Diazonamide Support Studies: Stereoselective Formation of the C10 Chiral Center in both the CDEFG and AEFG Fragments

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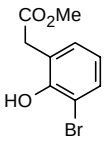
Supporting Information

Part 1. Experimental procedures

General Methods

Melting point determinations are uncorrected. Specific rotations were measured on a Jasco Dip-370 polarimeter and values are quoted in 10^{-1}degcm^{2}g^{-1}. Infrared spectra were recorded as thin films on salt plates on a Perkin-Elmer 781 spectrophotometer, with ν_{max} in inverse centimeters. Proton (^{1}H-NMR) and carbon (^{13}C-NMR) magnetic resonance spectra were obtained in $CDCl_3$ at 600 MHz or 500 MHz and 125 MHz, respectively (unless otherwise noted). The following abbreviations were utilized to describe peak patterns when appropriate: br=broad, s=single, d=doublet, t=triplet, q=quarter, quint=quintuplet and m=multiplet.

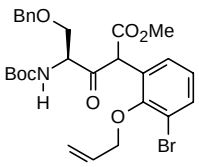
All air and moisture sensitive reactions were carried out under an atmosphere of dry argon using oven-dried or flame-dried glassware and standard syringe techniques. Tetrahydrofuran was distilled from sodium/benzophenone. Benzene and toluene were distilled from sodium. Dichloromethane, acetonitrile, 1,2-dichloroethane, triethylamine, pyridine, diisopropylamine and diisopropylethylamine were distilled from CaH_2. DMF and DMSO was pretreated with 4Å molecular sieves overnight and then distilled from 4Å molecular sieves under vacuum. 2,4,6-Collidine was distilled from CaH_2 under vacuum. Methanol was distilled over magnesium turnings. Anhydrous chloroform was purchased from Acros and used as received. Triphenylphosphine was recrystallized from CH_2Cl_2/hexanes in the freezer. Trityl chloride was recrystallized from isooctane. $Pb(OAc)_4$ was dried over solid KOH under vacuum for 3 h before use or washed with distilled Et_2O three times then dried under vacuum for 15 min. Flash chromatography was performed on Merck 60, 40-75 mesh silica gel using ethyl acetate-hexane mixtures as solvent unless otherwise indicated. Thin layer chromatography (TLC) was carried out on Whatman silica gel plates with UV detection.



Methyl (3-bromo-2-hydroxyphenyl)acetate (12). In a 250 mL round bottom flask fitted with a reflux condenser, 2-hydroxyphenylacetic acid (**11**, 12.50 g, 0.08 mol) was dissolved in methanol (125 mL) and conc. HCl (0.25 mL). The solution was heated under reflux overnight. The solvent was removed by vacuum and the crude product was redissolved in dichloromethane (100 mL) which was washed with sat. sodium carbonate (50 mL), water, and brine. The organic layers were then combined, dried with sodium sulfate and evaporated to afford the desired product as a white solid (12.55 g, 95 %) which was used without further purification. mp 70-71 °C; ^{1}H-NMR ($CDCl_3$): δ = 7.42 (dd, *J* = 8.5, 1.5 Hz, 1 H), 7.12 (d, *J* = 7.5 Hz, 1 H), 6.78 (t, *J* = 8.0 Hz, 1 H), 3.73 (s, 3 H), 3.71 (s, 2 H); ^{13}C-NMR ($CDCl_3$): δ = 174.1, 154.9, 131.0, 129.0, 120.4, 117.0, 52.6, 37.1. IR: (Nujol Mull) 3425, 2924, 1721, 1590, cm^{-1}; HRMS [M+H] for $C_9H_{11}O_3$, calcd., 167.07027, found, 167.06936.

In a 1000 mL round bottom flask, toluene (425 mL) and *t*-butylamine (13.5 mL, 9.4 g, 128.4 mmol) were added. The mixture was cooled to –30 °C (isopropanol and dry ice), and bromine (3.6 mL, 72.1 mmol, 0.8 equiv) was added dropwise into the reaction mixture. The resulting solution was stirred at -30 °C for an additional hour and then cooled to -78 °C by addition of more dry ice. 2-Hydroxyphenylacetic acid methyl ester (14.2 g, 86.2 mmol, 1.0 equiv) dissolved in dichloromethane was added slowly into the mixture and the reaction was allowed to warm to room temperature over a period of 6 h and stirred overnight. Water was then added into the reaction mixture and the organic layer was separated from the aqueous. The aqueous layer was extracted three times with dichloromethane and the combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography using ethyl acetate/hexanes (3/7) to afford the product as a yellow solid (13.5 g, 76%). mp 50-52 °C; ^{1}H-NMR ($CDCl_3$): δ = 7.42 (dd, *J* = 8.5, 1.5 Hz, 1 H), 7.12

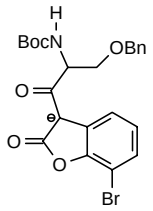
(d, J = 7.5 Hz, 1 H), 6.78 (t, J = 8.0 Hz, 1 H), 3.73 (s, 3 H), 3.71 (s, 2 H); ^{13}C-NMR ($CDCl_3$): δ = 172.5, 151.1, 131.7, 130.8, 122.4, 121.8, 111.2, 52.5, 36.8; IR (thin film): 3277, 2921, 1719, cm^{-1}; Anal. Calcd. for $C_9H_9BrO_3$: C, 44.11; H, 3.70. Found: C, 44.20; H, 3.82; HRMS [M+H] for $C_9H_9BrO_3$, calcd., 244.98061, found, 244.98078.



