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Synthesis of Optically Active 2- and 3- Indolylglycine Derivatives and their Oxygen Analogues

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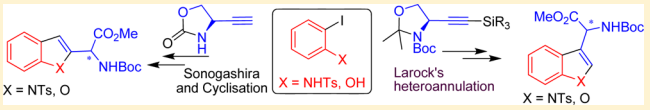
Supporting Information

ABSTRACT: 2-Indolylglycine derivative and its oxygen analogue have been synthesized by Sonogashira coupling followed by cyclization in one pot between 2-iodoheteroarenes and ethynyloxazolidinone where 3-indolylglycine derivative and its oxygen analogue have been synthesized from silylated internal alkyne using Larock's heteroannulation as the key reaction.



Synthesis of indolylglycines is getting importance because of their presence in various bis-indole alkaloids, namely, dragmacidins[1a] and hamacanthins.[1b] Moreover, they can be used in peptide synthesis to limit conformational flexibility, to enhance enzymatic stability and bioavailability compared to native peptides. Synthesis of optically active 3-indolyglycine derivative has been reported using three distinct approaches: (a) through Friedel–Crafts[2a−c] reaction taking the advantage of nucleophilic properties at 3-position of indole, (b) via Sharpless asymmetric aminohydroxylation,[2d] and (c) diastereoselective approach using chiral glyoxalate imines[2e] or optically active ylide.[2f] Other analogues such as 2-indolylglycine and 2-benzofuranyl glycine derivatives are found to be commercially available; however, to the best of our knowledge, there is no literature report on their synthesis except a racemic route of 2-benzofuranyl glycine.[2g] Herein, we describe the synthesis of these heteroaryl amino acid derivatives using chiral pool approach.

Retrosynthetic strategy **A** was used for the synthesis of 3-indolylglycine derivative **1a** and its "O" analogue **1b** using Larock's heteroannulation[3] as the key reaction, whereas retrosynthesis **B** was used for 2-indolylglycine derivative **2a** and its "O" analogue **2b** by way of intermediate **7**. In order to avoid epimerization at the α-C[4b] and undesired intramolecular nucleophilic (O or N) attack to Pd(II)−alkyne complexes,[4a,c] the masked form of propargylglycine derivative was chosen instead of propargylglycine derivative itself (Scheme 1).

Accordingly, acetylated 2-iodoaniline was treated with silylated internal alkyne **3a** under Larock's heteroannulation[3] condition to get 2,3-disubstitued indole derivative **4c**. Treatment of **4c** with TBAF at 0 °C resulted in **5c** due to simultaneous deprotection of sillyl and acetyl groups. Changing the protecting group from acetyl to tosyl enhanced the yield of hetero-annulation reaction, and the tosyl group remained unaffected under the condition of sillyl deprotection. Similarly, the oxygen-analogue **5b** was synthesized from 2-iodophenol, and a better yield was obtained when TBDMS-substituted internal alkyne **3b** was used instead of TMS-protected **3a**. Then oxazolidine deprotection[5] of **5a** and **5b** furnished Boc-protected amino alcohols **6a** and **6b**, respectively, which after oxidation[6,5] followed by esterification with diazomethane afforded the corresponding methyl esters **1a** and **1b** (Scheme 2). The internal alkynes (**3a** or **3b**)[7] were prepared according to the literature procedure from ethynyloxazolidine **12**,[8a] which in turn was synthesized from Garner's aldehyde[8b,c] using Bestmann–Ohira[8d,e] reagent.

For the synthesis of 2-indolylglycine, we initially followed Knight's[9] iodocyclization method on 2-alkynylaniline **8b** and obtained the desired product **9** in poor yield. When compound **8c** was subjected under Larock's[10] iodocyclisation condition, an unexpected nucleophilic attack of Boc led to the formation of **10** instead of expected indole derivative **11**. Cyclisation of **8a** using palladium catalysis[4c] resulted in a complex mixture. From this outcome we realized the problem associated with the N-protecting group of oxazolidine ring (Scheme 3).

In an attempt to solve the problem, acetonide protection was removed from ethynyloxazolidine **12**, and the resulting amino alcohol **13** on teartment with thionyl chloride furnished ethynyloxazolidinone **14**[11] (Scheme 4).

We were pleased to say that coupling of **14** with tosylated 2-iodoaniline under Sonogashira[12] condition gave the desired cyclized product **15a** in one pot. Protection of **15a** with Boc_2O and subsequent carbamate deprotection by cesium carbonate[13] gave Boc-protected amino alcohol **17a**. The alcohol was then converted to its methyl ester **2a** by means of two step oxidation[6] followed by treatment with diazomethane. Similarly, 2-benzofuranylglycine derivative **2b** has been synthesized from 2-iodophenol using the same protocol as stated for nitrogen analogue (Scheme 5).

In conclusion, the synthesis of optically active 2- and 3-indolylglycine derivatives and their oxygen analogues is described. Though the synthesis of 3-indolylglycine was reported by few groups but we are the first to report the synthesis of **1b**, **2a** and **2b** using chiral pool approach. It is anticipated that minor modifications of the starting materials and methods presented here should give various other analogues of these amino acids.

