 2.15 (s, 3H), 1.84 (m, 1H), 1.80 (br. s, 1H), 1.02 (d, $J = 6.8$ Hz, 3H), 0.89 (s, 9H), 0.64 (d, $J = 6.4$ Hz, 3H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, CDCl_3): δ 148.7, 148.5, 147.6, 147.2, 125.9, 124.9, 80.4, 78.1, 77.7, 64.4, 61.1, 61.0, 60.2, 60.1, 37.7, 35.2, 25.8, 18.1, 14.3, 9.3, 6.5, -4.2, -4.8; IR (film) $\nu_{\max}$ 3462, 2935, 1464 cm^{-1} ; HRMS(CI, NH_3) m/z calc'd for $\text{C}_{25}\text{H}_{45}\text{O}_7\text{Si}$ $[\text{M}+\text{H}]^+$ 485.2935, found: 485.2850.

3-Bromo-2,5,6-trimethoxybenzaldehyde

To a solution of 2,3,6-trimethoxybenzaldehyde⁴ (14.0 g, 71.4 mmol) in acetic acid (350 mL) was added sequentially sodium acetate (8.62 g, 105 mmol) and the dropwise addition of bromine (4.40 mL, 85.4 mmol). The reaction was stirred for 30 minutes before acetic acid was concentrated and residue was diluted with water. The aqueous layer was extracted with methylene chloride. The combined organic layers were dried with MgSO₄, filtered over silica gel, and concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel with (hexanes/EtOAc: 90/10) to yield 87% of 4-bromo-2,3,6-trimethoxybenzaldehyde (16.9 g, 62.1 mmol) as a light yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 10.32 (s, 1H), 7.26 (s, 1H), 3.89 (s, 3H), 3.84 (s, 3H), 3.82 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 189.1, 151.4, 151.0, 150.2, 123.8, 121.6, 112.4, 62.8, 62.3, 56.7 ppm; IR (film) ν_{max} 2939, 2843, 1695, 1563cm⁻¹; mp = 63-65 °C. HRMS(CI, NH₃) *m/z* calc'd for C₁₀H₁₂BrO₄ [M+H]⁺ 274.9919, Found 274.9910.

(2S,5S,6S)-Methyl-6-(3-bromo-2,5,6-trimethoxyphenyl)-

5-methyl-5,6-dihydro-2H-pyran-2-carboxylate

The (2*R*,3*S*)-(E)-methyl-3-(dimethyl(phenyl)silyl)-2-(trimethylsilyloxy)-hex-4-enoate (385.7 mg, 1.10 mmol) was placed in a round bottom flask equipped with a stir bar, 20 mL CH₂Cl₂, and 3-bromo-2,5,6-trimethoxybenzaldehyde (275.5 mg, 1.01 mmol). The mixture was then cooled to -78 °C and triflic acid (151.3 mg, 1.0 mmol) was added in one portion. The reaction was allowed to stir for 24 hours at -78 °C before a saturated

(4) For preparation of 2,3,6-trimethoxybenzaldehyde and 2,3,6-trimethoxy-4-nitrobenzaldehyde, see Andrus M. B.; Meredith E. L.; Hicken E. J.; Simmons B. L.; Glancey R. R.; Ma W. *J. Org. Chem.* **2003**, 68, 8162.

solution of NaHCO_3 (equal volume) was added. The solution was allowed to warm to room temperature on its own. The aqueous layer was then extracted with additional CH_2Cl_2 (3x). The combined organic extracts were placed over MgSO_4 , filtered and concentrated under vacuum to get a crude oil. The resulting crude dihydropyran was purified by column chromatography over silica gel with (hexanes/ CH_2Cl_2 /EtOH: 75/24/1) to yield 78% of pure dihydropyran (312.8 mg, 0.78 mmol) as light yellow oil. $[\alpha]_{\text{D}}^{20}$ -48.2 (*c* 3.60, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.03 (s, 1H), 5.88 (m, 2H), 4.91 (d, *J* = 12 Hz, 1H), 4.73 (s, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.82 (s, 3H), 3.74 (s, 3H), 3.12 (m, 1H), 0.73 (d, *J* = 9.8 Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 172.1, 150.7, 149.3, 132.2, 129.6, 122.5, 119.2, 76.8, 75.0, 74.3, 62.7, 61.3, 57.9, 56.8, 54.2, 31.8, 18.1 ppm; IR (film) ν_{max} 2956, 1742, 1563, 1475, 1425 cm^{-1} ; HRMS(CI, NH_3) *m/z* calc'd for $\text{C}_{17}\text{H}_{22}\text{BrO}_6$ $[\text{M}+\text{H}]^+$ 401.0600, Found 401.0604.

(2S,3S,5S,6S)-Methyl-6-(3-bromo-2,5,6-trimethoxyphenyl)-

3-hydroxy-5-methyl-tetrahydro-2H-pyran-2-carboxylate

(2S,5S,6S)-Methyl-6-(3-bromo-2,5,6-trimethoxyphenyl)-5-methyl-5,6-dihydro-2H-pyran-2-carboxylate (200.3 mg, 0.5 mmol) was placed in a round bottom flask equipped with 10 ml THF. The solution was cooled to 0 °C before borane-dimethyl sulfide complex (2.0M in THF, 0.8 mL) was added dropwise under an atmosphere of argon. The reaction mixture was allowed to warm up to room temperature and stirred for 6 hours. The mixture was cooled to 0 °C then a solution of sodium hydroxide in water (1.0M, 5.0 mL) and hydrogen peroxide (30% aqueous solution, 0.8 mL) were added. The mixture was stirred at 0 °C for 30 minutes and at room temperature for 1 hour before H_2O was added to dilute. The mixture was extracted five times with Et_2O (aqueous phase was saturated with solid NaCl each time). The combined organic extracts were dried over MgSO_4 , filtered, and concentrated under reduced pressure to get crude alcohol. The alcohol was purified by flash chromatography over silica gel with (hexanes/ EtOAc / Et_2O : 80/5/15) to

get colorless oil (165.3 mg, 79%). $[\alpha]_D^{20} + 3.2$ (c 0.60, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.04 (s, 1H), 5.02 (d, $J = 14.8$ Hz, 1H), 4.53 (s, 1H), 4.30 (s, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 3.80 (s, 3H), 3.78 (s, 3H), 3.01 (m, 1H), 2.58 (m, 1H), 1.94 (m, 1H), 1.40 (m, 1H), 0.64 (d, $J = 8.8$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 171.8, 150.9, 149.1, 129.6, 116.2, 112.6, 75.7, 75.0, 74.1, 73.7, 62.7, 61.3, 56.3, 52.2, 34.3, 26.7, 18.9 ppm; IR (film) ν_{max} 3450, 2945, 1742, 1475 cm^{-1} ; HRMS(CI, NH_3) m/z calc'd for $\text{C}_{17}\text{H}_{24}\text{BrO}_7$ $[\text{M}+\text{H}]^+$ 419.0705, Found 419.0710.