(4*S*) Methyl 2-(2-allyloxy-3-bromophenyl)-5-benzyloxy-3-oxo-4-[*N*-(Boc)amino]-pentanoate (13). To a solution of **12** (6.0 g, 24.5 mmol, 1.0 equiv) in acetone (55 mL) was added potassium carbonate (16 g, 115.7 mmol, 4.7 equiv) and allyl bromide (4.08 mL, 47 mmol, 2.0 equiv). The mixture was vigorously stirred overnight at room temperature. The solution was filtered and then evaporated under reduced pressure. The residue was then taken up with ethyl acetate, washed with water and brine, dried over sodium sulfate and evaporated. The residue was purified by either bulb to bulb distillation (160 °C at 0.26 mm) or silica gel chromatography using ethyl acetate/hexanes (1/9) to afford the desired product as a light yellow oil (6.4 g, 92%). ^{1}H-NMR: ($CDCl_3$) δ = 7.47 (dd, J = 7.5, 1.5 Hz, 1 H), 7.20 (dd, J = 7.5, 1.5 Hz, 1 H), 6.94 (dd, J = 7.5, 7.5 Hz, 1 H), 6.11 (m, 1H), 5.43 (dddd, J = 1.5, 1.5, 1.5, 17 Hz, 1 H), 5.27 (dd, J = 10, 1.5 Hz, 1 H), 4.94 (m, 2 H), 3.69 (s, 2 H), 3.68 (s, 3 H); ^{13}C-NMR: ($CDCl_3$) δ = 171.7, 154.5, 133.4, 132.9, 130.5, 130.2, 125.5, 118.1, 117.6, 74.3, 52.2, 36.0; IR: (thin film) 2941, 1806, 1740, 1639 cm^{-1}; HRMS [M+H] for $C_{12}H_{14}BrO_3$, calcd., 285.01208, found, 285.01502.

To a solution of *N*-Boc-Ser(OBn)-OH (4.03 g, 13.6 mmol, 1.0 equiv) in THF (100 mL) was added 1,1´-carbonyldiimidazole (2.32 g, 14.3 mmol, 1.05 equiv) under an argon atmosphere, and the mixture was stirred for 2 h. In another flask, an LDA solution was prepared at –78 °C by slow addition of *n*-BuLi (2.2 M solution, 12.4 mL, 27.2 mmol, 2.0 equiv) to THF (100 mL) and diisopropylamine (3.83 mL, 27.2 mmol, 2.0 equiv). The solution was stirred for 30 min at –78

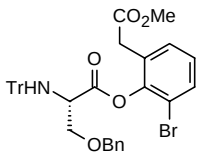
°C, followed by the addition of the allyl ether described above (7.8 g, 27.3 mmol, 2 equiv) in THF (30 mL). This solution was stirred for 1 h at –78 °C, and the *N*-Boc-Ser(OBn)-OH/CDI solution (above) was then added dropwise. The reaction mixture was slowly warmed to room temperature and stirred overnight. The solution was then quenched with saturated aqueous ammonium chloride (50 mL) and extracted with ethyl acetate (3×150 mL). The combined organic layers were then washed with brine, dried with magnesium sulfate, and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography eluting with hexanes/diethyl ether (8/2) to afford the desired product in 65% yield as a sticky foamy solid which is a mixture of enol/keto forms. $[\alpha]^{25}_{D}$ -8.0° (*c* 0.5 CH_2Cl_2); ^{1}H-NMR: δ = 13.15 (s), 7.52 (dd, *J* = 1.0, 8.0 Hz), 7.54 (bd), 7.48 (dd, *J* = 1.0, 8.0 Hz), 7.35-7.22 (m), 7.21, (d, *J* = 7.0 Hz), 7.18 (d, *J* = 6.5 Hz), 7.08 (dd, *J* = 1.0, 8.0 Hz), 7.024 (dd, *J* = 8.0, 8.0 Hz), 6.97 (dd, *J* = 8.0, 8.0 Hz), 6.88 (dd, *J* = 8.0, 8.0 Hz), 5.58 (s), 5.55 (s), 5.45-5.42 (m), 5.23 (ddd, *J* = 1.0, 9.5, 9.5 Hz), 5.20-5.10 (m), 4.61 (ddd, *J* = 3.5, 3.5, 8.5 Hz), 4.54 (ddd, *J* = 5.0, 5.0, 10.0 Hz), 4.48 (s), 4.35 (s), 4.32 (dd, *J* = 6.5, 6.5 Hz), 4.18 (ddd, *J* = 5.5, 5.5, 10.0 Hz), 3.93 (ddd, *J* = 3.0, 3.0, 10.0 Hz), 3.71 (s), 3.70 (s), 3.66 (dd, *J* = 1.5, 2.0 Hz), 3.53 (dd, *J* = 8.0, 8.0 Hz), 1.42 (s), 1.41 (s), 1.35 (s); ^{13}C-NMR: δ = 201.3. 172.9. 171.8. 170.4, 168.8, 168.6, 155.2, 154.3, 153.9, 137.8, 137.4, 134.0, 133.7, 133.6, 133.3, 132.9, 132.3, 129.9, 129.8, 128.4, 127.8, 127.7, 125.8, 125.6, 125.1, 118.7, 117.6, 117.4, 117.0, 101.5, 80.2, 79.8, 74.9, 74.1, 73.5, 73.4, 72.9, 70.4, 69.9, 69.4, 69.1, 60.1, 59.1, 55.1, 54.8, 53.6, 53.0, 52.8, 52.5, 52.2, 50.6, 50.2, 28.4; IR (thin film): 3426, 1708, 1651 cm^{-1}; Elemental Analysis: Theory C; 57.66, H 5.73. Found C; 57.69, H; 5.62; HRMS [M+H] for $C_{27}H_{33}BrO_7N$, calcd., 562.14349, found, 562.14167.



