Synthesis of *trans* (3*S*)-Amino-(4*R*)-Alkyl- and -(4*S*)-Aryl-Piperidines via Ring Closing Metathesis Reaction

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Experimental procedures, stereoassignments and characterization data for all reaction products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

General Experimental: All reagents were commercial grade and were used as received without further purification, unless otherwise specified. Commercially available anhydrous solvents were used for reactions conducted under inert atmosphere. Reagent grade solvents were used in all other cases, unless otherwise specified. Flash chromatography was performed on E. Merck silica gel 60 (230-400 mesh). Thin-layer chromatography was performed on E. Merck 60 F-254 precoated silica plates (250 mm layer thickness). The ¹H NMR spectra were recorded at 300 MHz. Chemical shifts for ¹H NMR spectra are expressed in parts per million downfield from tetramethylsilane. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; p, pentet; m, multiplet; br, broad. Coupling constants are given in Hertz (Hz). The ¹³C NMR spectra were recorded at 75 MHz. Chemical shifts for ¹³C NMR spectra are expressed in parts per million downfield from chloroform. Mass spectra were obtained by electrospray mass spectrometry utilizing an electrospray ionization (ESI) interface in flow injection analysis (FIA) mode equipped with an ESI interface. Melting points were taken on a capillary melting point apparatus. Optical rotations were measured with the use of a 10-cm cell at 20 °C.

(4*R*)-(1-Hydroxy-ethyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester. To a solution of Garner's aldehyde (2.80 g, 12.33 mmol) in anhydrous THF (50 mL) was added 3.0 M MeMgBr in Et₂O (4.52 mL, 13.65 mmol) dropwise at -78 °C under a N₂ atmosphere. The resulting solution was slowly warmed to room temperature in 3 hrs and then quenched with water. The mixture was partitioned between brine and EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc once. The combined organic layers were dried over anhydrous MgSO₄ and evaporated. The residue was purified by flash chromatography of silica-gel eluted with EtOAc:Hexanes (1:8) (R_f = 0.13 in EtOAc:Hexanes 1:4) to give 2.75 g (11.23 mmol, 91%). ¹H NMR (CDCl₃) δ 3.83-4.22 (m, 4H), 1.57-1.62 (m, 6H), 1.49 (s, 9H), 1.19-1.22 (m, 3H).

(4*R*)-(1-Hydroxy-propyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester.¹

(4R)-(1-Hydroxy-phenyl-methyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester.

(4R)-(Cyclopropyl-hydroxy-methyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester.

(4R)-Acetyl-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester (1a).

To a solution of oxalyl chloride (0.427 g, 4.895 mmol) in anhydrous CH₂Cl₂ (15 mL) was added DMSO (0.725 mL, 10.217 mmol) at –78 °C under a N₂ atmosphere. After stirring for 5 min, a solution of the alcohol (1.043 g, 4.257 mmol) in CH₂Cl₂ (5 mL) was added slowly to control the internal temperature under –65 °C. The resulting solution was stirred for 30 min at –78 °C and at this point Et₃N (3 mL, excess) was added. Stirring was continued for 5 min and the reaction solution was allowed to warm to room temperature and then quenched by addition of water. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ once. The combined extracts were dried over anhydrous MgSO₄ and evaporated. The residue was purified by flash chromatography of silica-gel eluted with EtOAc:Hexanes (1:4) (R_f = 0.35, in EtOAc:Hexanes 1:4) to give 0.95 g (3.910 mmol, 92%) as a colorless oil. ¹H NMR (CDCl₃) δ 4.25-4.44 (m, 1H), 4.09-4.20 (m, 1H), 3.90-4.01 (m, 1H), 2.20+2.22 (s+s, 3H, rotamers), 1.53+1.51 (s+s, 9H, rotamers), 1.42 (s, 6H). EIMS m/z 244 (m+H), 188 (m-Bu-*t*) 144 (m-Boc).

2,2-Dimethyl-(4R)-propionyl-oxazolidine-3-carboxylic acid *tert*-butyl ester (1b).

(4R)-Benzoyl-2,2-Dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester (1c).

(4R)-Cyclopropanecarbonyl-2,2-Dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester (1d).

