Use of Lithium Hexafluoroisopropoxide as a Mild Base for Horner–Wadsworth–Emmons Olefination of Epimerizable Aldehydes

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Supporting Information

Index:

General Experimental Procedures	S1
Materials	S2
Instrumentation	S2
Preparation of (2 <i>R</i> ,4 <i>S</i>)-6-(<i>tert</i> -Butyldiphenylsilyloxy)-2,4-dimethylhexanal	S3
Olefination of (2 <i>R</i> ,4 <i>S</i>)-6-(<i>tert</i> -Butyldiphenylsilyloxy)-2,4-dimethylhexanal	S6
Preparation of (2 <i>S</i> ,4 <i>S</i>)-6-(<i>tert</i> -Butyldiphenylsilyloxy)-2,4-dimethylhexanal	S9
Olefination of (2 <i>S</i> ,4 <i>S</i>)-6-(<i>tert</i> -Butyldiphenylsilyloxy)-2,4-dimethylhexanal	S13
Preparation of 1,2:3,4-Di- <i>O</i> -isopropylidene-D-galactohexodialdo-1,5-pyranose	S15
Olefination of 1,2:3,4-Di- <i>O</i> -isopropylidene-D-galactohexodialdo-1,5-pyranose	S16
Olefination of (<i>S</i>)-2-(<i>tert</i> -Butyl-dimethylsilyloxy)propionaldehyde	S17
Preparation of [(1 <i>S</i>)-[(1 <i>S</i> ,2 <i>S</i>)-1-Formyl-2-methylbutylcarbamoyl]-2-phenylethyl]carbamic Acid <i>tert</i> -Butyl Ester	S18
Olefination of [(1 <i>S</i>)-[(1 <i>S</i> ,2 <i>S</i>)-1-Formyl-2-methylbutylcarbamoyl]-2-phenylethyl]carbamic Acid <i>tert</i> -Butyl Ester	S20
Preparation of [(<i>S</i>)-1-[(<i>S</i>)-1-Methyl-2-oxoethylcarbamoyl]-2-phenylethyl]carbamic Acid <i>tert</i> -Butyl Ester	S22
Olefination of [(<i>S</i>)-1-[(<i>S</i>)-1-Methyl-2-oxoethylcarbamoyl]-2-phenylethyl]carbamic Acid <i>tert</i> -Butyl Ester	S24
³¹ P NMR Sample Preparation	S26

General Experimental Procedures: All reactions were performed in flame-dried glassware fitted with rubber septa under a positive pressure of argon, unless otherwise noted. Air- and moisture-sensitive liquids were transferred via syringe or stainless steel cannula. Organic solutions were concentrated by rotary evaporation (house vacuum, ca. 25–40 Torr) at ambient temperature.

Analytical thin-layer chromatography was performed using glass plates pre-coated with silica gel (0.25 mm, 60 Å pore size, 230–400 mesh, Merck KGA) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light (UV), and then were stained by submersion in aqueous ceric ammonium molybdate solution (CAM), ethanolic phosphomolybdic acid (PMA), basic aqueous potassium permanganate (KMnO₄), or an acidic solution of ninhydrin in *n*-butanol, followed by brief heating on a hot plate (~170 °C, 10–15 s). Flash-column chromatography was performed as described by Still et al.,¹ employing silica gel (60-Å pore size, 32–63 µm, standard grade, Sorbent Technologies).

Materials: Commercial reagents and solvents were used with the following exceptions. Dichloromethane, tetrahydrofuran, and ethyl ether were purified by the method of Pangborn et al.² Acetonitrile and *N,N*-diisopropylamine were distilled from calcium hydride at 760 Torr under an atmosphere of nitrogen. 1,1,1,3,3,3-Hexafluoroisopropanol was dried over 4-Å molecular sieves. Lithium chloride was flame-dried under vacuum and was stored in a drying oven at 150 °C. The dried solid was flame-dried in vacuo immediately prior to use. The molarity of commercial solutions of *n*-butyllithium was determined by titration against standard solutions of diphenylacetic acid (average of three determinations).³ Dess–Martin periodinane was prepared according to literature procedures.⁴ Barium hydroxide octahydrate was activated by heating to 150 °C in a drying oven for 1–2 h prior to use.⁵

Instrumentation: Proton magnetic resonance (¹H NMR) spectra were recorded on Varian Mercury 400 (400 MHz), Varian INOVA 500 (500 MHz), or Varian INOVA 600 (600 MHz) NMR spectrometers at 25 °C. Proton chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to residual protium in the NMR solvent (CHCl₃: δ 7.26, CD₂HClN: δ 1.93, CD₂HOD: δ 3.31). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), integration, and coupling constant (*J*) in Hertz (Hz). Carbon nuclear magnetic resonance (¹³C NMR) spectra were recorded on Varian Mercury 400 (100 MHz) or Varian INOVA 500 (125 MHz) NMR spectrometers at 25 °C. Carbon chemical shifts are

¹ Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

² Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.

³ Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879.

⁴ (a) Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537. (b) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.

⁵ Paterson, I.; Yeung, K.-S.; Smaill, J. B. *Synlett* **1993**, 774.

expressed in parts per million (ppm, δ scale) and are referenced to the carbon resonance of the NMR solvent (CDCl_3 : δ 77.0, CD_3CN : δ 1.3, CD_3OD : δ 49.0). Phosphorus nuclear magnetic resonance (^{31}P NMR) spectra were recorded on a Varian Mercury 400 (160 MHz) NMR spectrometer at 25 °C. Phosphorus chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to an external standard of 85% phosphoric acid in water. Samples for infrared (IR) spectroscopy were prepared as neat films by evaporation of dichloromethane solutions; infrared spectra were recorded using a Perkin–Elmer 1600 FT-IR spectrophotometer and were referenced to an internal polystyrene standard. Data are represented as follows: frequency of absorption (cm^{-1}) and intensity of absorption (s = strong, m = medium, w = weak, br = broad). High-resolution mass spectra were obtained at Harvard University Mass Spectrometry Facility.

(2R,4S)-6-(*tert*-Butyldiphenylsilyloxy)-2,4-dimethylhexanoic Acid N-[(1S,2S)-2-hydroxy-1-methyl-2-phenylethyl]-N-methylamide. A solution of *n*-butyllithium in hexanes (2.43 M, 16.7 mL, 40.7 mmol, 2.9 equiv) was added to a suspension of lithium chloride (7.66 g, 0.181 mol, 13 equiv) and *N,N*-diisopropylamine (6.40 mL, 45.7 mmol, 3.2 equiv) in tetrahydrofuran (50 mL) at –78 °C. The resulting suspension was warmed briefly to 0 °C, then was cooled to –78 °C. An ice-cold solution of (*S,S*)-*N*-(2-hydroxy-1-methyl-2-phenylethyl)-*N*-methylpropionamide⁶ (4.72 g, 21.3 mmol, 1.5 equiv) in tetrahydrofuran (100 mL, followed by two 3-mL rinses) was transferred into the reaction flask via cannula. The mixture was stirred at –78 °C for 80 min, at 0 °C for 20 min, and at 23 °C for 10 min. The mixture was cooled to 0 °C, and a solution of (*R*)-*tert*-butyl(4-iodo-3-methylbutoxy)diphenylsilane⁷ (6.43 g, 14.2 mmol, 1 equiv) in tetrahydrofuran (16 mL) was transferred to the reaction solution via cannula, and the resulting solution was stirred at 0 °C for 18.5 h and then at 23 °C for 22 h. The reaction solution was diluted with 50%-saturated aqueous ammonium chloride solution (100 mL), and the mixture was extracted with ethyl acetate (4 × 100

⁶ Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496.

⁷ (*R*)-*tert*-Butyl(4-iodo-3-methylbutoxy)diphenylsilane was prepared by asymmetric alkylation of (*S,S*)-*N*-(2-hydroxy-1-methyl-2-phenylethyl)-*N*-methylpropionamide (see ref 6). For an alternative preparative procedure, see: Ribe, S.; Kondru, R. K.; Beratan, D. N.; Wipf, P. *J. Am. Chem. Soc.* **2000**, *122*, 4608.

mL). The combined organic layers were dried over sodium sulfate and the solids were removed by filtration. The filtrate was concentrated and the product was purified by flash-column chromatography (30% ethyl acetate–hexanes, increasing to 40% ethyl acetate) to furnish (2*R*,4*S*)-6-(*tert*-butyldiphenylsilyloxy)-2,4-dimethylhexanoic acid *N*-[(1*S*,2*S*)-2-hydroxy-1-methyl-2-phenylethyl]-*N*-methylamide as a viscous, clear oil (6.86 g, 88%).

¹H NMR (5:1 rotamer ratio, asterisk denotes minor rotamer peaks, 500 MHz, CDCl₃) δ 7.67 (dd, 4H, *J* = 8, 1 Hz, ArH), 7.33 (m, 11H, ArH), 4.60 (t, 1H, *J* = 7.5, 6.5 Hz, CHOH), 4.55* (d, 1H, *J* = 7 Hz, CHOH), 4.40 (br, 1H, OH), 3.72* (m, 2H, CH₂OSi), 3.68 (m, 2H, CH₂OSi), 2.90* (s, 3H, NCH₃), 2.84 (s, 3H, NCH₃), 2.98* (m, 1H, CHC=O), 2.67 (m, 1H, CHC=O), 1.61 (m, 2H, CHN, CH), 1.55 (m, 1H, CH₂), 1.26 (m, 2H, CH₂, CH₂), 1.14 (m, 1H, CH₂), 1.11 (d, 3H, *J* = 6 Hz, CH₃), 1.07 (d, 3H, *J* = 6.5 Hz, CH₃), 1.05* (s, 9H, C(CH₃)₃), 1.04 (s, 9H, C(CH₃)₃), 1.00* (d, 3H, *J* = 7 Hz, CH₃), 0.88* (d, 3H, *J* = 6.5 Hz, CH₃), 0.75 (d, 3H, *J* = 6.5 Hz, CH₃); ¹³C (extra peaks are due to amide-bond rotamers, 100 MHz, CDCl₃) δ 179.2, 142.6, 135.6, 134.0, 129.5, 128.7, 128.4, 128.3, 127.6, 127.5, 126.9, 126.3, 76.7, 75.3, 62.2, 62.0, 58.4, 41.6, 39.5, 34.1, 33.1, 27.4, 26.9, 20.0, 19.8, 19.2, 18.3, 17.6, 15.5, 14.4; IR (thin film) cm⁻¹ 3385 (br, m, O–H), 1621 (s, C=O); HRMS (ES) *m/z* calcd for C₃₄H₄₇NO₃Si [M + H]⁺: 546.3403, found 546.3399; TLC (30% ethyl acetate–hexanes), R_f 0.52 (PMA).