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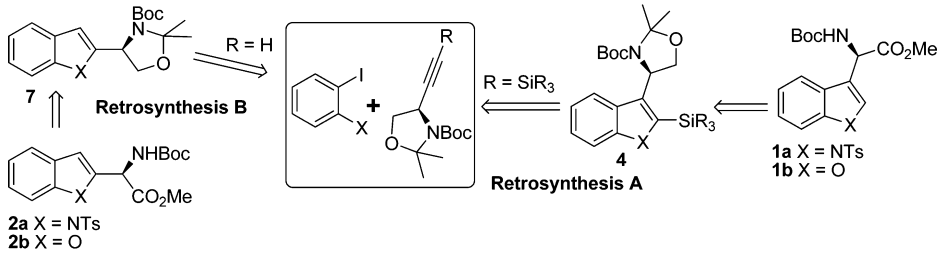
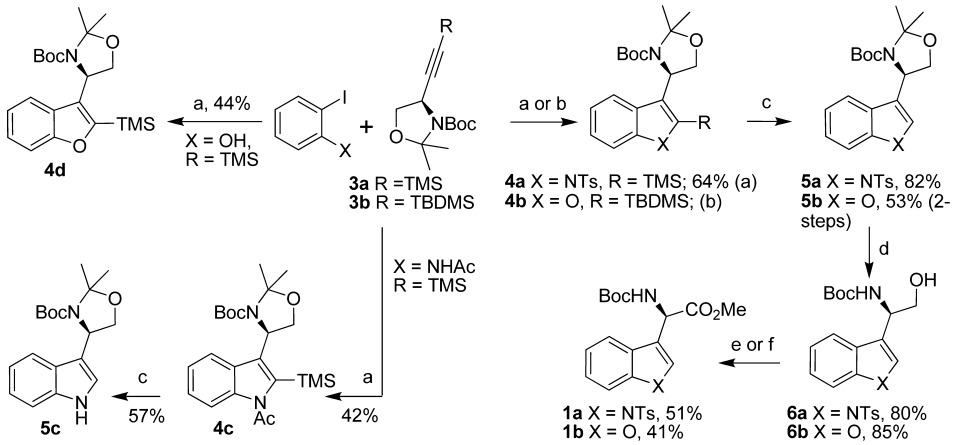
Scheme 1. Retrosynthetic Pathway

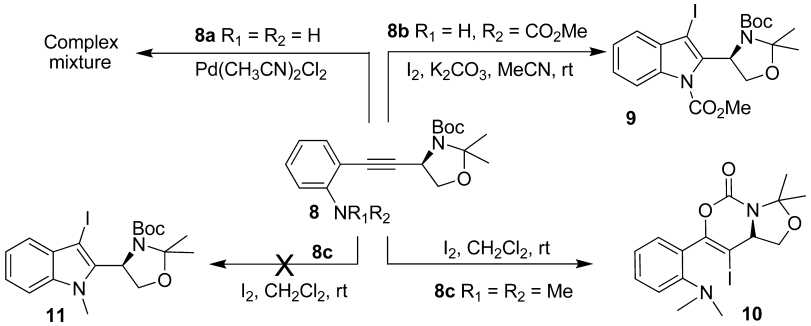


Scheme 2. Synthesis of 3-Indolylglycine Derivative and Its Oxygen Analogue[a]

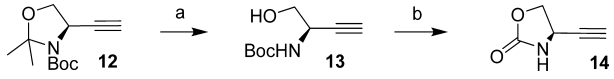


[a]Reaction conditions: (a) **3a**, $Pd(OAc)_2$, PPh_3, *n*-Bu_4Cl, DIPEA, DMF, 90 °C, 12 h; (b) **3b**, $Pd(OAc)_2$, LiCl, Na_2CO_3, DMF, 90 °C, 25 h; (c) TBAF, THF, 0 °C to rt, 2 h; (d) PTSA, MeOH, rt, 2 h; (e) (i) Dess−Martin periodinane, DCM, rt, 30 min, (ii) $NaClO_2$, NaH_2PO_4, *t*-BuOH, H_2O, rt, 1.5 h, (iii) CH_2N_2, ether, (for **1a**); (f) (i) 1 M Jones reagent, acetone, 0 °C, (ii) CH_2N_2, ether, (for **1b**).

Scheme 3. Attempted Synthesis toward 2-Substituted Indole Derivative



Scheme 4. Synthesis of Propargylcarbamate[a]



[a]Reaction conditions: (a) PTSA, MeOH, rt, 2 h, 61%; (b) $SOCl_2$ (distilled), THF, rt, 18 h, 80%.

EXPERIMENTAL SECTION

General Information. All reagents were purchased from commercial sources and used without further purification, unless otherwise stated. Petroleum ether (PE) refers to the fraction of petroleum boiling between 60 and 80 °C. THF is the abbreviation of tetrahydrofuran. All reactions were carried out in oven-dried glassware under an argon atmosphere using anhydrous solvents and standard syringe and septum techniques unless otherwise indicated. Organic extracts were dried over anhydrous Na_2SO_4 and then filtered prior to removal of all volatiles under reduced pressure on rotary evaporation. Chromatographic purification of products was accomplished using column chromatography on silica gels (mesh 100−200). Thin-layer chromatography (TLC) was carried out on aluminum sheets, silica gel 60 F254 (layer thickness 0.25 mm). Visualization of the developed chromatogram was performed by UV light and/or phosphomolybdic acid stains. Optical rotations were measured at stated temperature and solvent. Concentration was in gm/100 mL when $[\alpha]_D$ was recorded. ^1H and ^{13}C NMR spectra were recorded at 500 and 125 MHz, respectively, using $CDCl_3$ as solvent. Chemical shifts (δ) are given in ppm relative to the solvent residual peak or TMS as internal standard. The following abbreviations are used for multiplicity of NMR signals: s = singlet, d = doublet, t = triplet, m = multiplet, br = broad. High resolution mass spectra (HRMS) were measured in a QTOF I (quadrupole-hexapole-TOF) mass spectrometer.