Benzofuranone Salt 8-Boc. Compound **13** (0.22 g, 0.387 mmol, 1.0 equiv) was added to a flask, followed by THF (15 mL). After stirring, *trans*-dichlorobis(triphenylphosphine)palladium (II) (10 mg, 0.02 equiv) was added, followed by the dropwise addition of tributyltin hydride (0.10 mL, 0.113 mmol, 1.0 equiv) over 20 min. The reaction was followed by TLC and upon consumption of starting material (approx. 1 h) the mixture was concentrated *in vacuo.* The crude material was purified by silica gel column chromatography eluting with hexanes/ethyl acetate (6:1) yielding the desired material in 80% yield as an off-white solid composed of a mixture of enol/keto forms. ^{1}H-NMR ($CDCl_3$): 13.2-13.1 (m, 1 H), 7.44-7.04 (m, 5 H), 6.79-6.52 (m, 3 H), 6.15-5.77 (m, 1 H), 5.46-4.90 (m, 2 H), 4.80-4.00 (m, 4 H), 3.90-3.34 (m, 5 H), 1.55-1.23 (m, 9 H); ^{13}C-NMR ($CDCl_3$): δ = 201.1, 172.0, 169.5, 169.3, 169.2, 168.6, 158.8, 155.3, 155.1, 137.4, 136.7, 136.6, 133.1, 137.8, 132.6, 132.4, 132.2, 132.1, 132.0, 130.3, 130.2, 128.6, 128.5, 128.4, 128.1 127.8, 127.7, 127.6, 127.5, 125.2, 125.0, 123.1, 123.6, 122.7, 122.6, 122.5, 122.4, 121.9, 121.7, 121.0, 115.6, 111.2, 110.6 103.1, 103.0, 101.7, 77.5, 77.0, 76.5, 741, 73.7, 73.5, 73.4 73.1, 7.5, 69.4, 58.0, 55.8, 55.2, 55.1, 54.9, 53.8, 53.3, 52.7, 52.5, 52.2, 51.6, 28.7, 28.3, 14.1; IR (neat): 3364, 2978, 1743, 1731, 1714, 1694 cm^{-1}; HRMS-ES+ Calculated for $C_{24}H_{29}BrNO_7$ (M + H): 522.1127; Found 522.1125.

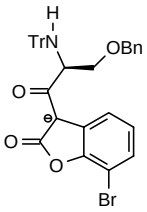
The phenol prepared above (0.175 g, 0.335 mmol, 1.0 equiv) was azeotroped with chloroform, then placed in a two neck flask and toluene (15 mL) was added, then cooled to 0 °C. A sodium methoxide solution (0.895 M, 0,375 mL, 0.334 mmol, 0.98 equiv) was added dropwise over 20 min. The solution was then allowed to warm up very slowly overnight to room temperature. The solution was then cooled, and evaporated under reduced pressure to yield 90% of a pure white solid. ^{1}H-NMR (DMSO-d_6): δ = 7.65 (d, J = 7.5 Hz, 1 H), 7.33-7.20 (m, 4 H), 6.90 (d, J = 8.0

Hz, 1 H), 6.79 (t, *J* = 8.0 Hz, 1 H), 6.26 (d, *J* = 8.0 Hz, 1 H), 5.32-5.28 (m, 1 H), 4.55-4.40 (m, 2 H), 1.38 (s, 9 H). ^{13}C-NMR (DMSO-d_6): δ = 186.0, 168.6, 154.7, 138.8, 128.2, 127.9, 127.6, 127.3, 127.1, 122.9, 121.3, 116.6, 99.5, 94.1, 71.6, 71.0, 27.9; IR (Nujol Mull): 3299, 2929, 1653 cm^{-1}; HRMS-ES+ Calculated for $C_{23}H_{23}BrNNa_2O_6$ (M+Na): 534.0504; Found 534.0506.

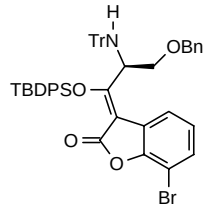


(*S*)-3-Benzyloxy-2-(tritylamino)-propionic acid, 2-bromo-6-methoxycarbonylmethylphenyl ester 14: To a solution of Tr-Ser(OBn)-OH (3.16 g, 7.22 mmol, 1.25 equiv) dissolved in methylene chloride (10 mL) was added dicyclohexylcarbodiimide (1.79 g, 8.66 mmol, 1.5 equiv) at 0 °C. The mixture was allowed to slowly warm to room temperature over 30 min at which time a white precipitate fell out of solution. The mixture was brought to 0 °C, and **12** (1.42 g, 5.77 mmol, 1.0 equiv) in methylene chloride (10 mL) and 4-dimethylaminopyridine (0.85 g, 6.93 mmol, 1.2 equiv) were added. The ice-bath was removed and the mixture was stirred at room temperature for 6 h. The resulting mixture was then filtered and the solvent was removed by vacuum. The resulting oil was dissolved in ethyl acetate (20 mL) and washed with 5% aqueous sodium bicarbonate (10 mL), 5% aqueous citric acid (10 mL), and brine (10 mL). The organic layer was dried with magnesium sulfate and evaporated. The crude material was purified by silica gel column chromatography eluting with hexanes/diethyl ether (8/2) yielding a white solid (3.38 g, 88%). mp 51-54 °C; $[\alpha]^{25}_{D}$ –24.5° (*c* 11.5., CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ = 7.58 (d, *J* = 8.1 Hz, 6 H), 7.54 (d, *J* = 7.9 Hz, 1 H), 7.31-7.17 (m, 15 H), 7.10 (t, *J* = 7.8 Hz, 1 H), 4.32 (d, *J* = 12.5 Hz, 1 H), 4.16 (d, *J* = 12.5 Hz, 1 H), 3.85-3.83 (m, 1 H), 3.60 (s, 3 H), 3.58 (d, *J* = 17.5 Hz, 1 H), 3.48 (d, *J* = 17.5 Hz, 1 H), 3.42 (d, *J* = 7.6 Hz, 1 H), 2.86 (d, *J* = 8.8 Hz, 1 H), 2.35 (dd, *J* = 4.3, 9.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ = 171.0, 170.6, 147.1, 146.4, 137.8, 132.5, 130.4, 129.5, 128.8, 128.4, 128.0, 127.8, 127.4, 126.7, 117.2, 73.2, 71.4, 70.5, 57.4, 52.2, 35.8; IR (Thin Film) 3303. 3032,

2931, 1740, 1704, 1650 cm^{-1}; HRMS for [M+Na] $C_{38}H_{35}NO_5BrNa$, calcd., 686.15126, found, 664.15137.