(2*R*,4*S*)-6-(*tert*-Butyldiphenylsilyloxy)-2,4-dimethylhexan-1-ol. A solution of *n*-butyllithium in hexanes (2.43 M, 20.2 mL, 49.0 mmol, 3.9 equiv) was added to a solution of *N,N*-diisopropylamine (7.40 mL, 52.8 mmol, 4.2 equiv) in tetrahydrofuran (50 mL) at –78 °C. The resulting solution was stirred at –78 °C for 10 min, then was warmed to 0 °C. After 10 min, borane–ammonia complex (1.72 g, 50.3 mmol, 4.0 equiv) was added in one portion. The resulting mixture was stirred at 0 °C for 15 min, then was warmed to 23 °C for 15 min. After cooling the mixture to 0 °C, a solution of (2*R*,4*S*)-6-(*tert*-butyldiphenylsilyloxy)-2,4-dimethylhexanoic acid *N*-[(1*S*,2*S*)-2-hydroxy-1-methyl-2-phenylethyl]-*N*-methylamide (6.86 g, 12.6 mmol, 1 equiv) in tetrahydrofuran (30 mL, followed by a 5-mL rinse) was added slowly via cannula, and the resulting

clear solution was stirred at 23 °C for 2 h. The reaction mixture was cooled to 0 °C and then was diluted slowly with aqueous hydrochloric acid solution (3 N, 120 mL). The mixture was stirred at 0 °C for 1 h and then was extracted with ethyl ether (4 × 45 mL). The combined organic layers were washed sequentially with aqueous hydrochloric acid solution (3 N, 20 mL), aqueous sodium hydroxide solution (2 N, 20 mL), and saturated aqueous sodium chloride solution (20 mL). The washed solution was dried over magnesium sulfate and the solids were removed by filtration. The filtrate was concentrated in vacuo and the product was purified by flash-column chromatography (10% ethyl acetate–hexanes initially, grading to 15% ethyl acetate–hexanes). Mixed fractions were pooled and re-purified chromatographically (analogous conditions) to provide in total 4.12 (85%) of (2*R*,4*S*)-6-(*tert*-butyldiphenylsilyloxy)-2,4-dimethylhexan-1-ol as a clear, colorless oil. HPLC analysis of the purified product showed it to be 98% de (Beckman Coulter Ultrasphere Silica column, 5 μm dp, 4.6 mm × 25 cm, 10% ethyl acetate–hexanes; retention time of (2*R*,4*S*)-6-(*tert*-butyldiphenylsilyloxy)-2,4-dimethylhexan-1-ol: 14 min, retention time of (2*S*,4*S*)-6-(*tert*-butyldiphenylsilyloxy)-2,4-dimethylhexan-1-ol: 17 min).

¹H NMR (500 MHz, CDCl₃) δ 7.68 (dd, 4H, *J* = 7.5, 1 Hz, ArH), 7.40 (m, 6H, ArH), 3.71 (m, 2H, CH₂OSi), 3.49 (dd, 1H, *J* = 10, 5 Hz, CH₂OH), 3.37 (dd, 1H, *J* = 10, 7 Hz, CH₂OH), 1.67 (m, 3H, CH, CH, CH₂), 1.28 (m, 3H, CH₂, CH₂, CH₂), 1.06 (s, 9H, C(CH₃)₃), 0.95 (m, 1H, CH₃), 0.91 (d, 3H, *J* = 7 Hz, CH₃), 0.85 (d, 3H, 6.5 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 135.8, 134.3, 129.8, 127.8, 68.6, 62.2, 41.3, 39.4, 33.3, 27.1, 26.9, 20.7, 19.4, 17.4; IR (thin film) cm⁻¹ 3342 (m, br, OH); HRMS (CI) *m/z* calcd for C₂₄H₃₆O₂Si [M + H]⁺: 385.2563, found 385.2568; TLC (20% ethyl acetate–hexanes), R_f 0.55 (PMA).

(2*R*,4*S*)-6-(*tert*-Butyldiphenylsilyloxy)-2,4-dimethylhexanal. Sodium bicarbonate (61.4 mg, 0.731 mmol, 4.0 equiv) and Dess–Martin periodinane⁸ (155 mg, 0.366 mmol, 2.0 equiv) were added in sequence to a solution of (2*R*,4*S*)-6-(*tert*-butyldiphenylsilyloxy)-2,4-dimethylhexan-1-ol (70.3

⁸ (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, 48, 4156. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, 113, 7277.

mg, 0.183 mmol, 1 equiv) in dichloromethane (0.76 mL) at 23 °C. After stirring at 23 °C for 30 min, the product solution was diluted with a mixture of saturated aqueous sodium thiosulfate solution (0.4 mL), saturated aqueous sodium bicarbonate solution (0.4 mL), and water (0.2 mL). The resulting solution was stirred vigorously until clear, then was diluted further with a mixture of saturated aqueous sodium thiosulfate solution (1.6 mL), saturated aqueous sodium bicarbonate solution (1.6 mL), and water (0.8 mL). The product was extracted with ethyl acetate (3 × 7 mL), and the combined organic layers were dried over sodium sulfate. The solids were removed by filtration, and the filtrate was concentrated in vacuo. The product was purified by flash-column chromatography (30% dichloromethane–pentane initially, grading to 35% dichloromethane–pentane) to afford (2*R*,4*S*)-6-(*tert*-butyldiphenylsilyloxy)-2,4-dimethylhexanal as a white solid (62.8 mg, 90%). Reduction of the purified product with NaBH₄ in CH₃OH followed by HPLC analysis (conditions given above) showed the de of (2*R*,4*S*)-6-(*tert*-butyldiphenylsilyloxy)-2,4-dimethylhexan-1-ol to be >98%, indicating that no detectable epimerization had occurred during oxidation to the aldehyde.

¹H NMR (500 MHz, CDCl₃) δ 9.58 (d, 1H, *J* = 2.5 Hz, CHO), 7.67 (d, 4H, *J* = 6.5 Hz, ArH), 7.40 (m, 6H, ArH), 3.70 (m, 2H, CH₂OSi), 2.39 (m, 1H, CH), 1.66 (m, 3H, CH₂, CH) 1.31 (m, 1H, CH₂), 1.14 (m, 1H, CH₂), 1.06 (d, 3H, *J* = 7 Hz, CH₃), 1.05 (s, 9H, C(CH₃)₃), 0.86 (d, *J* = 6.5 Hz, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 205.3, 135.6, 133.9, 129.6, 127.6, 61.7, 44.0, 39.1, 38.1, 27.0, 26.8, 19.9, 19.1, 13.9; IR (thin film) cm⁻¹ 1726 (s, C=O); HRMS (ES) *m/z* calcd for C₂₄H₃₄O₂Si [M + H]⁺: 383.2406, found 383.2410; TLC (10% ethyl acetate–hexanes), R_f 0.75 (CAM).

(E)-(4*R*,6*S*)-8-(*tert*-Butyldiphenylsilyloxy)-4,6-dimethyloct-2-enoic Acid Methyl Ester.

LiOCH(CF₃)₂ Conditions. A solution of *n*-butyllithium in hexanes (2.44 M, 44.0 μL, 0.107 mmol, 1.18 equiv) was added to a solution of 1,1,1,3,3,3-hexafluoroisopropanol (11.9 μL, 0.113 mmol, 1.24 equiv) in 1,2-dimethoxyethane (160 μL) at -14 °C (ice-salt bath). A solution of biphenyl in 1,2-dimethoxyethane (0.115 M, 10.0 μL, 1.15 μmol, 0.013 equiv) was added as an internal standard

for HPLC analysis. Following addition of trimethyl phosphonoacetate (16.0 μ L, 0.109 mmol, 1.2 equiv), a solution of (2*R*,4*S*)-6-(*tert*-butyldiphenylsilanyloxy)-2,4-dimethylhexanal (34.8 mg, 0.0910 mmol, 1 equiv) in 1,2-dimethoxyethane (110 μ L, followed by a 100- μ L rinse) was added to the reaction mixture, causing a white precipitate to form. The reaction solution was stirred overnight at -14°C in a cryobath and then was diluted with 50%-saturated aqueous ammonium chloride solution (4 mL). The product was extracted with dichloromethane (3×5 mL) and the combined organic layers were dried over sodium sulfate. The solids were removed by filtration, and the filtrate was concentrated in vacuo. HPLC analysis of the crude product mixture using biphenyl as an internal standard established the following product distribution: (*Z*)-(4*R*,6*S*)-8-(*tert*-butyldiphenylsilanyloxy)-4,6-dimethyloct-2-enoic acid methyl ester (2.0%), (*E*)-(4*R*,6*S*)-8-(*tert*-butyldiphenylsilanyloxy)-4,6-dimethyloct-2-enoic acid methyl ester (94.5%), and (*E*)-(4*S*,6*S*)-8-(*tert*-butyldiphenylsilanyloxy)-4,6-dimethyloct-2-enoic acid methyl ester (1.6%) (Beckman Coulter Ultrasphere Silica column, 5 μ m dp, 4.6 mm $\times$ 25 cm, 1:99 ethyl acetate–hexanes; retention time of biphenyl: 5 min; retention time of (*Z*)-(4*R*,6*S*)-8-(*tert*-butyldiphenylsilanyloxy)-4,6-dimethyloct-2-enoic acid methyl ester: 11 min; retention time of (*E*)-(4*R*,6*S*)-8-(*tert*-butyldiphenylsilanyloxy)-4,6-dimethyloct-2-enoic acid methyl ester: 19 min; retention time (*E*)-(4*S*,6*S*)-8-(*tert*-butyldiphenylsilanyloxy)-4,6-dimethyloct-2-enoic acid methyl ester: 21 min). The product was purified by flash-column chromatography (2% ethyl ether–pentane initially, grading to 4% ethyl ether–pentane) to afford (*E*)-(4*R*,6*S*)-8-(*tert*-butyldiphenylsilanyloxy)-4,6-dimethyloct-2-enoic acid methyl ester (38.1 mg, 95%).

