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A stereoselective synthesis of (2*S*,4*R*)-δ-hydroxyleucine methyl ester: a component of cyclomarin A

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Abstract—(2*S*,4*R*)-δ-Hydroxyleucine methyl ester, the *N*-demethyl analogue of an amino acid contained within the macrocycle of cyclomarin A, was successfully synthesized using Davis' asymmetric Strecker reaction.

1. Introduction

Cyclomarin A is a novel cyclic peptide isolated from a estuarine actinomycete, cultured from a sediment sample collected in Mission Bay, CA[1] (Fig. 1). Cyclomarin A is cytotoxic toward cancer cells with a mean IC_{50} of 2.6 μM against a panel of human cancer cell lines. Of greater interest is cyclomarin A's potent anti-inflammatory both in vitro and in vivo. The structure of cyclomarin A was deduced using a variety of spectroscopic methods. The number of non-coded amino acids contained with cyclomarin A has attracted significant attention from synthetic chemists[2–5] culminating in the synthesis of cyclomarin C[6], a close congener of cyclomarin A. En route to a total synthesis of cyclomarin A, we herein report the synthesis of (2*S*,4*R*)-δ-hydroxyleucine based on an Evans' asymmetric alkylation and Davis' asymmetric Strecker reaction.

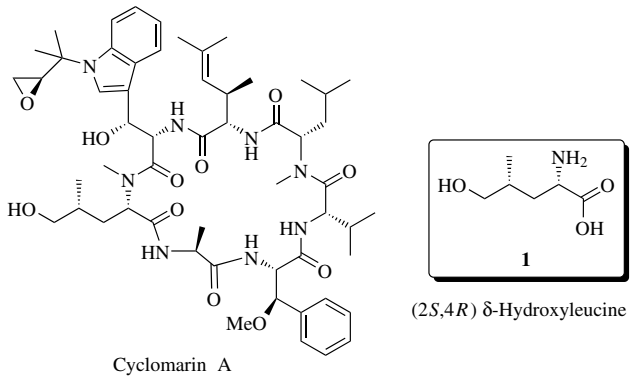
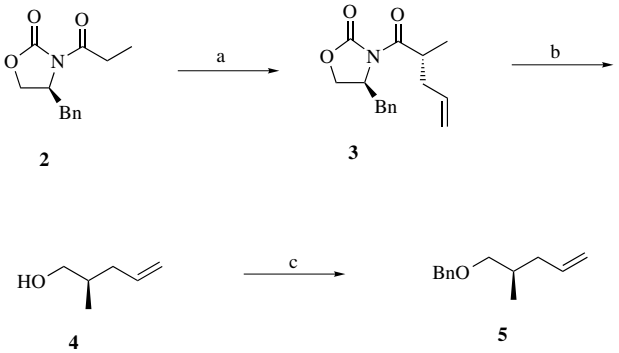


Figure 1. Cyclomarin A and (2*S*,4*R*) δ-hydroxyleucine **1**.

2. Results and discussion

Our goal was to develop a robust and general synthetic method based on an asymmetric alkylation and an asymmetric Strecker reaction. After examining a number of asymmetric alkylation conditions, we chose Evans' oxazolidinone method. This method would complement the route chosen by Wen et al. who used two Evans' alkylations to set the stereochemistry of both stereocenters.[6] The required propionyl oxazolidinone **2** was synthesized from (*S*)-phenylalanine[7,8] (Scheme 1).



Scheme 1. Reagents and conditions: (a) NaHMDS, allyl iodide, 77%; (b) $LiBH_4$, 88%; (c) NaH, BnBr, 74%.

