Efficient Synthesis of the γ-Amino-β-hydroxy Acid Subunit of Hapalosin

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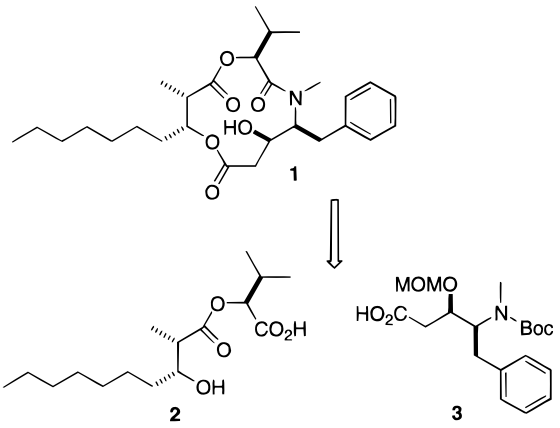
Introduction

The 1,2-amino alcohol substructure represents an important replacement of the peptide bond in a number of peptidomimetics.[1,2] Enantiomerically pure 1,2-amino alcohols allow the formation of heterocycles which rank among the most popular chiral auxiliaries. Moreover, this structural element can be found in amino sugars,[3] sphingosins,[4] and also some acids. Representative examples for the latter include statine and (3*S*,4*S*)-4-amino-3-hydroxy-5-phenylpentanoic acid, which are the key constituents of renin inhibitors.[5−7] Furthermore, the 3-hydroxy-4-amino acid related to **3** is part of the cyclic depsipeptide hapalosin (**1**) (Scheme 1).[8−12] This natural product turned out to be quite active in reversing multidrug resistance caused by overexpression of the P-glycoprotein. To synthesize analogues of hapalosin,[13,14] an efficient and flexible synthesis of the acid **3** was sought. The requirements to incorporate this substructure into hapalosin fragment **2** are protecting groups at the 3-hydroxy and the 4-*N*-methylamino function. Amino acids of type **3** are usually prepared by elongation of phenylalanine.[9−12] Other routes to the amino alcohol group involve the asymmetric hydrogenation of an enaminoketone,[15] the Sharpless aminohydroxylation reaction,[16] and the Lewis acid promoted coupling reactions of oxazins with nucleophiles.[17]

Scheme 1



Recognizing that the amino function might originate from a carboxylic group through a Curtius rearrangement,[3,18,19] we devised an aldol reaction/Curtius rearrangement strategy for compound **3** (Scheme 1). The realization of this route is presented in this paper.

Results

The two stereocenters of the target molecule were established by an Evans aldol reaction.[20] Thus, enolization of the acylated oxazolidinone **4** with di-*n*-butylboron triflate[21] in the presence of diisopropylethylamine at 0 °C followed by the addition of acrolein at −78 °C gave rise to the aldol product **5**.[22] The use of the Hünig's base proved to be crucial since with triethylamine the yield dropped to 10%. Subsequent hydrolysis with lithium hydroxide and hydrogen peroxide[23] furnished the acid **6**. With acid **6** being somewhat unstable, although it can be stored at −25 °C, it was used immediately in the next step. Treatment of **6** with diphenylphosphoryl azide and triethylamine and heating to 80 °C induced Curtius rearrangement[19] and intramolecular trapping[24] of the isocyanate to the oxazolidinone **7**. The vicinal coupling constant $J_{4,5} = 6.7$ Hz is in accord with a *syn*-orientation of the two substituents.[25] To facilitate the hydrolysis of the oxazolidinone **7**, it was converted to the corresponding BOC derivative **8**.[26] Stirring of **8** with cesium carbonate in methanol provided the N-protected amino alcohol **9** in 76% yield. The melting point as well as the optical rotation matched the reported values.[27,28] Both of these

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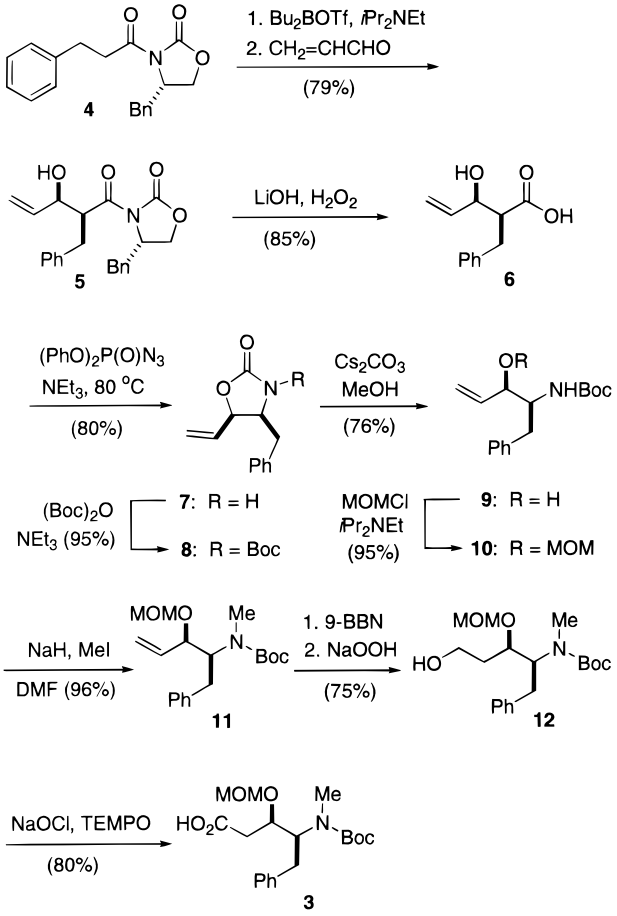
Scheme 2