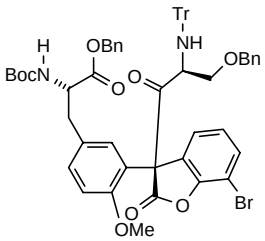


Benzofuranone Salt 8-Tr. Potassium hydride (0.403 g, 3.02 mmol, 1 equiv, 30% in oil) in THF (10 mL) was brought to -78 °C at which point a solution of **14** (2.00 g, 3.02 mmol, 1.0 equiv) dissolved in THF (10 mL) was added dropwise. The mixture was slowly allowed to warm to room temperature for 10 h. Solvent was removed by vacuum, resulting in an off-white solid (1.98 g, 99%) which was used without purification. ^{1}H-NMR (DMSO): δ = 7.47-7.45 (m, 6 H), 7.42 (dd, *J* = 1.0, 7.0 Hz, 1 H), 7.43-7.19 (m, 5 H), 7.11-7.05 (m, 6 H), 7.01-6.96 (m, 3 H), 6.76 (dd, *J* = 1.0, 7.0 Hz, 1 H), 6.64 (dd, *J* = 7.0, 7.0 Hz, 1 H), 4.60 (m, 1 H), 4.52 (d, *J* = 12.5 Hz, 1 H), 4.48 (d, *J* = 12.5 Hz, 1 H), 3.75 (bs, 1 H), 3.44 (dd, *J* = 6.0, 10.0 Hz, 1 H), 3.37 (dd, *J* = 3.5, 10.0 Hz, 1 H); ^{13}C-NMR (DMSO): δ = 168.3, 146.9, 139.3, 133.4, 128.7, 128.0, 127.2, 126.9, 125.7, 122.4, 120.3, 116.3, 98.9, 87.4, 74.1, 71.8, 70.3, 67.0, 25.1; IR: (thin film) 3394, 3292, 3058, 2866, 1683 cm^{-1}.



TBDPS derivative of Benzofuranone Salt 8-Tr. The potassium salt **8-Tr** (50 mg, 0.08 mmol, 1.0 equiv) was dissolved in THF (2 mL). The resulting solution was cooled to 0 °C and TBDPS-Cl (28 μL, 0.11 mmol, 1.5 equiv) was added dropwise. The reaction mixture was allowed to warm to room temperature and was stirred for 2 h. The solvent was then removed under vacuum and the crude product was purified by column chromatography using hexanes/ethyl acetate (7:3) on a column that was pre-treated with hexanes/ethyl acetate (7:3) with 1% triethylamine, yielding the desired product (32 mg, 49 %). ^{1}H NMR: δ = 7.79 (dd, *J* = 1.0, 6.5 Hz, 1 H), 7.54 (dd, *J* = 2.0, 8.0 Hz, 6 H), 7.72-7.23 (m, 24 H), 7.12-7.10 (m, 1 H), 6.96 (dd, *J* = 8.0, 8.0 Hz, 1 H), 4.94 (bs, 1 H), 4.47 (q, *J* = 12.5, 1 H), 3.77-3.73 (m, 1 H), 3.46 (bs, 1 H), 1.10 (s, 9 H); ^{13}C NMR: δ = 169.9, 150.1,

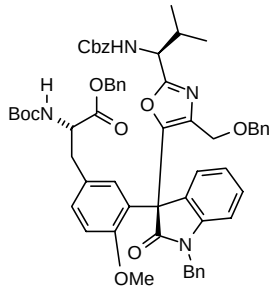
146.9, 146.7, 139.9, 136.8, 135.5, 135.3, 134.9, 132.6, 131.2, 130.4, 129.9, 129.8, 128.9, 128.7, 128.4, 128.2, 128.1, 127.9, 127.7, 126.2, 121.5, 119.0, 112.9, 82.2, 74.2, 70.9, 56.5, 26.8, 19.2.



EFG ring system 6-Tr. Benzofuranone salt **8-Tr** (0.677 g, 1.01 mmol, 1.0 equiv) was dissolved in 1,2-dichloroethane (10 mL) to which aryllead(IV) reagent **10** (1.73g, 2.25 mmol, 2.25 equiv) in 1,2-dichloroethane (10 mL) was added. The solution was stirred for 24 h at about 40 °C. Sodium sulfide solution (20 mL, 3% aq. solution) was added into the reaction and stirred for 15 min. The mixture was then filtered through Celite and the filter cake was washed with dichloromethane. The organic layer was separated and the aqueous layer was extracted with dichloromethane (10 mL x 2). The combined organic layer was washed with brine and dried over sodium sulfate. The solvent was then removed under vacuum and the crude residue was purified using silica gel column chromatography eluting with ethyl acetate/hexanes (3/7) to yield compound **6-Tr** (0.457 g, 45%). mp 160-162°C; $[\alpha]^{25}_{D}$ + 41.2 (c 0.5, $CHCl_3$); ^{1}H-NMR ($CDCl_3$): δ = 7.46-6.99 (m, 30 H), 6.71 (d, *J* = 8.5 Hz, 1 H), 5.17 (d, *J* =12.5 Hz, 1 H), 5.07 (d, *J* =12.5 Hz, 1 H), 4.97 (d, *J* = 8.5, 1 H), 4.38 (m, 1 H), 4.06 (m, 2 H), 3.87 (d, *J* = 11.5 Hz, 1 H), 3.51 (s, 3 H), 3.43 (m, 1 H), 2.80 (dd, *J* =14.5, 6.0 Hz, 1 H), 2.46 (dd, *J* = 13.5, 8.0 Hz, 1 H), 2.28 (dd, *J* = 10.0, 5.0 Hz, 1 H), 2.18 (d, *J* = 8.0 Hz, 1 H), 1.39 (s, 9 H); ^{13}C-NMR ($CDCl_3$): δ = 201.7, 173.8, 171.7, 156.2, 155.4, 151.4, 145.6, 137.3, 135.6, 132.5, 131.3, 130.4, 130.0, 128.8, 128.7, 128.5, 128.4, 128.3, 128.2, 127.8, 126.8, 126.6, 125.4, 124.7, 112.8, 102.6, 79.8, 72.4, 72.3, 69.9, 66.9, 62.7, 55.8, 54.8, 37.2, 28.4; IR ($CDCl_3$): 3349, 3061, 2931, 1801, 1714, 1607 cm^{-1}; HRMS for [M+H] $C_{59}H_{56}N_2O_9Br$, calcd., 1015.31637, found, 1015.31043.