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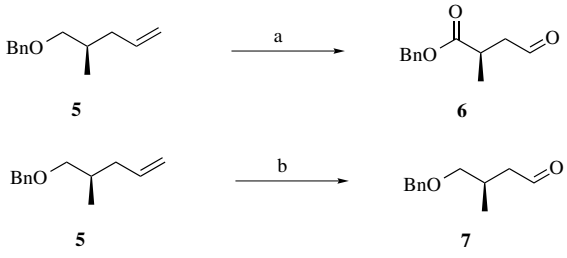
Enolization, followed by the addition of allyl iodide gave oxazolidinone **3** as the major diastereomer in greater than 96% de. Removal of the chiral auxiliary was accomplished under reductive conditions to give alcohol **4**, which was subsequently protected as its benzyl ether **5**.

With intermediate **5** in hand, we set out to interconvert the terminal alkene to the desired terminal aldehyde. Exposure of **5** to ozone gave lower than expected yields while further spectroscopic analysis showed that not only had the terminal olefin been oxidized but the benzyl ether had been oxidized to benzyl ester **6**, a well documented side reaction of benzyl ethers to ozone.[9,10] To circumvent this problem a new method was employed, a one pot dihydroxylation/periodate cleavage,[11] providing the desired aldehyde **7** in good yield (Scheme 2).

With the Strecker aldehyde precursor in hand, we reviewed a number of asymmetric Strecker conditions and chose Davis' asymmetric Strecker reaction.[12–14] This method uses a chiral *N*-sulfinimine as both a nitrogen source and chiral auxiliary. Condensation of an enantiopure *p*-toluenesulfinamide with an aldehyde in the presence of a dehydrating agent gives the desired sulfinimine [thiooxime (*S*)-oxide]. The addition of Et_2AlCN gives an amino nitrile, while aqueous acid cleaves the sulfinamide chiral auxiliary and hydrolyzes the nitrile group to afford the amino acid (Fig. 2). Having both aldehyde **7** and (*S*)-(+)-*p*-toluenesulfinamide in hand, the two starting materials were condensed with titanium ethoxide to give sulfinimine **8**. The key Strecker reaction was performed according to Davis' improved conditions[12] to afford the desired amino nitrile **9** in good yield and diastereoselectivity (Scheme 3).

All that remained to complete the synthesis of δ-OH-Leu was to remove the sulfinyl chiral auxiliary and hydrolyze the nitrile group. A variety of aqueous acidic and basic conditions were attempted, but in our hands none of the desired products could be isolated. The milder conditions developed by Davis in his synthesis of polyoxamic acid[15] gave amino nitrile **10** (Scheme 4). To our delight, exposure to methanolic hydrogen chloride overnight afforded **1** in good yield completing the synthesis of the methyl ester of (2*S*,4*R*) δ-hydroxyleucine.



Scheme 2. Reagents and conditions: (a) O_3, then DMS, 17%; (b) $K_2[OsO_2(OH)_4]$, KIO_4, 78%.

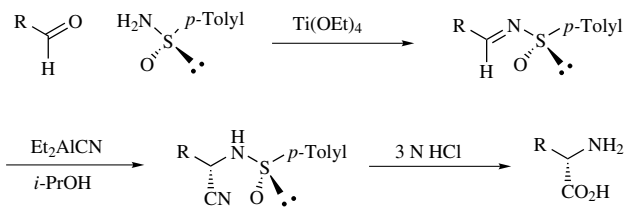
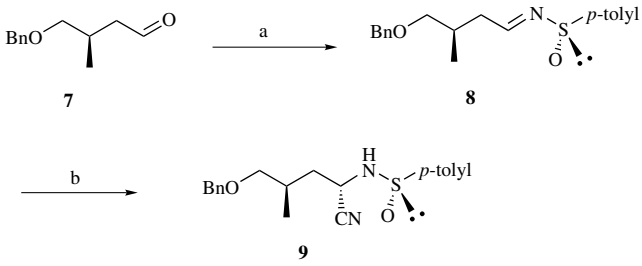
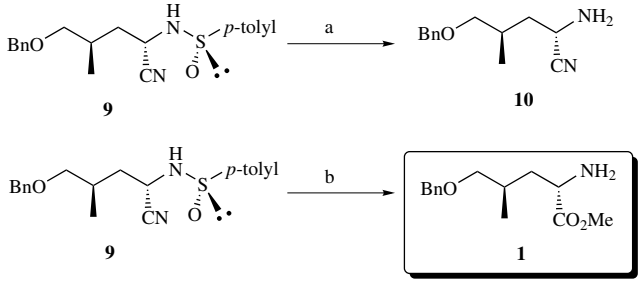


Figure 2. Davis' asymmetric Strecker reaction.