papers describe the synthesis of **9** by an addition of vinylmagnesium bromide to an α-amino aldehyde. However, this approach produces a mixture of both diastereomers which have to be separated. In the next step the hydroxyl group was protected with chloromethyl methyl ether (MOM chloride) to give compound **10**. This protecting group was chosen over a silicon-based one because the N-methylation conditions can cause cleavage of a neighboring silicon protecting group. Having the ether **10** in hand, N-methylation to the alkene **11** was achieved using sodium hydride (NaH) and methyl iodide (MeI).[9] The final steps served to establish the carboxylic function from the double bond. This was initiated by hydroboration of **11** using 9-borabicyclo[3.3.1]nonane (9-BBN) followed by oxidative workup.[25]

The resulting primary alcohol **12** was then oxidized to the carboxylic acid **3** by the use of sodium hypochlorite and TEMPO (Scheme 2).[16] These conditions proved to be superior in comparison to the oxidation with pyridinium dichromate (PDC) in DMF.

With a view to the synthesis of functionalized pyrrolidines, we investigated the conversion of the double bond to the carboxylic function with a free NH group in the molecule. This route was studied with the alkene **13** which is available by silylation of the alcohol **9**. As described above, hydroboration delivered the primary alcohol **14**. Oxidation of this compound with PDC in DMF gave directly the lactam **15**.[29] This could be opened under mild conditions to the methyl ester **16** (Scheme 3).

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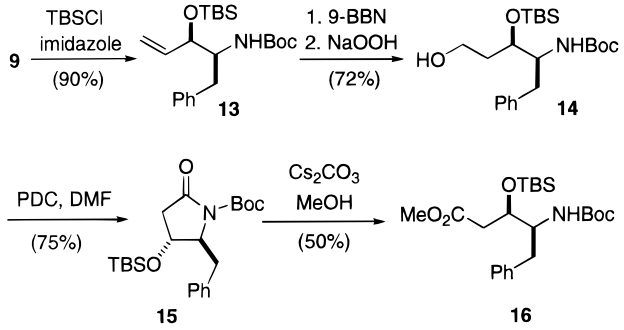
Scheme 3



In summary, we could show that the aldol reaction with acrolein followed by a Curtius rearrangement and conversion of the double bond to a terminal carboxylic function allows the stereocontrolled synthesis of γ-amino-β-hydroxy acids such as the one in hapalosin. Moreover, this strategy should open up a new route to optically active nitrogen heterocycles.[30]

Experimental Section

All melting points were recorded on a Büchi melting point B-540 apparatus. Optical rotations were recorded on a JASCO P-1020 polarimeter. IR spectra were recorded on a Jasco FT/IR-430 spectrometer. ^{1}H (250 MHz) and ^{13}C (62.5 MHz) spectra were recorded in $CDCl_3$. Unless mentioned, all the reactions were carried out under an argon atmosphere. Anhydrous solvents were obtained as follows: diethyl ether, tetrahydrofuran, and toluene by distillation from sodium and benzophenone; methylene chloride by distillation from calcium hydride; dimethylformamide was first stirred over calcium hydride, decanted, and distilled under reduced pressure. Tributylborane was prepared from boron trifluoride etherate and butylmagnesium bromide in dry ether under argon.[31] Di-*n*-butylboron triflate was prepared according to Mukaiyama's procedure.[21] The chiral auxiliary **4** was prepared according to the literature procedure.[32,33] Aqueous sodium hypochlorite (13% active chlorine, ACROS) was diluted to 0.43 M. Hünig's base was distilled from KOH before use. Triethylamine was distilled from calcium hydride prior to use. Column chromatography was performed with E. Merck 40−63 μm silica gel. Thin-layer chromatography was carried out with Polygram Sil G/UV$_{254}$ from Macherey-Nagel.