EFG ring system (15). Sodium hydride (60% suspension in mineral oil, 0.366 g, 9.1 mmol, 1.05 equiv) was stirred in THF (50 mL). To this solution is added *N*-benzyl oxindole **9** (5.58 g, 8.7 mmol, 1.0 equiv) in THF (50 mL) and the resulting mixture is allowed to react with stirring at room temperature for 15 min prior to concentration *in vacuo*. The resultant dry sodium salt of the *β*-ketoamide was stirred in chloroform (200 mL) and treated with a solution of aryllead(IV) reagent **10** (12.1 g, 15.7 mmol, 1.8 equiv) in chloroform (100 mL) over 15 min. The resultant solution was allowed to stir for 24 h at room temperature. The reaction was quenched with Na_2S (3% aq. solution, 100 mL) and passed through celite to remove solid material. The organic layer was separated and the aqueous layer extracted with chloroform (50 mL x 3). The combined organic layer was dried over sodium sulfate filtered and concentrated *in vacuo*. Column chromatography afforded the desired product as two separable isomers. **15**: (5.53 g, 62%) Mp: 72-74 °C; $[\alpha]^{25}_D$= -50.1, (c = 0.047 $CHCl_3$); ^{1}H-NMR ($CDCl_3$): δ = 7.41-7.40 (m, 5 H), 7.32-7.31 (m, 4 H), 7.26-7.13 (m, 21 H), 6.96-6.93 (m, 2 H), 6.85 (d, *J* = 5.9 Hz, 2 H), 6.74 (dd, *J* = 15.6, 7.8 Hz, 2 H), 6.63 (s, 1 H), 5.02 (dd, *J* = 11.2, 2.5 Hz, 2 H), 4.86-4.83 (m, 2 H), 4.52 (d, *J* = 15.1 Hz, 1 H), 4.24 (m, 1 H), 3.55 (d, *J* = 11.7 Hz, 1 H), 3.35 (d, *J* = 11.7 Hz, 1 H), 3.27 (s, 3 H), 2.93 (d, *J* = 8.3 Hz, 1 H), 2.89 (dd, *J* = 14.2, 5.4 Hz, 1 H), 2.74 (dd, *J* = 13.7, 6.4 Hz, 1 H), 2.49 (br, 1 H), 2.43 (d, *J* = 10.3 Hz, 1 H), 1.38 (s, 9 H); ^{13}C-NMR ($CDCl_3$): δ = 202.2, 173.9, 171.9, 157.0, 155.2, 146.5, 142.7, 137.8, 135.8, 135.4, 130.1, 129.0, 128.8, 128.8, 128.4, 128.2, 128.11, 128.07, 127.9, 127.82, 127.76, 127.3, 126.5, 123.0, 113.5, 108.8, 79.9, 72.2, 71.0, 69.0, 67.0, 66.8, 61.1, 56.3, 54.4, 44.3, 37.4, 28.4; IR (thin film) 3435, 3030, 1712, 1609; HRMS for $C_{66}H_{64}N_3O_8$ calcd. 1026.4688, found, 1026.4627. **minor isomer**: (0.714 g, 8%) Mp: 90-92 °C; $[\alpha]^{25}_D$= 11.4 (c=0.04 $CHCl_3$); ^{1}H-NMR ($CDCl_3$): δ = 7.49 (m, 2 H), 7.38-7.20 (m, 10 H), 7.27-7.25 (m, 3 H), 7.23-

7.20 (m, 4 H), 7.05-6.98(m, 9 H), 6.93-6.90 (m, 2 H), 6.62 (d, *J* = 8.3 Hz, 1 H), 5.32 (d, *J* = 2.2 Hz, 1 H), 5.26 (d, *J* = 2.2 Hz, 1 H), 4.88 (d, *J* = 7.8 Hz, 1 H), 4.74 (d, *J* = 15.1 Hz, 1 H), 4.59 (d, *J* = 14.7 Hz, 1 H), 4.45 (dd, *J* = 12.5, 4.6 Hz, 1 H), 4.28 (d, *J* = 12.2 Hz, 1 H), 4.10 (d, *J* = 12.2 Hz, 1 H), 3.86 (d, *J* = 5.3 Hz, 1 H), 3.24 (d, *J* = 7.8 Hz, 1 H), 3.13 (dd, *J* = 11.0, 5.0 Hz, 1 H), 3.09 (s, 3 H), 2.81 (dd, *J* = 13.5, 6.0 Hz, 1 H), 2.68 (dd, *J* = 13.5, 5.0 Hz, 1 H), 1.42 (s, 9 H); ^{13}C-NMR ($CDCl_3$): δ = 201.7, 175.6, 171.7, 156.0, 155.2, 146.4, 142.6, 138.3, 136.3, 135.6, 130.2, 129.8, 128.9, 128.8, 128.7, 128.6, 128.4, 128.3, 128.0, 127.8, 127.4, 126.7, 126.2, 123.0, 112.6, 108.1, 79.8, 72.7, 71.2, 70.3, 67.7, 67.3, 62.2, 55.6, 54.5, 44.8, 37.0, 28.5; IR (thin film) 3436, 2930, 1709 cm^{-1}; HRMS for $C_{66}H_{64}N_3O_8$ [M+H$^+$] calcd. 1026.4688, found 1026.4633.

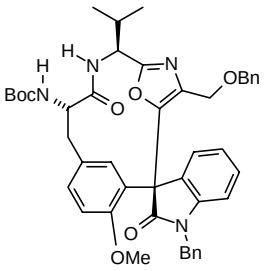


Oxazole (16). Compound **15** (2.11 g, 2.0 mmol) was dissolved in 50 mL of CH_2Cl_2, TFA (0.5 mL) was added dropwise at room temperature and the reaction mixture was stirred for 1 h. Solvent was removed *in vacuo* to yield the corresponding amine TFA salt, which was dried under high vacuum and used without further purification. In another flask, to a suspension of *Z*-Val-OH (1.036 g, 4.0 mmol, 2.0 equiv) and HOAt (0.411 g, 3.0 mmol, 1.5 equiv) in THF (40 mL) at 0 °C is added *i*-Pr_2NEt (3.4 mL, 20 mmol, 10 equiv) dropwise. The addition of CIP (0.804 g, 3.0 mmol, 1.5 equiv) to this mixture is followed by addition of a THF (20 mL) solution of the amine TFA salt. After stirring for 1 h at room temperature, the reaction was quenched with $KHSO_4$ (0.5 M, 50 mL) and extracted with ethyl acetate (30 mL x 3). The combined organic phase was washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by chromatography on silica gel to afford the desired compound as a foamy solid (1.79 g, 89%). mp: 80-82 C; $[\alpha]^{25}_D$= -114.5, (c = 0.047 $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ = 7.42 (d, *J* = 6.8 Hz, 1 H), 7.35-7.25 (m, 14 H), 7.19-7.18 (m, 5 H), 7.08 (t, *J* = 7.6