Scheme 3. Reagents and conditions: (a) (*S*)-(+)-*p*-toluenesulfinamide, $Ti(OEt)_4$, 84%; (b) Et_2AlCN, *i*PrOH, 92% yield, 91% de.



Scheme 4. Reagents and conditions: (a) Et_2O–HCl/H_2O, 74%; (b) methanol, HCl, 86%.

3. Conclusion

An efficient synthesis of (2*S*,4*R*) δ-hydroxyleucine methyl ester was accomplished in seven steps using a combination of asymmetric alkylation and Davis' asymmetric Strecker reaction. The approach is flexible and should allow for the synthesis of similar amino acids.

4. Experimental

4.1. General

Reactions requiring air-sensitive manipulations were conducted under an argon atmosphere. Methylene chloride was distilled from calcium hydride, tetrahydrofuran, and diethyl ether were distilled from sodium/benzophenone. Analytical TLC was performed on 0.25 mm E. silica gel 60 F_{254} plates. Silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography. NMR spectra were recorded on a 500 MHz spectrometer and calibrated by using residual undeuterated solvent or TMS as an internal reference. Chemical shifts (δ) were measured in parts per million, and coupling constants (J values) are in hertz (Hz).

Infrared spectra (IR) were recorded on an FT-IR spectrometer. High-resolution mass spectra (HRMS) were recorded using electrospray ionization (ESI). Optical rotations were recorded on a polarimeter at the sodium D line. Melting points were determined in an open capillary tube and are uncorrected.

4.2. (*S*)-4-Benzyl-3-((*R*)-2-methylpent-4-enoyl)oxazolidin-2-one 3

Oxazolidinone **2** (22.16 g, 0.095 mol) was dissolved in anhydrous THF (200 mL) under argon, and then cooled to −78 °C. NaHMDS (1.0 M in THF, 100 mL, 0.10 mol) was added dropwise and the reaction allowed to stir for 1 h at −78 °C. Allyl iodide (27 mL, 0.30 mol) was added dropwise and the mixture allowed to stir at −78 °C for 6 h. The reaction was checked by TLC. When the starting material was consumed, the reaction was quenched at −78 °C with satd NH_4Cl (250 mL) and allowed to warm to room temperature. The reaction mixture was treated with H_2O (500 mL) and Et_2O (750 mL). The organic layer was separated, washed with brine, dried over $MgSO_4$, and reduced in vacuo. The residue was purified by flash silica gel chromatography, eluting with 25% Et_2O/hexanes to give a pale oil (20.70 g, 80% yield): $[\alpha]_D^{20} = +98.0$ (*c* 0.9, $CHCl_3$); TLC (20% EtOAc/Hex), $R_f = 0.40$ ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34–7.21 (m, 5H), 5.87–5.79 (m, 1H), 5.12–5.05 (m, 2H), 4.70–4.66 (m, 1H), 4.21–4.14 (m, 2H), 3.87 (sext, $J = 6.8$, 1H), 3.29 (dd, $J = 3.3$, 13.4, 1H), 2.69 (dd, $J = 9.9$, 13.3, 1H), 2.53 (pent, $J = 5.6$, 1H), 2.24 (pent, $J = 7.0$, 1H), 1.19 (d, $J = 6.9$, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 176.5, 153.1, 135.4, 135.3, 129.4, 128.9, 127.3, 117.2, 66.0, 55.4, 38.1, 38.0, 37.2, 16.4; IR (thin film) 2977 w, 1779 s, 1698 s, 1454 m, 1386 s, 1934 m, 1242 m, 1210 s, 1098 w, 703 m; HRMS (EI): *m*/*z* calcd for $C_{16}H_{19}NO_3$-NA 296.1262, found 296.1253.