Experimental Procedures. *(R)-tert-Butyl 2,2-Dimethyl-4-(2-(trimethylsilyl)-1-tosyl-1H-indol-3-yl)oxazolidine-3-carboxylate (**4a**).* To a solution of tosylated 2-iodoaniline (100 mg, 0.27 mmol) and (*R*)-*tert*-butyl 2,2-dimethyl-4-(2-(trimethylsilyl)ethynyl)oxazolidine-3-

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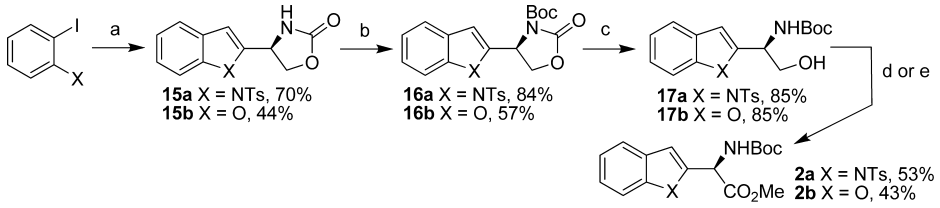
Scheme 5. Synthesis of 2-Indolylglycine Derivative and Its Oxygen Analogue[a]



[a]Reaction conditions: (a) **14**, $Pd(OAc)_2$, PPh_3, CuI, DIPA, DMF, 65 °C, 3 h (for **15a**), 12 h (for **15b**); (b) Boc_2O, THF, Et_3N, DMAP, rt, 16 h (for **16a**), 48 h (for **16b**); (c) Cs_2CO_3, MeOH, rt, 3 h; (d) (i) Dess−Martin periodinane, DCM, rt, 30 min, (ii) $NaClO_2$, NaH_2PO_4, *t*-BuOH, H_2O, rt, 1.5 h, (iii) CH_2N_2, ether (for **2a**); (e) (i) 1 M Jones reagent, acetone, 0 °C, (ii) CH_2N_2, ether (for **2b**).

carboxylate **3a** (90 mg, 0.30 mmol) in dry DMF (3 mL) was added $Pd(OAc)_2$ (6.0 mg, 0.027 mmol) followed by PPh_3 (28 mg, 0.11 mmol), and the reaction vessel was evacuated and flushed with argon three times. To the reaction mixture were added tetrabutyl-ammonium chloride (75 mg, 0.27 mmol) followed by diisopropylethylamine (DIPEA) (0.14 mL, 0.81 mmol) and again flushed with argon. It was heated at 90 °C for overnight. The reaction mixture was cooled to room temperature, and the solvent was removed. The crude residue was subjected for column purification, eluting with petroleum ether−AcOEt (93:7), to afford **4a** as waxy solid (94 mg, 64%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, 1H, J = 6.5 Hz), 7.73 (br m, 1H), 7.39 (d, 2H, J = 7.0 Hz), 7.21 (br s, 1H), 7.11 (t, 1H, J = 7.7 Hz), 7.03 (d, 2H, J = 8.0 Hz), 5.32 (br s, 1H), 3.97 (br s, 1H), 3.69 (br s, 1H), 2.24 (s, 3H), 1.78 (s, 3H), 1.61 (s, 3H), 0. 93−1.37 (2 br s, 9H), 0.57 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.4, 144.2, 140.6, 136.3, 134.4, 130.2, 129.8, 129.6, 129.1, 126.6, 125.4, 123.8, 120.6, 116.2, 95.3, 80.1, 69.0, 55.2, 28.1, 25.5, 21.6, 3.0; HRMS (ESI) $(M + Na)^+$ calculated for $C_{28}H_{38}N_2O_5SSiNa^+$ = 565.2168, found 565.2169.

*(R)-tert-Butyl 2,2-Dimethyl-4-(1-tosyl-1H-indol-3-yl)oxazolidine-3-carboxylate (**5a**).* To a solution of **4a** (80 mg, 0.15 mmol) in tetrahydrofuran (3 mL) was added tetrabutyl ammonium fluoride (0.18 mL of 1.0 M in THF, 0.18 mmol) at 0 °C, and the mixture was stirred at rt for 1 h. After removal of solvent the crude residue was charged directly into column, eluting with petroleum ether−AcOEt (92:8), to give **5a** as white foam (58 mg, 82%): $[\alpha]^{25}_D$ = −65.6 (*c* 1.79, $CHCl_3$); IR (neat/$CHCl_3$) ν 1697 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94−7.99 (br m, 1H), 7.73 (br s, 2H), 7.62 (d, 1H, J = 8.0 Hz), 7.43−7.48 (br m, 1H), 7.30 (br s, 1H), 7.20−7.25 (m, 3H), 5.22 (br s, 0.35 H), 5.06 (br s, 0.65 H), 4.26 (dd, 1H, J = 6.7, 8.7 Hz), 3.98 (d, 1H, J = 8.0 Hz), 2.32 (s, 3H), 1.17−1.78 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.1, 145.0, 135.5, 130.0, 128.7, 126.9, 124.8, 124.5, 124.0, 123.3, 119.8, 113.9, 94.7, 94.2*, 80.5, 80.1*, 68.6, 68.2*, 53.9, 28.5, 28.4, 27.4, 26.5*, 24.6, 23.5*, 21.6 (*Asterisk denotes conformer peaks); HRMS (ESI) $(M + Na)^+$ calculated for $C_{25}H_{30}N_2O_5SNa^+$ = 493.1773, found 493.1774.