(3*R*,4*S*)-4-[*N*-(*tert*-Butoxycarbonyl)-*N*-methylamino]-3-(methoxymethoxy)-5-phenylpentanoic Acid (3). Compound **12** (1.80 g, 5.10 mmol) was dissolved in acetone (40 mL) and added to an aqueous 5% $NaHCO_3$ solution (13.5 mL). This magnetically stirred heterogeneous mixture was cooled to 0 °C and treated sequentially with KBr (62 mg, 0.52 mmol) and TEMPO (0.84 g, 5.39 mmol). Sodium hypochlorite (15 mL, 6.45 mmol) was then added dropwise, while the mixture was vigorously stirred and maintained at 0 °C. After 1 h, additional NaOCl (5.8 mL, 2.50 mmol) was added, and stirring was continued at 0 °C for an another hour followed by addition of a 5% $NaHCO_3$ solution (19 mL). Following evaporation of the acetone, the aqueous layer was washed with ether (2 × 50 mL, to remove TEMPO impurities), acidified to pH 6 with 10% aqueous citric acid, and extracted with ethyl acetate (3 × 100 mL). The combined organic phases were washed with water and brine, dried over $NaSO_4$, and concentrated to give the crude acid. Pure acid **3** (1.5 g, 80%) was obtained by flash chromatography (petroleum ether/ethyl acetate, 1:1): TLC (40% ethyl acetate in petrol ether): $R_f = 0.37$; $[\alpha]^{22}_D = -39.8$ (*c* 0.6, $CHCl_3$); IR (neat)

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3449−2622 (br), 1733 (s), 1692 (s) cm^{-1}; ^1H NMR (both rotamers) δ 1.19 (br s, 9 H, minor), 1.25 (s, 9 H, major), 2.43−2.62 (complex, 6 H), 3.17 (dd, J = 11.1, 13.5, 2.7 Hz, 1H), 3.35 (s, 3 H, minor), 3.36 (s, 3 H, major), 4.04−4.15 (br m, 2 H), 4.66 (d, J = 7.1 Hz, 1H), 4.75 (d, J = 7.1 Hz, 1 H), 7.07−7.22 (m, 5 H); ^{13}C NMR (both rotamers) δ 28.1, 28.3, 34.5, 38.0, 56.2, 56.3, 76.5, 77.3, 97.1, 97.3, 126.2, 126.4, 128.3, 128.4, 129.0, 138.5, 155.7, 175.8; MS (EI), m/z (%) 368 [M^+ + 1] (10); HRMS (EI) calcd for $C_{19}H_{29}NO_6$ 367.19948, found 367.20129.

(4*S*)-4-Benzyl-3-[(2*S*,3*R*)-2-benzyl-3-hydroxy-4-pentenoyl]-1,3-oxazolidin-2-one (5). To a solution of **4**[32] (5.80 g, 18.7 mmol) in CH_2Cl_2 (38 mL) at 0 °C was added di-*n*-butylboron triflate (22.9 mL, 22.9 mmol, 1 M in CH_2Cl_2) dropwise. This was followed by the dropwise addition of Hünig's base (4.20 mL, 24.4 mmol). After 1 h at 0 °C, the solution was cooled to −78 °C and freshly distilled acrolein (1.9 mL, 28.1 mmol) was added over 2 min. After being stirred for 1 h at −78 °C, the reaction mixture was allowed to warm to room temperature over 1 h and kept at this temperature for 2 h. The mixture was poured into pH 7 buffer (42 mL), and then ether (55 mL) was added. The layers were separated, and the aqueous layer was extracted with ether (2 × 50 mL). The combined layers were washed with brine (30 mL), and the solvent was removed with a rotary evaporator. The residue was dissolved in methanol (55 mL), cooled to 0 °C, and treated dropwise with H_2O_2 (18.75 mL of a 30% aqueous solution). After 60 min at 0 °C, the mixture was diluted with water (55 mL), and most of the methanol was removed with a rotary evaporator. The aqueous layer was extracted with ether (3 × 50 mL). The combined organic layers were washed with cold 5% HCl (7 mL), saturated aqueous $NaHCO_3$ (15 mL), and brine (15 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 3:2) to give **5** as a colorless oil (5.4 g, 79%) which solidifies upon standing, mp 45.8−46.8 °C: TLC (petroleum ether/ethyl acetate, 3:2): R_f = 0.46; $[\alpha]^{23}_D$ +11.75 (*c* 1.22, $CHCl_3$); IR (neat) 3821 (s), 1777 (s), 1698 (s) cm^{-1}; ^1H NMR δ 2.17 (ddd, J = 4.3, 9.2, 4.0 Hz, 1 H), 2.80 (dd, J = 10.1, 3.4 Hz, 1 H), 2.91−3.09 (m, 2 H), 3.92 (dd, J = 6.1, 3.0 Hz, 1 H), 4.03 (dd, J = 1.2, 7.9 Hz, 1 H), 4.39−4.43 (m, 1 H), 4.52−4.62 (m, 2 H), 5.20 (dt, J = 10.4, 1.5 Hz, 1 H), 5.30 (dt, J = 17.1, 1.2 Hz, 1 H), 5.91 (ddd, J = 6.5, 4.2, 6.1 Hz, 1 H), 6.83−6.87 (m, 2 H), 7.10−7.21 (m, 8 H); ^{13}C NMR δ 33.8, 37.4, 49.8, 55.0, 65.8, 73.9, 117.1, 126.6 127.3, 128.5, 128.9, 129.4, 129.5, 135.1, 137.4, 138.8, 153.5, 174.0; MS (EI), m/z (%) 365 [M] (1); HRMS (EI) calcd for $C_{22}H_{23}NO_4$ 365.16273, found 365.16983.