4.3. (*R*)-2-Methylpent-4-en-1-ol 4

Oxazolidinone **3** (19.20 g, 69.6 mmol) was dissolved in anhydrous Et_2O (400 mL) under argon and cooled to 0 °C. Absolute ethanol (4.9 mL, 84 mmol) was added followed by the dropwise addition of $LiBH_4$ (2.0 M in THF, 41.7 mL, 84 mmol). The reaction was allowed to warm to room temperature overnight under argon. The reaction was quenched slowly with 1.0 M NaOH (400 mL) and allowed to stir until both layers were clear. The aqueous layer was separated and extracted twice with Et_2O, all the organic layers were combined, washed with brine, dried over $MgSO_4$, and reduced in vacuo. The residue was purified by flash silica gel chromatography, eluting with 25% Et_2O/pentane to give a pale oil (6.3 g, 88% yield): $[\alpha]_D^{20} = -1.8$ (*c* 0.4, $CHCl_3$); TLC (20% EtOAc/Hex), $R_f = 0.33$; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.84–5.78 (m, 1H), 5.07–5.00 (m, 2H), 3.54–3.45 (m, 2H), 2.19–2.15 (m, 1H), 1.97–1.94 (m, 1H), 1.76–1.72 (m, 1H), 1.34 (br s, 1H), 0.93 (d, $J = 6.7$, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 137.0, 116.1, 67.9, 37.9, 35.6, 16.4; IR (thin film) 3337 br, 3076 m, 2924 br s, 1640 s, 1458 s, 1381 m, 1104 m, 1044 s, 993 s, 911 s; HRMS (EI): *m*/*z* calcd for $C_6H_{13}O$ 101.0966, found 101.0960.

4.4. (*R*)-[(2-Methylpent-4-enyloxy)methyl]benzene 5

Alcohol **4** (6.00 g, 59.8 mmol) was slowly added to a suspension of NaH (2.15 g, 89.7 mmol) in dry DMF (100 mL) under argon. The reaction was cooled to 0 °C and benzyl bromide (8.5 mL, 72 mmol) added dropwise. The reaction was allowed to warm to room temperature and stirred overnight. The reaction was cautiously quenched with water (30 mL), and diluted with additional water (100 mL). The aqueous layer was extracted three times with Et_2O and the organic layers combined and washed with water and brine, dried over $MgSO_4$, and reduced in vacuo. The residue was purified by flash silica gel chromatography, eluting with 10% CH_2Cl_2/hexanes to give a pale oil (8.42 g, 74% yield): $[\alpha]_D^{20} = -1.6$ (*c* 1.2, $CHCl_3$); TLC (5% EtOAc/Hex), $R_f = 0.56$; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34–7.26 (m, 5H), 5.81–5.75 (m, 1H), 5.03–4.98 (m, 2H), 4.50 (s, 1H), 3.35–3.26 (m, 2H), 2.25–2.20 (m, 1H), 1.95–1.85 (m, 2H), 0.92 (d, $J = 6.5$, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 138.8, 137.0, 128.3, 127.5, 127.4, 115.9, 75.3, 73.0, 38.0, 33.4, 16.8; IR (thin film) 3064 w, 2975 m, 2908 m, 2855 m, 1640 w, 1496 w, 1454 m, 1363 m, 1099 s, 944 m, 912 s, 735 m, 697 s; HRMS (EI): *m*/*z* calcd for $C_{13}H_{18}O$ 190.1357, found 190.1350.

