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**Tandem Azidination- and Hydroazidation-Huisgen [3 + 2] Cycloadditions of
Ynamides. Syntheses of Chiral Amide Substituted Triazoles.**

authored by

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GENERAL PROCEDURES FOR SYNTHESIS OF CHIRAL AMIDE-SUBSTITUTED TRIAZOLES FROM YNAMIDES AND BENZYL AZIDE.

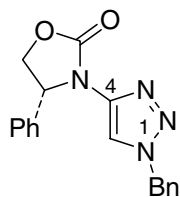
To a vial charged with ynamide **5** (50.0 mg, 0.267 mmol) were added CuSO₄·5H₂O (3.30 mg, 0.0134 mmol, 0.050 equiv), Na-Ascorbate (2.70 mg, 0.0134 mmol, 0.050 equiv), benzyl azide (37.0 μL, 0.294 mmol, 1.1 equiv), and *t*-butanol (0.50 mL). The mixture was stirred at rt for 2 min before H₂O (1 mL) was added. The reaction mixture was then vigorously stirred at rt for 12 h under nitrogen. After TLC showed that all ynamide **5** was consumed, the reaction mixture was diluted with H₂O (8 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with sat aq NaCl and dried over Na₂SO₄. Removal of solvent under reduced pressure gave crude triazole **7a**, which was purified via silica gel chromatography (using EtOAc/hexane as gradient eluent) to yield the pure triazole **7a** (70.0 mg, 82%) as a white solid.

GENERAL PROCEDURES FOR SYNTHESIS OF CHIRAL AMIDE-SUBSTITUTED TRIAZOLES FROM YNAMIDES AND IODOBENZENE (OR VINYL IODIDE): TANDEM AZIDINATION-[3 + 2].

To a solution of iodobenzene (0.086 mL, 157.0 mg, 0.77 mmol, 1.2 equiv) in DMSO/H₂O (4:1: 2.4 mL DMSO + 0.6 mL H₂O) were added K₂CO₃ (17.7 mg, 0.128 mmol, 0.20 equiv), *L*-proline (14.8 mg, 0.128 mmol, 0.20 equiv), CuSO₄·5H₂O (16.1 mg, 0.064 mmol, 0.10 equiv), Na-Ascorbate (25.4 mg, 0.128 mmol, 0.20 equiv), and sodium azide (58.4 mg, 0.90 mmol, 1.4 equiv). After the reaction mixture was stirred at 70 °C for 10 min, ynamide **5** (120.0 mg, 0.64 mmol, 1.0 equiv) in DMSO (3 mL) was added by syringe pump over 10 h. The reaction mixture was then vigorously stirred at 70 °C for an additional 2 h. After TLC showed all ynamide **5** was consumed, the reaction mixture was poured into dilute NH₄OH (15 mL), and then extracted by EtOAc (3 x 15 mL). The combined organic layers were washed with sat aq NaCl and dried over Na₂SO₄. Removal of solvent under reduced pressure gave crude triazole **17**, which was purified via silica gel chromatography (using EtOAc/hexane as gradient eluent) to yield the pure triazole **17** (147.0 mg, 75%) as a white solid.

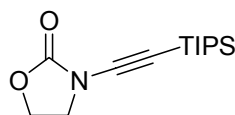
GENERAL PROCEDURES FOR TANDEM HYDROAZIDINATION-[3 + 2] CYCLOADDITIONS:

To a vial containing ynamide **5** (60.0 mg, 0.32 mmol) were added CuSO₄·5H₂O (8.10 mg, 0.032 mmol, 0.10 equiv), Na-Ascorbate (12.7 mg, 0.064 mmol, 0.20 equiv), phenyl acetylene (53.0 μL, 0.48 mmol, 1.50 equiv), sodium azide (29.2 mg, 0.45 mmol, 1.40 equiv), and *t*-butanol (1.1 mL). The mixture was stirred at rt for 2 min before H₂O (2.2 mL) was added. The reaction was then vigorously stirred at rt 24 h under nitrogen. After TLC showed all ynamide **5** was consumed, the reaction mixture was poured into dilute NH₄OH (8 mL), and extracted by EtOAc (3 x 10 mL). The combined organic layers were washed with sat aq NaCl and dried over Na₂SO₄. Removal of solvent under reduced pressure gave crude mixture of **18** and **38c**, which was purified via silica gel chromatography (using EtOAc/hexane as gradient eluent) to yield both **18** (22.0 mg, 31%) and **38c** (16.0 mg, 15%) as white solids.



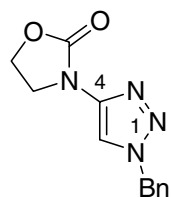
7a

$R_f = 0.38$ [50% EtOAc in hexanes]; mp 148-151 °C; $[\alpha]_D^{20} = -2.50$ (c 0.88, CHCl_3);
IR (film) cm^{-1} 3171(m), 3145(m), 3031(w), 2916(w), 1758(s), 1585(m), 1557(m), 1422(m), 1290(w),
1220(m), 1117(m), 1048(m), 1032(w); ^1H NMR (500 MHz, CDCl_3) δ 4.36 (dd, 1 H, $J = 4.5, 9.0$ Hz),
4.83 (dd, 1 H, $J = 9.0, 9.0$ Hz), 5.34-5.45 (m, 2 H), 5.65 (dd, 1 H, $J = 4.5, 9.0$ Hz), 7.21-7.24 (m, 2 H),
7.28-7.37 (m, 8 H), 7.81 (s, 1 H); ^{13}C NMR (125 MHz, CDCl_3) δ 54.8, 58.9, 71.3, 113.0, 126.4, 126.5,
128.2, 128.7, 128.8, 129.1, 134.2, 138.8, 143.1, 154.9; mass spectrum (ESI): m/e (% relative intensity)
321.4 (33) ($\text{M} + \text{H}$) $^+$, 343.4 (100) ($\text{M} + \text{Na}$) $^+$; HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{16}\text{N}_4\text{O}_2\text{Na}$ 343.1165, found
343.1160.