^1H NMR (500 MHz, CDCl_3) δ 7.67 (dd, 4H, $J = 6, 1$ Hz, ArH), 7.40 (m, 6H, ArH), 6.82 (dd, 1H, $J = 15.5, 15.5$ Hz), 5.79 (d, 1H, $J = 15.5$), 3.72 (s, 3H, OCH_3), 3.68 (m, 2H, CH_2OSi), 2.40 (m, 1H, CH), 1.63 (m, 1H, CH), 1.56 (m, 1H, CH_2), 1.34 (m, 2H, CH_2 , CH_2), 1.12 (m, 1H, CH_2), 1.04 (s, 9H, $\text{C}(\text{CH}_3)_3$), 1.02 (d, $J = 6.5$ Hz, CH_3), 0.81 (d, $J = 6.5$ Hz, CH_3); ^{13}C NMR (100 MHz, CDCl_3) δ 167.5, 155.0, 135.8, 134.2, 129.8, 127.8, 119.5, 62.0, 51.6, 44.0, 40.1, 34.4, 27.2, 27.1, 20.4, 19.6, 19.4; IR (thin film) cm^{-1} 1727 (s, C=O), 1657 (m, C=C-H); HRMS (CI) m/z calcd for $\text{C}_{27}\text{H}_{38}\text{O}_3\text{Si}$ [$\text{M} + \text{NH}_4$] $^+$: 456.2934, found 456.2927; TLC (5% ethyl ether–pentane), R_f 0.35 (CAM).

LiCl, DBU Conditions.⁹ To a suspension of lithium chloride (4.0 mg, 0.94 mmol, 1.2 equiv) in acetonitrile (0.41 mL) at 23 °C was added a solution of biphenyl in acetonitrile (88.8 mM, 10.0 μ L, 0.888 μ mol, 0.012 equiv, for use as an internal HPLC standard). Trimethyl phosphonoacetate (13.5 μ L, 0.0919 mmol, 1.2 equiv) and 1,8-diazabicyclo[5.4.0]undec-7-ene (11.5 μ L, 0.0766 mmol, 1.0 equiv) were added to the reaction mixture, followed by a solution of (2*R*,4*S*)-6-(*tert*-butyldiphenylsilyloxy)-2,4-dimethylhexanal (29.3 mg, 0.0766 mmol, 1 equiv) in acetonitrile (280 μ L, followed by a 230- μ L rinse). After stirring at 23 °C for 3 d, the product solution was diluted with 50%-saturated aqueous ammonium chloride solution (4 mL) and the mixture was extracted with dichloromethane (3 $\times$ 5 mL). The combined organic layers were dried over sodium sulfate, the solids were removed by filtration, and the filtrate was concentrated in vacuo. HPLC analysis of the crude product mixture using biphenyl as an internal standard established the following product distribution: (*Z*)-(4*R*,6*S*)-8-(*tert*-butyldiphenylsilyloxy)-4,6-dimethyloct-2-enoic acid methyl ester (3.0%), (*E*)-(4*R*,6*S*)-8-(*tert*-butyldiphenylsilyloxy)-4,6-dimethyloct-2-enoic acid methyl ester (89.9%), and (*E*)-(4*S*,6*S*)-8-(*tert*-butyldiphenylsilyloxy)-4,6-dimethyloct-2-enoic acid methyl ester (2.0%) (Beckman Coulter Ultrasphere Silica column, 5 μ m dp, 4.6 mm $\times$ 25 cm, 1:99 ethyl acetate–hexanes; retention time of biphenyl: 5 min; retention time of (*Z*)-(4*R*,6*S*)-8-(*tert*-butyldiphenylsilyloxy)-4,6-dimethyloct-2-enoic acid methyl ester: 11 min; retention time of (*E*)-(4*R*,6*S*)-8-(*tert*-butyldiphenylsilyloxy)-4,6-dimethyloct-2-enoic acid methyl ester: 19 min; retention time of (*E*)-(4*S*,6*S*)-8-(*tert*-butyldiphenylsilyloxy)-4,6-dimethyloct-2-enoic acid methyl ester: 21 min).

Ba(OH)₂ Conditions.⁵ Trimethyl phosphonoacetate (12.9 μ L, 0.0883 mmol, 1.0 equiv) was added to a suspension of barium hydroxide octahydrate (22.3 mg, 0.0706 mmol, 0.8 equiv) in

⁹ Blanchette, M. A.; Choy, W.; Davis, J. T.; Essinfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, 25, 2183.

tetrahydrofuran (200 mL) at 23 °C. A solution of biphenyl in tetrahydrofuran (108 mM, 10.0 μ L, 1.08 μ mol, 0.012 equiv, for use as an internal HPLC standard) was added via syringe, followed by a solution of (2*R*,4*S*)-6-(*tert*-butyldiphenylsilanyloxy)-2,4-dimethylhexanal (33.8 mg, 0.0883 mmol, 1 equiv) in 40:1 tetrahydrofuran–water (120 μ L, followed by a 100- μ L rinse). Because the resulting mixture was very viscous, an additional 100- μ L portion of 40:1 tetrahydrofuran–water was added. After stirring at 23 °C for 2d, the product solution was diluted with saturated aqueous sodium bicarbonate solution (6 mL) and dichloromethane (8 mL). The layers were separated, and the aqueous layer was extracted with dichloromethane (2 $\times$ 10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (1 $\times$ 6 mL), then were dried over sodium sulfate. The solids were removed by filtration, and the filtrate was concentrated in vacuo. HPLC analysis of the crude product mixture using biphenyl as an internal standard established the following product distribution: (*Z*)-(*4R*,6*S*)-8-(*tert*-butyldiphenylsilanyloxy)-4,6-dimethyloct-2-enoic acid methyl ester (3.8%), (*E*)-(*4R*,6*S*)-8-(*tert*-butyldiphenylsilanyloxy)-4,6-dimethyloct-2-enoic acid methyl ester (79.9%) and (*E*)-(*4S*,6*S*)-8-(*tert*-butyldiphenylsilanyloxy)-4,6-dimethyloct-2-enoic acid methyl ester (0.9%) (Beckman Coulter Ultrasphere Silica column, 5 μ m dp, 4.6 mm $\times$ 25 cm, 1:99 ethyl acetate–hexanes; retention time of biphenyl: 5 min; retention time of (*Z*)-(*4R*,6*S*)-8-(*tert*-butyldiphenylsilanyloxy)-4,6-dimethyloct-2-enoic acid methyl ester: 11 min; retention time of (*E*)-(*4R*,6*S*)-8-(*tert*-butyldiphenylsilanyloxy)-4,6-dimethyloct-2-enoic acid methyl ester: 19 min; retention time of (*E*)-(*4S*,6*S*)-8-(*tert*-butyldiphenylsilanyloxy)-4,6-dimethyloct-2-enoic acid methyl ester: 21 min).

(2*S*,4*S*)-6-(*tert*-Butyldiphenylsilanyloxy)-2,4-dimethylhexanoic Acid *N*-[(1*R*,2*R*)-2-hydroxy-1-methyl-2-phenylethyl]-*N*-methylamide. A solution of *n*-butyllithium in hexanes (2.16 M, 0.304 mL, 0.656 mmol, 4.0 equiv) was added to a suspension of lithium chloride (88.5 mg, 2.08 mmol, 13 equiv) and *N,N*-diisopropylamine (99.1 μ L, 0.707 mmol, 4.3 equiv) in tetrahydrofuran (0.5 mL) at –78 °C. The resulting suspension was warmed briefly to 0 °C, then was cooled to –78 °C. After stirring at –78 °C for 15 min, an ice-cold solution of (*R,R*)-*N*-(2-hydroxy-1-methyl-2-phenylethyl)-

N-methylpropionamide⁶ (76.2 mg, 0.344 mmol, 2.1 equiv) in tetrahydrofuran (0.6 mL, followed by a 0.18-μL rinse) was transferred into the reaction flask via cannula. The mixture was stirred at –78 °C for 1 h, at 0 °C for 20 min, and at 23 °C for 10 min. The mixture was cooled to 0 °C, and a solution of (*R*)-*tert*-butyl(4-iodo-3-methylbutoxy)diphenylsilane⁶ (74.3 mg, 0.164 mmol, 1 equiv) in tetrahydrofuran (0.46 mL) was transferred to the reaction solution via syringe. The resulting solution was stirred at 23 °C for 23 h. The reaction solution was diluted with 50%-saturated aqueous ammonium chloride solution (7 mL), and the mixture was extracted with ethyl acetate (4 × 10 mL). The combined organic layers were dried over sodium sulfate and the solids were removed by filtration. The filtrate was concentrated and the product was purified by flash-column chromatography (20% ethyl acetate–hexanes, increasing to 35% ethyl acetate) to furnish (2*S*,4*S*)-6-(*tert*-butyldiphenylsilanyloxy)-2,4-dimethylhexanoic acid [(1*R*,2*R*)-2-hydroxy-1-methyl-2-phenylethyl]methanamide as a viscous, clear oil (67.7 mg, 76%).