4.5. (*R*)-Benzyl 2-methyl-4-oxobutanoate 6

Olefin **5** (1.04 g, 5.49 mmol) was dissolved in CH_2Cl_2 (22 mL) and cooled to −78 °C, ozone was bubbled into the reaction until a pale blue color persisted, followed by argon for 10 min. The reaction was quenched with dimethyl sulfide (4.0 mL, 55 mmol) and allowed to warm to room temperature and stirred overnight. The reaction mixture was reduced in vacuo. The residue was purified by flash silica gel chromatography, eluting with 10% EtOAc/hexanes to give a pale oil (198 mg, 17% yield): $[\alpha]_D^{20} = +0.7$ (*c* 0.9, $CHCl_3$); TLC (10% EtOAc/Hex), $R_f = 0.34$; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.83 (t, $J = 1.5$, 1H), 8.02 (d, $J = 7$, 2H), 7.57 (d, $J = 7.4$, 1H), 7.45 (t, $J = 8.0$, 2H), 4.29 (q, $J = 5.4$, 1H), 4.17 (q, $J = 6.7$, 1H), 2.65–2.61 (m, 2H), 2.43–2.41 (m, 1H), 1.11 (d, $J = 6.8$, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 201.2, 166.4, 133.1, 130.0, 129.6, 128.4, 68.8, 47.9, 28.0, 17.1; IR (thin film) 2965 m, 1720 br s, 1601 w, 1452 m, 1391 w, 1315 m, 1275 br s, 1177 m, 1112 s, 1070 m, 1026 m; HRMS (EI): *m*/*z* calcd for $C_{12}H_{14}O_3Na$ 229.0841, found 229.0845.

4.6. (*R*)-4-(Benzyloxy)-3-methylbutanal 7

Under mechanical stirring, olefin **5** (4.00 g, 21.0 mmol) was dissolved in acetone (125 mL). The solution was diluted with water (40 mL), followed by addition of $K_2[OsO_2(OH)_4]$ (70 mg, 0.21 mmol) and $NaIO_4$ (9.89 g, 46.3 mmol). The reaction was complete after 6 h. The mixture was collected by filtration and the remaining salts washed twice with Et_2O. The filtrate was diluted with brine, the organic layer was separated, and the remaining aqueous layer washed with Et_2O. The organic layers were combined, washed twice with satd $Na_2S_2O_3$, brine, dried over $MgSO_4$, and reduced in vacuo. The residue was purified by flash silica gel chromatography,

eluting with 10% EtOAc/hexanes to give a pale oil (3.11 g, 78% yield): $[\alpha]_D^{20} = +8.9$ (*c* 0.7, $CHCl_3$); TLC (5% EtOAc/Hex), $R_f = 0.20$; ^1H NMR ($CDCl_3$, 500 MHz) δ 9.76 (t, $J = 2.2$, 1H), 7.36–7.26 (m, 5H), 4.49 (s, 2H), 3.42 (dd, $J = 5.2$, 9.1, 2H), 3.25 (dd, $J = 7.6$, 9.1, 1H), 2.55 (ddd, $J = 2.2$, 6.3, 16.2, 1H), 2.45–2.40 (m, 1H), 2.28 (ddd, $J = 2.1$, 6.9, 16.2, 1H), 0.99 (d, $J = 6.8$, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 202.3, 138.4, 128.2, 127.6, 127.5, 74.9, 73.0, 48.6, 29.1, 17.1; IR (thin film) 2930 w, 2856 m, 2723 w, 1723 s, 1454 m, 1363 m, 1099 m, 1028 w, 738 m, 698 m; HRMS (EI): *m*/*z* calcd for $C_{12}H_{16}O_2$ 192.1150, found 192.1156.