(2S,3S,5S,6S)-Methyl-3-[(R)-2-acetoxy-2-phenylacetoxy]-

6-(3-bromo-2,5,6-trimethoxyphenyl)-5-methyl-tetrahydro-2H-pyran-2-carboxylate

(2S,3S,5S,6S)-Methyl-6-(3-bromo-2,5,6-trimethoxyphenyl)-3-hydroxy-5-methyl-tetrahydro-2H-pyran-2-carboxylate (41.1 mg, 0.098 mmol) was added into a round bottom flask along with DCC (35.5 mg, 0.172 mmol), DMAP (3.0 mg, 0.026 mmol) and CH_2Cl_2 (3 mL). A solution of (*R*)-acetoxy mandelic acid (19.7 mg, 0.10 mmol) in CH_2Cl_2 (1.0 mL) was then added at room temperature and allowed to stir overnight. The solution was filtered and concentrated under vacuum to get cloudy oil. The oil was then purified over silica gel (hexanes/THF/EtOAc: 90/5/5) to get a clear oil (46.6mg, 80%). $[\alpha]_D^{20} + 17.6$ (c 2.50, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.48 (m, 2H), 7.38 (m, 3H), 7.02 (s, 1H), 5.93 (s, 1H), 5.46 (s, 1H), 4.87 (d, $J = 10.8$ Hz, 1H), 4.64 (s, 1H), 3.86 (s, 3H), 3.81 (s, 3H), 3.76 (s, 3H), 3.71 (s, 3H), 2.68 (m, 1H), 2.21 (s, 3H), 1.77 (dd, $J = 13.6, 2.3$ Hz, 1H), 1.36 (m, 1H), 0.47 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 170.5, 169.8, 168.4, 150.0, 148.2, 133.3, 129.3, 128.9, 128.8, 127.9, 127.4, 116.1, 75.7, 75.4, 74.8, 70.1, 69.8, 62.1, 61.4, 56.1, 52.3, 33.5, 26.4, 20.6, 17.2 ppm; IR (film) ν_{max} 2941, 1749,

1476, 1426 cm^{-1} ; HRMS(CI, NH_3) m/z calc'd for $\text{C}_{27}\text{H}_{32}\text{BrO}_{10}$ $[\text{M}+\text{H}]^+$ 595.1179, Found 595.1174.

(2S,3S,5S,6S)-Methyl-3-[(S)-2-acetoxy-2-phenylacetoxy]-6-(3-bromo-2,5,6-trimethoxyphenyl)-5-methyl-tetrahydro-2H-pyran-2-carboxylate

(2S,3S,5S,6S)-Methyl-6-(3-bromo-2,5,6-trimethoxyphenyl)-3-hydroxy-5-methyl-tetrahydro-2H-pyran-2-carboxylate (41.1 mg, 0.098 mmol) was added into a round bottom flask along with DCC (35.5 mg, 0.172 mmol), DMAP (3.0 mg, 0.026 mmol) and CH_2Cl_2 (3 mL). A solution of (S)-acetoxymandelic acid (19.7 mg, 0.10 mmol) in CH_2Cl_2 (1.0 mL) was then added at room temperature. The reaction was allowed to stir overnight at room temperature. The solution was filtered and concentrated under vacuum to get cloudy oil. The oil was then purified over silica gel (hexanes/THF/EtOAc: 90/5/5) to get a clear oil (46.6mg, 80%). $[\alpha]_{\text{D}}^{20} + 31.5$ (c 2.85, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.50 (m, 2H), 7.38 (m, 3H), 7.02 (s, 1H), 5.94 (s, 1H), 5.49 (s, 1H), 4.85 (d, J = 10.8 Hz, 1H), 4.41 (s, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 3.0 (br. s, 6H), 2.88 (m, 1H), 2.16 (s, 3H), 2.10 (dd, J = 13.8, 2.0 Hz, 1H), 1.51 (m, 1H), 0.57 (d, J = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 170.3, 169.8, 168.4, 149.9, 147.4, 133.4, 129.5, 128.9, 128.5, 127.9, 126.7, 116.2, 111.8, 76.5, 75.7, 74.8, 70.1, 61.9, 61.2, 56.1, 52.3, 33.7, 26.4, 20.7, 17.3 ppm; IR (film) ν_{max} 2944, 1747, 1474, 1373 cm^{-1} ; HRMS(CI, NH_3) m/z calc'd for $\text{C}_{27}\text{H}_{32}\text{BrO}_{10}$ $[\text{M}+\text{H}]^+$ 595.1179, Found 595.1181.

[(2S,3S,5S,6S)-Methyl-6-(3-bromo-2,5,6-trimethoxyphenyl)]-3-methoxy-5-methyl-tetrahydro-2H-pyran-2-carboxylate (1e**).**

A flame-dried 50 mL round bottom flask was charged with (2S,3S,5S,6S)-Methyl-6-(3-bromo-2,5,6-trimethoxyphenyl)-3-hydroxy-5-methyl-tetrahydro-2H-pyran-2-carboxylate (125.2 mg, 0.30 mmol), 20 mL of dry CH₂Cl₂, proton sponge (320.1 mg, 1.5 mmol) and 4Å molecular sieves (300 mg) were added followed by Me₃O⁺BF₄⁻ (222.4 mg, 1.5 mmol). The resulting heterogeneous, light yellow solution was stirred for 12 hours at room temperature. The mixture was then filtered over celite and purified by column chromatography over silica gel with (hexanes/CH₂Cl₂/Et₂O: 70/25/5) to get **1e** as colorless oil (125.7mg, 97%). [α]_D²⁰ + 12.6 (*c* 5.60, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.02 (s, 1H), 4.92 (d, *J* = 6.8 Hz, 1H), 4.63 (s, 1H), 3.86 (s, 3H), 3.81 (s, 3H), 3.79 (s, 3H), 3.78 (s, 3H), 3.70 (m, 1H) 3.41 (s, 3H), 2.91 (m, 1H), 2.05 (m, 1H), 1.24 (m, 1H), 0.57 (d, *J* = 7.2 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 171.8, 150.3, 148.8, 129.6, 116.3, 112.7, 75.7, 75.0, 74.1, 73.7, 62.3, 61.5, 56.4, 56.3, 52.2, 33.7, 26.0, 18.0 ppm; IR (film) $\nu_{\max}$ 2938, 1746, 1475, 1425 cm⁻¹; HRMS(CI, NH₃) *m/z* calc'd for C₁₈H₂₆BrO₇ [M+H]⁺ 433.0862, Found 433.0864.

[(2R,3S,5S,6S)-6-(3-Bromo-2,5,6-trimethoxyphenyl)-3-methoxy-5-methyl-tetrahydro-2H-pyran-2-yl]methanol (1h**).** (See the general procedure for reduction of methyl ester to alcohol on SI-5 to obtain 98% yield from **1e**). [α]_D²⁰ + 22.8 (*c* 3.12, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.03 (s, 1H), 4.67 (d, *J* = 14.4 Hz, 1H), 4.13 (m, 2H), 3.85 (s, 3H), 3.82 (s, 3H), 3.79 (s, 3H), 3.70 (m, 2H), 3.38 (s, 3H), 2.91 (m, 1H), 2.22 (br s, 1H), 2.02 (m, 1H), 1.39 (m, 1H), 0.65 (d, *J* = 9.2 Hz,

3H); ^{13}C NMR (75 MHz, CDCl_3) δ 150.3, 148.3, 129.6, 116.7, 116.3, 112.1, 75.7, 74.5, 72.6, 62.3, 61.6, 59.9, 56.4, 52.2, 33.9, 26.4, 18.2 ppm; IR (film) ν_{max} 3430, 2938, 1746, 1475, 1425 cm^{-1} ; HRMS(CI, NH_3) m/z calc'd for $\text{C}_{17}\text{H}_{25}\text{BrNaO}_6$ $[\text{M}+\text{Na}]^+$ 427.0732, Found 427.0735.

(2S,5S,6S)-6-(3-Benzyloxy-5-bromo-2-methoxy-phenyl)-5-methyl-5,6-dihydro-2H-pyran-2-carboxylic acid methyl ester (8b).

