SUPPORTING INFORMATION

Synthetic Applications of Lithiated *N*-Boc Allylic Amines as Asymmetric Homenolate Equivalents

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I. General Procedures and Instrumentation.

All glassware used in lithiation reactions was either flame dried or oven dried, and cooled under a nitrogen atmosphere. Solvents and reagents were used as received, unless noted. Toluene and dichloromethane were freshly distilled from CaH_2 under N_2 prior to use. Tetrahydrofuran (THF) was distilled from Na/benzophenone under N_2 . DMF was distilled over Linde type 4A molecular sieves. *n*-BuLi in hexane was used at a concentration determined by titration with *N*-pivaloyl-*o*-toluidine.¹ (–)-Sparteine was distilled under N_2 from CaH_2 prior to first use.

Analytical thin layer chromatography was carried out on Merck silica gel plates with QF-254 indicator. The products were revealed with UV light or exposure to ceric ammonium molybdate (CAM). Flash chromatography was performed with 230-400 mesh silica gel (Merck) and petroleum ether and ethyl acetate as obtained directly from the bottles. Preparative HPLC was performed with a Dynamax 60A column coupled to a Rainin HPX pump system attached to a Rheodyne 7125 Syringe Loading Sample Injector and a Knauer UV detector (254 nm). Analytical chiral stationary phase HPLC was performed on a Rainin HPLX pump system coupled to a Rainin Dynamax Model UV-C Absorbance Detector. Either a 5 μm Rexchrom Reversible, covalent Pirkle (*S,S*)-Whelk-O column (Regis Chemical Co., Morton Grove, IL 60053-9975, 25 cm x 4.6 mm i.d.) or a ChiralPak AD column (Daicel Chemical Industries, Ltd., 25 cm x 4.6 mm i.d.) with isopropanol/hexane mobile phase was used to affect enantiomeric separations.

^1H and ^{13}C NMR spectra were obtained at the University of Illinois VOICE NMR Laboratory on either a Varian Unity 400 (400 MHz ^1H ; 100 MHz ^{13}C) or a Varian Unity 500 (500 MHz ^1H ; 126 MHz ^{13}C). Chemical shifts (δ) are reported in ppm relative to the solvent (acetone-*d*₆: 2.05 ppm, ^1H ; 29.22, 205.7 ppm, ^{13}C ; or chloroform-*d*: 7.26 ppm, ^1H ; 77.23 ppm, ^{13}C). Peak multiplicities are indicated by: s (singlet), d (doublet), t (triplet), q (quartet), qn (quintet), sept (septet) and br (broad). Coupling constants (*J*) are reported in hertz (Hz). X-ray crystallographic data was acquired at the University of Illinois George L. Clark X-Ray Facility. Elemental analyses were carried out by the University of Illinois Microanalytical Service Laboratory. Mass spectrometric data was acquired at the University of Illinois Mass Spectrometry Laboratory by electron ionization (EI) or fast atom bombardment (FAB) technique. The purity of compounds was determined to be > 95% by ^{13}C NMR when HRMS was used to determine elemental composition. Melting points were acquired on a Thomas-Hoover melting point apparatus and are uncorrected. Diastereomeric purity was determined by ^1H NMR.

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¹ Suffert, J. *J. Org. Chem.* **1989**, *54*, 510.

“Standard workup” refers to dilution with ether, separation of phases, extraction of the aqueous layer with ether (3x), combination of the organic phases, drying with MgSO₄ and concentration by rotary evaporation.

II. Experimental Procedures

Representative Lithiation/Substitution of *N*-(*t*-Butoxycarbonyl)-*N*-(4-methoxyphenyl)-(*E*)-2-buten-1-amine (**11**): Preparation of (*S*)-*N*-(*t*-Butoxycarbonyl)-*N*-(4-methoxyphenyl)-3-methyl-(*Z*)-1,5-hexadien-1-amine (**13**) and (*R*)-*N*-(*t*-Butoxycarbonyl)-*N*-(4-methoxyphenyl)-3-methyl-(*E*)-1,5-hexadien-1-amine (**14**)

To a stirring solution of **11** (428 mg, 1.55 mmol) and (–)-sparteine (0.50 mL, 2.16 mmol) under N₂ in toluene (25 mL, 0.062 M) was added *n*-BuLi (1.23 mL, 1.85 mmol). The reaction mixture immediately turned bright yellow. After stirring for 45 minutes, allyl bromide (0.27 mL, 3.09 mmol) was added dropwise. The mixture was stirred at –78 °C for 2 hr, and then quenched with MeOH (1 mL). Standard workup afforded the crude product as a yellow oil, which was purified by column chromatography (90:10 petroleum ether:EtOAc) to give the product as a mixture of isomers. The *E* enecarbamate was isolated as a colorless oil in 26% yield (130 mg). The *Z* enecarbamate **13** was isolated as a colorless oil in 51% yield (249 mg). A trace amount of the α -isomer **15** was observed by crude ¹H nmr and was inseparable from the *Z* enecarbamate by chromatography. The enantiomeric ratio of the *Z* enecarbamate **13** was determined directly to be 94:6 by CSP-HPLC ((*S*, *S*)-Whelk-O column, 2.5% *i*-PrOH/hexane, 1.0 mL/min). The major enantiomer (*R*) had a retention time of 10.10 minutes while the retention time of the minor enantiomer (*S*) was 11.32 minutes. ¹H NMR (acetone-*d*₆, 400 MHz) δ 0.66 (d, 3H, *J* = 6.6 Hz, CH₃), 1.41 (s, 9H, C(CH₃)₃), 1.77 (m, 2H, CH₂), 1.92 (m, 1H, CH₃CH), 3.78 (s, 3H, OCH₃), 4.61 (t, 1H, *J* = 9.8 Hz, CH=CHN), 4.82 (m, 2H, CH=CH₂), 5.51 (m, 1H, CH=CH₂), 6.47 (d, 1H, *J* = 9.0 Hz, CH=CHN), 6.89–6.91 (m, 2H, ArH), 7.17–7.19 (m, 2H, ArH). ¹³C NMR (acetone-*d*₆, 100 MHz) δ 19.3, 27.7, 30.3, 41.1, 55.1, 80.3, 113.9, 115.4, 126.9, 128.4, 130.7, 135.5, 137.0, 153.3, 158.0. HRMS-FAB (*M*+1) Calcd for C₁₉H₂₈NO₃: 318.2069 Found, 318.2068.

The *Z* enecarbamate **13** was isomerized to the *E* isomer **19** according to the following protocol. To a solution of **13** (83 mg, 0.262 mmol) in CH₂Cl₂ (3 mL, 0.087 M) under N₂ at rt was added trifluoroacetic anhydride (37 μ L, 0.262 mmol). The mixture was allowed to stir for 10 min and

trifluoroacetic acid was then added (2 μ L, 0.026 mmol). The solution stirred for 1 hr, was quenched with anhydrous MeOH (1 mL) and poured into NaHCO₃ (10 mL). The organic layer was separated and the aqueous layer was washed with CHCl₂ (3 x 10 mL). The organic layers were combined, washed with 1M KOH (1 x 25 mL) and brine (1 x 25 mL), dried over MgSO₄ and concentrated to give a clear colorless oil **19** (65 mg, 70%). The resulting E enecarbamate **19** had optical activity of $[\alpha]^{20}_{\text{D}} = +20.2$ ($c = 5.06$ in CHCl₃) and was spectroscopically (¹H and ¹³C NMR) and chromatographically (TLC and preparative HPLC) identical to **14**.