(2*S*,3*R*)-2-Benzyl-3-hydroxy-4-pentenoic Acid (6). To a solution of the oxazolidinone **5** (5.0 g, 13.7 mmol) in tetrahydrofuran−distilled water (3:1, v/v, 205 mL) was added H_2O_2 (30% aqueous solution, 7.75 mL, 68.42 mmol) at 0 °C via syringe over a 5-min period. This was followed by the addition of lithium hydroxide (1.15 g, 27.37 mmol), dissolved in water (27 mL). Some gas evolved from the clear solution. After stirring for 1 h at 0 °C and for 15 h at room temperature, the excess H_2O_2 was quenched by the addition of sodium sulfite (8.62 g, 68.4 mmol) in distilled water (41 mL). The bulk of the tetrahydrofuran was removed by rotary evaporation at a bath temperature of 25−30 °C, and the resulting mixture was extracted with dichloromethane (3 × 60 mL) to remove the oxazolidinone auxiliary. The aqueous layer was cooled in an ice bath and acidified to pH 2 with aqueous 1 N hydrochloric acid. The resulting cloudy solution was then extracted with ether (5 × 60 mL). The combined ether extracts were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (50% ethyl acetate in petroleum ether) to give **6** (2.4 g, 85%) as a colorless oil: TLC (petroleum ether/ethyl acetate, 1:1) R_f = 0.38; $[\alpha]^{25}_D$ = −12.85 (*c* 0.16, $CHCl_3$); IR (neat) 3412−2056 (br), 1709 (s) cm^{-1}; ^1H NMR δ 2.77−3.01 (m, 3 H), 4.30 (td, J = 3.2, 1.4 Hz, 1 H), 5.18 (dt, J = 10.4, 1.2 Hz, 1 H), 5.27 (dt, J = 17.4, 1.3 Hz, 1 H), 5.78−5.91 (m, 1 H), 6.64 (br s, 2 H), 7.07−7.26 (m, 5 H); ^{13}C NMR δ 33.0, 52.8, 73.0, 117.7, 126.6, 128.6, 128.9, 136.7, 138.8, 178.7; MS (EI), m/z (%) 206 [M^+] (35), 188 (50), 143 (82).

(4*S*,5*R*)-4-Benzyl-5-vinyl-1,3-oxazolidin-2-one (7). The hydroxy acid **6** (2.00 g, 9.66 mmol) was dissolved in dry toluene (21 mL), diphenylphosphoryl azide (3.13 mL, 14.49 mmol) followed by triethylamine (3.16 mL, 22.71 mmol) was added, and the resulting mixture was heated at 80 °C for 4 h. After cooling the reaction mixture to room temperature, the toluene was removed under reduced pressure. The residue was partitioned between ethyl acetate and saturated aqueous $NaHCO_3$. The organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a black residue, which was purified by flash chromatography (40% ethyl acetate in petroleum ether) providing **7** (1.58 g, 80%) as light yellow oil: TLC (40% ethyl acetate in petroleum ether) R_f = 0.33; $[\alpha]^{23}_D$ = −118.5 (*c* 1.04, $CHCl_3$); IR (neat) 3278 (s), 1750 (s) cm^{-1}; ^1H NMR δ 2.54 (dd, J = 2.5, 11.0 Hz, 1 H), 2.74 (dd, J = 9.6, 4.0 Hz, 1 H), 3.96−4.08 (m, 1 H), 5.06 (dd, J = 6.7, 1.2 Hz, 1 H), 5.10 (dd, J = 1.2, 0.9 Hz, 1 H), 5.38 (dt, J = 10.4, 1.2 Hz, 1 H), 5.47 (dt, J = 17.4, 1.3 Hz, 1 H), 5.84−5.97 (m, 1 H), 7.07−7.10 (m, 2 H), 7.15−7.30 (m, 3 H); ^{13}C NMR δ 37.5, 57.2, 80.1, 120.4, 127.2, 129.0, 129.1, 130.78, 136.8, 158.3; MS (EI), m/z (%) 204 [M^+ + 1] (5.9); HRMS (EI) calcd for $C_{12}H_{13}NO_2$ 203.09463, found 203.09147.