(4R)-Isopropenyl-2,2-Dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester. To a suspension of $\text{Ph}_3\text{PCH}_3\text{Br}$ (3.750 g, 10.494 mmol) in anhydrous THF (20 mL) in a cold water bath was added *t*-BuOK (1.180 g, 1.5 mmol) in one portion under N_2 . The resulting yellow suspension was stirred at room temperature for 10 min and then a solution of **1a** (1.70 g, 6.996 mmol) in THF (10 mL) was added. Stirring was continued for 10 min and brine was added to quench the reaction. The mixture was extracted with EtOAc, dried over anhydrous MgSO_4 and evaporated. The residue was purified by flash chromatography of silica-gel eluted with EtOAc:Hexanes (1:4) (R_f = 0.45) to give 1.462 g (6.066 mmol, 87%) as a colorless oil. $[\alpha]_D^{20} = +9.2^\circ$ ($c = 3.2$ in CHCl_3). ^1H NMR (CDCl_3) δ 4.74-4.88 (m, 2H), 4.14-4.34 (m, 1H), 4.00 (dd, $J = 3.3, 9.0$ Hz, 1H), 3.65 (dd, $J = 3.0, 9.0$ Hz, 1H), 1.62+1.60 (s+s, 6H, rotamers), 1.43+1.39 (s+s, 9H, rotamers); ^{13}C NMR (CDCl_3) δ 152.4, 144.5+143.5 (rotamers), 111.5, 94.4+94.0 (rotamers), 80.3+79.6 (rotamers), 67.9+67.5 (rotamers), 62.7, 28.5, 26.7+25.9 (rotamers), 24.8+23.5 (rotamers), 18.7. EIMS m/z 242 ($m+\text{H}$), 186 ($m\text{-Bu-}t$), 142 ($m\text{-Boc}$), 128 ($m\text{-Boc-CH}_4$).

(4S)-(1-Ethyl-vinyl)-2,2-Dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester.

2,2-Dimethyl-(4S)-(1-phenyl-vinyl)-oxazolidine-3-carboxylic acid *tert*-butyl ester.

(4*S*)-(1-Cyclopropyl-vinyl)-2,2-Dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester.

((1*S*)-Hydroxymethyl-2-methyl-allyl)-carbamic acid *tert*-butyl ester (2a). A solution of the 2,2-dimethyl-oxazolidine (1.462 g, 6.066 mmol) and *p*-TsOH (0.115 g, 0.607 mmol) in MeOH (50 mL) was heated at reflux for 48 hrs. After cooling, Et₃N (0.85 mL, 6.066 mmol) was added followed by (Boc)₂O (0.661 g, 3.033 mmol) and stirring was continued at room temperature for additional 2 hrs. The solvent was evaporated and the residue was purified by flash chromatography of silica-gel eluted with EtOAc:Hexanes (1:4) (*R*_f = 0.18 in EtOAc:Hexanes 1:4) to give 1.462 g (6.066 mmol, 87%) as a white solid. m.p. 55-57 °C. [α]_D²⁰ = -25.5 ° (c = 4.5 in CHCl₃). ¹H NMR (CDCl₃) δ 5.17 (br, 1H), 4.97 (s, 1H), 4.94 (s, 1H), 4.09 (br, 1H), 3.68 (t, *J* = 4.5 Hz, 2H), 2.62 (t, *J* = 6.0 Hz, 1H), 1.78 (s, 3H), 1.45 (s, 9H); ¹³C NMR (CDCl₃) δ 156.3, 142.9, 112.4, 80.0, 63.9, 57.7, 28.6, 20.5. EIMS *m/z* 224 (*m*+Na), 202 (*m*+H), 146 (*m*-Bu-*t*), 128 (*m*-Bu-*t*-H₂O), 102 (*m*-Boc).

((2*S*)-Ethyl-1-Hydroxymethyl-allyl)-carbamic acid *tert*-butyl ester (2b).

((1*S*)-Hydroxymethyl-2-phenyl-allyl)-carbamic acid *tert*-butyl ester (2c).

((2*S*)-Cyclopropyl-1-Hydroxymethyl-allyl)-carbamic acid *tert*-butyl ester (2d).