The enantiomers of the original E enecarbamate **14** could not be separated by analytical HPLC. The enantiomeric ratio was determined by comparison of optical rotations with the isomerized E enecarbamate **19**. The optical activity of **14** is $[\alpha]^{20}_{\text{D}} = -19.6$ ($c = 3.40$ in CHCl₃), which corresponds to an enantiomeric ratio of 92:8, favoring the opposite major enantiomer when compared with **19**. The E enecarbamates were observed spectroscopically. ¹H NMR (acetone-*d*₆, 400 MHz) δ 0.91 (d, 3H, $J = 6.8$ Hz, CH₃), 1.37 (s, 9H, C(CH₃)₃), 1.95 (tt, 2H, $J = 7.1, 1.2$ Hz, CH₂), 2.20 (sept, 1H, $J = 6.8$ Hz, CH₃CH), 3.81 (s, 3H, OCH₃), 4.26 (dd, 1H, $J = 14.2, 7.8$ Hz, CH=CHN), 4.93 (m, 2H, CH=CH₂), 5.70 (m, 1H, CH=CH₂), 6.94-7.10 (m, 5H, CH=CHN; ArH). ¹³C NMR (acetone-*d*₆, 100 MHz) δ 20.4, 27.7, 34.8, 42.2, 55.0, 80.3, 114.4, 115.5, 116.1, 129.0, 129.9, 132.2, 137.3, 152.6, 158.9. HRMS-FAB (M+1) Calcd for C₁₉H₂₈NO₃: 318.2069 Found, 318.2068.

(R)-3-Benzyl-N-(*t*-butoxycarbonyl)-N-(4-methoxyphenyl)-(Z)-1-buten-1-amine (16), (S)-3-Benzyl-N-(*t*-butoxycarbonyl)-N-(4-methoxyphenyl)-(E)-1-buten-1-amine (17), and N-(*t*-Butoxycarbonyl)-N-(4-methoxyphenyl)-1-phenyl-(E)-3-penten-2-amine (18). Compounds **16-18** were obtained using **11** as the substrate and benzyl bromide as electrophile following a procedure similar to that reported for the preparation of **13** and **14**. The crude product was purified by column chromatography (90:10 petroleum ether:EtOAc) to afford the product as a mixture of isomers. The E enecarbamate **16** was isolated as a colorless oil in 14% yield. The Z enecarbamate **17** and the α -isomer **18** were chromatographically inseparable and isolated as a colorless oil in 39% yield in a ratio of ~82:18 Z enecarbamate: α -isomer. The enantiomers of the α -isomer were not baseline separable by chiral analytical chromatography, but the enantiomeric ratio was determined to be > 80:20. The enantiomeric ratio of the Z enecarbamate **16** was determined directly to be 94:6 by CSP-HPLC ((*S*, *S*)-Whelk-O column, 1.5% *i*-PrOH/hexane, 1.0 mL/min). The major enantiomer (*R*) had a retention time of 15.71

minutes while the retention time of the minor enantiomer (*S*) was 17.95 minutes. ^1H NMR (acetone- d_6 , 400 MHz) δ 0.63 (d, 3H, J = 6.3 Hz, CH_3), 1.38 (s, 9H, $\text{C}(\text{CH}_3)_3$), 2.12 (X of ABX, m, 1H, CH_3CH), 2.30 (ABX, 2H, ν_a = 2.39 ppm; ν_b = 2.22 ppm; J_{AB} = 12.9 Hz; J_{AX} = 6.3 Hz; J_{BX} = 7.9 Hz; PhCH_2), 3.81 (s, 3H, OCH_3), 4.64 (t, 1H, J = 9.8 Hz, $\text{CH}=\text{CHN}$), 6.44 (d, 1H, J = 9.0 Hz, $\text{CH}=\text{CHN}$), 6.89-7.21 (m, 9H, ArH). HRMS-FAB ($M+1$) Calcd for $\text{C}_{23}\text{H}_{30}\text{NO}_3$: 368.2226 Found, 368.2225.

The *Z* enecarbamate **16** was isomerized to the *E* isomer **isom-16** according to the protocol described above for **13**. The resulting *E* enecarbamate **isom-16** had optical activity of $[\alpha]_{\text{D}}^{20}$ = +63.9 (c = 0.75 in CHCl_3) and was spectroscopically (^1H and ^{13}C NMR) and chromatographically (TLC and preparative HPLC) identical to **17**.

The enantiomers of the original *E* enecarbamate **17** could not be separated by analytical HPLC. The enantiomeric ratio was determined by comparison of optical rotations with the isomerized *E* enecarbamate **isom-16**. The optical activity of **17** is $[\alpha]_{\text{D}}^{20}$ = -70.7 (c = 0.44 in CHCl_3), which corresponds to an enantiomeric ratio of 98:2, favoring the opposite major enantiomer when compared with **isom-16**. The *E* enecarbamate **17** was observed spectroscopically. ^1H NMR (acetone- d_6 , 400 MHz) δ 0.91 (d, 3H, J = 6.3 Hz, CH_3), 1.34 (s, 9H, $\text{C}(\text{CH}_3)_3$), 2.41 (sept, 1H, J = 6.8 Hz, CH_3CH), 2.49 (m, 2H, CH_2) 3.82 (s, 3H, OCH_3), 4.26 (dd, 1H, J = 14.4, 7.8 Hz, $\text{CH}=\text{CHN}$), 6.94-7.26 (m, 10H, $\text{CH}=\text{CHN}$; ArH). ^{13}C NMR (acetone- d_6 , 125 MHz) δ 20.3, 27.6, 27.6, 36.9, 44.3, 54.9, 80.3, 114.4, 116.2, 125.9, 128.2, 129.0, 129.5, 129.9, 132.2, 140.9, 158.9. HRMS-FAB ($M+1$) Calcd for $\text{C}_{23}\text{H}_{30}\text{NO}_3$: 368.2226 Found, 368.2227.

Representative Lithiation/Substitution of *N*-(*t*-Butoxycarbonyl)-3-cyclohexyl-*N*-(4-methoxyphenyl)-(*E*)-2-propene-1-amine (12**): Preparation of (*R*)-*N*-(*t*-Butoxycarbonyl)-3-cyclohexyl-*N*-(4-methoxyphenyl)-(*Z*)-1,5-hexadien-1-amine (**23**), (*S*)-*N*-(*t*-Butoxycarbonyl)-3-cyclohexyl-*N*-(4-methoxyphenyl)-(*E*)-1,5-hexadien-1-amine (**24**), and *N*-(*t*-Butoxycarbonyl)-1-cyclohexyl-*N*-(4-methoxyphenyl)-(*E*)-1,5-hexadien-3-amine (**25**)**

To a stirring solution of **12** (400 mg, 1.16 mmol) and (–)-sparteine (0.37 mL, 1.62 mmol) under N_2 in toluene (20 mL, 0.058 M) was added *n*-BuLi (0.92 mL, 1.39 mmol). The reaction mixture immediately turned bright yellow. After stirring for 45 minutes, allyl bromide (0.20 mL, 2.31 mmol) was added dropwise. The mixture was stirred at -78°C for 2 hr, and then quenched with MeOH (1 mL). Standard workup afforded the crude product as a yellow oil, which was purified by column

chromatography (90:10 petroleum ether:EtOAc) to give the product as a mixture of isomers. The E enecarbamate **24** was isolated as a colorless oil in 31% yield (137 mg). The Z enecarbamate **23** and the α -isomer **25** were chromatographically inseparable and isolated as a colorless oil in 42% yield (186 mg) in a ratio of ~1:1. The enantiomeric ratio of the Z enecarbamate **23** was determined directly to be 57:43 by CSP-HPLC ((S, S)-Whelk-O column, 2.5% *i*-PrOH/hexane, 1.0 mL/min). The major enantiomer (*R*) had a retention time of 15.39 minutes while the retention time of the minor enantiomer (*S*) was 12.88 minutes. The Z enecarbamate **23** was isomerized to the E isomer **isom-23** according to the protocol described above for **13**. The resulting E enecarbamate **isom-23** had optical activity of $[\alpha]_D^{20} = -4.6$ ($c = 0.44$ in CHCl_3) and was spectroscopically (^1H and ^{13}C NMR) and chromatographically (TLC and preparative HPLC) identical to **24**.