(4*S*,5*R*)-4-Benzyl-3-(*tert*-butoxycarbonyl)-5-vinyl-1,3-oxazolidin-2-one (8). A solution of oxazolidinone **7** (1.3 g, 6.40 mmol) in tetrahydrofuran (30 mL) was treated with $(Boc)_2O$ (1.82 g, 8.34 mmol) and triethylamine (1.07 mL, 7.68 mmol) in the presence of DMAP (0.16 g, 1.28 mmol) and the mixture stirred at room temperature for 5.30 h. Excess $(Boc)_2O$ was quenched by the addition of *N*,*N*-diethylenediamine (0.17 mL, 1.28 mmol) and the mixture stirred for 10 min. Then ether (100 mL) was added to the reaction mixture which was washed successively with a 1 M aqueous $KHSO_4$ solution, water, a saturated aqueous $NaHCO_3$ solution, water, and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (30% ethyl acetate in petroleum ether) to give **8** (1.84 g, 95%) as colorless needles, mp 72−73 °C: TLC (30% ethyl acetate in petroleum ether) R_f = 0.65; $[\alpha]^{21}_D$ = −13.5 (*c* 1.0, $CHCl_3$); IR (KBr) 3606 (w), 3429 (w), 3059 (s), 1803 (s), 1719 (s) cm^{-1}; ^1H NMR δ 1.41 (s, 9 H), 2.85 (d, J = 2.1 Hz, 1 H), 2.87 (s, 1 H), 4.54 (q, J = 6.8 Hz, 1 H), 4.92−4.98 (m, 1 H), 5.29 (dt, J = 10.7, 1.2 Hz, 1 H), 5.44 (dt, J = 17.1, 1.2 Hz, 1 H), 5.62−5.75 (m, 1 H), 7.10−7.25 (m, 5 H); ^{13}C NMR δ 27.8, 35.6, 59.5, 78.1, 83.9, 120.4, 126.9, 128.7, 129.6, 129.7, 136.4, 148.9, 151.6; MS (EI), m/z (%) 247 [M^+ + 1 − *t*-Bu] (7).

(3*R*,4*S*)-*N*-(*tert*-Butoxycarbonyl)-4-amino-3-hydroxy-5-phenylpent-1-ene (9). A mixture of the oxazolidinone **8** (1.80 g, 5.94 mmol) in methanol (80 mL) and cesium carbonate (0.774 g, 2.38 mmol) was stirred for 25 h at room temperature. Then the reaction was quenched with citric acid, and the product was extracted with ethyl acetate, dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification of the residue by flash chormatography (20% ethyl acetate in petroleum ether) gave 1.26 g (76%) of **9** as colorless needles, mp 124.5 °C, lit.[27] 125−126.5 °C: TLC (hexane/ethyl acetate, 2:1): R_f = 0.65; $[\alpha]^{23}_D$ = −23.9 (*c* 0.5, $CHCl_3$), lit.[27] $[\alpha]^{25}_D$ = −23 (*c* 1.0, $CHCl_3$); IR (KBr) 3356 (s), 1686 (s) cm^{-1}; ^1H NMR δ 1.29 (s, 9 H), 2.61−2.82 (m, 1 H), 2.78 (dd, J = 8.9, 5.5 Hz, 1 H), 3.00 (br s, 1 H), 3.90 (br s, 1 H), 4.16 (s, 1 H), 4.53 (br d, J = 6.4 Hz, 1 H), 5.22 (dt, J = 10.4, 1.6 Hz, 1 H), 5.30 (dt, J = 17.4, 1.6 Hz, 1 H), 5.87 (dddd, J = 1.3, 5.5, 4.9, 5.8 Hz, 1 H), 7.11−7.26 (m, 5 H); ^{13}C NMR δ 28.3, 36.0, 56.5, 74.6, 79.778, 116.9, 126.4, 128.4, 129.3, 137.0, 138.1, 156.4; MS (EI), m/z (%) 278 [M^+ + 1] (3.7).