¹H NMR (5:1 rotamer ratio, asterisk denotes minor rotamer peaks, 500 MHz, CDCl₃) δ 7.66 (dd, 4H, *J* = 7, 1.5 Hz, ArH), 7.34 (m, 11H, ArH), 4.60 (t, 1H, *J* = 7.5, 7 Hz, CHOH), 4.55* (d, 1H, *J* = 6.5 Hz, CHOH), 4.39 (br, 1H, OH), 3.73* (m, 2H, CH₂OSi), 3.69 (m, 1H, CH₂OSi), 3.63 (m, 1H, CH₂OSi), 2.99* (m, 1H, CHC=O), 2.90* (s, 3H, NCH₃), 2.82 (s, 3H, NCH₃), 2.66 (m, 1H, CHC=O), 1.61 (m, 2H, CHN, CH), 1.33 (m, 4H, CH₂, CH₂), 1.11 (d, 3H, *J* = 7.5 Hz, CH₃), 1.06 (d, 3H, *J* = 7 Hz, CH₃), 1.04 (s, 9H, C(CH₃)₃), 0.98* (d, 3H, *J* = 6.5 Hz, CH₃), 0.86* (d, 3H, *J* = 6 Hz, CH₃), 0.79 (d, 3H, *J* = 6.5 Hz, CH₃); ¹³C (extra peaks are due to amide-bond rotamers, 100 MHz, CDCl₃) δ 179.4, 142.6, 135.5, 134.0, 134.0, 129.6, 128.7, 128.4, 128.3, 127.6, 127.6, 127.5, 126.9, 126.3, 76.5, 75.2, 62.0, 61.9, 59.0 (br), 58.1, 41.1, 39.9, 34.2, 33.2, 27.2, 27.0, 26.9, 19.6, 19.5, 19.2, 17.6, 17.0, 15.5, 14.4; IR (thin film) cm^{–1} 3418 (br, m, O–H), 1621 (s, C=O); HRMS (ES) *m/z* calcd for C₃₄H₄₇NO₃Si [M + H]⁺: 546.3403, found 546.3401; TLC (30% ethyl acetate–hexanes), R_f 0.39 (PMA).

(2*S*,4*S*)-6-(*tert*-Butyldiphenylsilanyloxy)-2,4-dimethylhexan-1-ol. A solution of *n*-butyllithium in hexanes (2.43 M, 3.60 mL, 8.76 mmol, 3.9 equiv) was added to a solution of *N,N*-diisopropylamine

(1.32 mL, 9.43 mmol, 4.2 equiv) in tetrahydrofuran (10 mL) at $-78\text{ }^{\circ}\text{C}$. The resulting solution was stirred at $-78\text{ }^{\circ}\text{C}$ for 10 min, then was warmed to $0\text{ }^{\circ}\text{C}$. After 10 min, borane–ammonia complex (308 mg, 8.98 mmol, 4.0 equiv) was added in one portion. The resulting mixture was stirred at $0\text{ }^{\circ}\text{C}$ for 15 min and at $23\text{ }^{\circ}\text{C}$ for 15 min. After cooling the mixture to $0\text{ }^{\circ}\text{C}$, a solution of (2*S*,4*S*)-6-(*tert*-butyldiphenylsilyloxy)-2,4-dimethylhexanoic acid *N*-[(1*R*,2*R*)-2-hydroxy-1-methyl-2-phenylethyl]-*N*-methylamide (1.23 g, 2.24 mmol, 1 equiv) in tetrahydrofuran (10 mL, followed by a 6-mL rinse) was added slowly via cannula, and the resulting clear solution was stirred at $23\text{ }^{\circ}\text{C}$ for 2 h. The reaction mixture was cooled to $0\text{ }^{\circ}\text{C}$, then was diluted slowly with aqueous hydrochloric acid solution (3 N, 15 mL). After stirring at $0\text{ }^{\circ}\text{C}$ for 1 h, the product solution was extracted with ethyl ether (4 $\times$ 15 mL). The combined organic layers were washed sequentially with aqueous hydrochloric acid solution (3 N, 15 mL), aqueous sodium hydroxide solution (2 N, 15 mL), and saturated aqueous sodium chloride solution (15 mL). The washed solution was dried over magnesium sulfate and the solids were removed by filtration. The filtrate was concentrated in vacuo and the product was purified by flash-column chromatography (15% ethyl acetate–hexanes initially, grading to 20% ethyl acetate–hexanes). Mixed fractions were pooled and re-purified chromatographically (analogous conditions) to provide in total 779 mg (90%) of (2*S*,4*S*)-6-(*tert*-butyldiphenylsilyloxy)-2,4-dimethylhexan-1-ol as a clear, colorless oil. HPLC analysis of the purified product showed it to be 96% de (Beckman Coulter Ultrasphere Silica column, 5 μm dp, 4.6 mm $\times$ 25 cm, 10% ethyl acetate–hexanes; retention time of (2*S*,4*S*)-6-(*tert*-butyldiphenylsilyloxy)-2,4-dimethylhexan-1-ol: 17 min, retention time of (2*R*,4*S*)-6-(*tert*-butyldiphenylsilyloxy)-2,4-dimethylhexan-1-ol: 14 min).

^1H NMR (500 MHz, CDCl_3) δ 7.68 (dd, 4H, $J = 7.5, 1\text{ Hz}$, ArH), 7.40 (m, 6H, ArH), 3.71 (m, 2H, CH_2OSi), 3.46 (dd, 1H, $J = 10.5, 5.5\text{ Hz}$, CH_2OH), 3.39 (dd, 1H, $J = 10.5, 7\text{ Hz}$, CH_2OH), 1.72 (m, 2H, CH, CH), 1.57 (m, 1H, CH_2), 1.40 (m, 1H, CH_2), 1.28 (br, 1H, OH), 1.15 (m, 1H, CH_2), 1.06 (m, 1H, CH_2), 1.05 (s, 9H, $\text{C}(\text{CH}_3)_3$), 0.89 (d, $J = 6.5\text{ Hz}$, CH_3), 0.82 (d, $J = 6.5\text{ Hz}$, CH_3); ^{13}C NMR (125 MHz, CDCl_3) δ 135.8, 134.3, 129.8, 127.8, 69.2, 62.2, 40.8, 40.7, 33.4, 27.1, 26.7, 19.6, 19.4, 16.5; IR (thin film) cm^{-1} 3345 (br, OH); HRMS (CI) m/z calcd for $\text{C}_{24}\text{H}_{36}\text{O}_2\text{Si}$ [$\text{M} + \text{H}$] $^+$: 385.2563, found 385.2560; TLC (20% ethyl acetate–hexanes), R_f 0.33 (CAM).

(2*S*,4*S*)-6-(*tert*-Butyldiphenylsilyloxy)-2,4-dimethylhexanal. Sodium bicarbonate (78.0 mg, 0.929 mmol, 4.0 equiv) and the Dess–Martin periodinane⁸ (196.8 mg, 0.464 mmol, 2.0 equiv) were added in sequence to a solution of (2*S*,4*S*)-6-(*tert*-butyldiphenylsilyloxy)-2,4-dimethylhexan-1-ol (89.3 mg, 0.232 mmol, 1 equiv) in dichloromethane (1.0 mL) at 23 °C. After stirring at 23 °C for 30 min, the product solution was diluted with a mixture of saturated aqueous sodium thiosulfate solution (0.8 mL), saturated aqueous sodium bicarbonate solution (0.8 mL), and water (0.4 mL). The resulting solution was stirred vigorously until clear, then was diluted with a mixture of saturated aqueous sodium thiosulfate solution (3.2 mL), saturated aqueous sodium bicarbonate solution (3.2 mL), and water (1.6 mL). The product was extracted with ethyl acetate (3 × 10 mL), and the combined organic layers were dried over sodium sulfate. The solids were removed by filtration, and the filtrate was concentrated in vacuo. The product was subjected to flash-column chromatography (30% dichloromethane–pentane initially, grading to 40% dichloromethane–pentane) to afford pure (2*S*,4*S*)-6-(*tert*-butyldiphenylsilyloxy)-2,4-dimethylhexanal as a white solid (71.2 mg, 80%).

¹H NMR (400 MHz, CDCl₃) δ 9.60 (d, 1H, *J* = 1.6 Hz, **CHO**), 7.66 (dd, 4H, *J* = 8, 1.6 Hz, **ArH**), 7.40 (m, 6H, **ArH**), 3.70 (m, 2H, **CH₂OSi**), 2.40 (m, 1H, **CH**), 1.76 (m, 1H, **CH**) 1.55 (m, 2H, **CH₂**, **CH₂**), 1.42 (m, 1H, **CH₂**), 1.26 (m, 1H, **CH₂**), 1.06 (d, 3H, *J* = 8 Hz, **CH₃**), 1.05 (s, 9H, **C(CH₃)₃**), 0.84 (d, *J* = 6.8 Hz, **CH₃**); ¹³C NMR (100 MHz, CD₃CN) δ 206.3, 136.4, 134.9, 130.7, 128.7, 62.7, 44.7, 40.6, 38.2, 27.6, 27.2, 19.7, 19.4, 13.5; IR (thin film) cm⁻¹ 1725 (s, C=O); HRMS (ES) *m/z* calcd for C₂₄H₃₄O₂Si [**M + H**]⁺: 383.2406, found 383.2404; TLC (40% dichloromethane–pentane), R_f 0.40 (CAM).

(*E*)-(4*S*,6*S*)-8-(*tert*-Butyldiphenylsilyloxy)-4,6-dimethyloct-2-enoic Acid Methyl Ester.