*(R)-tert-Butyl 4-(Benzofuran-3-yl)-2,2-dimethyloxazolidine-3-carboxylate (**5b**).* To a solution of 2-iodophenol (109 mg, 0.495 mmol) and (*R*)-*tert*-butyl 4-(2-(*tert*-butyldimethylsilyl)ethynyl)-2,2-dimethyloxazolidine-3-carboxylate **3b** (140 mg, 0.413 mmol) in dry DMF (3 mL) were added lithium chloride (17 mg, 0.41 mmol) and sodium carbonate (131 mg, 1.24 mmol). The reaction vessel was evacuated and flushed with argon three times. Then $Pd(OAc)_2$ (10 mg, 0.041 mmol) was added to it. The reaction mixture was again flushed with argon and heated at 90 °C for 25 h. The reaction mixture was cooled to room temperature, and the solvent was removed under reduced pressure. The crude residue was subjected for column purification, eluting with petroleum ether−AcOEt (96:4), to afford a mixture of **4b** (major) and **3b** as colorless liquid (127 mg).

To a solution of the mixture of **4b** and **3b** (125 mg, 0.29 mmol with respect to **4b**) in tetrahydrofuran (4 mL) was added tetrabutylammonium fluoride (0.28 mL of 1.0 M in THF, 0.28 mmol) at 0 °C, and the mixture was stirred at rt for 1 h. After removal of solvent the crude residue was charged directly into column, eluting with petroleum ether−AcOEt (96:4), to give **5b** as white foam (70 mg, 53% after 2 steps): $[\alpha]^{25}_D$ = −61.5 (*c* 1.17, $CHCl_3$); IR (neat/$CHCl_3$) ν 1697 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (br s, 1H), 7.54−7.61 (br m, 1H), 7.48 (d, 1H, J = 8.0 Hz), 7.29−7.30 (m, 1H), 7.23−7.26 (m, 1H), 5.09−5.24 (br m, 1H), 4.27−4.30 (dd, J = 6.7, 8.7 Hz), 4.11 (br s, 1H), 1.26−1.77 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.8, 152.2, 143.5, 143.0*, 125.9, 124.5, 122.7, 121.4, 120.3, 111.8, 94.7, 94.2*, 80.6, 80.3*, 68.5, 67.9*, 52.9, 28.5, 27.4, 26.4*, 24.7, 23.6* (*Asterisk denotes conformer peaks); HRMS (ESI) $(M + Na)^+$ calculated for $C_{18}H_{23}NO_4Na^+$ = 340.1525, found 340.1525.

*tert-Butyl (R)-2-Hydroxy-1-(1-tosyl-1H-indol-3-yl)ethylcarbamate (**6a**).* To a solution of **5a** (50 mg, 0.106 mmol) in methanol (1.5 mL) was added *p*-toluensulfonic acid (PTSA) monohydrate (10 mg, 0.053 mmol), and the mixture was stirred at room temperature for 2 h. The solution was then neutralized with saturated aqueous $NaHCO_3$, diluted with AcOEt (2 mL), and washed with brine (2 × 1 mL). The organic phase was dried (Na_2SO_4) and concentrated. The residue was eluted from a column with petroleum ether−AcOEt (7: 3) to give **6a** (37 mg, 80%) as white foam: $[\alpha]^{25}_D$ = −36.4 (*c* 1.33, $CHCl_3$), lit.[2d] $[\alpha]^{20}_D$ = +38.6 (*c* 1.25, $CHCl_3$, antipode of **6a**); IR (neat/$CHCl_3$) ν 1699, 3392 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, 1H, J = 8.0 Hz), 7.76 (d, 2H, J = 8.0 Hz), 7.54−7.56 (m, 2H), 7.33 (t, 1H, J = 7.5 Hz), 7.21−7.26 (m, 3H), 5.06−5.10 (m, 2H), 3.97 (s, 2H), 2.34 (s, 3H), 2.25 (br s, 1H), 1.45 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.1, 145.2, 135.4, 135.3, 130.1, 129.2, 127.0, 125.2, 123.8, 123.5, 121.1, 119.9, 113.9, 80.3, 65.1, 49.6, 28.4, 21.6; HRMS (ESI) $(M + Na)^+$ calculated for $C_{22}H_{26}N_2O_5SNa^+$ = 453.1460, found 453.1460.

*tert-Butyl (R)-1-(Benzofuran-3-yl)-2-hydroxyethylcarbamate (**6b**).* To a solution of **5b** (52 mg, 0.16 mmol) in methanol (2.0 mL) was added *p*-toluenesulfonic acid (PTSA) monohydrate (15 mg, 0.08 mmol), and the mixture was stirred at room temperature for 2.5 h. The solution was then neutralized with saturated aqueous $NaHCO_3$, diluted with AcOEt (3 mL), and washed with brine (2 × 1.5 mL). The organic phase was dried (Na_2SO_4) and concentrated. The residue was eluted from a column with petroleum ether−AcOEt (8: 2) to give **6b** (38 mg, 85%) as white foamy solid: $[\alpha]^{25}_D$ = −20.3 (*c* 3.05, $CHCl_3$); IR (neat/$CHCl_3$) ν 1695, 3319 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60−7.61 (m, 2H), 7.48 (d, 1H, J = 8.5 Hz), 7.31 (t, 1H, J = 7.5 Hz), 7.24 (t, 1H, J = 7.7), 5.23 (br s, 1H), 5.06 (br s, 1H), 3.98 (m, 2H), 2.72 (br s, 1H), 1.45 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.2, 155.6, 142.4, 126.4, 124.9, 123.0, 120.1, 119.3, 111.9, 80.4, 65.2, 49.1, 28.5; HRMS (ESI) $(M + Na)^+$ calculated for $C_{15}H_{19}NO_4Na^+$ = 300.1212, found 300.1211.