4.7. (S_s,3*R*)-(+)-4-(Benzyloxy)-3-methylbutylidene-*p*-toluenesulfinamide 8

Aldehyde **7** (2.34 g, 12.2 mmol) was added to a solution of anhydrous CH_2Cl_2 (175 mL) and (*S*)-(+)-*p*-toluenesulfinamide (1.89 g, 12.2 mmol). After the slow addition of $Ti(OEt)_4$ (12.8 mL, 60.9 mmol), the reaction was heated at reflux for 2 h, then cooled to 0 °C, followed by the slow addition of water (250 mL). The turbid mixture was filtered through Celite, the Celite pad then washed twice with CH_2Cl_2, and the organic layer separated, dried over $MgSO_4$ and reduced in vacuo. The residue was purified by flash silica gel chromatography, eluting with 10% EtOAc/hexanes to give a pale oil (3.33 g, 84% yield): $[\alpha]_D^{20} = +37.0$ (*c* 4.0, $CHCl_3$); TLC (20% EtOAc/Hex), $R_f = 0.30$; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.25 (t, $J = 5.1$, 1H), 7.54 (d, $J = 8.1$, 2H), 7.34–7.25 (m, 7H), 4.44 (s, 2H), 3.36–3.33 (m, 1H), 3.28–3.25 (m, 1H), 2.67–2.26 (m, 1H), 2.39–2.23 (m, 4H), 2.25–2.23 (m, 1H), 0.96–0.93 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.4, 141.8, 141.5, 138.3, 129.6, 128.3, 127.5, 127.4 124.4, 74,7, 73.0, 40.0, 31.4, 21.3, 16.9; IR (thin film) 3029 w, 2957 m, 2871 m, 1619 s, 1494 m, 1454 m, 1363 m, 1097 s, 1073 s, 810 m, 738 m, 699 m; HRMS (EI): *m*/*z* calcd for $C_{19}H_{23}O_2N_1SNa$ 352.1347, found 352.1354.

4.8. (S_s,2*S*,4*R*)-(+)-*N*-(*p*-Toluenesulfinyl)-2-amino-5-(benzyloxy)-4-methylpentanenitrile 9

Sulfinimine **8** (100 mg, 0.30 mmol) was dissolved in anhydrous THF (15 mL) in a flame-dried, round-bottomed flask, under argon and the solution cooled to −78 °C. In a separate flame-dried round-bottomed flask, THF (5 mL) was added, under argon, and cooled to 0 °C, Et_2AlCN (1.0 M toluene, 0.45 mL, 0.45 mmol) was added followed by *i*PrOH (0.02 mL, 0.30 mmol). The reaction was allowed to stir at 0 °C for 10 min and then cannulated into the round-bottomed flask at −78 °C and allowed to stir for 10 min. It was warmed to room temperature and stirred overnight. The reaction was cooled to −78 °C, quenched with satd NH_4Cl, and warmed to room temperature. The reaction was filtered through celite and the celite pad washed twice with EtOAc. All the organic filtrates were combined, washed with brine, dried over $MgSO_4$, and reduced in vacuo. The crude residue was examined ^1H NMR ($CDCl_3$, 500 MHz) to determine a 91% de by integration of the methyl protons. The residue was purified by flash silica gel chromatography, eluting with 20% EtOAc/hexanes to give a pale oil (0.98 mg, 92% yield): $[\alpha]_D^{20} = +10.7$ (*c* 0.7, $CHCl_3$); TLC (20% EtOAc/Hex), $R_f = 0.11$; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.55 (d, $J = 8.2$, 2H), 7.37–7.28 (m, 7H), 5.65 (d, $J = 7.2$, 1H), 4.52 (q, $J = 8.2$, 2H), 4.25 (q, $J = 7.1$, 1H), 3.47 (dd, $J = 4.3$, 9.4, 1H), 2.00–1.94 (m, 1H), 1.84–1.79 (m, 1H), 0.96 (d, $J = 6.9$, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 142.0, 139.6, 137.5, 129.8, 128.5, 127.9, 127.8, 126.0, 118.7, 74.8, 73.3, 40.1, 30.6, 21.3, 17.5; IR (thin film) 3192 br m, 2924 m, 1596 w, 1564 m, 1454 m, 1364 m, 1090 s, 1067 s, 813 m, 739 m, 699 m, cm^{-1}; HRMS (EI): *m*/*z* calcd for $C_{20}H_{24}O_2N_2SNa$ 379.1456, found 379.1452.