Hz, 1 H), 7.00 (dd, *J* = 8.5, 2.2 Hz, 1 H), 6.87 (d, *J* = 7.8 Hz, 2 H), 6.83 (d, *J* = 8.3 Hz, 1 H), 6.77-6.75 (m, 2 H), 6.31 (br, 1 H), 5.77-5.77 (m, 1 H), 5.41 (d, *J* = 8.3 Hz, 2 H), 5.11 (s, 1 H), 5.02 (d, *J* = 12.2 Hz, 2 H), 4.90-4.82 (m, 3 H), 4.73 (d, *J* = 15.6 Hz, 1 H), 4.44 (dd, *J* = 13.4, 5.6 Hz, 2 H), 4.12 (dd, *J* = 8.3, 5.4 Hz, 1 H), 3.78 (s, 3 H), 3.61 (dd, *J* = 18.6, 11.7 Hz, 1 H), 3.56 (dd, *J* = 10.3, 3.4 Hz, 1 H), 3.15 (dd, *J* = 10.3, 2.0 Hz, 1 H), 2.93 (dd, *J* = 13.9, 5.6 Hz, 1 H), 2.81 (dd, *J* = 14.2, 5.9 Hz, 1 H), 2.24-2.16 (m, 1 H), 1.37 (s, 9 H), 0.99 (d, *J* = 6.4 Hz, 2 H), 0.91 (d, *J* = 6.8 Hz, 2 H); ^{13}C-NMR ($CDCl_3$): δ = 200.2, 173.2, 171.7, 170.3, 156.5, 156.4, 155.2, 142.7, 137.1, 136.5, 135.5, 135.3, 130.9, 129.5, 129.1, 129.0, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 127.8, 127.7, 126.8, 126.4,126.8, 126.4, 123.4, 124.7, 113.2, 109.3, 80.0, 72.9, 68.5, 67.1, 65.2, 60.4, 56.6, 56.3, 54.4, 44.3, 37.3, 31.6, 28.4, 19.3, 17.5; IR (thin film) 3326.7, 2965.6, 1713.7, 1498.3, 1259.3, 1217.4, 1168.8, 752.0, 697.3 cm^{-1}; HRMS for $C_{60}H_{65}N_4O_{11}$ [$M+H^+$] calcd., 1017.4644, found 1017.4673.

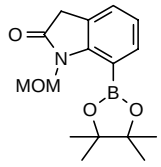
To a stirred solution of hexachloroethane (69.8 mg, 0.3 mmol, 3.0 equiv) and triphenylphosphine (77.6 mg, 0.3 mmol, 3.0 equiv) in anhydrous acetonitrile (5 mL) was added triethylamine (0.14 mL, 1.0 mmol, 10 equiv). After 5 min, the valine addition product from the above reaction (101.6 mg, 0.1 mmol, 1 equiv) in acetonitrile (5 mL) was added in one portion. The temperature was raised to 80 °C and the reaction was heated for 5h. The solvent was evaporated and the residue was stirred in ether (20 mL) for 15 min. The solution was then filtered and evaporated. The residue was purified by flash chromatography, yielding oxazole **16 (**30 mg, 31%) as white foam along with recovered starting material (13.1 mg, 13%). Mp: 64-66 °C; $[\alpha]^{25}_D$= 85.1, (c=0.050 $CHCl_3$); ^{1}H-NMR ($CDCl_3$): δ = 7.33-7.16 (m, 22 H), 7.00 (d, *J* = 8.3 Hz, 1 H), 6.89 (d, *J* = 7.3 Hz, 1 H), 6.87 (d, *J* = 1.0 Hz, 1 H), 6.74 (d, *J* = 7.8 Hz, 2 H), 6.69 (d, *J* = 8.8 Hz, 1 H), 5.71 (d, *J* = 8.3 Hz, 1 H), 5.26 (d, *J* = 8.3 Hz, 1 H), 5.13-5.05 (m, 4 H), 4.92 (d, *J* = 15.6 Hz, 1 H),

4.77-4.72 (m, 2 H), 4.55 (q, *J* = 5.4 Hz, 1 H), 4.23 (s, 2 H), 4.01 (s, 2 H), 3.30 (s, 3 H), 3.04 (dd, *J* = 13.9, 5.1 Hz, 1 H), 2.79 (dd, *J* = 13.7, 7.8 Hz, 1 H), 2.18-2.11 (m, 1 H), 1.34 (s, 9 H), 0.93 (d, *J* = 6.8 Hz, 3 H), 0.88 (d, *J* = 6.3 Hz, 3 H); ^{13}C-NMR ($CDCl_3$): δ = 174.9, 172.0, 162.8, 156.2, 155.9, 155.4, 144.9, 143.0, 138.3, 136.5, 136.1, 135.5, 135.3, 130.8, 130.0, 129.4, 128.8, 128.6, 128.6, 128.4, 128.4, 128.11, 128.08, 127.9, 127.8, 127.6, 127.5, 125.6, 122.5, 112.6, 109.0, 79.8, 72.5, 67.0, 63.6, 55.8, 55.5, 55.1, 54.7, 44.4, 37.8, 32.9, 29.8, 28.4, 18.7, 18.3; IR (thin film): 3018.5, 1716.9, 1500.8, 1216.1, 753.7, 667.9 cm^{-1}; HRMS for $C_{60}H_{63}N_4O_{10}$ [M+H$^+$] calcd. 999.4539, found, 999.4594.