The enantiomeric ratio of the α -isomer **25** was not determined. The enantiomers of the original E enecarbamate **24** could not be separated by analytical HPLC. The enantiomeric ratio was determined by comparison of optical rotations with the isomerized E enecarbamate **isom-23**. The optical activity of **24** is $[\alpha]_D^{20} = +11.3$ ($c = 3.22$ in CHCl_3), which corresponds to an enantiomeric ratio of 67:33, favoring the opposite major enantiomer when compared with **isom-23**. The E enecarbamate **24** was observed spectroscopically. ^1H NMR (acetone- d_6 , 500 MHz) δ 0.69-1.28 (m, 5H, Cy), 1.36 (s, 9H, $\text{C}(\text{CH}_3)_3$), 1.46-2.18 (m, 9H, Cy; CyCH ; PhCH_2), 3.80 (s, 3H, OCH_3), 4.13 (dd, 1H, $J = 14.2, 9.5$ Hz, $\text{CH}=\text{CHN}$), 4.91 (m, 2H, $\text{CH}=\text{CH}_2$), 5.69 (m, 1H, $\text{CH}=\text{CH}_2$), 6.95-7.09 (m, 5H, $\text{CH}=\text{CHN}$; ArH). ^{13}C NMR (acetone- d_6 , 100 MHz) δ 26.6, 26.6, 26.7, 27.7, 29.4, 31.5, 37.6, 41.9, 46.6, 55.0, 80.3, 112.9, 114.4, 115.1, 129.8, 130.3, 132.3, 137.9, 152.5, 158.8. HRMS-FAB ($M+1$) Calcd for $\text{C}_{24}\text{H}_{36}\text{NO}_3$: 386.2965 Found, 386.2694.

26 **27** **28**

(*R*)-*N*-(*t*-Butoxycarbonyl)-3-cyclohexyl-*N*-(4-methoxyphenyl)-4-phenyl-(*Z*)-1-buten-1-amine (**26**), (*S*)-*N*-(*t*-Butoxycarbonyl)-3-cyclohexyl-*N*-(4-methoxyphenyl)-4-phenyl-(*E*)-1-buten-1-amine (**27**), and *N*-(*t*-Butoxycarbonyl)-4-cyclohexyl-*N*-(4-methoxyphenyl)-1-phenyl-(*E*)-3-buten-2-amine (**28**). Compounds **26-28** were obtained using **12** as the substrate and benzyl bromide as electrophile following a procedure similar to that reported for the preparation of **23-25**. The crude product was purified by column chromatography (90:10 petroleum ether:EtOAc) to afford the product as a mixture of isomers. The E enecarbamate was isolated as a colorless oil in 11% yield. The Z enecarbamate **26** and the α -isomer **28** were chromatographically inseparable and isolated as a colorless oil in 49% yield in a

ratio of ~80:20 α -isomer:Z enecarbamate. The enantiomeric ratio of the Z enecarbamate **26** was determined directly to be 55:45 by CSP-HPLC (ChiralPak AD column, 0.5% *i*-PrOH/hexane, 1.0 mL/min). The major enantiomer (*R*) had a retention time of 12.41 minutes while the retention time of the minor enantiomer (*S*) was 8.27 minutes. ^1H NMR (acetone- d_6 , 500 MHz) δ 0.94-1.23 (m, 7H, Cy), 1.38 (s, 9H, C(CH $_3$) $_3$), 1.43-1.95 (m, 6H, Cy; CyCH), 2.35 (ABX, 2H, ν_a = 2.45 ppm; ν_b = 2.24 ppm; J_{AB} = 16.2 Hz; J_{AX} = 6.6 Hz; J_{BX} = 7.2 Hz; PhCH $_2$), 3.81 (s, 3H, OCH $_3$), 4.75 (t, 1H, J = 10.3 Hz, CH=CHN), 6.57 (d, 1H, J = 9.0 Hz, CH=CHN), 6.77-7.28 (m, 9H, ArH). ^{13}C NMR (acetone- d_6 , 125 MHz) δ 26.6, 27.6, 28.3, 28.7, 30.9, 37.6, 40.7, 42.5, 55.1, 55.1, 80.1, 113.9, 125.7, 128.0, 128.6, 129.3, 129.7, 140.9, 153.2, 157.9. HRMS-FAB ($M+1$) Calcd for C $_{28}$ H $_{38}$ NO $_3$: 436.2852 Found, 436.2851.

The E isomer **27** was observed spectroscopically. The enantiomeric ratio was not determined. ^1H NMR (acetone- d_6 , 400 Mz) δ 0.76-1.22 (m, 6H, Cy), 1.31 (s, 9H, C(CH $_3$) $_3$), 1.41-1.71 (m, 5H, Cy), 2.11 (sept, 1H, J = 4.9 Hz, CyCH), 2.37 (dd, 1H, J = 13.2, 9.3 Hz, PhCH $_2$), 2.75 (dd, 1H, J = 13.2, 5.4 Hz, PhCH $_2$), 3.83 (s, 3H, OCH $_3$), 4.12 (dd, 1H, J = 14.2, 10.0 Hz, CH=CHN), 6.73 (d, 1H, J = 14.2 Hz, CH=CHN), 6.94-7.27 (m, 9H, ArH). ^{13}C NMR (acetone- d_6 , 125 MHz) δ 26.5, 26.6, 26.7, 27.6, 27.6, 29.3, 31.7, 39.5, 41.9, 48.9, 55.0, 80.2, 112.6, 114.3, 125.7, 128.1, 129.6, 129.8, 130.4, 132.3, 141.5, 152.4, 158.9. HRMS-FAB ($M+1$) Calcd for C $_{28}$ H $_{38}$ NO $_3$: 436.2852 Found, 436.2851.

The enantiomeric ratio of the α -isomer **28** was determined directly to be 72:28 by CSP-HPLC (ChiralPak AD column, 0.5% *i*-PrOH/hexane, 1.0 mL/min). The major enantiomer had a retention time of 7.44 minutes while the retention time of the minor enantiomer was 9.65 minutes. The α -isomer **28** was observed spectroscopically. ^1H NMR (acetone- d_6 , 500 MHz) δ 0.94-1.29 (m, 6H, Cy), 1.34 (br-s, 9H, C(CH $_3$) $_3$), 1.41-1.68 (m, 4H, Cy), 1.90 (m, 1H, CHCH=CHCHN), 2.75 (dd, 1H, J = 13.4, 7.3 Hz, PhCH $_2$), 3.15 (dd, 1H, J = 13.7, 8.1 Hz, PhCH $_2$), 3.76 (s, 3H, OCH $_3$), 4.62 (q, 1H, J = 7.6 Hz, CHN), 5.47 (ABX, 2H, ν_a = 5.52 ppm; ν_b = 5.41 ppm; J_{AB} = 15.6 Hz; J_{AX} = 7.4 Hz; J_{BX} = 6.6 Hz; CyCH=CH; CyCH=CH), 6.74-6.81 (m, 4H, ArH), 7.17-7.28 (m, 5H, ArH). ^{13}C NMR (acetone- d_6 , 125 MHz) δ 25.8, 26.1, 27.9, 27.9, 32.8, 32.8, 39.8, 40.6, 54.9, 54.9, 63.0, 79.0, 113.5, 126.3, 127.0, 128.3, 129.7, 130.3, 138.8, 139.4, 154.5, 158.4. HRMS-FAB ($M+1$) Calcd for C $_{28}$ H $_{38}$ NO $_3$: 436.2852 Found, 436.2851.