(2R,3S)-(E)-Methyl-3-(dimethyl(phenyl)silyl)-2-(trimethylsilyloxy)-hex-4-enoate (385.7 mg, 1.10 mmol) was placed in a round bottom flask equipped with a stir bar, 20 mL CH_2Cl_2 , and 3-(benzyloxy)-5-bromo-2-methoxybenzaldehyde⁵ (320.5 mg, 1.01 mmol). The mixture was then cooled to -78°C and triflic acid (151.3 mg, 1.00 mmol) was added in one portion. The reaction was allowed to stir for 24 hours at -78°C before a saturated solution of NaHCO_3 (equal volume) was added. The solution was allowed to warm to room temperature on its own. The aqueous layer was then extracted with additional CH_2Cl_2 (3x). The combined organic extracts were dried over MgSO_4 , filtered and concentrated under vacuum to get a crude oil. The resulting crude dihydropyran was purified by column chromatography over silica gel with (hexanes/EtOAc: 95/5) to get 87% of pure product (388.3 mg, 0.87 mmol) as colorless oil. $[\alpha]_{\text{D}}^{20}$ - 24.9 (c 1.02, CHCl_3); ^1H NMR (CDCl_3 , 400 MHz): δ 7.43-7.30 (m, 5H), 7.17 (d, J = 1.6 Hz, 1H); 7.02 (d, J = 2.0 Hz, 1H), 5.89 (qt, J = 9.6, 2.4 Hz, 2H), 5.06 (s, 2H), 4.87 (s, 1H), 4.85 (d, J = 5.2 Hz, 1H), 3.88 (s, 3H), 3.73 (s, 3H), 2.36 (m, 1H), 0.78 (d, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3): δ 171.3, 152.2, 146.8, 136.21, 136.20, 133.9, 128.6, 128.1, 127.3, 123.0, 122.3, 116.8, 116.7, 73.2, 72.7, 70.8, 61.1, 52.0, 35.4, 16.0; IR (film) ν_{max} 2956, 1750, 1578, 1477 cm^{-1} ; HRMS(CI, Na) m/z calc'd for $\text{C}_{22}\text{H}_{24}\text{BrO}_5$ $[\text{M}+\text{H}]^+$ 447.3190, found: 447.3184.

(5) Wrona, I. E.; Gabarda, A. E.; Evano, G.; Panek, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 15026.

[(2*R*,3*S*,5*S*,6*S*)-6-(3-Benzyloxy-5-bromo-2-methoxyphenyl)-3-methoxy-5-methyl-tetrahydro-pyran-2-yl]-methanol (9b**).**

The dihydropyran **8b** (223.1 mg, 0.5 mmol) was placed in a round bottom flask equipped with 10 mL THF. The solution was cooled to 0 °C before borane-dimethyl sulfide complex (2.0 M in THF, 0.8 mL) was added dropwise under an atmosphere of argon. The reaction mixture was allowed to warm up to room temperature and stirred for 8 hours. The mixture was cooled to 0 °C then a solution of sodium hydroxide in water (1.0 M, 5.0 mL) and a solution of 30% aqueous hydrogen peroxide (0.8 mL) were added. The mixture was stirred at 0 °C for 30 minutes and at room temperature for 1 hour before H₂O was added. The mixture was extracted five times with ethyl ether (aqueous phase was saturated with solid NaCl each time). The combined organic extracts were dried over MgSO₄, filtered, and concentrated under reduced pressure to obtain the crude alcohol.

The crude oil was placed in a flame-dried 50 mL round bottom flask charged with 20 mL of dry CH₂Cl₂. Proton sponge (535.1 mg, 2.5 mmol) and 4Å molecular sieves (300 mg) were added followed by Me₃O⁺BF₄⁻ (370.2 mg, 2.5 mmol). The resulting heterogeneous light yellow solution was stirred for 12 hours at room temperature. The mixture was then filtered through silica and concentrated to obtain a crude oil.

The crude ester was reduced to **9b** using general procedure (SI-5). The crude oil was purified by column chromatography over silica gel with (hexanes/CH₂Cl₂/Et₂O: 70/25/5) to get **9b** as colorless oil (126.3 mg, 56%). $[\alpha]_D^{20} +19.6$ (c 0.26, CHCl₃); ¹H NMR (CDCl₃, 400 MHz): δ 7.43-7.29 (m, 5H), 7.22 (d, *J* = 2.0 Hz, 1H), 7.03 (d, *J* = 2.4 Hz, 1H), 5.05 (s, 2H), 4.59 (d, *J* = 10.4 Hz, 1H), 4.11 (dd, *J* = 10.4, 4.4 Hz, 1H), 4.02 (apt. t, *J* = 10.8 Hz, 1H), 3.84 (s, 3H), 3.54 (dd, *J* = 11.2, 4.4 Hz, 1H), 3.39 (s, 3H), 3.23 (apt. q, *J* = 1.6 Hz, 1H), 2.20 (m, 1H), 2.06 (dt, *J* = 14.8, 2.4 Hz, 1H), 1.47 (dd, *J* = 12.4, 3.6 Hz, 1H), 0.72 (d, *J* = 6.4 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 152.2, 147.0, 136.2, 135.5,

128.6, 128.2, 127.4, 122.9, 117.0, 116.7, 75.8, 74.2, 71.2, 71.0, 61.2, 59.8, 56.4, 33.2, 29.2, 17.7; IR (film) $\nu_{\max}$ 3438, 2931, 1576, 1472 cm^{-1} ; HRMS(CI, Na) m/z calc'd for $\text{C}_{22}\text{H}_{27}\text{BrNaO}_5$ $[\text{M}+\text{Na}]^+$ 473.0940, found: 473.0768.

(2S,5S,6S)-Methyl-5-methyl-6-(2,3,6-trimethoxy-5-nitrophenyl)-5,6-dihydro-2H-pyran-2-carboxylate (8a).

Anti-(2*R*,3*S*,*E*)-crotylsilane (385.9 mg, 1.10 mmol) was placed in a round bottom flask equipped with a stir bar, 20 mL CH_2Cl_2 and 2,3,6-trimethoxy-5-nitrobenzaldehyde⁴ (243.1 mg, 1.01 mmol). The mixture was then cooled to -78°C and triflic acid (151.3 mg, 1.0 mmol) was added in one portion. The reaction was allowed to stir for 24 hours at -78°C before a saturated solution of NaHCO_3 (equal volume) was added and allowed to warm to room temperature. The aqueous layer was then extracted with additional CH_2Cl_2 (3x). The combined organic extracts were placed over MgSO_4 , filtered and concentrated under vacuum to get a crude oil. The resulting crude dihydropyran was purified by column chromatography over silica gel with (hexanes/ CH_2Cl_2 /EtOH: 65/34/1) to get 63% of the dihydropyran as a light yellow oil. $[\alpha]_{\text{D}}^{20}$ - 35.2 (c 1.51, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.45 (s, 1H), 5.83 (m, 2H), 4.96 (d, J = 9.6 Hz, 1H), 4.83 (br s, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 3.78 (s, 3H), 3.72 (s, 3H), 3.01 (m, 1H), 0.71 (d, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 171.8, 149.3, 147.6, 139.2, 134.5, 122.2, 108.9, 76.2, 74.9, 73.0, 72.8, 64.0, 61.8, 58.3, 52.3, 31.7, 16.7 ppm; IR (film) $\nu_{\max}$ 2951, 1751, 1576, 1521, 1479 cm^{-1} ; HRMS(CI, Na) m/z calc'd for $\text{C}_{17}\text{H}_{22}\text{NO}_8$ $[\text{M}+\text{H}]^+$ 368.1345, Found 3689.1341.

(2S,3S,5S,6S)-Methyl-3-methoxy-5-methyl-6-(2,3,6-trimethoxy-5-nitrophenyl)-tetrahydro-2H-pyran-2-carboxylate (1c).