(3*R*,4*S*)-*N*-(*tert*-Butoxycarbonyl)-4-amino-3-(methoxymethoxy)-5-phenylpent-1-ene (10). Chloromethyl methyl ether (4.00 mL, 49.6 mmol) was added dropwise to a cooled (0 °C) solution of the alcohol **9** (3.00 g, 10.8 mmol) and diisopropylethylamine (17 mL, 100 mmol) of CH_2Cl_2 (15 mL). The reaction mixture was stirred at this temperature for 1 h and then at room temperature for 8 h. Water was added, the two phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phases were washed with 1 N HCl (3 × 50 mL), water, and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (30% ethyl acetate in petroleum ether as eluent) to give the ether **10** (3.3 g, 95%) as colorless crystals, mp 93−94 °C: TLC (30% ethyl acetate in petroleum ether): R_f = 0.5; $[\alpha]^{21}_D$ = −82.2 (*c* 1.0, $CHCl_3$); IR (KBr) 3382 (s), 3083 (m), 3058 (m), 1687 (s), 1032 (s) cm^{-1}; ^1H NMR δ 1.25 (s, 9 H), 2.63 (dd, J = 3.4, 10.7 Hz, 1 H), 2.89 (dd, J = 9.5, 4.6 Hz, 1 H), 3.32 (s, 3 H), 3.91 (br s, 1 H), 4.11 (dd, J = 4.2, 6.7 Hz, 1 H), 4.62 (d, J = 6.7 Hz, 1 H), 5.23 (d, J = 15.6 Hz, 1 H), 5.26

(dt, J = 17.5, 1.2 Hz, 1 H), 5.64−5.78 (m, 1 H), 7.08−7.23 (m, 5 H); ^{13}C NMR δ 28.3, 35.7, 54.9, 55.8, 79.2, 94.6, 119, 126.2, 128.3, 129.3, 135.1, 138.4, 155.4; MS (EI), *m*/*z* (%) 322 [M + 1] (0.1), 266 (0.2).

(3*R*,4*S*)-4-[*N*-(*tert*-Butoxycarbonyl)-*N*-methylamino]-3-(methoxymethoxy)-5-phenylpent-1-ene (11). To a cooled (0 °C, ice bath) solution of **10** (2.50 g, 7.79 mmol) and MeI (1.0 mL, 15.6 mmol) in DMF (30 mL) was added NaH (0.405 g, 10.12 mmol, 60% in mineral oil) in portions. After complete addition, the ice bath was removed, and the mixture was stirred at room temperature for 15 h. The reaction was quenched with saturated aqueous NH_4Cl, and much of the DMF was removed in vacuo. The mixture was extracted with ethyl acetate (3 × 30 mL), and the organic layers were washed with water, dried, filtered, and concentrated. The resulting thick liquid was purified by flash chromatography (15% ethyl acetate in petroleum ether) to give **11** (2.50 g, 96%) as a colorless oil: TLC (20% ethyl acetate in petroleum ether): R_f = 0.63; $[\alpha]^{22}_D$ = −154.4 (*c* 0.3, $CHCl_3$); IR (neat) 1694 (s) cm^{-1}; ^{1}H NMR (both rotamers, 1:1.4) δ 1.18 (s, 9 H, minor), 1.24 (s, 9 H, major), 2.46 (br s, 3 H, minor), 2.59 (br s, 3 H, major), 2.77−2.83 (complex, 1 H), 3.15 (ddd, J = 14.4, 5.2, 3.7 Hz, 1 H), 3.34 (s, 3 H, minor), 3.35 (s, 3 H, major), 4.03 (br s, 1 H), 4.18 (br s, 1 H), 4.50 (d, J = 6.7 Hz, 1 H), 4.69 (dd, J = 1.6, 5.1 Hz, 1 H), 5.16−5.25 (complex, 2 H), 5.51−5.72 (m, 1 H), 7.08−7.21 (m, 5 H); ^{13}C NMR (both rotamers) δ 28.2, 28.3, 34.3, 34.6, 55.9, 56.0, 78.6, 79.07, 79.13, 79.5, 93.8, 94.0, 119.2, 119.8, 126.0, 126.2, 128.2, 128.3, 129.0, 135.4, 136.0, 138.9, 155.6; MS (EI), *m*/*z* (%) 336 [M$^+$ + 1] (7); HRMS calcd for $C_{19}H_{29}NO_4$ 335.20965, found 335.21414.