32

(5S)-1-Benzyl-5-phenyl-hexahydro-cyclopenta[c]isoxazole (32). To a stirring solution of **30** (60 mg, 0.345 mmol) in toluene (3 mL, 0.12 M) was added benzylhydroxylamine hydrochloride (121

mg, 0.759 mmol), triethylamine (0.11 mL, 0.759 mmol) and molecular sieves. The mixture was allowed to stir overnight at rt and was monitored by TLC. When no starting material remained, the mixture was poured into water. The organic layer was removed and the aqueous layer was extracted with ether (3 x 25 mL). The combined organic layers were dried and concentrated to provide crude **32** as a light yellow oil. Column chromatography (90:10 petroleum ether:EtOAc) provided the product as a white solid (78 mg, 81%): m.p. = 55-57 °C. The diastereomers were easily separable by column chromatography and were isolated in a ratio of 80:20. Crystals of the major diastereomer suitable for X-ray crystallography were grown by recrystallization from EtOH. The more retained minor diastereomer was obtained as a white solid and was characterized spectroscopically: ^1H NMR (acetone- d_6 , 400 MHz) δ 1.71 (m, 1H, $\text{CH}_2\text{CHCH}_2\text{O}$), 1.82 (m, 1H, $\text{CH}_2\text{CHCH}_2\text{O}$), 1.98 (m, 2H, CH_2CHN), 3.24 (qt, 1H, $J = 8.1$ Hz, PhCH), 3.45 (sept, 1H, $J = 6.1$ Hz, CHCH_2O), 3.49 (m, 1H, CHN), 3.57 (dd, 1H, $J = 8.4, 6.3$ Hz, CH_2O), 3.99 (AB, 2H, $J = 13.4$ Hz; $\nu_a = 4.03$ ppm; $\nu_b = 3.95$ ppm, PhCH_2), 4.25 (t, 1H, $J = 8.6$ Hz, CH_2O), 7.19-7.44 (m, 10H, ArH). ^{13}C NMR (acetone- d_6 , 100 MHz) δ 38.9, 42.8, 47.5, 61.1, 71.6, 72.4, 72.8, 126.2, 127.0, 127.3, 128.1, 128.4, 129.1, 138.8, 144.1. HRMS-FAB ($M+1$) Calcd for $\text{C}_{19}\text{H}_{22}\text{NO}$: 279.1623 Found, 279.1623. The less retained major diastereomer was obtained as a white solid and was characterized spectroscopically: ^1H NMR (acetone- d_6 , 400 MHz) δ 1.53 (m, 1H, $\text{CH}_2\text{CHCH}_2\text{O}$), 1.66 (q, 1H, $J = 11.5$ Hz, $\text{CH}_2\text{CHCH}_2\text{O}$), 2.14 (m, 1H, CH_2CHN), 2.34 (m, 1H, CH_2CHN), 3.01 (sept, 1H, $J = 6.1$ Hz, CHCH_2O), 3.20 (m, 1H, CHN), 3.59 (dd, 1H, $J = 8.5, 2.7$ Hz, CH_2O), 3.69 (q, 1H, $J = 8.1$ Hz, CH_2O), 3.90 (AB, 2H, $J = 13.4$ Hz; $\nu_a = 3.96$ ppm; $\nu_b = 3.84$ ppm, PhCH_2), 4.11 (m, 1H, PhCH), 7.14-7.40 (m, 10H, ArH). ^{13}C NMR (acetone- d_6 , 125 MHz) δ 40.2, 40.8, 46.3, 47.6, 59.6, 71.5, 71.5, 126.3, 127.1, 127.1, 128.3, 128.6, 129.2, 138.7, 143.9. Anal. Calcd for $\text{C}_{19}\text{H}_{21}\text{NO}$: C, 81.68; H, 7.58; N, 5.01 Found: C, 81.27; H, 7.48; N, 5.15.

33

(5S)-1-Methyl-5-phenyl-hexahydro-cyclopenta[c]isoxazole (33). To a stirring solution of **30** (55 mg, 0.316 mmol) in toluene (3 mL, 0.08 M) was added methylhydroxylamine hydrochloride (45 mg, 0.54 mmol), triethylamine (75 μL , 0.54 mmol) and molecular sieves. The mixture was heated to reflux for 8 hr. After complete conversion to product, a procedure similar to that for the preparation of **32** (vide supra) was then followed except the aqueous layer was extracted with CHCl_3 . Column chromatography (50:50 petroleum ether:EtOAc) followed by preparative HPLC provided the product **33** (69% yield) as a mixture of two easily separable diastereomers in a ratio of 78:22. The less retained

minor diastereomer was obtained as a colorless oil (9 mg, 15%). ^1H NMR (acetone- d_6 , 400 MHz) δ 1.68-1.96 (m, 4H, $\text{CH}_2\text{CHCH}_2\text{O}$, CHCH_2O , CHCHN), 2.60 (s, 3H, CH_3), 3.12 (m, 1H, CHCHN), 3.15 (qt, 1H, $J = 7.8$ Hz, CHN), 3.33 (sept, 1H, $J = 6.1$ Hz, PhCH), 3.38 (m, 1H, CH_2O), 4.10 (t, 1H, $J = 8.3$ Hz, CH_2O), 7.14-7.29 (m, 5H, ArH). ^{13}C NMR (acetone- d_6 , 100 MHz) δ 38.7, 39.0, 42.8, 43.7, 47.9, 72.3, 73.7, 126.2, 127.3, 128.4, 144.1. HRMS-FAB ($M+1$) Calcd for $\text{C}_{13}\text{H}_{18}\text{NO}$: 204.1388 Found, 204.1387. The more retained major diastereomer was obtained as a colorless oil (35 mg, 54%). ^1H NMR (acetone- d_6 , 400 MHz) δ 1.50 (q, 1H, $J = 12.2$ Hz, $\text{CH}_2\text{CHCH}_2\text{O}$), 1.60 (m, 1H, $\text{CH}_2\text{CHCH}_2\text{O}$), 2.20-2.34 (m, 2H, CHCH_2O , CHCHN), 2.53 (s, 3H, CH_3), 3.03 (sept, 1H, $J = 5.9$ Hz, CHCHN), 3.15 (m, 1H, CHN), 3.45 (br-s, 1H, PhCH), 3.54 (dd, 1H, $J = 8.5, 2.9$ Hz, CH_2O), 4.07 (br-s, 1H, CH_2O), 7.14-7.29 (m, 5H, ArH). ^{13}C NMR (acetone- d_6 , 100 MHz) δ 39.7, 40.7, 43.1, 46.6, 47.9, 70.8, 73.8, 126.3, 127.0, 128.5, 143.9. HRMS-FAB ($M+1$) Calcd for $\text{C}_{13}\text{H}_{18}\text{NO}$: 204.1388 Found, 204.1387.