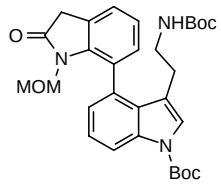


Macrolactam (5). Under an atmosphere of hydrogen, degassed methanol (5 mL) was added to a mixture of oxazole **16** (30.1 mg, 30 μmol), followed by palladium on carbon (2.8 mg, 10% weight). The solution was stirred for 2 h and then filtered through a pad of celite. Solvent was removed *in vacuo* and the residue was dried under high vacuum. The residue was then dissolved in a premixed solution of DMF/CH_2Cl_2 (1:2, 100mL, final concentration 3x10^{-4} M). HATU (24.5 mg, 64 μmol) and 2,4,6-collidine (26 μl, 0.20 mmol) were added sequentially and the resulting solution was stirred overnight at room temperature. Solvents were removed *in vacuo* by short path distillation with the temperature of the oil bath less than 50 °C. The desired product **5** was isolated via preparative TLC as a white solid (6.8 mg, 30%). $[\alpha]^{25}_D$ = 92.3, (c = 0.014 $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ = 7.31 (d, *J* = 6.8 Hz, 2 H), 7.24-7.21 (m, 4 H), 7.17-7.10 (m, 6 H), 7.01 (s, 1 H), 6.93 (d, *J* = 6.4 Hz, 1 H), 6.81 (t, *J* = 7.6 Hz, 1 H), 6.74-6.71 (m, 2 H), 6.29 (br, 1 H), 4.90-4.76 (m, 3 H), 4.45 (m, 1 H), 4.11 (d, *J* = 11.7 Hz, 1 H), 4.03 (d, *J* = 11.7 Hz, 1 H), 3.72 (d, *J* = 12.2 Hz, 1 H), 3.60 (d, *J* = 11.7 Hz, 1 H), 3.33 (s, 3 H), 3.08 (d, *J* = 11.2 Hz, 1 H), 2.93 (t, *J* = 12.2 Hz, 1 H), 2.31-2.24 (m, 1 H), 1.33 (s, 9 H), 1.01 (d, *J* = 6.3

Hz, 1 H), 0.92 (d, *J* = 6.6 Hz, 1 H); ^{13}C-NMR ($CDCl_3$): δ = 174.9, 172.7, 165.0, 156.4, 155.4, 143.7, 138.3, 136.4, 129.6, 128.9, 128.7, 128.2, 128.0, 127.8, 127.6, 127.4, 125.8, 121.9, 112.6, 128.7, 79.4, 71.9, 63.7, 56.1, 55.4, 55.0, 54.6, 44.3, 37.3, 31.2, 28.3, 19.2, 19.1; IR (thin film): 3306.0, 2920.0, 1730.5, 1657.2, 1611.6, 1529.9, 1466.5, 1365.8, 1258.1, 1169.2, 1070.5, 1027.2, 748.2 cm^{-1}; HRMS for $C_{45}H_{49}N_4O_7$ [M+H$^+$] calcd 757.3596 found 757.3584.

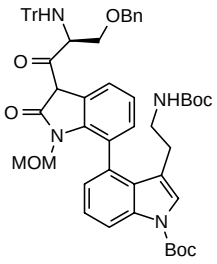


***N*-methoxymethyl-7-(4´,4´,5´,5´,-tetramethyl-1´,3´-dixoaborolan-2´-yl) oxindole (18):** Compound **17** (0.10 g, 0.39 mmol, 1.0 equiv), bis(pinacolato)diboron (0.121 g, 0.47 mmol, 1.2 equiv), and potassium acetate (0.195 g, 1.17 mmol, 3.0 equiv) were dissolved in 1,2-dimethoxyethane (5 mL) in a microwave reaction tube. The mixture was degassed via freeze-pump-thaw method (x4). Catalyst $Pd(dppf)_2$ (0.06 g, 0.08 mmol, 0.2 mmol) was quickly added and the reaction tube was sealed. The mixture was heated in the microwave for 10 min at 250 W (avg. temp. = 150 °C). The mixture was then cooled and filtered. The resulting black liquid was partitioned between dichloromethane and water. The organic layer was then collected, washed with brine, dried with magnesium sulfate, and concentrated *in vacuo*. The resulting black oil was purified by column chromatography using hexanes/ethyl acetate (8:2) yielding recovered **17** (0.6 g, 60%) and the desired material **18** (0.39 g, 33%). ^{1}H-NMR: δ = 7.50 (d, *J* = 7.5 Hz, 1 H), 7.30 (d, *J* = 7.5 Hz, 1 H), 7.06 (dd, *J* = 7.5, 7.5 Hz, 1 H), 5.52 (s, 2 H), 3.59 (s, 2 H), 3.17 (s, 3 H), 1.39 (s, 12 H); ^{13}C-NMR: δ = 176.4, 145.7, 134.1, 126.2, 124.0, 122.3, 84.6, 71.5, 55.5, 25.5, 25.8, 25.2; IR (thin film): 3056, 2977, 1721, 1606 cm^{-1}; HRMS for [M+H] $C_{16}H_{23}NO_4B$, calcd., 304.17147, found, 304.17292.



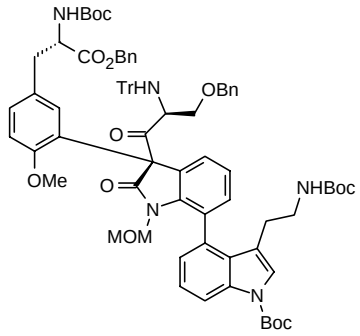
CDEF-ring System (20). Oxindole **18** (0.240 g, 0.79 mmol, 1.0 equiv), tryptamine derivative **19** (0.345 g, 0.79 mmol, 1.0 equiv), and potassium