The dihydropyran **8a** (183.4 mg, 0.5 mmol) was placed in a round bottom flask equipped with 10 mL THF. The solution was cooled to 0 °C at that point borane-dimethyl sulfide complex (2.0 M in THF, 0.9 mL) was added dropwise under an atmosphere of argon. The reaction mixture was allowed to warm up to room temperature and stirred for 8 hours. The mixture was cooled to 0 °C and a solution of sodium hydroxide in water (1.0 M, 5.0 mL) and hydrogen peroxide (30% wt, 1.4 mL) were added. The mixture was stirred at 0 °C for 30 minutes and at room temperature for 1 hour before H₂O was added to dilute. The mixture was extracted with Et₂O (5x, aqueous phase was saturated with solid NaCl each time). The combined organic extracts were dried over MgSO₄, filtered, and concentrated under reduced pressure to get crude alcohol.

The crude oil was placed in flame-dried 25 mL round bottom flask 20 mL of dry CH₂Cl₂, proton sponge (535.1 mg, 2.5 mmol) and 4Å molecular sieves (300 mg) were added followed by Me₃O⁺BF₄⁻ (370.2 mg, 2.5 mmol). The resulting heterogeneous light yellow solution was stirred for 12 hours at room temperature. The mixture was then filtered through silica and concentrated to obtain a crude oil. The crude oil was purified by column chromatography over silica gel with (hexanes/CH₂Cl₂/Et₂O: 80/15/5) to get 68% yield of the 3-methoxyl tetrahydropyran as yellow oil (135.6 mg, 0.34 mmol). $[\alpha]_D^{20} + 9.9$ (*c* 2.70, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.40 (s, 1H), 4.99 (d, *J* = 3.8 Hz, 1H), 4.61 (s, 1H), 3.91(s, 3H), 3.83 (s, 3H), 3.81 (m, 1H), 3.76 (s, 3H), 3.72(s, 3H), 3.42 (s, 3H), 2.95 (m, 1H), 2.05 (m, 1H), 1.22 (m, 1H), 0.56 (d, *J* = 6.2 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 171.6, 152.3, 148.7, 130.5, 108.7, 107.8, 81.0, 78.1, 74.9, 73.7, 63.7, 61.8, 59.3, 56.3, 52.3, 33.6, 25.8, 17.8 ppm; IR (film) $\nu_{\max}$ 2942, 1746, 1521, 1475, 1336 cm⁻¹; HRMS(CI, Na) *m/z* calc'd for C₁₈H₂₅NNaO₉ [M+Na]⁺ 422.1427, found: 422.1425.

[(2R,3S,5S,6S)-3-Methoxy-5-methyl-6-(2,3,6-trimethoxy-5-nitrophenyl)-tetrahydro-2H-pyran-2-yl]methanol (9a). (See the general procedure for reduction of methyl ester to alcohol on SI-5 to obtain 97% reduced from ester **1c** as a light yellow oil); $[\alpha]_{\text{D}}^{20} + 3.1^\circ$ (*c* 0.84, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.36 (s, 1H), 5.01 (d, *J* = 3.8 Hz, 1H), 4.61 (br s, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 3.81 (m, 1H), 3.79 (s, 3H), 3.44 (m, 2H), 3.41 (s, 3H), 2.93 (m, 1H), 2.20 (br s, 1H), 2.05 (m, 1H), 1.24 (m, 1H), 0.62 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 152.5, 148.9, 130.2, 107.7, 107.5, 81.0, 78.1, 73.6, 71.7, 63.7, 61.5, 59.3, 56.4, 36.2, 34.5, 25.8 19.5 ppm; IR (film) ν_{max} 3467, 2952, 1521, 1475 cm^{-1} ; HRMS(CI, Na) *m/z* calc'd for $\text{C}_{17}\text{H}_{25}\text{NO}_8[\text{M}]^+$ 371.1580, Found 371.1582.

(2R,3R,4R,5S,6S)-3,4,5-Trimethoxy-2-methoxymethyl-6-(2,4,6-trimethoxy-phenyl)-tetrahydro-pyran (11). (Prepared from the alkylation⁶ of 2,4,5-trimethoxy- β -D-glucopyranoside⁷ in 75% yield). $[\alpha]_{\text{D}}^{20} - 2.5^\circ$ (*c* 0.44, CHCl_3); ^1H NMR (CDCl_3 , 400 MHz): δ 6.08 (s, 2H), 4.68 (d, *J* = 10 Hz, 1H), 3.95 (m, 1H), 3.77 (s, 3H), 3.76 (s, 3H), 3.75 (s, 3H), 3.65 (s, 3H), 3.63-3.54 (obsc. m, 3H), 3.56 (s, 3H), 3.35 (s, 3H), 3.25-3.18 (m, 2H), 3.11 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3): δ 161.0, 160.7, 159.7, 107.3, 91.5, 90.6, 88.9, 81.1, 79.8, 79.0, 72.3, 71.6, 60.6, 60.2, 59.4, 59.1, 56.0, 55.5, 55.0; IR (film) ν_{max} 2937, 2835, 1603, 1461, 1202 cm^{-1} ; HRMS(CI, Na) *m/z* calc'd for $\text{C}_{19}\text{H}_{30}\text{NaO}_8[\text{M}+\text{Na}]^+$ 409.1838, found: 409.1806.

(6) Wang, H.; Sun, L.; Glazechnik, S.; Zhao, K. *Tetrahedron Lett.* **1995**, 36, 2953.

(7) For the preparation of the polyol see: Stewart, A. O.; Williams, R. M. *J. Am. Chem. Soc.* **1985**, 107, 4289.

General procedure for reductive opening of 5-aryl pyrans

Condition A (Room temperature):

Triethyl silane (5 equiv.) was placed in a round bottom flask containing a stir bar and a 0.1-0.5M solution of the appropriate pyran (0.1 mmol) in CH₂Cl₂. To this solution Sc(OTf)₃ (2.0 equiv.) was added and allowed to stir for 24 hours at room temperature. Water was then added and the mixture was allowed to stir for 10 minutes before being extracted with CH₂Cl₂ (3x). The combined organic extracts were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel to yield the desired alcohol. The aqueous layer was washed with CH₂Cl₂ and concentrated under reduced pressure to recover Sc(OTf)₃.

Condition B (Microwave):

Triethyl silane (5 equiv.) was placed in a microwave tube containing a stir bar and a 0.1-0.5M solution of the appropriate pyrans (0.1 mmol) in CH₂Cl₂ at ambient temperature. To the solution Sc(OTf)₃ (0.25-1.0 equiv.) was then added. The tube was sealed and irradiated in a microwave (300 watts, 70 PSI and 100 °C) for 20 to 60 minutes before water was added. The mixture was allowed to stir for 10 minutes then extracted with additional CH₂Cl₂ (3x). The combined organic extracts were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel to yield the desired alcohol. The aqueous solution was washed with CH₂Cl₂ and concentrated under reduced pressure to recover Sc(OTf)₃.

(2S,5S)-Methyl-2-hydroxy-5-methyl-6-phenylhexanoate

(2a). (Condition A (60 hours) provided **2a** from **1a** in 67% overall yield as colorless oil; Condition B (2.0 equiv. Sc(OTf)₃) provided **2a** from **1a** in 71% overall yield as colorless

oil); $[\alpha]_D^{20} + 1.7$ (*c* 2.20, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.14-7.22 (m, 5H), 4.17 (dd, *J* = 5.8, 2.8 Hz, 1H), 3.74 (s, 3H), 2.69 (s, 1H), 2.61 (q, *J* = 6.0 Hz, 1H), 2.38 (q, *J* = 5.8 Hz, 1H), 1.77 (m, 3H), 1.49 (m, 1H), 1.21 (m, 1H), 0.82 (d, *J* = 6.4 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 175.9, 141.4, 129.4, 128.4, 126.0, 70.9, 52.7, 43.7, 35.0, 32.2, 31.7, 19.4 ppm; IR (film) $\nu_{\max}$ 3466, 3025, 2953, 1734, 1495, 1453 cm⁻¹; HRMS(CI, Na) *m/z* calc'd for C₁₄H₂₀O₃ [M]⁺ 236.1412, Found 236.1407.