34

(5S)-Phenyl-1-iso-propyl-hexahydro-cyclopenta[c]isoxazole (34). To a stirring solution of **30** (175 mg, 1.00 mmol) in CHCl_3 (10 mL, 0.10 M) was added isopropylhydroxylamine hydrochloride (247 mg, 2.21 mmol), triethylamine (0.31 mL, 2.21 mmol) and molecular sieves. After 24 hr, starting material and nitron intermediate were observed by TLC, so the mixture was heated to reflux overnight. After complete conversion to product, a procedure similar to that for the preparation of **32** (vide supra) was then followed except the aqueous layer was extracted with CHCl_3 . Column chromatography (70:30 petroleum ether:EtOAc) followed by preparative HPLC provided the product **34** (73% yield) as a mixture of two easily separable diastereomers in a ratio of 84:16. The less retained minor diastereomer was obtained as a colorless oil (28 mg, 12%). ^1H NMR (CDCl_3 , 400 MHz) δ 1.14 (d, 3H, $J = 6.1$ Hz, CH_3), 1.21 (d, 3H, $J = 6.3$ Hz, CH_3), 1.80 (m, 2H, $\text{CH}_2\text{CHCH}_2\text{O}$), 1.96 (m, 1H, CH_2CHN), 2.15 (m, 1H, CH_2CHN), 2.89 (qt, 1H, $J = 6.3$ Hz, CHCH_2O), 3.19 (qt, 1H, $J = 7.3$ Hz, PhCH), 3.43 (sept, 1H, $J = 6.1$ Hz, $(\text{CH}_3)_2\text{CH}$), 3.55 (dd, 2H, $J = 8.6, 6.6$ Hz, CH_2O), 4.13 (t, 1H, $J = 8.6$ Hz, CHN), 7.19-7.33 (m, 5H, ArH). The more retained major diastereomer was obtained as a colorless oil (142 mg, 61%). ^1H NMR (CDCl_3 , 400 MHz) δ 1.12 (d, 3H, $J = 6.1$ Hz, CH_3), 1.19 (d, 3H, $J = 4.9$ Hz, CH_3), 1.60 (q, 1H, $J = 12.2$ Hz, $\text{CH}_2\text{CHCH}_2\text{O}$), 1.87 (m, 1H, $\text{CH}_2\text{CHCH}_2\text{O}$), 2.34 (m, 2H, CH_2CHN), 2.87 (m, 1H, CHCH_2O), 3.03 (s, 1H, $J = 5.9$ Hz, $(\text{CH}_3)_2\text{CH}$), 3.10 (m, 1H, PhCH), 3.65 (dd, 1H, $J = 8.5, 3.2$ Hz, CH_2O), 3.74 (br-s, 1H, CHN), 3.97 (t, 1H, $J = 7.8$ Hz, CH_2O), 7.19-7.33 (m, 5H, ArH). ^{13}C NMR (CDCl_3 , 100 MHz) δ

20.9, 21.2, 41.0, 47.0, 48.0, 54.2, 69.8, 72.1, 126.5, 127.2, 128.6, 143.4. HRMS-FAB (M+1) Calcd for C₁₅H₂₂NO: 232.1701 Found, 232.1702.

35

Representative Lithiation and Substitution of *N*-(*t*-Butoxycarbonyl)-*N*-(4-methoxyphenyl)-3-phenyl-(*E*)-2-propene-1-amine (6): Synthesis of (3*S*)-*N*-(*t*-Butoxycarbonyl)-3,6-diphenyl-*N*-(4-methoxyphenyl)-(1*Z*,5*E*)-hexadien-1-amine (35). To a stirring solution of **6** (205 mg, 0.60 mmol) in toluene (12 mL, 0.05 mmol) was added (–)-sparteine (0.19 mL, 0.84 mmol). The mixture was cooled to –78 °C and *n*-BuLi (0.962 mL, 0.52 mmol) was added dropwise. After stirring for 1 hr at –78 °C, cinnamyl bromide (0.18 mL, 1.21 mmol) was added and reactions continued to stir for 2 hr. The mixture was then quenched with MeOH (1 mL), warmed to rt, and poured into water. The layers were separated and the aqueous layer was extracted with ether (3 x 50 mL). The combined organic layers were dried over MgSO₄ and concentrated to provide **35** as a yellow oil. Column chromatography and preparative HPLC allowed separation of the desired product **35** (276 mg, 93%) as a colorless oil from a small amount of the α-substituted isomer. The enantiomeric ratio of **35** was determined directly to be 98:2 by CSP-HPLC ((*S,S*-Whelk-O column, 15% *i*-PrOH/hexanes, 1.0 mL/min). The major enantiomer (*S*) had a retention time of 12.2 minutes while the retention time of the minor enantiomer (*R*) was 9.9 minutes. ¹H NMR (acetone-*d*₆, 400 MHz) δ 1.37 (s, 9H, O(CH₃)₃), 2.34 (m, 2H, CH₂), 3.13 (m, 1H, PhCH), 3.78 (s, 3H, OCH₃), 5.09 (t, 1H, *J* = 9.5 Hz, CH=CHN), 5.93 (m, 1H, CH=CHPh), 6.25 (d, 1H, *J* = 9.8 Hz, CH=CHPh), 6.65 (d, 1H, *J* = 9.1 Hz, CH=CHN), 6.85-7.29 (m, 14H, ArH). ¹³C NMR (acetone-*d*₆, 100 MHz) δ 27.7, 40.4, 42.3, 55.1, 80.5, 114.0, 121.0, 126.1, 126.2, 127.1, 127.5, 127.6, 128.3, 128.4, 128.7, 131.4, 135.2, 138.0, 144.2, 153.3, 158.2. HRMS-FAB (M-1) Calcd for C₃₀H₃₂NO₃: 454.2382 Found, 454.2389.

37

(3*R*,5*S*)-1-Benzyl-3,5-diphenyl-hexahydro-cyclopenta[c]isoxazole (37). To a stirring solution of **35** (146 mg, 0.32 mmol) in CHCl₃ (5 mL, 0.06 M) was added 6M HCl (2 mL). The mixture stirred at rt for 2 hr and was poured into H₂O. The layers were separated and the aqueous layer was washed with CH₂Cl₂. The combined organic layers were dried over MgSO₄ and concentrated to provide crude **36** as a yellow oil. The aldehyde **36** was purified by column chromatography (90:10 petroleum ether:EtOAc)

but was inseparable from the α -substituted isomer that is not prone to hydrolysis (75 mg, 94% combined yield). The aldehyde was characterized spectroscopically: ^1H NMR (CDCl_3 , 400 MHz) δ 2.60 (m, 2H, $\text{CH}_2\text{CH}=\text{CH}$), 2.85 (m, 2H, CH_2CHO), 3.44 (qt, 1H, $J = 7.1$ Hz, PhCH), 6.12 (m, 1H, $\text{CH}=\text{CHPh}$), 6.44 (m, 1H, $\text{CH}=\text{CHPh}$), 7.26-7.40 (m, 10H, ArH), 9.73 (t, 1H, $J = 2.0$ Hz, CHO). ^{13}C NMR (CDCl_3 , 100 MHz) δ 40.4, 40.5, 49.6, 126.4, 127.1, 127.5, 127.8, 128.8, 129.0, 130.8, 132.7, 137.6, 143.7, 202.0. To a stirring solution of the aldehyde **36** (75 mg, 0.30 mmol) in CHCl_3 (3 mL, 0.10 M) was added benzyloxyamine hydrochloride (86 mg, 0.54 mmol), triethylamine (75 μL , 0.54 mmol) and molecular sieves. The mixture was stirred for 36 hr at room temperature and was poured into H_2O when no starting material remained by TLC. The layers were separated and the aqueous layer was washed with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over MgSO_4 , and concentrated to provide crude **37** as a mixture of two diastereomers (dr = 84:16). The diastereomers were separated by column chromatography (90:10 petroleum ether:EtOAc) and preparative HPLC to provide pure **37** in 64% yield. The less retained minor diastereomer was obtained as a colorless oil and was characterized spectroscopically by ^1H NMR and by mass. A small amount of the α -substituted impurity remained inseparable from the minor diastereomer. ^1H NMR (CDCl_3 , 400 MHz) δ 1.66 (m, 1H, CH_2CHCHO), 1.83 (m, 2H, CH_2CHCHO ; CH_2CHN), 2.11 (m, 1H, CH_2CHN), 3.04 (q, 1H, $J = 8.3$ Hz, CHCHO), 3.60 (m, 2H, CHN ; PhCHCH_2), 4.16 (AB, 2H, $J = 13.4$ Hz; $\nu_a = 4.34$ ppm; $\nu_b = 3.98$ ppm, PhCH_2), 4.66 (d, 1H, $J = 7.8$ Hz, PhCHO), 7.20-7.48 (m, 15H, ArH). HRMS-FAB ($M+1$) Calcd for $\text{C}_{25}\text{H}_{26}\text{NO}$: 356.2014 Found, 356.2016. The more retained major diastereomer was obtained as a white solid (m.p. = 104 $^\circ\text{C}$) and was characterized spectroscopically by ^1H and ^{13}C NMR and by mass. ^1H NMR (CDCl_3 , 400 MHz) δ 1.78 (m, 1H, CH_2CHCHO), 2.00 (m, 2H, CH_2CHN), 2.30 (m, 1H, CH_2CHCHO), 3.09 (qt, 1H, $J = 9.5$ Hz, PhCHCH_2), 3.29 (sept, 1H, $J = 6.3$ Hz, CHCHO), 3.63 (m, 1H, CHN), 4.13 (AB, 2H, $J = 12.9$ Hz; $\nu_a = 4.26$ ppm; $\nu_b = 3.99$ ppm, PhCH_2), 4.94 (d, 1H, $J = 6.3$ Hz, PhCHO), 7.22-7.48 (m, 15H, ArH). ^{13}C NMR (CDCl_3 , 100 MHz) δ 38.9, 38.9, 49.5, 58.0, 62.2, 73.5, 86.4, 126.6, 126.7, 127.2, 127.7, 128.0, 128.5, 128.7, 128.7, 129.8, 137.1, 140.4, 143.5. HRMS-FAB ($M+1$) Calcd for $\text{C}_{25}\text{H}_{26}\text{NO}$: 356.2014 Found, 356.2016.