*tert-Butyl (R)-(Methoxycarbonyl)(1-tosyl-1H-indol-3-yl)-methylcarbamate (**1a**).* To a solution of amino alcohol **6a** (25 mg, 0.058 mmol) in dichloromethane (1 mL) was added solid periodinane (27 mg, 0.064 mmol) portion wise, and the mixture was stirred for 0.5 h. After consumption of starting material (TLC), it was diluted with ether (1.6 mL), and the resulting suspension was added to 1.3 (M) NaOH (0.6 mL). The reaction mixture was stirred for 15 min, and the ether layer was washed with 0.6 mL of 1.3 M NaOH and 2 mL of water. The organic layer was dried, filtered, concentrated in vacuo and used in the next step without any purification.

To a solution of the above crude aldehyde in *t*-BuOH (0.16 mL) and 2-methyl-2-butene (0.08 mL) was added a solution of $NaClO_2$ (20 mg) and NaH_2PO_4 (20 mg) in H_2O (0.3 mL) at rt. The reaction mixture was stirred for 1.5 h and diluted with saturated aqueous NH_4Cl solution (0.5 mL). The organic layer was extracted with AcOEt (3 × 1.5 mL). The combined organic layers were dried, filtered and concentrated in vacuo to give the crude product, which was purified by silica gel column

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chromatography, eluting with petroleum ether−AcOEt (60:40), to afford the corresponding acid as white foam (15 mg).

To the solution of above acid (15 mg, 0.034 mmol) in ether (1 mL) was added excess ethereal diazomethane at 0 °C, and the mixture was stirred for 10 min. After evaporation of ether it was directly charged into column, eluting with DCM−AcOEt (95:5), to give **1a** as a waxy solid (13.5 mg, 51%, after 3 steps from amino alcohol **6a**): $[\alpha]^{26}_{D} = -25.7$ (*c* 0.76, $CHCl_3$); IR (neat/$CHCl_3$) ν 1714, 1745, 3443 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, 1H, *J* = 8.5 Hz), 7.76 (d, 2H, *J* = 8.5 Hz), 7.63 (d, 1H, *J* = 8.0 Hz), 7.57 (s, 1H), 7.33 (t, 1H, *J* = 7.7 Hz), 7.22−7.26 (m, 3H), 5.58 (d, 1H, *J* = 7 Hz), 5.43 (d, 1H, *J* = 6.0 Hz), 3.74 (s, 3H), 2.34 (s, 3H), 1.44 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 155.0, 145.3, 135.4, 135.2, 130.1, 128.8, 127.1, 125.3, 124.8, 123.7, 120.1, 118.3, 113.8, 80.6, 53.0, 50.5, 28.4, 21.7; HRMS (ESI) $(M + Na)^+$ calculated for $C_{23}H_{26}N_2O_6SNa^+$ = 481.1409, found 481.1408.

*tert-Butyl (R)-(Methoxycarbonyl)(benzofuran-3-yl)-methylcarbamate (**1b**).* To a solution of amino alcohol **6b** (20 mg, 0.072 mmol) in acetone (1 mL) at 0 °C was added freshly prepared Jones reagent (1 M, 0.22 mL, 0.22 mmol) dropwise under nitrogen. After completion of the reaction (TLC), it was quenched with isopropyl alcohol (0.25 mL) and partitioned with AcOEt (15 mL) and saturated NH_4Cl (5 mL). After stirring the solution for 1 h, the aqueous layer was separated and re-extracted with AcOEt (15 mL), and the combined organic layers were dried, filtered, and concentrated in vacuo to about 5 mL in volume. The solution of the crude acid was cooled to 0 °C. Excess ethereal diazomethane was added, and the reaction was stirred for 10 min. The diazomethane was blown off with nitrogen, and the organic layer was washed with aqueous $NaHCO_3$ (4 mL), saturated NH_4Cl (4 mL), dried, filtered, and concentrated in vacuo to give the crude product, which was purified by column chromatography, eluting with DCM−AcOEt (95:5), to afford **1b** (9 mg, 41%) as white foam: $[\alpha]^{25}_{D} = -75.1$ (*c* 0.99, $CHCl_3$); IR (neat/$CHCl_3$) ν 1714, 1747, 3363 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.65−7.67 (m, 2H), 7.49 (d, 1H, *J* = 8.0 Hz), 7.31−7.34 (m, 1H), 7.25−7.28 (m, 1H), 5.60 (d, 1H, *J* = 7.0 Hz), 5.50 (br s, 1H), 3.76 (s, 3H), 1.45 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 155.7, 155.1, 143.3, 125.7, 125.1, 123.2, 120.2, 116.9, 111.9, 80.6, 53.0, 49.6, 28.4; HRMS (ESI) $(M + Na)^+$ calculated for $C_{16}H_{19}NO_5Na^+$ = 328.1161, found 328.1161.