LiOCH(CF₃)₂ Conditions. A solution of *n*-butyllithium in hexanes (2.47 M, 80.3 μ L, 0.198 mmol, 1.18 equiv) was added to a solution of 1,1,1,3,3,3-hexafluoroisopropanol (21.9 μ L, 0.208 mmol, 1.24 equiv) in 1,2-dimethoxyethane (315 μ L) at $-14\text{ }^\circ\text{C}$ (ice-salt bath). Following addition of trimethyl phosphonoacetate (29.3 μ L, 0.202 mmol, 1.2 equiv), a solution of (2*S*,4*S*)-6-(*tert*-butyldiphenylsilyloxy)-2,4-dimethylhexanal (64.1 mg, 0.168 mmol, 1 equiv) in 1,2-dimethoxyethane (200 μ L, followed by a 185- μ L rinse) was added to the reaction mixture, causing a white precipitate to form. The reaction solution was stirred overnight at $-14\text{ }^\circ\text{C}$ in a cryobath, then was diluted with 50%-saturated aqueous ammonium chloride solution (8 mL). The product was extracted with dichloromethane (3 $\times$ 10 mL) and the combined organic layers were dried over sodium sulfate. The solids were removed by filtration, and the filtrate was concentrated in vacuo. ¹H NMR analysis of the crude reaction product revealed that the ratio of (*E*)- and (*Z*)-isomers was >19:1. Flash-column chromatographic purification (2% ethyl ether–pentane initially, grading to 5% ethyl ether–pentane) afforded (*E*)-(4*S*,6*S*)-8-(*tert*-butyldiphenylsilyloxy)-4,6-dimethyloct-2-enoic acid methyl ester (69.2 mg, 94%). HPLC analysis of the purified product showed it to be 95% de (Beckman Coulter Ultrasphere Silica column, 5 μ m dp, 4.6 mm $\times$ 25 cm, 1:99 ethyl acetate–hexanes; retention time of (*E*)-(4*S*,6*S*)-8-(*tert*-butyldiphenylsilyloxy)-4,6-dimethyloct-2-enoic acid methyl ester: 21 min, retention time of (*E*)-(4*R*,6*S*)-8-(*tert*-butyldiphenylsilyloxy)-4,6-dimethyloct-2-enoic acid methyl ester: 19 min).

¹H NMR (500 MHz, CDCl₃) δ 7.67 (dd, 4H, *J* = 6, 1 Hz, ArH), 7.40 (m, 6H, ArH), 6.86 (dd, 1H, *J* = 16, 16 Hz), 5.77 (d, 1H, *J* = 16.5), 3.73 (s, 3H, OCH₃), 3.69 (m, 2H, CH₂OSi), 2.38 (m, 1H, CH), 1.68 (m, 1H, CH), 1.61 (m, 1H, CH₂), 1.34 (m, 1H, CH₂, CH₂), 1.23 (m, 2H, CH₂), 1.05 (s, 9H, C(CH₃)₃), 1.01 (d, *J* = 7 Hz, CH₃), 0.82 (d, *J* = 6.5 Hz, CH₃); ¹³C (100 MHz, CDCl₃) δ 167.6, 155.5, 135.8, 134.2, 129.8, 127.8, 119.2, 62.0, 51.6, 43.7, 39.6, 34.2, 27.2, 27.1, 19.9, 19.5, 19.4; IR (thin film) cm⁻¹ 1726 (s, C=O), 1657 (m, C=C–H); HRMS (CI) *m/z* calcd for C₂₇H₃₈O₃Si [M + NH₄]⁺: 456.2934, found 456.2941; TLC (5% ethyl ether–pentane), R_f 0.35 (CAM).

LiCl, DBU Conditions.⁹ A solution of biphenyl in acetonitrile (148 mM, 15.0 μ L, 2.22 μ mol, 0.012 equiv, for use as an internal HPLC standard) was added to a suspension of lithium chloride (9.5 mg, 0.223 mmol, 1.2 equiv) in acetonitrile (1.0 mL) at 23 °C. Trimethyl phosphonoacetate (32.7 μ L, 0.223 mmol, 1.2 equiv) and 1,8-diazabicyclo[5.4.0]undec-7-ene (27.8 μ L, 0.186 mmol, 1.0 equiv) were added to the reaction mixture, followed by a solution of (2*S*,4*S*)-6-(*tert*-butyldiphenylsilyloxy)-2,4-dimethylhexanal (71.2 mg, 0.186 mmol, 1 equiv) in acetonitrile (0.7 mL, followed by a 0.6-mL rinse). After stirring at 23 °C for 2 d, the product solution was diluted with 50%-saturated aqueous ammonium chloride solution (10 mL) and the product was extracted with dichloromethane (3 $\times$ 10 mL). The combined organic layers were dried over sodium sulfate, the solids were removed by filtration, and the filtrate was concentrated in vacuo. HPLC analysis of the crude product mixture using biphenyl as an internal standard established the following product distribution: (*Z*)-(4*S*,6*S*)-8-(*tert*-butyldiphenylsilyloxy)-4,6-dimethyloct-2-enoic acid methyl ester (3.8%), (*E*)-(4*S*,6*S*)-8-(*tert*-butyldiphenylsilyloxy)-4,6-dimethyloct-2-enoic acid methyl ester (86.0%) and (*E*)-(4*R*,6*S*)-8-(*tert*-butyldiphenylsilyloxy)-4,6-dimethyloct-2-enoic acid methyl ester (4.9%) (Beckman Coulter Ultrasphere Silica column, 5 μ m dp, 4.6 mm $\times$ 25 cm, 1:99 ethyl acetate–hexanes; retention time of biphenyl: 5 min; retention time of (*Z*)-(4*S*,6*S*)-8-(*tert*-butyldiphenylsilyloxy)-4,6-dimethyloct-2-enoic acid methyl ester: 11 min; retention time of (*E*)-(4*R*,6*S*)-8-(*tert*-butyldiphenylsilyloxy)-4,6-dimethyloct-2-enoic acid methyl ester: 19 min; retention time of (*E*)-(4*S*,6*S*)-8-(*tert*-butyldiphenylsilyloxy)-4,6-dimethyloct-2-enoic acid methyl ester: 21 min).

1,2:3,4-Di-*O*-isopropylidene-D-galactohexodialdo-1,5-pyranose.¹⁰ Potassium bromide (105 mg, 0.882 mmol, 0.97 equiv), saturated aqueous bicarbonate solution (15 mL), and the stable free radical 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) (12.8 mg, 0.0819 mmol, 0.09 equiv) were added sequentially to a solution of 1,2:3,4-di-*O*-isopropylidene- α -D-galactopyranose (237 mg, 0.909 mmol, 1 equiv) in dichloromethane (30 mL) at 0 °C.¹¹ Addition of aqueous sodium hypochlorite solution (0.7 M, 1.31 mL, 0.919 mmol, 1.0 equiv) produced a red, biphasic mixture. After stirring for 25 min at 0 °C, the product solution was diluted with aqueous saturated sodium thiosulfate solution (10 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (1 $\times$ 25 mL). The aqueous layer was then diluted with saturated aqueous sodium chloride solution (5 mL) and the resulting solution was extracted with dichloromethane (1 $\times$ 25 mL). The combined organic layers were dried over sodium sulfate, the solids were removed by filtration, and the filtrate was concentrated in vacuo to afford 1,2:3,4-di-*O*-isopropylidene-D-galactohexodialdo-1,5-pyranose as a clear oil (210 mg, 89%).

¹H NMR (400 MHz, CDCl_3) δ 9.62 (s, 1H, CHO), 5.67 (d, 1H, J = 5.2 Hz, CHCHO), 4.64 (dd, 1H, J = 8, 2.4 Hz, CHOC(CH₃)₂), 4.60 (dd, 1H, J = 8, 2.4, CHOC(CH₃)₂), 4.38 (dd, 1H, J = 5.2, 2.4 Hz, CHOC(CH₃)₂), 4.19 (d, 1H, J = 2.4 Hz, CHOC(CH₃)₂), 1.51 (s, 3H, CH₃), 1.44 (s, 3H, CH₃), 1.35 (s, 3H, CH₃), 1.32 (s, 3H, CH₃); ¹³C NMR (100 MHz, CDCl_3) δ 200.3, 110.0, 109.0, 96.2, 73.2, 71.7, 70.4, 70.3, 26.0, 25.7, 24.8, 24.2; IR (thin film) cm^{-1} 1741 (m, C=O), 1070 (s, C–O); HRMS (ES) m/z calcd for $\text{C}_{12}\text{H}_{18}\text{O}_6$ [$\text{M} + \text{H}$]⁺: 259.1181, found 259.1176; TLC (10% ethyl acetate–dichloromethane), R_f 0.29 (UV, CAM).

¹⁰ For another preparative procedure see: Bose, A. K.; Banik, B. K.; Mathur, C.; Wagle, D. R.; Manhas, M. S. *Tetrahedron* **2000**, 56, 5603.

¹¹ (a) Anelli, P. L.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem.* **1987**, 52, 2559. (b) Leanna, M. R.; Sowin, T. J.; Morton, H. E. *Tetrahedron Lett.* **1992**, 33, 5029.

Methyl (*E*)-6,7-Dideoxy-1,2:3,4-di-*O*-isopropylidene- α -D-galacto-oct-5-enopyranuronate.

LiOCH(CF₃)₂ Conditions. A solution of *n*-butyllithium in hexanes (2.47 M, 388 μ L, 0.959 mmol, 1.18 equiv) and trimethyl phosphonoacetate (143 μ L, 0.975 mmol, 1.2 equiv) were added in sequence to a solution of 1,1,1,3,3,3-hexafluoroisopropanol (106 μ L, 1.01 mmol, 1.24 equiv) in 1,2-dimethoxyethane (1.53 mL) at -14 °C. A solution of 1,2:3,4-di-*O*-isopropylidene-D-galactohexodialdo-1,5-pyranose (210 mg, 0.813 mmol, 1 equiv) in 1,2-dimethoxyethane (1.0 mL, followed by one 0.86-mL rinse) was added via cannula, causing a white precipitate to form. The light orange suspension was stirred for 30 min at -14 °C. The product mixture was diluted with water (0.4 mL) and the solvents were removed in vacuo. ¹H NMR analysis of the crude product mixture showed the product to be >95% de with an *E*:*Z* ratio of >19:1. The product was purified by flash-column chromatography (15% ethyl ether–pentane initially, grading to 25% ethyl ether–pentane) to afford methyl (*E*)-6,7-dideoxy-1,2:3,4-di-*O*-isopropylidene- α -D-galacto-oct-5-enopyranuronate (228 mg, 89%). Spectral data are in agreement with those published.¹²

LiCl, DBU Conditions.⁹ Trimethyl phosphonoacetate (118 μ L, 0.806 mmol, 1.2 equiv) and 1,8-diazabicyclo[5.4.0]undec-7-ene (101 μ L, 0.672 mmol, 1.0 equiv) were added in sequence to a suspension of lithium chloride (34.2 mg, 0.806 mmol, 1.2 equiv) in acetonitrile (3.8 mL). A solution of 1,2:3,4-di-*O*-isopropylidene-D-galactohexodialdo-1,5-pyranose (174 mg, 0.672 mmol, 1 equiv) in acetonitrile (3 mL, followed by a 1.6-mL rinse) was added via cannula, causing a white precipitate to form. After stirring at 23 °C for 10 min, the product solution was diluted with water (1.0 mL). Volatile solvents were removed in vacuo and the product was purified by flash-column

¹² Tronchet, J. M. J.; Massoud, M. A. M. *Helv. Chim. Acta* **1979**, 62, 1632.

chromatography (15% ethyl ether–pentane initially, grading to 30% ethyl ether–pentane) to afford, separately, methyl (*E*)-6,7-dideoxy-1,2:3,4-di-*O*-isopropylidene- α -D-galacto-oct-5-enopyranuronate (172 mg, 81%) and methyl (*Z*)-6,7-dideoxy-1,2:3,4-di-*O*-isopropylidene- α -D-galacto-oct-5-enopyranuronate (20 mg, 10%). Spectral data agree for both isomers are in agreement with published data.¹²

(*E*)-(S)-4-(*tert*-Butyldimethylsilyloxy)pent-2-enoic Acid Methyl Ester.