(1S,2S,4S)-1-Amino-N-benzyl-2-hydroxymethyl-4-phenyl cyclopentane (38). To a stirring solution of **32** (153 mg, 0.548 mmol) in 10 M AcOH (10 mL, 0.06 M) in a three-necked round bottom flask was added Zn dust (717 mg, 10.97 mmol). A reflux condenser was attached and the mixture was

heated to 55 °C. After stirring for 3 hr, the mixture was cooled to rt, diluted with water, basified with 6 M KOH, and extracted with CH₂Cl₂ (3 x 25 mL). The organic layers were combined, dried (MgSO₄), and concentrated to provide **38** as a pure colorless oil (130 mg, 85%) requiring no further purification. ¹H NMR (acetone-*d*₆, 400 MHz) δ 1.65 (m, 2H, CH₂CHOH), 2.09 (m, 1H, CHCH₂OH), 2.36 (m, 2H, CH₂CHNH), 2.98 (m, 1H, CHNH), 3.30 (br-s, 1H, OH), 3.39 (m, 1H, PhCH), 3.71 (d, 2H, *J* = 5.8 Hz, CH₂OH), 3.82 (AB, 2H, *J* = 13.2 Hz; *v*_a = 3.87 ppm; *v*_b = 3.76 ppm, PhCH₂), 7.13-7.39 (m, 10H, ArH). ¹³C NMR (acetone-*d*₆, 125 MHz) δ 36.6, 41.8, 43.2, 43.2, 52.8, 60.5, 63.2, 126.0, 126.9, 127.2, 128.3, 128.4, 128.5, 141.2, 145.6. HRMS-FAB (*M*+1) Calcd for C₁₉H₂₄NO: 282.1858 Found, 282.1857.

(1*S*,2*S*,4*S*)-1-Amino-*N*-benzyl-*N*-(*t*-butoxycarbonyl)-2-hydroxymethyl-4-phenylcyclopentane (39**).** To a stirring solution of **38** (55 mg, 0.195 mmol) in MeOH (3 mL, 0.07 M) was added NaHCO₃ (115 mg, 1.37 mmol). (Boc)₂O (0.13 mL, 0.585 mmol) was then added and the mixture was stirred at rt overnight. The mixture was poured into water and extracted with CH₂Cl₂ (3 x 25 mL). The combined organic layers were dried (MgSO₄) and concentrated to provide the crude product as a yellow oil. Purification by column chromatography (80:20 petroleum ether:EtOAc) provided **39** (57 mg, 77%) as a colorless oil. ¹H NMR (CDCl₃, 500 MHz) δ 1.45 (s, 9H, C(CH₃)₃), 1.78 (q, 1H, *J* = 11.8 Hz, CH₂CHCH₂OH), 2.16 (br-m, 3H, CH₂CHCH₂OH, CH₂CHN), 2.55 (m, 1H, CHCH₂OH), 2.92 (br-s, 1H, OH), 3.02 (m, 1H, PhCH), 3.66 (m, 2H, CH₂OH), 4.37 (m, 2H, PhCH₂), 4.63 (br-m, 1H, CHN), 7.18-7.33 (m, 10H, ArH). ¹³C NMR (CDCl₃, 100 MHz) δ 28.6, 28.6, 35.9, 37.4, 42.8, 59.5, 60.7, 63.1, 80.7, 126.4, 126.6, 127.0, 127.3, 128.6, 128.7, 139.7, 144.4, 157.2. HRMS-FAB (*M*+1) Calcd for C₂₄H₃₁NO₃: 382.2382 Found, 382.2383.

(1*R*,2*S*,4*S*)-2-Amino-*N*-benzyl-*N*-(*t*-butoxycarbonyl)-4-phenyl-1-cyclopentanecarboxylic acid (40**).** To protected amino alcohol **39** (57 mg, 0.150 mmol) was added 1.5 mL of solvent (1:1:1.5 CH₃CN:CCl₄:H₂O) and NaIO₄ (128 mg, 0.598 mmol). RuCl₃ (0.7 mg, 0.022 mmol) was then added and the colorless solution became yellowish brown in color. The mixture was allowed to stir overnight.

H₂O was then added and the solution was poured into a separatory funnel and washed with CH₂Cl₂ (3 x 25 mL). The organic layers were combined, dried (MgSO₄), and concentrated. The light brown oil was dissolved in ether and filtered through a pad of Celite. Concentration of the filtered solution provided the product **40** (52 mg, 88%) which was carried directly to the subsequent deprotection reaction without further purification. ¹H NMR (acetone-*d*₆, 400 MHz) Note: Restricted rotation causes severe broadening of peaks. δ 1.45 (br-s, 9H, C(CH₃)₃), 2.14 (br-s, 1H, CH₂CHN), 2.20 (m, 1H, CH₂CHN), 2.35 (t, 2H, *J* = 8.5 Hz, CH₂CHCOOH), 2.97 (m, 1H, PhCH), 3.48 (m, 1H, CHCOOH), 4.44 (m, 1H, CHN), 4.74 (br-m, 2H, PhCH₂), 7.19-7.63 (m, 10H, ArH). ¹³C NMR (CDCl₃, 100 MHz) δ 28.6, 35.9, 37.8, 42.9, 46.3, 49.2, 59.8, 80.9, 126.8, 126.9, 127.4, 127.4, 128.6, 128.7, 139.8, 143.5, 156.4, 180.0. HRMS-FAB (M+1) Calcd for C₂₄H₃₀NO₄: 396.2175 Found, 396.2176.