*(R)-4-Ethynyloxazolidin-2-one (**14**).* To a solution of **12** (550 mg, 2.0 mmol) in methanol (12 mL) was added *p*-toluenesulfonic acid (PTSA) monohydrate (190 mg, 1.0 mmol), and the mixture was stirred at rt for 3 h. The solution was then neutralized with saturated aqueous $NaHCO_3$, diluted with AcOEt (30 mL), and washed with brine (2 × 10 mL). The organic phase was dried (Na_2SO_4) and concentrated. The residue was eluted from a column with petroleum ether−AcOEt (7: 3) to give **13** (226 mg, 61%) as colorless oil.

Thionyl chloride (0.43 mL, 6 mmol) was added to the solution of aminoalcohol **13** (226 mg, 1.2 mmol) in 12 mL of dry THF under argon atmosphere, and the reaction mixture was stirred at room temperature for 18 h. Evaporation of the solvent under reduced pressure gave the crude, which was purified by flash chromatography (1:1 ethyl acetate/petroleum ether) to get pure propargylcarbamate **14** as yellowish solid (106 mg, 80%): $[\alpha]^{26}_{D} = -7.7$ (*c* 1.67, $CHCl_3$); IR (neat/$CHCl_3$) ν 3246, 2121, 1761 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.08 (br s, 1H), 4.54−4.61(m, 2H), 4.36−4.40 (m, 1H), 2.48 (s, 1H); HRMS (ESI) $(M + H)^+$ calculated for $C_5H_6O_2N^+$ = 112.0399, found 112.0393.

*(R)-4-(1-Tosyl-1H-indol-2-yl)oxazolidin-2-one (**15a**).* To a stirred degassed solution of *N*-tosyl-2-iodoaniline (184 mg, 0.49 mmol) and **14** (50 mg, 0.45 mmol) in diisopropylamine (5.0 mL) and DMF (2.0 mL) under nitrogen were added $Pd(OAc)_2$ (10 mg, 0.045 mmol), PPh_3 (47 mg, 0.18 mmol) and copper iodide (8.5 mg, 0.045 mmol), respectively. The yellowish solution was degassed again and heated at 65 °C for 3 h. After solvent evaporation in vacuo, the residue was directly charged into column, eluting with petroleum ether:AcOEt (1:1), to give **15a**, 112 mg (70%) as yellowish white foam: $[\alpha]^{26}_{D} = +146.7$ (*c* 2.00, $CHCl_3$); IR (neat/$CHCl_3$) ν 1755, 3271 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, 1H, *J* = 8.5 Hz), 7.62 (d, 2H, *J* = 8.5 Hz), 7.48 (d, 1H, *J* = 7.5 Hz), 7.33 (t, 1H, *J* = 8.0 Hz), 7.21−7.27 (m, 3H), 6.80 (s, 1H), 6.60 (s, 1H), 5.50 (dd, 1H, *J* = 4.0, 8.5 Hz), 4.88 (t, 1H, *J* = 8.8 Hz), 4.48 (dd, 1H, *J* = 4.5, 9.0 Hz), 2.35 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.2, 145.6, 139.9, 137.5, 135.3, 130.3, 128.8, 126.3, 125.3, 124.2, 121.5, 114.5, 109.2, 71.6, 51.2, 21.6; HRMS (ESI) $(M + Na)^+$ calculated for $C_{18}H_{16}N_2O_4SNa^+$ = 379.0728, found 379.0727.

*(S)-4-(Benzofuran-2-yl)oxazolidin-2-one (**15b**).* To a stirred degassed solution of 2-iodophenol (54 mg, 0.25 mmol) and **14** (25 mg, 0.22 mmol) in diisopropylamine (3.0 mL) under nitrogen were added $Pd(OAc)_2$ (5 mg, 0.022 mmol), PPh_3 (23 mg, 0.088 mmol) and copper iodide (4 mg, 0.022 mmol), respectively. The yellowish solution was degassed again and heated at 65 °C for 12 h. After solvent evaporation in vacuo the residue was directly charged into column, eluting with petroleum ether:AcOEt (1:1), to give **15b**, 20 mg (44%) as yellowish white solid: $[\alpha]^{26}_{D} = -12.4$ (*c* 0.66, $CHCl_3$); IR (neat/$CHCl_3$) ν 1707, 1741, 3244 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, 1H, *J* = 7.5 Hz), 7.46 (d, 1H, *J* = 8.5 Hz), 7.29−7.32 (m, 1H), 7.23−7.26 (m, 1H), 6.73 (s, 1H), 6.22 (s, 1H), 5.11 (dd, 1H, *J* = 5.5, 9.0 Hz), 4.70−4.74 (m, 1H), 4.54 (dd, 1H, *J* = 5.7, 8.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.4, 155.4, 154.2, 127.7, 125.1, 123.4, 121.5, 111.5, 104.6, 69.1, 50.5; HRMS (ESI) $(M + Na)^+$ calculated for $C_{11}H_{10}NO_3^+$ = 204.0655, found 204.0654.