(2S,5S)-Methyl-2-hydroxy-5-methyl-6-(naphthalen-2-yl)-hexanoate (2b). (Condition A provided **2b** from **1b** in 83% overall yield as colorless oil; Condition B (2.0equiv. Sc(OTf)₃) provided **2b** from **1b** in 86% overall yield as colorless oil); $[\alpha]_D^{20} + 22.3$ (*c* 2.41, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.74 (m, 3H), 7.55 (s, 1H), 7.40 (m, 2H), 7.26 (d, *J* = 8.0 Hz, 1H), 4.18 (dd, *J* = 7.1, 3.2 Hz, 1H), 3.71 (s, 3H), 2.69 (q, *J* = 5.8 Hz, 1H), 2.57 (q, *J* = 5.9 Hz, 1H), 2.22 (br s, 1H), 1.79 (m, 3H), 1.48 (m, 1H), 1.21 (m, 1H), 0.87 (d, *J* = 8.0 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 175.9, 138.9, 133.7, 132.2, 128.1, 127.9, 127.8, 127.6, 127.5, 126.0, 125.3, 70.8, 52.7, 43.9, 35.0, 32.2, 31.8, 19.5 ppm; IR (film) $\nu_{\max}$ 3471, 3052, 2952, 1734, 1599, 1507, 1437 cm⁻¹; HRMS(CI, Na) *m/z* calc'd for C₁₈H₂₂O₃ [M]⁺ 286.1569, Found 286.1562.

(2S,3S,5R)-Methyl-2-hydroxy-3-methoxy-5-methyl-6-(2,3,6-trimethoxy-5-nitrophenyl)-hexanoate³ (2c). (Condition A provided **2c** from **1c** in 82% overall yield as light yellow oil); $[\alpha]_D^{20} + 0.3$ (*c* 2.70, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.35 (s, 1H), 4.42 (dd, *J* = 5.5, 3.0 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.84 (s, 3H), 3.78 (s, 3H), 3.52 (dt, *J* = 9.7, 3.0 Hz, 1H), 3.38 (s, 3H), 2.88 (d, *J* = 5.7 Hz, 1H),

2.63 (dd, $J = 12.4, 6.2$ Hz, 1H), 2.53 (dd, $J = 12.9, 8.7$ Hz, 1H), 2.09-1.96 (m, 1H), 1.75 (m, 1H), 1.17 (m, 1H), 0.81 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 173.3, 152.8, 148.4, 148.0, 138.3, 131.1, 107.1, 81.0, 71.9, 62.6, 61.1, 58.3, 56.3, 52.7, 37.3, 32.2, 30.2, 19.5 ppm; IR (film) ν_{max} 3498, 2952, 1736, 1518, 1479, 1424 cm^{-1} HRMS(CI, Na) m/z calc'd for $\text{C}_{18}\text{H}_{27}\text{NNaO}_9$ 424.1584, Found 424.1588. Found to be identical to previous reports of **2c**.⁴

(2S,5S)-Methyl-6-(4-(dimethylamino)phenyl)-2-hydroxy-5-methylhexanoate (2d). (Condition **A** provided **2d** from **1d** in 73% overall yield as light yellow oil); $[\alpha]_{\text{D}}^{20} + 2.7$ (c 2.01, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.01 (d, $J = 8.8$ Hz, 2H), 6.68 (d, $J = 8.8$ Hz, 2H), 4.16 (m, 1H), 3.75 (s, 3H), 2.91 (s, 6H), 2.67 (s, 1H), 2.53 (dd, $J = 16.2, 4.8$ Hz, 1H), 2.26 (dd, $J = 16.2, 4.8$ Hz, 1H), 1.67 (m, 3H), 1.50 (m, 1H), 1.18 (m, 1H), 0.82 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 175.7, 140.0, 139.6, 130.3, 122.4, 70.5, 52.5, 42.9, 34.8, 32.2, 32.0, 31.5, 19.1 ppm; IR (film) ν_{max} 3474, 2952, 2801, 1739 cm^{-1} ; HRMS(CI, Na) m/z calc'd for $\text{C}_{16}\text{H}_{26}\text{NO}_3$ $[\text{M}]^+$ 280.1913, Found 280.1917.

(2S,3S,5R)-Methyl-6-(3-bromo-2,5,6-trimethoxyphenyl)-2-hydroxy-3-methoxy-5-methylhexanoate (2e). (Condition **A** provided **2e** from **1e** in 87% overall yield as colorless oil in 2.5g; Condition **B** (2.0 equiv. $\text{Sc}(\text{OTf})_3$) provided **2e** from **1e** in 89% overall yield as colorless oil); $[\alpha]_{\text{D}}^{20} + 3.7^\circ$ (c 2.20, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 6.92 (s, 1H), 4.43 (m, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 3.77 (s, 3H), 3.74 (s, 3H), 3.55 (m, 1H), 3.40 (s, 3H), 2.87 (d, 1H), 2.61 (dd, $J = 16.2, 3.8$ Hz, 1H), 2.45 (dd, $J = 16.2, 3.8$ Hz, 1H), 2.02 (m, 1H), 1.71 (m, 1H), 1.12 (m, 1H), 0.80 (d, $J = 9.2$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 173.5, 150.0, 147.7, 130.2,

114.3, 110.8, 81.2, 72.2, 61.3, 60.8, 58.4, 56.3, 52.7, 37.5, 33.0, 32.0, 30.6, 19.6 ppm; IR (film) $\nu_{\max}$ 3469, 2933, 1739, 1475 cm^{-1} ; HRMS(CI, Na) m/z calc'd for $\text{C}_{18}\text{H}_{27}\text{BrO}_7$ $[\text{M}]^+$ 434.0940, Found 434.0941.

(2S,5S)-5-methyl-6-phenylhexane-1,2-diol (2f). (Condition **A** provided **2f** from **1f** in 78% overall yield as colorless oil; Condition **B** (2.0 equiv. $\text{Sc}(\text{OTf})_3$) provided **2f** from **1f** in 71% overall yield as colorless oil); $[\alpha]_{\text{D}}^{20} + 33.4$ (c 2.90, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.25 (m, 5H), 3.62 (m, 2H), 3.42 (m, 1H), 2.62 (dd, $J = 13.6, 4.2$ Hz, 1H), 2.37 (dd, $J = 13.6, 4.2$ Hz, 1H), 1.96 (s, 1H), 1.69 (m, 2H), 1.48 (m, 3H), 0.85 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 141.3, 128.6, 128.1, 127.6, 79.3, 73.2, 61.6, 35.4, 27.7, 25.1, 18.4 ppm; IR (film) $\nu_{\max}$ 3352, 3026, 2925, 160, 1494, 1454 cm^{-1} ; HRMS(CI, Na) m/z calc'd for $\text{C}_{13}\text{H}_{20}\text{O}_2$ $[\text{M}+\text{Na}]^+$ 231.1361, Found 231.1359.