LiOCH(CF₃)₂ Conditions. A solution of *n*-butyllithium in hexanes (2.53 M, 85.8 μ L, 0.217 mmol, 1.18 equiv) and trimethyl phosphonoacetate (32.4 μ L, 0.221 mmol, 1.2 equiv) were added in sequence to a solution of 1,1,1,3,3,3-hexafluoroisopropanol (24.0 μ L, 0.228 mmol, 1.24 equiv) in 1,2-dimethoxyethane (0.66 mL) at $-14\text{ }^{\circ}\text{C}$. Neat (*S*)-2-(*tert*-butyldimethylsilyloxy)propionaldehyde¹³ (34.7 mg, 0.184 mmol, 1 equiv) was added via syringe, followed by two 50- μ L acetonitrile rinses of the syringe, causing a white precipitate to form. After stirring for 40 min at $-14\text{ }^{\circ}\text{C}$, the product solution was diluted with water (0.5 mL). The mixture was further diluted with saturated aqueous ammonium chloride solution (5 mL) and the product was extracted with dichloromethane (3×7 mL). The combined organic layers were dried over sodium sulfate, the solids were removed by filtration, and the dried solution was concentrated in vacuo. ¹H NMR analysis of the crude reaction product revealed that the ratio of (*E*)- and (*Z*)-isomers was >19:1. The product was purified by flash-column chromatography (2% ethyl ether–pentane initially, grading to 5% ethyl ether–pentane) to afford the volatile products (*E*)-(S)-4-(*tert*-butyldimethylsilyloxy)pent-2-enoic acid methyl ester (34.8 mg, 77%) and (*Z*)-(S)-4-(*tert*-butyldimethylsilyloxy)pent-2-enoic acid methyl ester (0.9 mg, 2%). The *E*-isomer was determined to be >95% ee by ¹H NMR analysis of its Mosher ester.¹⁴ Spectral data are in agreement with those published.¹⁵

¹³ Defosseux, M.; Blanchard, N.; Meyer, C.; Cossy, J. *J. Org. Chem.* **2004**, *69*, 4626.

¹⁴ Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

¹⁵ Grée, D.; Vallerie, L.; Grée, R.; Toupet, L.; Washington, I.; Pelicier, J.-P.; Villacampa, M.; Pérez, J. M.; Houk, K. N. *J. Org. Chem.* **2001**, *66*, 2374.

LiCl, DBU Conditions.⁹ To a suspension of lithium chloride (9.4 mg, 0.221 mmol, 1.2 equiv) in acetonitrile (2.2 mL) were added sequentially trimethyl phosphonoacetate (32.4 μ L, 0.221 mmol, 1.2 equiv) and 1,8-diazabicyclo[5.4.0]undec-7-ene (27.5 μ L, 0.184 mmol, 1 equiv). Neat (*S*)-2-(*tert*-butyldimethylsilyloxy)propionaldehyde (34.7 mg, 0.184 mmol, 1 equiv) was added via syringe, followed by two 50- μ L acetonitrile rinses of the syringe, causing a white precipitate to form. After stirring the reaction solution at 23 $^\circ$ C for 1.75 h, water (0.5 mL) was added. The mixture was further diluted with saturated aqueous ammonium chloride solution (5 mL), and the product was extracted with dichloromethane (3 $\times$ 7 mL). The combined organic layers were dried over sodium sulfate, the solids were removed by filtration, and the dried solution was concentrated in vacuo. ^1H NMR analysis of the crude reaction mixture revealed that the ratio of (*E*)- and (*Z*)-isomers was 15:1. The product was purified by flash-column chromatography (2% ethyl ether–pentane initially, grading to 5% ethyl ether–pentane) to afford, separately, the volatile products (*E*)-(*S*)-4-(*tert*-butyldimethylsilyloxy)pent-2-enoic acid methyl ester (33.1 mg, 74%) and (*Z*)-(*S*)-4-(*tert*-butyldimethylsilyloxy)pent-2-enoic acid methyl ester (2.0 mg, 4%). The (*E*)-isomer was determined to be >95% ee by ^1H NMR analysis of its Mosher ester.¹⁴

[(1*S*)-[(1*S*,2*S*)-1-Hydroxymethyl-2-methylbutylcarbamoyl]-2-phenylethyl]carbamic Acid *tert*-Butyl Ester. *N,N*-Diisopropylethylamine (394 μ L, 2.26 mmol, 1.2 equiv) and (*S*)-(+)-isoleucinol (221mg, 1.89 mmol, 1 equiv) were added sequentially to a solution of *N*-Boc-L-phenylalanine (500 mg, 1.89 mmol, 1 equiv) and *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU) (788 mg, 2.07 mmol, 1.1 equiv) in dichloromethane (50 mL) at 23 $^\circ$ C. The cloudy yellow solution was stirred at 23 $^\circ$ C for 4.5 h. The product solution was concentrated in vacuo and then was partitioned between ethyl acetate (50 mL) and saturated aqueous ammonium chloride solution (30 mL). The aqueous layer was extracted with ethyl acetate

(1 × 50 mL), and the combined organic layers were washed with saturated ammonium chloride solution (2 × 30 mL), saturated aqueous sodium bicarbonate solution (2 × 30 mL), and saturated aqueous sodium chloride solution (1 × 30 mL). The organic layer was dried over sodium sulfate, the solids were removed by filtration, and the filtrate was concentrated in vacuo. The product was purified by flash-column chromatography (40% ethyl acetate–hexanes initially, grading to 50% ethyl acetate–hexanes) to yield [(1*S*)-[(1*S*,2*S*)-1-hydroxymethyl-2-methylbutylcarbamoyl]-2-phenylethyl]carbamic acid *tert*-butyl ester as a white solid (601 mg, 87%).

¹H NMR (500 MHz, CD₃OD) δ 7.28–7.18 (m, 5H, ArH), 4.28 (dd, 1H, *J* = 9.5, 6 Hz, CHBn), 3.69 (m, 1H, CHCH₂OH), 3.50 (m, 2H, CH₂OH), 3.09 (dd, 1H, *J* = 14, 5.5 Hz, CH₂Ph), 2.82 (dd, 1H, *J* = 14, 9 Hz, CH₂Ph), 1.64 (m, 1H, CH(CH₃)CH₂CH₃), 1.49 (m, 1H, CH₂CH₃), 1.36 (s, 9H, C(CH₃)₃), 1.11 (m, 1H, CH₂CH₃), 0.91 (d, 3H, *J* = 6.5 Hz, CH₃), 0.88 (t, 3H, *J* = 7.5 Hz, CH₃); ¹³C NMR (100 MHz, CD₃OD) δ 174.1, 157.5, 138.7, 130.4, 129.3, 127.6, 80.5, 62.7, 57.5, 56.7, 39.0, 36.3, 28.6, 26.0, 15.9, 11.7; IR (thin film) cm⁻¹ 3414 (m, br, O–H), 3339 (m, H–N), 1651 (s, C=O); mp 118.5–119 °C; HRMS (ES) *m/z* calcd for C₂₀H₃₂N₂O₄ [M + H]⁺: 365.2440, found 365.2438; TLC (30% ethyl acetate–hexanes), R_f 0.26 (UV, ninhydrin).

[(1*S*)-[(1*S*,2*S*)-1-Formyl-2-methylbutylcarbamoyl]-2-phenylethyl]carbamic Acid *tert*-Butyl Ester. Potassium bromide (34.7 mg, 0.292 mmol, 0.97 equiv), saturated aqueous sodium bicarbonate solution (5 mL), the stable free radical 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) (4.2 mg, 0.0271 mmol, 0.09 equiv), and aqueous sodium hypochlorite solution (0.7 M, 418 μL, 0.301 mmol, 1.0 equiv) were added in sequence to a solution of [(1*S*)-[(1*S*,2*S*)-1-hydroxymethyl-2-methylbutylcarbamoyl]-2-phenylethyl]carbamic acid *tert*-butyl ester (110 mg, 0.301 mmol, 1 equiv) in dichloromethane (10 mL) at 0 °C.¹¹ The biphasic, orange mixture was stirred at 0 °C for 20 min. The product solution was diluted with saturated aqueous sodium thiosulfate solution (5 mL) and saturated aqueous sodium bicarbonate solution (5 mL), then was extracted with dichloromethane (2 × 10 mL). The aqueous layer was then diluted with saturated aqueous sodium chloride solution (5

mL) and the resulting solution was extracted with dichloromethane (1 × 10 mL). The combined organic layers were dried over sodium sulfate and the solids were removed by filtration. The filtrate was concentrated in vacuo to provide [(1*S*)-[(1*S*,2*S*)-1-formyl-2-methylbutylcarbamoyl]-2-phenylethyl]carbamic acid *tert*-butyl ester as a white foam (109 mg, 100%). ¹H NMR analysis showed the product to be >95% de.