*(R)-tert-Butyl 2-Oxo-4-(1-tosyl-1H-indol-2-yl)oxazolidine-3-carboxylate (**16a**).* To a well stirred solution of **15a** (110 mg, 0.31 mmol) in dry THF (8 mL) was added Et_3N (0.06 mL, 0.44 mmol), Boc_2O (107 mg, 0.49 mmol). After 10 min DMAP (3.8 mg, 0.031 mmol) was added, and the reaction was stirred at room temperature for 16 h. After that the solution was concentrated under reduced pressure, and the residue was purified by column chromatography with petroleum ether:AcOEt (80:20) as eluent to give **16a** (119 mg, 84%): $[\alpha]^{26}_{D}$ = +91.5 (*c* 0.73, $CHCl_3$); IR (neat/$CHCl_3$) ν 1718, 1817 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, 1H, *J* = 8.5 Hz), 7.75 (d, 2H, *J* = 8.5 Hz), 7.48 (d, 1H, *J* = 8.0 Hz), 7.31 (t, 1H, *J* = 7.5 Hz), 7.23−7.26 (m, 3H), 6.63 (s, 1H), 6.04 (d, 1H, *J* = 7.5 Hz), 4.71 (t, 1H, *J* = 8.8 Hz), 4.42 (dd, 1H, *J* = 2.5, 9.0 Hz), 2.35 (s, 3H), 1.42 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.0, 149.1, 145.6, 138.4, 137.2, 135.3, 130.3, 128.8, 126.8, 125.4, 124.2, 121.4, 114.4, 108.4, 84.5, 68.6, 54.0, 28.0, 21.7; HRMS (ESI) $(M + Na)^+$ calculated for $C_{23}H_{24}N_2O_6SNa^+$ = 479.1253, found 479.1254.

*(S)-tert-Butyl 4-(Benzofuran-2-yl)-2-oxooxazolidine-3-carboxylate (**16b**).* To a stirred solution of **15b** (20 mg, 0.098 mmol) in dry THF (2 mL) were added Et_3N (0.02 mL, 0.14 mmol), Boc_2O (34 mg, 0.15 mmol). After 10 min DMAP (1.2 mg, 0.001 mmol) was added, and the reaction was stirred at room temperature for 48 h. After that the solution was concentrated under reduced pressure, and the residue was purified by column chromatography with petroleum ether:AcOEt (80:20) as eluent to give **16b** (17 mg, 57%): $[\alpha]^{26}_{D} = -102.0$ (*c* 0.97, $CHCl_3$); IR (neat/$CHCl_3$) ν 1716, 1801 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, 1H, *J* = 8.0 Hz), 7.48 (d, 1H, *J* = 8.5 Hz), 7.32 (t, 1H, *J* = 7.2 Hz), 7.24−7.27 (m, 1H), 6.73 (s, 1H), 5.46 (dd, 1H, *J* = 4.2, 8.7 Hz), 4.61 (t, 1H, *J* = 8.7 Hz), 4.45 (dd, 1H, *J* = 4.0, 9.0 Hz), 1.42 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ; 155.1, 153.1, 151.8, 148.8, 127.7, 125.2, 123.4, 121.5, 111.6, 105.2, 84.6, 66.0, 53.0, 28.0; HRMS (ESI) $(M + Na)^+$ calculated for $C_{16}H_{17}NO_5Na^+$ = 326.1004, found 326.1005.

*tert-Butyl (R)-2-Hydroxy-1-(1-tosyl-1H-indol-2-yl)ethylcarbamate (**17a**).* To a well stirred solution of **16a** (100 mg, 0.22 mmol) in dry MeOH (4 mL) was added Cs_2CO_3 (15 mg, 0.044 mmol) in one portion, and the solution was stirred at room temperature for 3 h. Then the solution was neutralized with solid citric acid and concentrated under reduced pressure. The residue was dissolved in AcOEt (15 mL), washed with brine (15 mL), H_2O (15 mL) and dried over Na_2SO_4. The residue was purified by column chromatography using petroleum ether:AcOEt (7:3) as eluent to give **17a** (80 mg, 85%) as waxy solid: $[\alpha]^{26}_{D} = +174.2$ (*c* 1.58, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, 1H, *J* = 8.5 Hz), 7.87 (d, 2H, *J* = 7.0 Hz), 7.41 (d, 1H, *J* = 7.5 Hz), 7.24−7.26 (m, 1H,), 7.17−7.20 (m, 3H), 6.69 (s, 1H), 5.74 (s, 1H), 5.55 (d, 1H, *J* = 5.5 Hz), 4.03−4.10 (m, 2H), 2.30 (s, 3H), 1.84 (br s, 1H), 1.48 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.6, 145.0, 140.5, 137.7, 134.8, 129.9, 129.6, 127.2, 124.7, 124.0, 120.9, 115.2, 111.0, 80.0, 65.5, 51.6, 28.5, 21.6; HRMS (ESI) $(M + Na)^+$ calculated for $C_{22}H_{26}N_2O_5SNa^+$ = 453.1460, found 453.1457.