4.9. (2*S*,4*R*)-2-Amino-5-(benzyloxy)-4-methylpentanenitrile 10

Nitrile **9** (178 mg, 0.80 mmol) was dissolved in 2.0 M HCl in Et_2O (5.0 mL) and stirred under argon for 5 min, while a white precipitate formed. After the addition of a few drops of water, the reaction was allowed to stir under argon overnight. The solvent was removed under reduced pressure and quenched with satd K_2CO_3. The aqueous layer was then extracted three times with EtOAc. The organic layers were combined, washed with brine, dried over $MgSO_4$, and reduced in vacuo. The residue was purified by flash silica gel chromatography, eluting with 10% EtOAc/hexanes to give a pale oil (113 mg, 74% yield): $[\alpha]_D^{20} = +8.0$ (*c* 0.6, $CHCl_3$); TLC (50% EtOAc/Hex), $R_f = 0.18$; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.37–7.26 (m, 5H), 4.50 (s, 3H), 3.81 (t, $J = 7.4$, 1H), 3.41–3.38 (m, 1H), 3.32–3.29 (m, 1H), 2.16–2.08 (m, 1H), 1.94–1.84 (m, 1H), 1.67–1.59 (m, 3H), 0.98 (d, $J = 6.7$, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 138.7, 128.8, 128.1, 128.0, 122.7, 75.6, 73.5, 42.2, 40.4, 30.8, 17.5; IR (thin film) 3380 w, 2956 w, 2859 m, 2358 s, 1455 m, 1363 m, 1095 s, cm^{-1}; HRMS (CI): *m*/*z* calcd for $C_{12}H_{18}ON$ 192.1388, found 192.1386.

4.10. (2*S*,4*R*)-Methyl 2-amino-5-(benzyloxy)-4-methylpentanoate 1

Nitrile **9** (126 mg, 0.58 mmol) was dissolved in MeOH (5.0 mL) under argon and then cooled to 0 °C. HCl gas was bubbled through the solution for 1 min. The round-bottomed flask was then sealed and allowed to stir overnight at room temperature. The reaction was then slowly poured into satd $NaHCO_3$ (50 mL) and more $NaHCO_3$ added to keep the solution basic. The aqueous layer was extracted three times with EtOAc, the organic layers were combined, washed with brine, dried over $MgSO_4$, and reduced in vacuo. The residue was purified by flash silica gel chromatography, eluting with 10% CH_3CN/CH_2Cl_2 to give a yellow oil (79 mg, 86% yield): $[\alpha]_D^{20} = -36.0$ (*c* 1.1, $CHCl_3$); TLC (100% EtOAc), $R_f = 0.15$; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.36–7.26 (m, 5H), 4.52–4.73 (m, 2H), 3.71 (s, 3H), 3.58 (t, $J = 6.8$, 1H), 3.34 (d, $J = 6.0$, 2H), 2.20–1.94 (m, 1H), 1.88–1.83 (m, 1H), 1.71 (br s, 2H), 1.46–1.40 (m, 1H), 0.99 (d, $J = 6.8$, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 176.6, 138.5, 128.3, 127.5, 127.5, 75.4, 73.0, 52.7, 51.9, 39.6, 30.4, 17.8; IR (thin film) 2928 m, 2854 m, 1736 s, 1454 m, 1363 w, 1200 m, 1172 m,

1095 m, 737 m, 698 m; HRMS (EI): m/z calcd for $C_{14}H_{22}O_3N$ 252.1600, found 252.1611.

Acknowledgments

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