Toluene-4-sulfonic acid (2*S*)-*tert*-butoxycarbonylamino-3-methyl-but-3-enyl ester. A solution of the alcohol (0.630 g, 3.134 mmol), *p*-TsCl (0.722 g, 3.761 mmol) and Et₃N (0.527 mL, 3.761 mmol) in CH₂Cl₂ (15 mL) was heated at reflux for 3 hrs. After cooling, the solvent was evaporated and the residue was purified by flash chromatography of silica-gel eluted with EtOAc:Hexanes (1:8) (*R*_f = 0.50 in EtOAc:Hexanes 1:4) to give 0.921 g (2.594 mmol, 83%) as a white solid. m.p. 70-72 °C. [α]_D²⁰ = -47.3° (c = 3.2 in CHCl₃). ¹H NMR (CDCl₃) δ 7.78 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.4 Hz, 2H), 4.93 (s, 1H), 4.90 (s, 1H), 4.89 (br, 1H), 4.23 (br, 1H), 4.10 (d, *J* = 4.5 Hz, 2H), 2.45 (s, 3H), 1.67 (s, 3H), 1.42 (s, 9H); ¹³C NMR (CDCl₃) δ 155.3, 145.3, 141.0, 132.8, 130.2, 128.2, 113.6, 80.2, 70.2, 54.4, 28.6, 21.9, 20.2. EIMS *m/z* 378 (m+Na), 356 (m+H), 146 (m-Bu-*t*), 128 (m-Bu-*t*-TsOH-p), 102 (m-Boc-TsOH-p).

Toluene-4-sulfonic acid (2*S*)-*tert*-butoxycarbonylamino-3-ethyl-but-3-enyl ester.

Toluene-4-sulfonic acid (2*S*)-*tert*-butoxycarbonylamino-3-phenyl-but-3-enyl ester.

Toluene-4-sulfonic acid (2*S*)-*tert*-butoxycarbonylamino-3-cyclopropyl-but-3-enyl ester.

(((1S)-Allyl-*tert*-butoxycarbonyl-amino)-2-methyl-allyl)-carbamic acid *tert*-butyl ester (3a). A solution of the tosylate (0.910 g, 2.563 mmol) in allylamine (5 mL) was heated at reflux for 5 hrs. The excess allylamine was removed by evaporation on a rotary evaporator. The residue was used for the next step without purification.

The crude amine (0.269, 1,121 mmol) was dissolved in CH_2Cl_2 (10 mL) and $(\text{BOC})_2\text{O}$ (0.367 g, 1.684 mmol) was added. The resulting solution was stirred at room temperature for 4 hrs. The solvent was evaporated and the residue was purified by flash chromatography of silica-gel eluted with EtOAc:Hexanes (1:20 and the 1:10) ($R_f = 0.90$ in EtOAc:Hexanes 1:4) to give 0.269 g (0.791mmol, 71%) as a colorless oil. ^1H NMR (CDCl_3) δ 5.62-5.89 (m, 1H), 5.16 (s, 1H), 5.12 (s, 1H), 4.95 (s, 1H), 4.89 (s, 1H), 3.91-4.24.25 (m, 2H), 3.64-3.80 (m, 2H), 2.88-3.40 (m, 1H), 1.74 (s, 3H), 1.38-1.54 (m, 18H). EIMS m/z 341 (m+H), 285 (m-Bu-*t*), 241 (m-Boc), 229 (m-2xBu-*t*), 185 (m-Bu-*t*-Boc), 141 (m-2xBoc).

(((1*S*)-Allyl-(2,2,2-trifluoro-acetyl)-amino)-methyl)-2-ethyl-allyl)-carbamic acid *tert*-butyl ester (3b). A solution of the tosylate (0.910 g, 2.563 mmol) in allylamine (5 mL) was heated at reflux for 5 hrs. The excess allylamine was removed by evaporation on a rotary evaporator and further dried in high vacuum.

The residue was dissolved in CH₂Cl₂ (10 mL) and Et₃N (0.257 mL, 2.563 mmol) was added followed by trifluoroacetic anhydride (0.543 mL, 3.845 mmol) at room temperature. The resulting solution was stirred for 2 hrs and then washed with saturated NaHCO₃. The organic layer was separated and the aqueous layer was extracted once with CH₂Cl₂. The combined extracts were dried over anhydrous MgSO₄ and evaporated. The residue was purified by flash chromatography of silica-gel eluted with EtOAc:Hexanes (1:20 and the 1:10) (R_f = 0.76 in EtOAc:Hexanes 1:4) to give 0.555 g (1.586 mmol, 62%) as a colorless oil.

(((1*S*)-Allyl-(2,2,2-trifluoro-acetyl)-amino)-methyl)-2-phenyl-allyl)-carbamic acid *tert*-butyl ester (3c).