(3*R*,4*S*)-4-[*N*-(*tert*-Butoxycarbonyl)-*N*-methylamino]-3-(methoxymethoxy)-1-hydroxy-5-phenylpentane (12). To a solution of the alkene **11** (2.00 g, 5.97 mmol) in THF (50 mL) was added 9-borabicyclo[3.3.1]nonane (35.8 mL, 0.5 M solution in hexane, 17.9 mmol) at room temperature. The reaction mixture was stirred for 20 h before it was treated successively with EtOH (11 mL), 6 N NaOH (3.7 mL), and 30% H_2O_2 (7.3 mL). The mixture was heated at 50 °C for 1 h, cooled to room temperature, and extracted several times with ethyl acetate. The combined organic layers were washed with water and brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The pure alcohol **12** (1.58 g, 75%) was obtained by flash chromatography (50% ethyl acetate in petroleum ether) as colorless oil: TLC (50% ethyl acetate in petroleum ether): R_f = 0.3; $[\alpha]^{25}_D$ = −17.8 (*c* 0.9, $CHCl_3$); IR (neat) 3445 (s), 1689 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) (both rotamers) δ 1.15 (s, 3 H, minor), 1.25 (s, 3 H, major), 1.44−1.97 (m, 2 H), 2.21 (br s, 1 H), 2.49 (s, 3 H, minor), 2.61 (br s, 3 H, major), 2.76−2.81 (complex, 1 H), 3.07 (td, J = 13.7, 3.1 Hz, 1 H), 3.38 (s, 3 H, minor), 3.41 (s, 3 H, major), 3.61−3.83 (m, 2 H), 3.88 (br s, 1 H), 4.19 (br s, 1 H), 4.67 (deformed t, J = 6.3, 4.6 Hz, 1 H), 4.73 (deformed t, J = 4.0, 6.7 Hz, 1 H), 7.07−7.22 (m, 5 H); ^{13}C NMR (both rotamers) δ 28.1, 28.3, 31.1, 34.1, 34.6, 56.2, 56.4, 58.8, 79.6, 79.8, 97.4, 97.7, 126.1, 126.3, 128.4, 128.9, 129.0, 138.8, 155.5, 155.9; MS (EI), *m*/*z* (%) 354 [M$^+$ + 1] (2.2); HRMS (EI) calcd for $C_{19}H_{31}NO_5$ 353.22022, found 353.22531.

(3*R*,4*S*)-*N*-(*tert*-Butoxycarbonyl)-4-amino-3-(*tert*-butyldimethylsilyloxy)-5-phenylpent-1-ene (13). A mixture of **9** (1.20 g, 4.33 mmol), *tert*-butyldimethylsilyl chloride (2.24 g, 9.53 mmol), and imidazole (1.29 g, 19.06 mmol) in DMF (7 mL) was stirred under an argon atmosphere for 2 h. After dilution with ether (50 mL), the mixture was washed with water (5 × 10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a pale yellow oil which was purified by flash chromatography (5% ethyl acetate in petroleum ether) to give 1.52 g (90%) of **13** as colorless crystals, mp 50−51 °C: TLC (10% ethyl acetate in petroleum ether) R_f = 0.74; $[\alpha]^{22}_D$ = −18.9 (*c* 0.6, $CHCl_3$); IR (neat) 3454 (m), 3370 (m), 3275 (m), 1705 (s), 1699 (s) cm^{-1}; ^{1}H NMR δ 0.02 (d, J = 8.2 Hz, 6 H), 0.91 (t, J = 3.1 Hz, 9 H), 1.33 (s, 9 H), 2.63 (dd, J = 14.0, 10.1 Hz, 1 H), 2.87 (dd, J = 9.7, 4.7 Hz, 1 H), 3.86 (br s, 1 H), 4.33 (br s, 1 H), 4.48 (br d, J = 8.5 Hz, 1 H), 5.18 (br d, J = 10.4 Hz, 1 H), 5.31 (dt, J = 17.4, 1.7 Hz, 1 H), 5.80−5.92 (m, 1 H), 7.13−7.28 (m, 5 H); ^{13}C NMR δ −5.0, −4.4, 18.3, 25.9, 28.4, 34.9, 56.3, 74.8, 79.1, 116.2, 126.1, 128.3, 129.2, 138.1, 138.8, 155.4; MS (EI), *m*/*z* (%) 392 [M + 1] (16); HRMS (EI) calcd for $C_{22}H_{37}NO_3Si$ 391.25427, found 391.25229.

(3*R*,4*S*)-*N*-(*tert*-Butoxycarbonyl)-4-amino-3-(*tert*-butyldimethylsilyloxy)-1-hydroxy-5-phenylpentane (14). To a solution of **13** (1.50 g, 3.84 mmol) in THF (33 mL) was added 9-borabicyclo[3.3.1]nonane (11.2 mL, 0.5 M solution in hexane, 5.60 mmol) at room temperature. The reaction mixture was stirred for 20 h before it was treated successively with EtOH (7 mL), 6 N NaOH (2.4 mL), and 30% H_2O_2 (4.7 mL). The mixture was heated at 50 °C for 1 h, cooled to room temperature, and extracted with ethyl acetate several times. The combined organic layers were washed with water and brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. Pure **14** (1.13 g, 72%) was obtained by flash chromatography (25% ethyl acetate in petroleum ether) as colorless oil: TLC (30% ethyl acetate in petroleum ether): R_f = 0.45, $[\alpha]^{23}_D$ = −24.9 (*c* 1.0, $CHCl_3$); IR (neat) 3453 (s), 1699 (s) cm^{-1}; ^{1}H NMR δ −0.01 (d, J = 2.43 Hz, 6 H), 0.85 (t, J = 3.1 Hz, 9 H), 1.25 (s, 9 H), 1.71 (dd, J = 6.4, 6.1 Hz, 2 H), 2.48−2.66 (m, 2 H), 2.80−2.89 (m, 1 H), 3.66 (br d, J = 6.7 Hz, 1 H), 3.69 (br d, J = 5.5 Hz, 1 H), 3.81 (br s, 1 H), 3.90 (br s, 1 H), 4.51 (d, J = 8.6 Hz, 1 H), 7.17−7.23 (m, 2 H), 7.08−7.14 (m, 3 H); ^{13}C NMR δ −4.5, −4.6, 18.1, 25.9, 28.3, 36.1, 55.6, 59.4, 72.1, 79.4, 126.3, 128.4, 129.2, 138.7, 155.7; MS (EI), *m*/*z* (%) 410 [M$^+$ + 1] (6); HRMS (EI) calcd for $C_{22}H_{40}NO_4Si$ 410.272663, found 410.26828.