carbonate (0.543 g, 3.93 mmol, 5.0 equiv) were dissolved in 1,2-dimethoxyethane (4 mL) and water (1 mL). The reaction mixture was degassed via freeze-pump-thaw method (x4). Catalyst $Pd(dppf)_2$ (28 mg, 0.04 mmol, 0.05 mmol) was quickly added and the reaction mixture was heated to 80 °C for 10 h. The solvent was then removed under vacuum and the crude mixture was dissolved in dichloromethane and filtered through a plug of silica gel. The filtrate was concentrated and the resulting oil was purified by column chromatography using hexanes/ethyl acetate (7:3), yielding the desired material as a white solid in 80% yield. mp 68-72 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.29 (d, *J* = 8.0 Hz, 1 H), 7.42 (s, 1 H), 7.35-7.37 (m, 2 H), 7.28-7.25 (m, 1 H), 7.19-7.08 (m, 2 H), 4.44 (d, *J* = 9.8 Hz, 1 H) 4.36 (d, *J* = 9.8 Hz, 1 H), 4.31 (bs, 1 H), 3.71 (d, *J* = 22.5 Hz, 1 H), 3.65 (d, *J* = 22.5 Hz, 1 H), 3.11-3.01 (m, 1 H), 2.95-2.84 (m, 1 H), 2.67 (s, 3 H), 2.34-2.26 (m, 1 H), 2.26-2.18 (m, 1 H), 1.68 (s, 9 H), 1.40 (s, 9 H); ^{13}C-NMR: δ = 176.47, 155.94, 149.73, 141.00, 135.99, 131.70, 128.43, 125.51, 125.38, 124.83, 124.47, 124.24, 124.17, 123.66, 122.19, 118.38, 115.26, 71.07, 55.34, 48.15, 44.01, 40.08, 39.76, 36.92, 35.81, 32.13, 28.59, 28.42, 26.47; IR (thin film): 3373, 2977, 2930, 1727, 1420, 1368, 1159 cm^{-1}; HRMS for [M+Na] $C_{30}H_{37}N_3O_6Na$, calcd., 558.25746, found, 558.25672.



Serine derivative (21). To a solution of imidazole (44.5 mg, 0.65 mmol, 5.0 equiv) in THF (1 mL) was added lithium hydride (5.3 mg, 0.65 mmol, 5.0 equiv). The heterogeneous mixture was refluxed for 1 h then allowed to cool to ambient temperature. A solution of Tr-Ser(OBn)-Im (0.09 g, 0.18 mmol, 1.4 equiv) in THF (1 mL) followed by a solution of **20** (0.07 g, 0.13 mmol, 1.0 equiv) in THF (1 mL) were added to the reaction. The reaction was stirred overnight at room temperature, quenched with aqueous sat. ammonium chloride (5 mL) and extracted with ethyl acetate (3 mL x 3). The organic layers were combined, washed with brine, dried with magnesium sulfate, filtered,

and concentrated *in vacuo* to give the crude product which was purified by semi-prep HPLC to give a white glass (72 mg, 58%) as a mixture of enol-keto forms. mp 78-81 °C; $[\alpha]^{25}_{D}$ = 80.0, (*c* 0.05, CD_3Cl); see Supporting Information for ^{1}H- and ^{13}C-NMR spectra: IR (thin film): 3426, 3060, 2930, 1731, 1713, 1656 cm^{-1}; HRMS for [M-CH_3O] $C_{58}H_{59}N_4O_7$, calcd., 923.43783, found, 923.47453.



CDEFG product (22). Sodium hydride (2.1 mg, 0.055 mmol, 1.0 equiv) was added to a solution of **21** (0.053 g, 0.055 mmol, 1.0 equiv) in THF (1 mL) at 0 °C. The mixture was stirred for 30 min, the solvent was removed and the resulting sodium salt was dried under high vacuum for 1 h to remove trace amounts of THF. The sodium salt was then suspended in 1,2-dichloroethane (1 mL) and aryllead(IV) reagent **10** (0.084 g, 0.110 mmol, 2.0 equiv) in 1,2-dichloroethane (1 mL) was added. The resulting mixture was stirred overnight at 40 °C. The resulting mixture was quenched with 3% aqueous Na_2S (1 mL) and filtered though a bed of celite, which was washed with methylene chloride (1 mL x 3). The organic layer was separated, washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue was put through a short plug of silica using ethyl acetate to flush. The resulting solution was concentrated and resulting crude solid was purified by HPLC to give the major isomer (35 mg, 47%) and a minor isomer (5 mg, 7%). mp 112 °C (decomposed); $[\alpha]^{25}_{D}$ = -190.0, (*c* 0.01, $CDCl_3$); ^{1}H-NMR (600 MHz): δ = 8.29-8.28 (m, 1 H), 7.43-6.93 (m, 29 H), 6.87-6.83 (m, 2 H), 6.77 (d, *J* = 8.4 Hz, 1 H), 6.70 (d, *J* = 8.4 Hz, 1 H), 5.21-5.10 (m, 2 H), 5.10-5.08 (m, 2 H), 5.02-4.98 (m, 2 H), 4.88 (t, *J* = 7.8 Hz, 1 H), 4.61 (q, *J* = 6.0 Hz, 1 H), 4.56 (d, *J* = 8.4 Hz, 1 H), 4.48 (t, *J* = 5.2 Hz, 1 H), 4.00 (d, *J* = 9.6 Hz, 1 H), 4.06-3.96 (m, 2 H), 3.92-3.79 (m, 2 H), 3.79 (s, 3 H), 3.77-3.75 (m, 2 H), 3.73 (s, 3 H), 3.55-3.58 (m,

2 H), 3.41 (d, J = 8.4 Hz, 2 H), 1.70 (s, 9 H), 1.69 (s, 9 H), 1.56 (s, 9 H); ^{13}C-NMR: δ = 177.5, 167.8, 162.4, 160.7, 154.3, 153.8, 153.4, 151.5, 151.4, 151.3, 151.2, 141.2, 134.8, 134.7, 134.4, 133.6, 133.2, 133.1, 132.7, 131.7, 125.9, 115.1, 88.8, 83.5, 82.5, 71.2, 71.0, 61.1, 60.7, 60.6, 60.5, 60.1, 59.6, 41.2, 35.5, 33.3, 32.8, 30.7; IR (thin film): 3419, 3351, 3060, 2930, 1747, 1722, 1715; HRMS for [M+H] $C_{81}H_{88}N_5O_{13}$, calcd., 1338.63731, found, 1338.64223.