(2S,5S)-5-Methyl-6-(naphthalen-1-yl)hexane-1,2-diol (2g). (Condition **A** provided **2g** from **1g** in 93% overall yield as colorless oil; Condition **B** (1.0 equiv. $\text{Sc}(\text{OTf})_3$) provided **2g** from **1g** in 89% overall yield as colorless oil) $[\alpha]_{\text{D}}^{20} + 60.2$ (c 4.48, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.98 (d, $J = 8.6$ Hz, 1H), 7.84 (d, $J = 8.6$ Hz, 1H), 7.70 (d, $J = 9.0$ Hz, 1H), 7.46 (m, 2H), 7.36 (m, 1H), 7.25 (d, $J = 6.4$ Hz, 1H), 3.63 (m, 2H), 3.40 (m, 1H), 3.11 (dd, $J = 17.8, 3.8$ Hz, 1H), 2.79 (dd, $J = 17.8, 4.6$ Hz, 1H), 2.12 (s, 1H), 1.91 (m, 2H), 1.55 (m, 1H), 1.43 (m, 2H), 0.90 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 137.5, 134.1, 132.4, 129.0, 127.5, 126.9, 125.8, 125.6, 125.5, 124.2, 72.8, 67.0, 41.1, 34.4, 33.1, 30.9, 19.9 ppm; IR (film) $\nu_{\max}$ 3367, 3064, 2926, 1595, 1509, 1458 cm^{-1} ; HRMS(CI, Na) m/z calc'd for $\text{C}_{17}\text{H}_{22}\text{O}_2$ $[\text{M}]^+$ 258.1620, Found 258.1620.

(2R,3S,5R)-6-(3-Bromo-2,5,6-trimethoxyphenyl)-3-methoxy-5-methylhexane-1,2-diol (2h). (Condition **A** provided **2h** from **1h** in 88% overall yield as colorless oil; Condition **B** (0.25 equiv. Sc(OTf)₃) provided **2h** from **1h** in 80% overall yield as colorless oil); $[\alpha]_{\text{D}}^{20}$ - 4.8 (*c* 2.20, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 6.89 (s, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 3.71 (s, 3H), 3.58 (m, 2H), 3.33 (s, 3H), 3.18 (m, 1H), 2.95 (m, 1H), 2.58 (dd, *J* = 13.6, 3.6 Hz, 1H), 2.43 (dd, *J* = 13.6, 4.2 Hz, 1H), 2.18 (br s, 2H), 1.99 (m, 1H), 1.59 (m, 1H), 1.22 (m, 1H), 0.82 (d, *J* = 6.8 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 150.1, 149.7, 130.1, 114.3, 110.6, 90.1, 73.1, 63.4, 61.2, 60.9, 60.6, 58.2, 56.1, 37.9, 33.0, 30.4, 19.7 ppm; IR (film) ν_{max} 3450, 2938, 1475, 1425 cm⁻¹; HRMS(CI, Na) *m/z* calc'd for C₁₇H₂₇BrNaO₆ [M+Na]⁺ 429.0889, Found 429.0885.

(2S,5R)-2-Hydroxy-5-methyl-6-(2,3,5,6-tetramethoxy-4-methyl-phenyl)-hexanoic acid methyl ester (2i). (Condition **A** provided **2i** from **1i** in 78% overall yield as colorless oil).³ $[\alpha]_{\text{D}}^{20}$ - 16.9 (*c* 0.82, CHCl₃); ¹H NMR (CDCl₃, 400 MHz): δ 4.19 (m, 1H), 3.78 (s, 3H), 3.75 (s, 12H), 2.70 (br. s, 1H), 2.56 (dd, *J* = 16.8, 8.0 Hz, 1H), 2.38 (dd, *J* = 16.8, 11.6 Hz, 1H), 2.14 (s, 3H), 1.89 (m, 1H), 1.73 (m, 1H), 1.64 (m, 1H), 1.37 (m, 2H), 0.84 (d, *J* = 9.2 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 175.8, 147.7, 147.3, 125.9, 123.3, 70.7, 60.4, 60.1, 52.3, 33.7, 32.0, 31.9, 31.1, 19.7, 9.1; IR (film) ν_{max} 3478, 2951, 1740, 1462, 1406 cm⁻¹; HRMS(CI, Na) *m/z* calc'd for C₁₉H₃₀NaO₇ [M+Na]⁺ 393.1889, found: 393.1910.

(2S,3R,4R,5S)-3,5-Dimethyl-6-(2,3,5,6-tetramethoxy-4-methyl-phenyl)-hexane-1,2,4-triol (2j). (Condition **A** provided **2j** from **1j** in 62% overall yield as colorless oil); $[\alpha]_{\text{D}}^{20} + 65.5$ (*c* 1.02, CHCl_3); ^1H NMR (CDCl_3 , 400 MHz): δ 3.81 (s, 6H), 3.75 (s, 6H), 3.63 (s, 1H), 3.48 (s, 2H), 3.29 (br. s, 2H), 3.17 (d, $J = 10.8$ Hz, 1H), 2.65 (dd, $J = 13.2, 4.4$ Hz, 1H), 2.46 (t, $J = 12.4$ Hz, 1H), 2.15 (s, 3H), 2.00 (m, 1H), 1.76 (m, 1H), 0.97 (d, $J = 6.8$ Hz, 3H), 0.67 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3): δ 147.7, 147.3, 124.4, 124.1, 73.7, 73.4, 63.5, 60.9, 60.3, 37.3, 35.9, 28.4, 13.3, 12.8, 9.1; IR (film) ν_{max} 3425, 2936, 1462, 1406, 1077 cm^{-1} ; HRMS(CI, Na) m/z calc'd for $\text{C}_{19}\text{H}_{33}\text{O}_7$ $[\text{M}+\text{H}]^+$ 373.2226, found: 373.2221.

(2R,3S)-5-Phenyl-pentane-1,2,3-triol (2k). (Condition **A** (48 hours) provided **2k** from **1k** in 50% overall yield from 1-phenyl-2-deoxy-D-ribose⁸ as colorless oil; Condition **B** (2.0 equiv. $\text{Sc}(\text{OTf})_3$) provided **2k** from **1k** in 51% overall yield from 1-phenyl-2-deoxy-D-ribose as colorless oil); $[\alpha]_{\text{D}}^{20} - 26.0$ (*c* 0.15, CHCl_3); ^1H NMR (CD_3OD , 400 MHz): δ 7.25-7.19 (m, 4H), 7.14-7.11 (m, 1H), 3.72 (dd, $J = 12.4, 4.0$ Hz, 1H), 3.56 (d, $J = 6.8$ Hz, 1H), 3.54-3.42 (m, 2H), 2.85 (m, 1H), 2.63 (m, 1H), 1.97 (m, 1H), 1.68 (m, 1H); ^{13}C NMR (75 MHz, CD_3OD): δ 143.7, 129.5, 129.3, 126.7, 76.3, 72.8, 64.7, 36.3, 32.9; IR (film) ν_{max} 3329, 2919, 1454, 1041 cm^{-1} ; HRMS(CI, Na) m/z calc'd for $\text{C}_{11}\text{H}_{16}\text{O}_3$ $[\text{M}]^+$ 196.1099, found: 196.1080.