(((1*S*)-Allyl-(2,2,2-trifluoro-acetyl)-amino)-methyl)-2-cyclopropyl-allyl)-carbamic acid *tert*-butyl ester (3d).

1-*tert*-Butoxycarbonyl-(3*S*)-*tert*-butoxycarbonyl-amino-4-methyl-1,2,3,6-tetrahydro-pyridine (4a). A solution of the diene (0.255 g, 0.750 mmol) and $\text{Cl}_2\text{Ru}(\text{CHPh})(\text{P}(c\text{-hexyl})_3)_2$ (0.054 g, 0.075 mmol) in CH_2Cl_2 was heated at reflux for 4 hrs under an argon atmosphere. After cooling, the solvent was evaporated and the residue was purified by flash chromatography of silica-gel eluted with EtOAc:Hexanes (1:8) ($R_f = 0.65$ in EtOAc:Hexanes 1:4) to give 0.200 g (0.641 mmol, 86%) as a light brown oil. $[\alpha]_D^{20} = -13.5^\circ$ ($c = 2.6$ in CHCl_3). ^1H NMR (CDCl_3) δ 5.50 (s, 1H), 4.62 (d, $J = 9$ Hz, 1H), 3.80-4.38 (m, 3H), 4.33-4.64 (m, 1H), 3.03-3.22 (m, 1H), 1.75 (m, 3H), 1.43-1.47 (m, 18H); ^{13}C NMR (CDCl_3) δ 155.8, 155.4, 132.6, 80.0, 79.6, 49.1, 46.6, 43.0, 28.6, 20.8. EIMS m/z 313 ($m+\text{H}$), 257 ($m\text{-Bu-}t$), 213 ($m\text{-Boc}$), 201 ($m\text{-2xBu-}t$), 157 ($m\text{-Bu-}t\text{-Boc}$), 113 ($m\text{-2xBoc}$).

1-(2,2,2-Trifluoro-acetyl)-(3*S*)-*tert*-butoxycarbonyl-amino-4-ethyl-1,2,3,6-tetrahydro-pyridine (4b).

1-(2,2,2-Trifluoro-acetyl)-(3*S*)-*tert*-butoxycarbonyl-amino-4-phenyl-1,2,3,6-tetrahydro-pyridine (4c).

1-(2,2,2-Trifluoro-acetyl)-(3*S*)-*tert*-butoxycarbonyl-amino-(4*R*)-propyl-piperidines.

(3*S*)-amino-(4*R*)-methylpiperidine (7a). A solution of di-Boc protected piperidine **5a** (95 mg, 0.255 mmol) dissolved in 1,4-dioxane (5 mL) and conc. HCl (1 mL) was stirred at room temperature for 30 min. The volatiles were evaporated to give 65 mg (0.250 mmol, 98%) as a white solid. m.p. 65-67 °C. $[\alpha]_D^{20} = -5.8^\circ$ ($c = 2.3$ in MeOH). ^1H NMR (CDCl_3) δ 3.67 (ddd, $J = 1.0, 4.0, 12.2$ Hz, 1H), 3.45 (dddd, $J = 1.0, 2.0, 3.8, 12.8$ Hz, 1H), 3.29 (ddd, $J = 4.3, 11.6, 11.6$ Hz, 1H), 3.10 (dd, $J = 11.6, 11.6$ Hz, 2H), 2.07 (dddd, $J = 3.3, 5.8, 8.9, 14.7$ Hz, 1H), 1.96 (m, 1H), 1.65 (m, 1H), 1.17 (d, $J = 6.6$ Hz, 3H).

(3*S*)-amino-(4*S*)-methylpiperidine (8a). The same deprotection procedure was used to deprotect the piperidine **6a**. $[\alpha]_D^{20} = -15.5^\circ$ ($c = 2.5$ in MeOH). ^1H NMR (CDCl_3) δ 3.83 (br, 1H), 3.45-3.51 (m, 2H), 3.22-3.42 (m, 2H), 2.48 (br, 1H), 1.88-2.15 (m, 2H), 1.20 (d, $J = 6.6$ Hz, 3H).

References:

- 1). Due to rotamers present in most of the *tert*-amide intermediates in the synthesis of (3*S*)-amino-(4*R*)-alkyl- and (3*S*)-amino-(4*S*)-phenyl-piperidines, the authors preferred to include ¹H and ¹³C NMR spectra for ethyl, phenyl and cyclopropyl intermediates and their products to better illustrate complex spectroscopic data.