***tert*-Butyl (2*S*,3*R*)-2-Benzyl-3-[*tert*-butyl(dimethyl)silyloxy]-5-oxo-1-pyrrolidinecarboxylate (15)**. A mixture of the alcohol **14** (0.500 g, 1.23 mmol), PDC (1.73 g, 4.60 mmol), and DMF (5.5 mL) was stirred at room temperature for 18 h. The resulting mixture was poured into water (35 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The extract was washed with 5% HCl (1 × 50 mL) and brine (1 × 50 mL), dried with $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography (25% ethyl acetate in petroleum ether) to give compound **15** (0.37 g, 75%) as a colorless oil which solidified, mp 71−72 °C: TLC (25% ethyl acetate in petroleum ether): R_f = 0.57; $[\alpha]^{21}_D$ = +10.7 (*c* 1.0, $CHCl_3$); IR (neat) 1788 (s), 1703 (s) cm^{-1}; ^{1}H NMR δ −0.31 (d, J = 4.3 Hz, 6 H), 0.66 (t, J = 3.1 Hz, 9 H), 1.52 (s, 9 H), 2.22 (d, J = 17.7 Hz, 1 H), 2.43 (dd, J = 3.1, 10.4 Hz, 1 H), 2.57 (dd, J = 12.2, 5.5 Hz, 1 H), 3.11 (dd, J = 10.1, 3.5 Hz, 1 H), 3.99 (d, J = 4.9 Hz, 1 H), 4.08 (dd, J = 6.7, 3.7 Hz, 1 H), 7.11−7.30 (m, 5 H); ^{13}C NMR δ −5.2, 17.7, 25.6, 28.2, 38.0, 41.4, 66.9, 69.2, 83.1, 127.1, 128.9, 129.3, 136.7, 150.1, 172.8; MS (EI), *m*/*z* (%) 406 [M$^+$ + 1] (3.7); HRMS (EI) calcd for $C_{22}H_{35}NO_4Si$ 405.23353, found 405.23498.

Methyl (3*R*,4*S*)-4-[(*tert*-Butoxycarbonyl)amino]-3-[*tert*-butyl(dimethyl)silyloxy]-5-pentanoate (16). To a stirred solution of **15** (0.500 g, 1.23 mmol) in methanol (15 mL) was added cesium carbonate (0.081 g, 0.25 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 2 h. Then it was quenched with citric acid, and the product was extracted with ethyl acetate, dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification of the residue by flash chromatography (15% ethyl acetate in petroleum ether) gave 0.271 g (50%) of the ester **16** as colorless oil: TLC (20% ethyl acetate in petroleum ether): R_f = 0.64; $[\alpha]^{22}_D$ = −19.7 (*c* 0.38, $CHCl_3$); IR (neat) 1741 (s), 1703 (s) cm^{-1}; ^{1}H NMR δ 0.00 (s, 3 H), 0.06 (d, J = 1.5 Hz, 3 H), 0.85−0.89 (complex, 9 H), 1.27 (s, 9 H), 2.47 (d, J = 2.8 Hz, 1 H), 2.50 (d, J = 1.5 Hz, 1 H), 2.92 (dd, J = 9.5, 4.6 Hz, 1 H), 2.53−2.56 (m, 1 H), 3.81 (s, 3 H), 4.07 (br s, 1 H), 4.24 (br s, 2 H), 4.40 (br s, 1 H), 7.13−7.28 (m, 5 H); ^{13}C NMR δ −4.7, 18.1, 25.9, 28.3, 35.9, 39.9, 51.7, 56.3, 71.4, 79.3, 126.3, 128.4, 129.2, 138.3, 155.2, 171.7; MS (EI), *m*/*z* (%) 364 [M$^+$ − O*t*Bu]; HRMS (EI) calcd for $C_{23}H_{39}NO_5Si$ − O*t*Bu 364.19441, found 364.19110.

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Supporting Information Available: NMR spectra of compounds prepared. This material is available free of charge via the Internet at http://pubs.acs.org.

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