(2R,3R,4R,5S)-1,3,4,5-Tetramethoxy-6-(2,4,6-trimethoxy-phenyl)-hexan-2-ol (2l). (Condition **A** (48 hours) provided **2l** from **1l** in 65% overall yield as colorless oil; Condition **B** (2.0 equiv. $\text{Sc}(\text{OTf})_3$) provided **2l** from **1l**

(8) Chaudhuri, N. C.; Kool, E. T. *Tetrahedron Lett.* **1995**, 36, 1795.

in 61% overall yield as colorless oil). $[\alpha]_{\text{D}}^{20} + 29.7$ (c 0.47, CHCl_3); ^1H NMR (CDCl_3 , 400 MHz): δ 6.10 (s, 2H), 3.79 (s, 9H), 3.59 (m, 1H), 3.54 (s, 3H), 3.51 (m, 1H), 3.41 (s, 3H), 3.38 (m, 1H), 3.35 (s, 3H), 3.27 (s, 1H), 3.47 (m, 2H), 3.14 (s, 3H), 2.99 (dd, $J = 13.2, 8.4$ Hz, 1H), 2.86 (dd, $J = 8.4, 4.8$ Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3): δ 159.7, 159.0, 107.1, 90.4, 80.6, 78.7, 77.4, 73.8, 71.1, 59.3, 59.1, 58.1, 57.4, 55.5, 55.2, 23.4; IR (film) ν_{max} 3483, 2930, 2832, 1610, 1460 cm^{-1} ; HRMS(CI, Na) m/z calc'd for $\text{C}_{19}\text{H}_{32}\text{NaO}_8$ $[\text{M}+\text{Na}]^+$ 411.1995, found: 411.1845.

(2R,3S,5R)-6-(3-Benzyloxy-5-bromo-2-methoxy-

phenyl)-3-methoxy-5-methyl-hexane-1,2-diol (10b). (Condition A provided **10b** from **9b** in 63% overall yield as colorless oil); $[\alpha]_{\text{D}}^{20} - 1.8^\circ$ (c 0.80, CHCl_3); ^1H NMR (CDCl_3 , 400 MHz): δ 7.50-7.30 (m, 5H), 6.95 (d, $J = 2.0$ Hz, 1H), 6.88 (d, $J = 2.4$ Hz, 1H), 5.05 (s, 2H), 3.80 (s, 3H), 3.73 (m, 2H), 3.65 (t, $J = 7.2$ Hz, 1H), 3.44 (m, 1H), 3.40 (s, 3H), 2.61 (dd, $J = 13.2, 6.0$ Hz, 1H), 2.37 (dd, $J = 13.2, 8.4$ Hz, 1H), 1.93 (m, 1H), 1.64 (m, 1H), 1.22 (m, 1H), 0.87 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3): δ 152.5, 147.0, 136.5, 136.4, 128.6, 128.3, 127.4, 125.7, 115.7, 115.4, 81.4, 72.6, 70.9, 63.3, 60.6, 58.5, 37.8, 37.7, 30.7, 19.6; IR (film) ν_{max} 3411, 2931, 1575, 1471, 1093 cm^{-1} ; HRMS(CI, Na) m/z calc'd for $\text{C}_{22}\text{H}_{29}\text{BrNaO}_5$ $[\text{M}+\text{Na}]^+$ 475.1096, found: 475.1096. Found to be identical to previous reports of **10b**.⁵

(2R,3S,5R)-3-Methoxy-5-methyl-6-(2,3,6-trimethoxy-

5-nitrophenyl)hexane-1,2-diol (10a). (Condition A provided **10a** from **9a** in 84% overall yield as light yellow oil); $[\alpha]_{\text{D}}^{20} - 14.8^\circ$ (c 1.20, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.38 (s, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 3.82 (s, 3H), 3.57 (m, 2H), 3.5 (m, 1H), 3.40 (m, 1H), 3.38 (s, 3H), 2.65 (dd, $J = 13, 6.5$ Hz, 1H), 2.55 (dd, $J = 13, 6.5$ Hz, 1H),

1.98 (m, 1H), 1.59 (m, 1H), 1.28 (m, 1H), 0.86 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 152.8, 148.7, 147.8, 138.5, 130.8, 107.3, 81.5, 73.0, 63.4, 62.5, 60.9, 58.4, 56.2, 37.9, 32.5, 30.4, 19.7 ppm; IR (film) ν_{max} 3450, 2942, 1485, 1425 cm^{-1} ; HRMS(CI, Na) m/z calc'd for $\text{C}_{17}\text{H}_{27}\text{NNaO}_8$ $[\text{M}+\text{Na}]^+$ 396.1634, Found 329.1638. Found to be identical to previous reports of **10a**.⁹

(2*S*,5*S*,6*R*)-methyl-2-hydroxy-5-methyl-6-phenylnon-8-

enoate (3a). (2*S*,5*S*,6*S*)-methyl-5-methyl-6-phenyl-tetrahydro-2H-pyran-2-carboxylate (**1a**) (23.4 mg, 0.10 mmol) was placed in a round-flask containing a stir bar, 2.0 mL CH_2Cl_2 and allyltrimethylsilane (228.1 mg, 2.0 mmol). To the solution $\text{Sc}(\text{OTf})_3$ (98.4 mg, 0.20 mmol) was then added. The solution was stirred for 2 days before 5 mL water was added. The mixture was allowed to stir for 10 minutes then extracted with additional CH_2Cl_2 (3 ml x 3). The combined organic extracts were dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel with (hexanes/EtOAc: 90/10) to yield 81% (dr=1.7/1) of (2*S*,5*S*)-methyl-2-hydroxy-5-methyl-6-phenylnon-8-enoate (22.4 mg, 81.1 μmol) as light yellow oil. ^1H NMR (^1H NMR (400 MHz, CDCl_3 , 1.7:1 diastereomeric ratio, asterisk denotes minor isomer peaks); δ 7.26 (m, 5H), 7.17* (m, 5H), 5.58 (m, 1H), 5.56* (m, 1H), 4.90 (m, 2H), 4.86* (m, 2H), 4.16 (m, 1H), 4.19* (m, 1H), 3.67 (s, 3H), 3.67* (s, 3H), 2.56 (d, $J = 6.0$ Hz, 1H), 2.62* (d, $J = 8.4$ Hz, 1H), 2.40 (m, 2H), 2.38* (m, 2H), 1.66 (m, 3H), 1.60* (m, 3H), 1.42 (m, 2H), 1.44* (m, 2H), 1.18 (m, 1H), 1.20* (m, 2H) 0.92 (d, $J = 6.4$ Hz, 3H), 0.72* (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 175.6, 137.3, 128.6, 127.9, 125.9, 115.6, 70.5, 52.5, 51.3, 43.5, 37.5, 31.8, 29.5, 28.9, 16.9 ppm; IR (film) ν_{max} 3487, 2955, 2239, 1736, 1446, 1221 cm^{-1} ; HRMS(CI, Na) m/z calc'd for $\text{C}_{17}\text{H}_{24}\text{NaO}_3$ $[\text{M}+\text{Na}]^+$ 299.1623, Found 299.1627.

(9) Andrus M. B.; Meredith E. L.; Sekhar B. B. V. S. *Org. Lett.* **2001**, 3, 259.