42

(3S)-6-Aza-6-benzyl-3-phenyl-bicyclo[3.2.0]heptan-7-one (42). To a stirring solution of **40** (27 mg, 0.067 mmol) in CH₂Cl₂ (1 mL, 0.07M) was added approximately 0.25 mL of 30% TFA in CH₂Cl₂. The mixture was allowed to stir at rt for 12 hr and was monitored by TLC. Concentrated TFA (0.25 mL) was then added and the reaction stirred until complete consumption of starting material was observed. Upon consumption of starting material, the TFA/CH₂Cl₂ mixture was removed *in vacuo*. Residual TFA was removed by azeotroping with CHCl₃ and toluene *in vacuo*. The crude, deprotected amino acid **41** was dissolved in CH₃CN (1.5 mL, 0.045 M) and NEt₃ (14 μL, 0.10 mmol) was added. A small amount of white precipitate immediately formed and the reaction was stirred for 10 min. PPh₃ (21 mg, 0.08 mmol) and 2,2'-dipyridyl disulfide (Aldrithiol, 18 mg, 0.08 mmol) were then added. The mixture became a milky yellow color. The reaction was outfitted with a condenser and heated to 60 °C for 8 hr. The yellow homogenous reaction mixture was then diluted with H₂O and washed with EtOAc (3 x 25 mL). The organic layers were combined, washed with brine, dried over MgSO₄ and concentrated to provide crude **42** as a yellow oil. Column chromatography (50:50 petroleum ether:EtOAc) provided pure **42** (12 mg, 65%) as a colorless oil. ¹H NMR (CDCl₃, 500 MHz) δ 2.01 (m, 2H, CH₂CHC=O), 2.08 (ddd, 1H, *J* = 16.7, 8.8, 7.7 Hz, CH₂CHN), 2.52 (ddd, 1H, *J* = 14.2, 5.1, 3.2 Hz, CH₂CHN), 3.58 (qt, 1H, *J* = 7.1 Hz, PhCH), 3.62 (m, 1H, CHC=O), 3.88 (AB, 2H, *J* = 15.0 Hz; *v*_a = 4.28 ppm; *v*_b = 3.47 ppm, PhCH₂), 7.12-7.36 (m, 10H, ArH). ¹³C NMR (CDCl₃, 100 MHz) δ 29.3, 35.6,

44.4, 46.2, 55.6, 58.1, 126.3, 126.7, 127.8, 128.6, 128.6, 129.0, 135.8, 143.5, 169.9. IR (CHCl₃) 1742 cm⁻¹; HRMS-FAB (M+1) Calcd for C₁₉H₂₀NO: 278.1545 Found, 278.1546.

43

6-Aza-(3S)-phenyl-bicyclo[3.2.0]heptan-7-one (43). A three-necked 15 mL round bottom flask was outfitted with a glass stir bar, a dry ice/acetone condenser, and an NH₃ lecture bottle inlet. The flask was cooled to -78 °C and NH₃ (approximately 5 mL) was condensed inside the flask. Protected β-lactam **42** dissolved in THF (0.5 mL, 0.12M) was added dropwise with a syringe. Small bits of sodium were added until the dark blue color persisted. The reaction was allowed to stir for 5 min, whereupon NH₄Cl (s) was added to quench the sodium. When the mixture was colorless, the reaction was allowed to warm to rt and the NH₃ evaporated. The residue was then dissolved in sat. NH₄Cl. The aqueous mixture was washed with CH₂Cl₂ (3 x 25 mL). The combined organic layers were washed with H₂O and brine, dried over MgSO₄ and concentrated to provide crude **43** as a colorless oil. The product was further purified by column chromatography (90:10 CHCl₃:MeOH) to provide pure **43** (8 mg, 67%) as a colorless oil. ¹H NMR (CDCl₃, 400 MHz) δ 2.09 (ddd, 1H, *J* = 13.9, 6.6, 2.7 Hz, CH₂CHN), 2.16 (m, 1H, CH₂CHC=O), 2.26 (m, 1H, CH₂CHC=O), 2.44 (ddd, 1H, *J* = 13.9, 6.4, 4.2 Hz, CH₂CHN), 3.60 (qt, 1H, *J* = 7.6 Hz, PhCH), 3.68 (m, 1H, CHC=O), 4.20 (m, 1H, CHN), 5.66 (br-s, 1H, NH), 7.18-7.34 (m, 5H, ArH). ¹³C NMR (CDCl₃, 100 MHz) δ 30.8, 38.7, 47.8, 55.0, 57.2, 126.4, 126.9, 128.6, 143.7, 171.2. HRMS-FAB (M+1) Calcd for C₁₂H₁₄NO: 188.1075 Found, 188.1075.

44

(1R,2S,4S)-2-Amino-N-benzyl-N-(t-butoxycarbonyl)-4-phenyl-1-cyclopentanecarboxylic acid (44). CH₂Cl₂ (0.5 mL) and oxalyl chloride (21 μL, 0.25 mmol) were added to a flame-dried flask and cooled to -78 °C. DMSO (32 μL, 0.45 mmol) was dissolved in CH₂Cl₂ (0.25 mL) and added to the reaction mixture. After stirring for 30 min, the alcohol **39** (34 mg, 0.09 mmol), dissolved in CH₂Cl₂ (1 mL), was added dropwise. After stirring at -78 °C for 1.5 hr, diethylisopropylamine (0.14 mL, 0.82 mmol) was added and the reaction was warmed to rt. The mixture was poured into 1M HCl (25 mL) and the layers were separated. The organic layer was washed with 1M HCl (1 x 10 mL), H₂O (2 x 5 mL), and brine (1 x 5 mL), dried over MgSO₄ and concentrated to provide crude **44** as a light yellow oil.

Column chromatography (80:20 petroleum ether:EtOAc) provided the pure **44** as a colorless oil in 86% yield (29 mg). Approximately 10% of the epimerized product was observed by ^1H NMR. ^1H NMR (CDCl_3 , 400 MHz) Note: Restricted rotation causes severe broadening of peaks. δ 1.47 (s, 9H, $\text{C}(\text{CH}_3)_3$), 2.02 (m, 1H, CH_2CHN), 2.13 (q, 1H, $J = 11.5$ Hz, CH_2CHN), 2.20 (m, 1H, CH_2CHCHO), 2.40 (m, 1H, CH_2CHCHO), 2.92 (sept, 1H, $J = 6.3$ Hz, PhCH), 3.20 (br-s, 1H, CHCHO), 4.35-4.48 (br-m, 3H, CHN ; CH_2Ph), 7.18-7.36 (m, 10H, ArH), 9.73 (s, 1H, CHO). ^{13}C NMR (CDCl_3 , 125 MHz) δ 28.6, 33.3, 38.1, 42.8, 51.8, 55.1, 60.4, 80.7, 126.7, 127.1, 127.3, 127.4, 128.7, 128.8, 139.1, 143.3, 155.8, 203.2. HRMS-FAB ($M+1$) Calcd for $\text{C}_{24}\text{H}_{30}\text{NO}_3$: 380.2226 Found, 380.2226.

(1S,2S,4S)-2-Amino-N-benzyl-N-(t-butoxycarbonyl)-4-phenyl-1-cyclopentanecarboxylic acid (45). To a stirring solution of **44** (9 mg, 0.02 mmol) in EtOH (1 mL, 0.02M) was added NaHCO_3 . The flask was outfitted with a reflux condenser and heated to 110 $^\circ\text{C}$ for 3 hr. The mixture was then cooled to rt and filtered over Celite to afford the epimerized product **45** (8 mg, 90%), which required no further purification. ^1H NMR (CDCl_3 , 400 MHz) Note: Restricted rotation causes severe broadening of peaks. δ 1.48 (br-s, 9H, $\text{C}(\text{CH}_3)_3$), 2.09 (m, 2H, CH_2CHN ; CH_2CHCHO), 2.14 (qt, 1H, $J = 11.7$ Hz, CH_2CHN), 2.33 (m, 1H, CH_2CHCHO), 2.90 (m, 1H, PhCH), 3.20 (m, 1H, CHCHO), 4.35-4.58 (br-m, 3H, CHN ; CH_2Ph), 7.18-7.36 (m, 10H, ArH), 9.65 (s, 1H, CHO). ^{13}C NMR (CDCl_3 , 125 MHz) δ 28.6, 29.9, 32.3, 42.8, 50.4, 58.6, 61.7, 80.9, 126.7, 126.7, 127.1, 127.5, 128.7, 128.7, 128.8, 139.1, 143.3, 202.5. HRMS-FAB ($M+1$) Calcd for $\text{C}_{24}\text{H}_{30}\text{NO}_3$: 380.2226 Found, 380.2223.