¹H NMR (500 MHz, CD₃CN) δ 9.43 (s, 1H, CHO), 7.30–7.20 (m, 5H, ArH), 6.90 (br, s, 1H, NH), 5.58 (br, d, 1H, *J* = 5 Hz, BocNH), 4.30 (m, 2H, NHCH), 3.10 (dd, 1H, *J* = 14, 5.5 Hz, CH₂Ph), 2.86 (dd, 1H, *J* = 13.5, 8.5 Hz, CH₂Ph), 1.97 (m, 1H, CH(CH₃)CH₂CH₃), 1.41 (m, 1H, CH₂CH₃), 1.34 (s, 9H, C(CH₃)₃), 1.20 (m, 1H, CH₂CH₃), 0.91 (d, 3H, *J* = 7 Hz, CH₃), 0.88 (d, 3H, *J* = 7 Hz, CH₃); ¹³C NMR (100 MHz, CD₃CN) δ 201.8, 173.0, 156.4, 138.6, 130.3, 129.3, 127.6, 80.0, 63.6, 56.6, 38.5, 36.3, 28.5, 25.8, 16.0, 11.9; IR (thin film) cm⁻¹ 3311 (m, NH), 1732 (m, C=O), 1657 (s, C=O); HRMS (ES) *m/z* calcd for C₂₀H₃₀N₂O₄ [M + H]⁺: 363.2284, found 363.2278; TLC (20% ethyl acetate–dichloromethane), R_f 0.58 (UV, ninhydrin).

(*E*)- and (*Z*)-4-[(2*S*)-*tert*-Butoxycarbonylamino-3-phenylpropionylamino]-5-methylhept-2-enoic Acid Methyl Ester.

LiOCH(CF₃)₂ Conditions. A solution of *n*-butyllithium in hexanes (2.59 M, 68.3 μL, 0.177 mmol, 1.18 equiv) was added to a solution of 1,1,1,3,3,3-hexafluoroisopropanol (19.6 μL, 0.186 mmol, 1.24 equiv) in 1,2-dimethoxyethane (280 μL) at -14 °C (ice-salt bath). Trimethyl phosphonoacetate (26.4 μL, 0.180 mmol, 1.2 equiv) was added to the reaction mixture, followed by a solution of [(1*S*)-[(1*S*,2*S*)-1-formyl-2-methylbutylcarbamoyl]-2-phenylethyl]carbamic acid *tert*-butyl ester (54.4 mg, 0.150 mmol, 1 equiv) in 1,2-dimethoxyethane (145 μL, followed by two 100-μL rinses), causing a white precipitate to form. The reaction mixture was stirred overnight in a cryobath at -14 °C, then was diluted with dichloromethane (6 mL) and 50%-saturated aqueous ammonium chloride solution (6 mL). The layers were separated and the aqueous portion was extracted with

dichloromethane (2 × 10 mL). The combined organic layers were dried over sodium sulfate and the solids were removed by filtration. The filtrate was concentrated in vacuo, and the product was purified by flash-column chromatography (20% ethyl acetate–hexanes initially, grading to 30% ethyl acetate–hexanes) to afford a mixture of (*E*)- and (*Z*)-(4*S*,5*S*)-4-[(2*S*)-*tert*-butoxycarbonylamino-3-phenylpropionylamino]-5-methylhept-2-enoic acid methyl ester as a white solid (58.9 mg, 94%). ¹H NMR analysis showed the *E*-olefin to be >95% de. HPLC analysis of the purified product revealed that the ratio of (*E*)- to (*Z*)-isomers was >26:1 (Beckman Coulter Ultrasphere Silica column, 5 μm dp, 4.6 mm × 25 cm, 15:85 ethyl acetate–hexanes; retention time of (*E*)-(4*S*,5*S*)-4-[(2*S*)-*tert*-butoxycarbonylamino-3-phenylpropionylamino]-5-methylhept-2-enoic acid methyl ester: 25 min; retention time of (*Z*)-(4*S*,5*S*)-4-[(2*S*)-*tert*-butoxycarbonylamino-3-phenylpropionylamino]-5-methylhept-2-enoic acid methyl ester: 30 min). Preparative HPLC provided pure (*E*)-(4*S*,5*S*)-4-[(2*S*)-*tert*-butoxycarbonylamino-3-phenylpropionylamino]-5-methylhept-2-enoic acid methyl ester (Beckman Coulter Ultrasphere Silica column, 5 μm dp, 10 mm × 25 cm, 15:85 ethyl acetate–hexanes; retention time: 39 min).

¹H NMR (500 MHz, CDCl₃) δ 7.32–7.20 (m, 5H, ArH), 6.69 (dd, *J* = 15.5, 5.5 Hz, HC=CHCO₂CH₃), 5.93 (d, 1H, *J* = 8 Hz, NH), 5.67 (d, 1H, *J* = 15.5 Hz, HC=CHCO₂CH₃), 5.04 (s, br, 1H, BocNH), 4.50 (m, 1H, CHCH=CH), 4.29 (dd, 1H, *J* = 14, 8 Hz, CHBn), 3.73 (s, 3H, CO₂CH₃), 3.10 (dd, 1H, *J* = 14, 7 Hz, CH₂Ph), 3.03 (dd, 1H, *J* = 14, 8 Hz, CH₂Ph), 1.55 (m, 1H, CH(CH₃)CH₂CH₃), 1.43 (s, 9H, C(CH₃)₃), 1.36 (m, 1H, CH₂CH₃), 1.04 (m, 1H, CH₂CH₃), 0.87 (t, 3H, *J* = 7.5 Hz, CH₃), 0.80 (d, 3H, *J* = 7.0 Hz, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 170.7, 166.5, 155.5, 146.0, 136.6, 129.2, 128.8, 127.1, 121.6, 80.4, 56.3, 54.2, 51.5, 38.6, 37.9, 28.2, 25.1, 15.1, 11.4; IR (thin film) cm⁻¹ 3327 (m, N–H), 1727 (s, C=O); mp 117.5–119 °C; HRMS (ES) *m/z* calcd for C₂₃H₃₄N₂O₅ [M + H]⁺: 419.2546, found 419.2533; TLC (30% ethyl acetate–hexanes), R_f 0.36.

LiCl, DBU Conditions.⁹ Trimethyl phosphonoacetate (26.4 μL , 0.180 mmol, 1.2 equiv) and 1,8-diazabicyclo[5.4.0]undec-7-ene (22.4 μL , 0.150 mmol, 1.0 equiv) were added sequentially to a suspension of lithium chloride (7.7 mg, 0.18 mmol, 1.2 equiv) in acetonitrile (0.88 mL) at 23 $^\circ\text{C}$. A solution of [(1*S*)-[(1*S*,2*S*)-1-formyl-2-methylbutylcarbamoyl]-2-phenylethyl]carbamic acid *tert*-butyl ester (54.4 mg, 0.150 mmol, 1 equiv) in acetonitrile (0.6 mL, followed by a 0.4-mL rinse) was added via cannula, and the reaction mixture was stirred at 23 $^\circ\text{C}$ for 18 h. The product solution was diluted with dichloromethane (6 mL) and 50%-saturated aqueous ammonium chloride solution (6 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (2 $\times$ 10 mL). The combined organic layers were dried over sodium sulfate, the solids were removed by filtration, and the filtrate was concentrated in vacuo. The product was purified by flash-column chromatography (20% ethyl acetate–hexanes initially, grading to 30% ethyl acetate–hexanes) to afford a mixture of (*E*)- and (*Z*)-[(4*S*,5*S*)-4-[(2*S*)-*tert*-butoxycarbonylamino]-3-phenylpropionylamino]-5-methylhept-2-enoic acid methyl ester as a white solid (57.8 mg, 92%). ^1H NMR analysis showed the product to be >95% de, with an *E:Z* ratio of 12:1.

[(1*S*)-[(1*S*)-2-Hydroxy-1-methylethylcarbamoyl]-2-phenylethyl]carbamic Acid *tert*-Butyl Ester. *N,N*-Diisopropylethylamine (394 μL , 2.26 mmol, 1.2 equiv) and (*S*)-(+)-2-amino-1-propanol (147 μL , 1.88 mmol, 1 equiv) were added sequentially to a solution of *N*-Boc-L-phenylalanine (500 mg, 1.88 mmol, 1 equiv) and HATU (788 mg, 2.07 mmol, 1.1 equiv) in dichloromethane (50 mL) at 23 $^\circ\text{C}$. After being stirred at 23 $^\circ\text{C}$ for 15 h, the product solution was concentrated in vacuo, then was partitioned between saturated aqueous ammonium chloride solution (30 mL) and ethyl acetate (50 mL). The aqueous layer was extracted with ethyl acetate (1 $\times$ 50 mL), and the combined organic layers were washed with the following solutions in sequence: saturated aqueous ammonium chloride solution (2 $\times$ 30 mL), saturated aqueous sodium bicarbonate

solution (2 × 30 mL), saturated aqueous ammonium chloride solution (2 × 30 mL), and saturated aqueous sodium chloride solution (2 × 30 mL). The organic layer was dried over sodium sulfate, the solids were removed by filtration, and the dried solution was concentrated in vacuo. The solid was purified by flash-column chromatography (30% hexanes–ethyl acetate, grading to 20% hexanes–ethyl acetate) to provide [(1*S*)-[(1*S*)-2-hydroxy-1-methylethylcarbamoyl]-2-phenylethyl]carbamic acid *tert*-butyl ester a white solid (582 mg, 96%).

¹H NMR (500 MHz, CDCl₃) δ 7.35–7.23 (m, 5H, ArH), 5.69 (d, 1H, *J* = 6.5 Hz, BocNH), 5.08 (br, s, 1H, NH), 4.25 (q, 1H, *J* = 9 Hz, CHBn), 3.97 (m, 1H, CH₃), 3.48 (m, 1H, CH₂OH), 3.35 (m, 1H, CH₂OH), 3.10 (dd, 1H, *J* = 17, 7.5 Hz, CH₂Ph), 2.99 (dd, 1H, *J* = 17, 9.5 Hz, CH₂Ph), 2.08 (br, s, 1H, OH), 1.43 (s, 9H, C(CH₃)₃), 1.06 (d, 3H, *J* = 8.5 Hz, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 171.6, 155.5, 136.7, 129.3, 128.6, 126.9, 80.2, 66.1, 56.1, 47.5, 38.7, 28.2, 16.6; IR (thin film) cm⁻¹ 3300 (m, H–N), 1651 (s, C=O); mp 113.5–114.5 °C; HRMS (ES) *m/z* calcd for C₁₇H₂₆N₂O₄ [M + H]⁺: 323.1971, found 323.1968; TLC (90% ethyl acetate–hexanes), R_f 0.35 (UV, ninhydrin).