(2*S*,5*S*,6*R*)-methyl-6-azido-2-hydroxy-5-methyl-6-phenylhexanoate (3b). (2*S*,5*S*,6*S*)-methyl-5-methyl-6-phenyl-tetrahydro-2H-pyran-2-carboxylate (**1a**) (23.4 mg, 0.10 mmol) was placed in a microwave tube containing a stir bar, 1.0 mL CH₂Cl₂ and TMSN₃ (230.1 mg, 2.01 mmol). To the solution Sc(OTf)₃ (98.4 mg, 0.20 mmol) was then added. The tube was sealed and irradiated in a microwave (300 watts, 70 PSI and 100 °C) for 60 minutes before water was added. The mixture was allowed to stir for 10 minutes then extracted with additional CH₂Cl₂ (3 ml x 3). The combined organic extracts were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel with (hexanes/EtOAc: 85/15) to yield 91% (dr=1.4/1) of (2*S*,5*S*)-methyl-6-azido-2-hydroxy-5-methyl-6-phenylhexanoate (25.3 mg, 91.1 μmol) as light yellow oil. ¹H NMR (400 MHz, CDCl₃, 1.4 : 1 diastereomeric ratio, asterisk denotes minor isomer peaks); δ 7.36 (m, 5H), 7.21* (m, 5H), 4.20 (m, 1H), 4.22* (m, 1H), 3.72 (s, 3H), 3.76* (s, 3H), 2.78 (d, *J* = 5.2 Hz, 1H), 2.69* (d, *J* = 8.6 Hz, 1H), 1.86 (m, 2H), 1.81* (m, 2H), 1.75 (m, 2H), 1.69* (m, 2H), 1.40 (m, 1H), 1.40* (m, 1H), 1.19 (m, 1H), 1.08* (m, 1H), 0.92 (d, *J* = 6.4 Hz, 3H); 0.72* (d, *J* = 6.4 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 175.4, 138.6, 128.8, 128.1, 127.7, 71.7, 70.2, 52.5, 38.3, 31.6, 28.5, 15.3 ppm; IR (film) ν_{max} 3480, 2955, 2098, 1736, 1453, 1249 cm⁻¹; HRMS(CI, Na) *m/z* calc'd for C₁₄H₁₉N₃NaO₃ [M+Na]⁺ 300.1324, Found 300.1328.

(2*S*,5*S*,6*R*)-methyl-6-cyano-2-hydroxy-5-methyl-6-phenylhexanoate (3c). (2*S*,5*S*,6*S*)-methyl-5-methyl-6-phenyl-tetrahydro-2H-pyran-2-carboxylate (**1a**) (23.4 mg, 0.10 mmol) was placed in a microwave tube containing a stir bar, 1.0 mL CH₂Cl₂ and TMSCN (49.5 mg, 0.50 mmol). To the solution Sc(OTf)₃ (98.4 mg, 0.20 mmol) was then added. The tube was sealed and irradiated in a microwave (300 watts, 70 PSI and 100 °C) for 20 minutes before water was added. The mixture was

allowed to stir for 10 minutes then extracted with additional CH₂Cl₂ (3 ml x 3). The combined organic extracts were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel with (hexanes/EtOAc: 85/15) to yield 43% (dr=4/1) of (2*S*,5*S*)-methyl-6-cyano-2-hydroxy-5-methyl-6-phenylhexanoate (11.3 mg, 43.1 μmol) as light yellow oil. ¹H NMR (400 MHz, CDCl₃, 4:1 diastereomeric ratio, asterisk denotes minor isomer peaks); δ 7.38 (m, 5H), 7.24* (m, 5H), 4.17 (m, 1H), 4.14* (m, 1H), 3.82 (d, *J* = 6.4 Hz, 1H), 3.66* (d, *J* = 10.4 Hz, 1H), 3.77 (s, 3H), 3.72* (s, 3H), 2.76 (d, *J* = 4.8 Hz, 1H), 2.70* (d, *J* = 9.6 Hz, 1H), 1.96 (m, 1H), 2.00* (m, 1H), 1.81 (m, 1H), 1.79* (m, 1H), 1.76 (m, 2H), 1.75* (m, 2H), 1.49 (m, 1H), 1.42* (m, 1H), 0.97 (d, *J* = 6.4 Hz, 3H), 1.02* (d, *J* = 6.4 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 184.6, 175.3, 134.7, 128.8, 127.7, 119.2, 70.1, 52.7, 43.5, 38.3, 31.7, 30.2, 15.6 ppm; IR (film) ν_{max} 3476, 2925, 2239, 1736, 1494, 1451 cm⁻¹; HRMS(CI, Na) *m/z* calc'd for C₁₅H₁₉NNaO₃ [M+Na]⁺ 284.1263, Found 284.1261.

Assignment of Stereochemistry of Azide 3b

The stereochemistry of the benzylic position in the resulting acyclic products found in table 3 was determined through a two step sequence; reduction and lactam formation of **3b**. Upon chromatographic separation, each diastereomer was fully characterized to secure the correct stereochemical assignment of the opened products (See below for details). Analysis of the three-bond coupling constants (³J_{H1,H2} = 4.2 Hz) correlating to the C5 and C6 stereogenic centers in the ¹H-NMR spectrum of the “major” lactam permitted the stereochemical assignment as a *cis* configuration. Analysis of the three-bond coupling constants (³J_{H1,H2} = 11.2 Hz) correlating to the C5 and C6 stereogenic centers in the ¹H-NMR spectrum of the “minor” lactam permitted the stereochemical assignment as a *trans* configuration. In addition, a NOESY 1D was performed on the C6 protons of both isomers giving responses supporting the three-bond coupling constants described above (See below for observed n.O.e responses). The absolute stereochemistry of the

C2 hydroxyl group and the C5 methyl group is based on the mechanism previously described for the [4+2]-annulation.¹ The remaining two examples in table 3 (**3a** and **3c**) were assigned by analogy with **3b**.

Azide **3b** (110.0 mg, 0.397 mmol) was dissolved in THF (2.0 mL) followed by the addition of 10% palladium on carbon (25.0 mg). The reaction was stirred under an atmosphere over 12 hours. The mixture was filtered through silica gel and concentrated to obtain a yellow colored oil *ca.* 93.0 mg (93%). The amine was dissolved in benzene (5.0 mL) and heated to 90°C for 7 days. The reaction was concentrated and the residue was purified by flash chromatography to over silica gel (CHCl₃/MeOH: 99/1 to 95/5) to yield the desired lactams 42.0 mg (46%) “major isomer” and 35.0 mg (43%) “minor isomer”.

“Major isomer” (3S,6S,7R)-3-Hydroxy-6-methyl-7-phenylazepan-2-one; [α]_D²⁰ - 2.4 (*c* 1.3, CHCl₃); colorless oil; ¹H NMR (400 MHz, CDCl₃) δ 7.30 (m, 5H), 6.57 (s, 1H), 4.79 (d, *J* = 4.2 Hz, 1H), 4.29 (d, *J* = 9.6 Hz, 1H), 3.92 (s, 1H), 2.16 (m, 1H), 1.93 (m, 2H), 1.69 (m, 2H), 1.08 (d, *J* = 7.6 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 177.7, 139.0, 128.6, 127.5, 127.1, 71.6, 60.0, 38.9, 29.8, 28.7, 17.9 ppm; IR (film) ν_{max} 3415, 3216, 2925, 1653, 1457, 1332 cm⁻¹; HRMS(CI, NH₃) *m/z* calc'd for C₁₄H₁₉O₃ [M+Na]⁺ 242.1157, Found 242.1157.

“Minor isomer” (3S,6S,7S)-3-Hydroxy-6-methyl-7-phenylazepan-2-one; [α]_D²⁰ - 15.7 (*c* 1.6, CHCl₃); white solid, mp 122-123 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.32 (m, 3H), 7.22 (m, 2H), 5.85 (s, 1H), 4.28 (d, *J* = 11.2 Hz, 1H), 4.06 (s, 1H), 3.98 (dd, *J* = 9.6, 4.0

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Hz, 1H), 2.12 (m, 2H), 1.98 (m, 1H), 1.74 (m, 1H), 1.64 (m, 1H), 0.53 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 177.0, 140.8, 129.2, 128.4, 126.8, 70.1, 63.9, 38.9, 36.5, 33.1, 20.3 ppm; IR (film) ν_{max} 3413, 3216, 2925, 1653, 1456, 1330 cm^{-1} ; HRMS(CI, NH_3) m/z calc'd for $\text{C}_{14}\text{H}_{19}\text{O}_3$ $[\text{M}+\text{Na}]^+$ 242.1157, Found 242.1157.

Observed n.O.e's for both "Major" and "Minor" lactams.

"Major isomer"

"Minor isomer"