*(S)-tert-Butyl 1-(Benzofuran-2-yl)-2-hydroxyethylcarbamate (**17b**).* To a well stirred solution of **16b** (17 mg, 0.056 mmol) in dry

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MeOH (1 mL) was added Cs_2CO_3 (3.6 mg, 0.011 mmol) in one portion, and the solution was stirred at room temperature for 3 h. Then the solution was neutralized with solid citric acid and concentrated under reduced pressure. The residue was dissolved in AcOEt (4 mL), washed with brine (2 mL), H_2O (2 mL) and dried over Na_2SO_4. The residue was purified by silica gel chromatography using petroleum ether:AcOEt (7:3) as eluent to give **17b** (13 mg, 85%) as white foamy solid: $[\alpha]^{26}_D$ = −60.9 (*c* 1.19, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, 1H, *J* = 7.5 Hz), 7.43 (d, 1H, *J* = 8.0 Hz), 7.19−7.27 (m, 2H), 6.64 (s, 1H), 5.40 (d, 1H, *J* = 7.5 Hz), 5.00 (br s, 1H), 4.01 (br m, 1H), 3.92−3.94 (m, 1H), 2.48 (br s, 1H), 1.45 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.8, 155.4, 155.0, 128.2, 124.3, 123.0, 121.1, 111.3, 104.2, 80.4, 64.3, 51.3, 28.5; HRMS (ESI) $(M + Na)^+$ calculated for $C_{15}H_{19}NO_4Na^+$ = 300.1212, found 300.1212.

*tert-Butyl (R)-(Methoxycarbonyl)(1-tosyl-1H-indol-2-yl)-methylcarbamate (**2a**).* To a solution of amino alcohol **17a** (50 mg, 0.116 mmol) in dichloromethane (2 mL) was added solid periodinane (55 mg, 0.13 mmol) portion wise, and the mixture was stirred for 0.5 h. It was then diluted with ether (3.0 mL), and the resulting suspension was added to 1.3 (M) NaOH (1.2 mL). After stirring the mixture for 15 min, ether layer was washed with 1.2 mL of 1.3 M NaOH and 4 mL of water. The organic layer was dried, filtered, concentrated in vacuo and used in the next step without further purification.

To a solution of the aldehyde in *t*-BuOH (0.32 mL) and 2-methyl-2-butene (0.16 mL) was added a solution of $NaClO_2$ (40 mg) and NaH_2PO_4 (40 mg) in H_2O (0.6 mL) at rt. The reaction mixture was stirred for 1.5 h and diluted with saturated aqueous NH_4Cl solution (1 mL). The organic layer was extracted with AcOEt (3 × 3 mL). The combined organic layers were dried, filtered and concentrated in vacuo to give the crude product, which was purified by column chromatography, eluting with petroleum ether−AcOEt (60:40), to afford the corresponding acid as white foam (32 mg).

To the solution of above acid (32 mg, 0.072 mmol) in ether (2 mL) was added excess ethereal diazomethane at 0 °C, and the mixture was stirred for 15 min. After evaporation of ether, it was directly charged into column, eluting with DCM−AcOEt (95:5), to obtain **2a** as a waxy solid (28 mg, 53%): $[\alpha]^{26}_D$ = −52.2 (*c* 1.85, $CHCl_3$); IR (neat/$CHCl_3$) ν 1708, 1735, 3371 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, 1H, *J* = 9.5 Hz), 7.73 (d, 2H, *J* = 8.5 Hz), 7.48 (d, 1H, *J* = 7.5 Hz), 7.19−7.26 (m, 4H), 6.78 (s, 1H), 6.10 (d, 1H, *J* = 8.5 Hz), 5.85 (br s, 1H), 3.74 (s, 3H), 2.34 (s, 3H), 1.45 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2, 155.2, 145.1, 136.9, 136.6, 135.8, 129.9, 128.8, 127.1, 125.3, 123.8, 121.5, 114.6, 113.3, 80.5, 53.1, 52.7, 28.5, 21.7; HRMS (ESI) $(M + Na)^+$ calculated for $C_{23}H_{26}N_2O_6SNa^+$ = 481.1409, found 481.1409.

*(R)-Methyl 2-(Benzofuran-2-yl)-2-(tert-butoxycarbonylamino)-acetate (**2b**).* To a solution of amino alcohol **17b** (12 mg, 0.043 mmol) in acetone (0.70 mL) at 0 °C was added freshly prepared Jones reagent (1 M, 0.13 mL, 0.13 mmol) dropwise under nitrogen. After completion of the reaction (TLC), it was quenched with isopropyl alcohol (0.14 mL) and partitioned with AcOEt (10 mL) and saturated NH_4Cl (3.5 mL). After stirring the solution for 1 h, the aqueous layer was separated and re-extracted with AcOEt (10 mL), and the combined organic layers were dried, filtered, and concentrated in vacuo to about 5 mL in volume. The solution of the crude acid was cooled to 0 °C. Excess ethereal diazomethane was added to it, and the reaction was stirred for 10 min. The organic layer was washed with aqueous $NaHCO_3$ (3 mL), saturated NH_4Cl (3 mL), dried, filtered, and concentrated in vacuo to give the crude product, which was purified by column chromatography, eluting with DCM−AcOEt (95:5), to afford **2b** (5.6 mg, 43%) as white foam: $[\alpha]^{26}_D$ = −110.3 (*c* 0.44, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, 1H, *J* = 7.5 Hz), 7.45 (d, 1H, *J* = 8.0 Hz), 7.29 (t, 1H, *J* = 7.5 Hz), 7.23 (t, 1H, *J* = 7.5 Hz), 6.75 (s, 1H), 5.62 (m, 2H), 3.79 (s, 3H), 1.45 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.4, 155.1, 155.0, 151.8, 128.0, 124.9, 123.2, 121.5, 111.6, 105.5, 80.8, 53.3, 52.2, 28.4; HRMS (ESI) $(M + Na)^+$ calculated for $C_{16}H_{19}NO_5Na^+$ = 328.1161, found 328.1162.

■ ASSOCIATED CONTENT

Supporting Information

Spectroscopic data as well as copies of the spectra of all new compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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