[(*S*)-1-[(*S*)-1-Methyl-2-oxoethylcarbamoyl]-2-phenylethyl]carbamic Acid *tert*-Butyl Ester.

Potassium bromide (8.5 mg, 0.0716 mmol, 0.97 equiv), saturated aqueous sodium bicarbonate solution (1.2 mL), and a solution of the stable free radical 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) in dichloromethane (0.064 M, 0.10 mL, 6.4 μmol, 0.09 equiv) were added sequentially to a solution of [(1*S*)-[(1*S*)-2-hydroxy-1-methylethylcarbamoyl]-2-phenylethyl]carbamic acid *tert*-butyl ester (23.8 mg, 0.0738 mmol, 1 equiv) in dichloromethane (2.5 mL) at 0 °C.¹¹ Addition of aqueous sodium hypochlorite solution (0.7 M, 103 mL, 0.0738 mmol, 1.0 equiv) produced an orange, biphasic mixture. After stirring at 0 °C for 20 min, the product solution was diluted with dichloromethane (3 mL), saturated aqueous sodium thiosulfate solution (3 mL), and saturated aqueous sodium bicarbonate solution (3 mL). The layers were separated and the aqueous portion was extracted with dichloromethane (1 × 5 mL). The aqueous layer was then diluted with saturated aqueous sodium chloride solution (3 mL), and the resulting mixture was extracted with

dichloromethane (1 × 5 mL). The combined organic layers were dried over sodium sulfate and the solids were removed by filtration. The filtrate was concentrated in vacuo, to provide [(*S*)-1-[(*S*)-1-methyl-2-oxoethylcarbamoyl]-2-phenylethyl]carbamic acid *tert*-butyl ester as a white foam (22.5 mg, 95%). ¹H NMR analysis of the purified product showed it to be >95% de.

¹H NMR (500 MHz, CD₃CN) δ 9.35 (s, 1H, CHO), 7.32–7.22 (m, 5H, ArH), 7.04 (s, br, 1H, NH), 5.53 (s, br, 1H, BocNH), 4.30 (s, br, CHBn), 4.16 (p, 1H, CHCHO), 3.11 (dd, 1H, *J* = 13.5, 5 Hz, CH₂Ph), 2.86 (dd, 1H, *J* = 13.5, 11 Hz, CH₂Ph), 1.34 (s, 9H, C(CH₃)₃), 1.21 (d, 3H, *J* = 7.5 Hz, CH₃); ¹³C NMR (100 MHz, CD₃CN) δ 201.9, 173.3, 156.8, 139.0, 130.8, 129.8, 128.0, 80.5, 57.0, 55.7, 39.3, 28.9, 14.7; IR (thin film) cm⁻¹ 3296 (m, N–H), 1735 (m, C=O); HRMS (ES) *m/z* calcd for C₁₇H₂₄N₂O₄ [M + H]⁺: 321.1814, found 321.1804; TLC (50% ethyl acetate–dichloromethane), R_f 0.50 (UV, ninhydrin).

(*E*)- and (*Z*)-(*S*)-4-[(*S*)-2-*tert*-Butoxycarbonylamino-3-phenylpropionylamino]pent-2-enoic Acid Methyl Ester.

LiOCH(CF₃)₂ Conditions. A solution of *n*-butyllithium in hexanes (2.59 M, 67.0 μL, 0.173 mmol, 1.18 equiv) was added to a solution of 1,1,1,3,3,3-hexafluoroisopropanol (19.2 μL, 0.182 mmol, 1.24 equiv) in 1,2-dimethoxyethane (280 μL) at -14 °C (ice-salt bath). Trimethyl phosphonoacetate (25.9 μL, 0.174 mmol, 1.2 equiv) was added to the reaction mixture, followed by a solution of [(*S*)-1-[(*S*)-1-methyl-2-oxoethylcarbamoyl]-2-phenylethyl]carbamic acid *tert*-butyl ester (47.2 mg, 0.147 mmol, 1 equiv) in 1,2-dimethoxyethane via syringe (130 μL, followed by two 100-μL washes of the syringe), causing a white precipitate to form. The reaction mixture was stirred overnight in a cryobath at -12 °C, then was diluted with dichloromethane (6 mL) and 50%-saturated aqueous ammonium chloride solution (6 mL). The layers were separated and the aqueous portion was extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried over sodium sulfate and the solids were removed by filtration. The filtrate was concentrated in vacuo, and the product was purified by flash-column chromatography (25% ethyl acetate–hexanes initially, grading

chromatography (20% ethyl acetate–hexanes initially, grading to 30% ethyl acetate–hexanes) to afford a mixture of (*E*)- and (*Z*)-(*S*)-4-[(*S*)-2-*tert*-butoxycarbonylamino-3-phenylpropionylamino)-pent-2-enoic acid methyl ester as a white solid (46.3 mg, 84%). ¹H NMR analysis of the purified product showed it to be 80% de, with an *E*:*Z* ratio of 7:1.

Ba(OH)₂ Conditions.⁵ Trimethyl phosphonoacetate (14.4 μ L, 0.0983 mmol, 1.0 equiv) was added to a suspension of barium hydroxide octahydrate (24.8 mg, 0.0786 mmol, 0.8 equiv) in tetrahydrofuran (250 μ L) at 23 $^\circ$ C. [(*S*)-1-[(*S*)-1-Methyl-2-oxoethylcarbamoyl]-2-phenylethyl]-carbamic acid *tert*-butyl ester (33.8 mg, 0.0883 mmol, 1 equiv) was added via syringe as a solution in 40:1 tetrahydrofuran–water (145 μ L, followed by a 100- μ L rinse and a 50- μ L rinse). After stirring at 23 $^\circ$ C for 2 h, the product solution was diluted with saturated aqueous sodium bicarbonate solution (6 mL), and the product was extracted with dichloromethane (3 $\times$ 10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (1 $\times$ 6 mL), then were dried over sodium sulfate. The solids were removed by filtration and the filtrate was concentrated in vacuo. The product was purified by flash-column chromatography (25% ethyl acetate–hexanes initially, grading to 32% ethyl acetate–hexanes) to afford a mixture of (*E*)- and (*Z*)-(*S*)-4-[(*S*)-2-*tert*-butoxycarbonylamino-3-phenylpropionylamino)pent-2-enoic acid methyl ester as a white solid (28.3 mg, 77%). ¹H NMR analysis of the purified product showed it to be 87% de with an *E*:*Z* ratio of 10:1.

³¹P NMR Experiments and Sample Preparation

Spectrum of Trimethyl Phosphonoacetate in 1,2-Dimethoxyethane and Deuterium Oxide.

Trimethyl phosphonoacetate (29.3 μ L, 0.202 mmol, 1 equiv) was dissolved in 1,2-dimethoxyethane

or deuterium oxide (0.7 mL). The solution was transferred via cannula to an NMR tube. ^{31}P NMR (160 MHz, 1,2-dimethoxyethane) δ 23.3; (160 MHz, D_2O) δ 26.8.

Spectrum of Trimethyl Phosphonoacetate and Lithium Hexafluoroisopropoxide. A solution of *n*-butyllithium in hexanes (2.47 M, 80.1 μL , 0.198 mmol, 0.98 equiv) was added to a solution of 1,1,1,3,3,3-hexafluoroisopropanol (21.9 μL , 0.208 mmol, 1.03 equiv) in 1,2-dimethoxyethane (0.7 mL) at -14°C . Trimethyl phosphonoacetate (29.3 μL , 0.202 mmol, 1 equiv) was added via syringe and the solution was allowed to warm to 23°C before being transferred via cannula to an NMR tube. ^{31}P NMR (160 MHz, 1,2-dimethoxyethane) δ 32.7, 23.7 (br).

Spectrum of Trimethyl Phosphonoacetate and Lithium *tert*-Butoxide. A solution of lithium *tert*-butoxide in hexanes (1.0 M, 198 μL , 0.198 mmol, 1.0 equiv) was added to a solution of trimethyl phosphonoacetate (29.0 μL , 0.198 mmol, 1 equiv) in 1,2-dimethoxyethane. The solution was transferred via cannula to an NMR tube. ^{31}P NMR (160 MHz, 1,2-dimethoxyethane) δ 44.1, 32.7, 24.5. This solution was concentrated in vacuo and re-dissolved in deuterium oxide for comparison with lithium dimethylphosphonoacetate. ^{31}P NMR (160 MHz, D_2O) δ 31.0, 21.3.

Spectrum of Lithium Dimethylphosphono-2,2-dideuteroacetate. Trimethyl phosphonoacetate (0.200 μL , 0.136 mmol, 1 equiv) was added to a solution of lithium hydroxide monohydrate (57.1 mg, 0.136 mmol, 1.0 equiv) in deuterium oxide (1.36 mL).¹⁶ After being stirred for 45 min, an aliquot of the product solution (ca. 40 μL) was transferred to an NMR tube and diluted with

¹⁶ Floyd, D. M.; Fritz, A. W. *Tetrahedron Lett.* **1981**, 22, 2847.

deuterium oxide (ca. 0.45 mL). ^1H NMR (400 MHz, D_2O) δ 3.80 (d, 6H, $J = 11.2$ Hz, $\text{P}(\text{OCH}_3)_2$), 3.35 (s, 3H, CH_2); ^{31}P NMR (160 MHz, D_2O) δ 31.1. HRMS (ES) m/z calcd for $\text{C}_4\text{H}_6\text{D}_2\text{LiO}_5\text{P}$ [$\text{M} - \text{Li}^+$] $^-$: 169.0233, found 169.0230.