Representative Lithiation/Transmetalation/Substitution of N-(t-Butoxycarbonyl)-N-(4-methoxyphenyl)-3-phenyl-(E)-2-propene-1-amine (6): Synthesis of (3R,4S,6S,7S)-7-Benzoxymethyl-N-(t-butoxycarbonyl)-4-hydroxy-N-(4-methoxyphenyl)-3,6,7-triphenyl-(E)-1-hepten-1-amine (52). To a stirring solution of **6** (52 mg, 0.152 mmol) in toluene (2.5 mL, 0.06 M) under N_2 was added (–)-sparteine (49 μL , 0.212 mmol). The solution was cooled to -78 $^\circ\text{C}$ and the internal temperature of the reaction mixture was monitored by a thermocouple. $n\text{-BuLi}$ (0.12 mL, 0.182 mmol) was added dropwise, ensuring that the temperature of the mixture did not exceed -76 $^\circ\text{C}$. The bright yellow solution was allowed to stir for 30 min, whereupon Et_2AlCl (0.17 mL, 0.303 mmol, 1.8 M solution in

toluene) was added dropwise with careful temperature control. The solution became colorless within 2 min and was allowed to stir for 1 hr. A solution of aldehyde **50** (100 mg, 0.303 mmol) in 0.5 mL toluene was then added, ensuring that the temperature of the mixture did not exceed $-76\text{ }^{\circ}\text{C}$. The reaction was allowed to stir at $-78\text{ }^{\circ}\text{C}$ for 3 hr, and was then quenched with MeOH (1 mL) and allowed to warm to rt. The solution was diluted with ether and poured onto 50 mL of 2M HCl. The organic layer was removed, and the aqueous layer was washed with ether (3 x 25 mL). The combined organic layers were dried (MgSO_4) and concentrated to provide the crude product as a yellow oil. The crude product was purified by column chromatography (80:20 petroleum ether:EtOAc) to afford **52** as a colorless oil (73 mg, 75%). The E geometrical isomer was obtained with a dr of 92:8. The diastereomers were separated by preparative HPLC with a solvent system of 90:10 hexanes:EtOAc. ^1H NMR (acetone- d_6 , 400 MHz) δ 1.40 (s, 9H, $\text{C}(\text{CH}_3)_3$), 1.91 (m, 2H, CH_2CHOH), 2.21 (m, 1H, CH_2CHOH), 3.19 (d, 1H, $J = 4.9\text{ Hz}$, OH), 3.22 (m, 1H, PhCHCH_2), 3.35 (dd, 1H, $J = 9.8, 4.2\text{ Hz}$, PhCHCH=CHN), 3.62 (m, 1H, CHOH), 3.80 (s, 3H, OCH_3), 4.32 (AB, 2H, $J = 11.7\text{ Hz}$, $\nu_a = 4.39\text{ ppm}$; $\nu_b = 4.25\text{ ppm}$, PhCH_2), 4.52 (d, 1H, $J = 7.1\text{ Hz}$, PhCH_2OCH), 4.79 (dd, 1H, $J = 14.2, 9.8\text{ Hz}$, CH=CHN-), 6.89-7.36 (m, 25H, ArH, CH=CHN-). ^{13}C NMR (acetone- d_6 , 100 MHz) δ 27.7, 37.4, 49.4, 51.3, 55.0, 70.7, 72.9, 80.4, 86.1, 108.9, 114.4, 125.9, 126.3, 127.3, 127.4, 127.5, 127.6, 128.0, 128.0, 128.1, 128.3, 128.5, 129.2, 129.9, 131.9, 132.2, 139.2, 141.0, 142.7, 144.7, 152.5, 158.8. HRMS-FAB ($M+1$) Calcd for $\text{C}_{44}\text{H}_{47}\text{NO}_5$: 670.3532 Found, 670.3530.

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(4R,5S)-5-(2S,3S-Diphenyl-3-benzyloxy-propyl)-4-phenyl-butyrolactone (54). To a stirring solution of **52** (72 mg, 0.108 mmol) in MeOH (1.5 mL, 0.072 M) at rt was added methanesulfonic acid (3.5 μL , 0.054 mmol). The reaction was allowed to stir overnight and was then poured into a mixture of KOH (15 mL) and brine (15 mL). The white, cloudy solution was extracted with ether (3 x 20 mL). The combined organic layers were dried over MgSO_4 , filtered, and concentrated to give a light yellow oil. The crude product **53** was purified by column chromatography (90:10 petroleum ether:EtOAc) to afford colorless oil **53** as an equal mixture of two diastereomers in 79% yield (41 mg). The diastereomers were not separated and were carried directly to the subsequent *m*-CPBA/ $\text{BF}_3\cdot\text{OEt}_2$ oxidation reaction. To a stirring solution of **53** (41 mg, 0.086 mmol) in CH_2Cl_2 (2 mL, 0.043 M) was added *m*-CPBA (44 mg, 0.257 mmol) and $\text{BF}_3\cdot\text{OEt}_2$ (3.2 μL , 0.026 mmol). The cloudy reaction mixture was allowed to stir overnight and was then poured into aq. NaHSO_3 (25 mL). The organic layer was

removed and the aqueous layer washed with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with aq. NaHCO_3 , dried over MgSO_4 , filtered and concentrated to afford the crude **54** as a light yellow oil. The crude product was purified by column chromatography (90:10 petroleum ether:EtOAc) to afford white solid **54** in 76% yield: m.p. = 155-157 °C. Crystals suitable for X-ray analysis were grown by recrystallization from EtOH. ^1H NMR (CDCl_3 , 500 MHz) δ 2.33 (m, 1H, OCHCH_2), 2.53 (m, 1H, OCHCH_2), 2.77 (ABX, 2H, $\nu_a = 2.89$ ppm; $\nu_b = 2.63$ ppm; $J_{AB} = 17.7$ Hz; $J_{AX} = 8.7$ Hz; $J_{BX} = 10.4$ Hz; $\text{CH}_2\text{C}=\text{O}$), 2.94 (X of ABX, 1H, PhCHCHO), 3.24 (q, 1H, $J = 8.6$ Hz, $\text{PhCHCH}_2\text{CHO}$), 4.28 (AB, 2H, $J = 11.8$ Hz, $\nu_a = 4.41$ ppm; $\nu_b = 4.14$ ppm; PhCH_2), 4.30 (d, 1H, $J = 7.9$ Hz, PhCHO), 4.54 (q, 1H, $J = 8.1$ Hz, $\text{PhCHCH}_2\text{CHO}$), 6.63-7.34 (m, 20H, ArH). ^{13}C NMR (CDCl_3 , 125 MHz) δ 29.9, 37.6, 38.6, 48.6, 49.1, 60.6, 70.8, 85.7, 126.7, 127.5, 127.7, 127.8, 127.8, 128.0, 128.2, 128.2, 128.5, 128.6, 129.3, 138.5, 139.5, 140.3, 141.1, 175.8. HRMS-FAB ($M+1$) Calcd for $\text{C}_{32}\text{H}_{31}\text{NO}_3$: 463.2273 Found, 463.2273.