S1

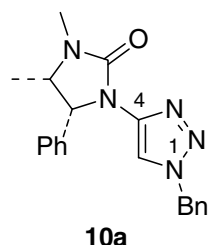
$R_f = 0.66$ [50% EtOAc in hexanes];
IR (film) cm^{-1} 2944(m), 2867(w), 1763(s), 1480(w), 1461(w), 1401(m), 1199(m), 1109(m), 1035(m); ^1H
NMR (300 MHz, CDCl_3) δ 1.00-1.11 (m, 21 H), 3.95 (dt, 2 H, $J = 1.5, 7.8$ Hz), 4.43 (dt, 2 H, $J = 1.5,$
7.8 Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 11.2, 18.6, 47.0, 62.8, 70.0, 93.0, 155.8; mass spectrum (ESI):
 m/e (% relative intensity) 290.2 (100) ($\text{M} + \text{Na}$) $^+$; HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{25}\text{NO}_2\text{SiNa}$ 290.1547,
found 290.1552.



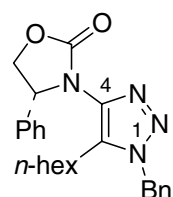
9a

$R_f = 0.12$ [50% EtOAc in hexanes]; mp 146-147 °C;
IR (film) cm^{-1} 3585(w), 3164(w), 3138 (w), 2987(w), 2920(w), 1745(s), 1590(m), 1439(m), 1421(w),
1244(m), 1217(m), 1108(m), 1031(m); ^1H NMR (500 MHz, CDCl_3) δ 4.17-4.23 (m, 2 H), 4.49-4.55 (m,
2 H), 5.46 (s, 2 H), 7.24-7.28 (m, 2 H), 7.31-7.36 (m, 3 H), 7.82 (s, 1 H); ^{13}C NMR (125 MHz, CDCl_3) δ

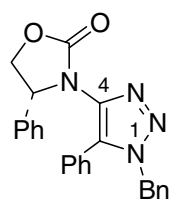
43.6, 54.8, 63.4, 111.8, 128.1, 128.8, 129.1, 134.4, 144.0, 154.8; mass spectrum (ESI): m/e (% relative intensity) 267.1 (100) ($M + Na$)⁺; HRMS (ESI) calcd for $C_{12}H_{12}N_4O_2Na$ 267.0852, found 267.0845.



$R_f = 0.14$ [50% EtOAc in hexanes]; mp 206-207 °C; $[\alpha]_D^{20} = 44.2$ (c 0.76, $CHCl_3$); IR (film) cm^{-1} 3176(w), 3033(w), 2890(w), 2361(m), 2340(m), 1699(s), 1583(m), 1430(m), 1405(m), 1267(m), 1206(m); ¹H NMR (500 MHz, $CDCl_3$) δ 0.86 (d, 3 H, $J = 6.5$ Hz), 2.83 (s, 3 H), 3.95-4.05 (m, 1 H), 5.29-5.42 (m, 2 H), 5.50 (d, 1 H, $J = 14.5$ Hz), 7.15-7.40 (m, 10 H), 7.88 (s, 1 H); ¹³C NMR (125 MHz, $CDCl_3$) δ 14.8, 28.4, 54.3, 56.1, 60.6, 111.7, 127.5, 127.9, 128.0, 128.2, 128.5, 128.9, 134.4, 136.1, 144.5, 157.7; mass spectrum (ESI): m/e (% relative intensity) 348.3 (2500) ($M + H$)⁺, 370.3 (100) ($M + Na$)⁺; HRMS (ESI) calcd for $C_{20}H_{22}N_5O$ 348.1819, found 348.1824.

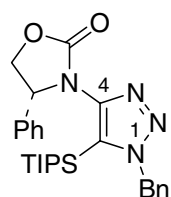


$R_f = 0.46$ [50% EtOAc in hexanes]; $[\alpha]_D^{20} = -51.8$ (c 1.24, $CHCl_3$); IR (film) cm^{-1} 3033(w), 2954(m), 2928(m), 2858(m), 1766(s), 1591(m), 1457(m), 1408(m), 1213(m), 1109(m), 1037(m); ¹H NMR (500 MHz, $CDCl_3$) δ 0.84 (t, 3 H, $J = 7.5$ Hz), 0.98-1.11 (m, 6 H), 1.13-1.23 (m, 2 H), 2.26-2.32 (m, 1 H), 2.51-2.58 (m, 1 H), 4.45 (dd, 1 H, $J = 7.5, 9.0$ Hz), 4.87 (dd, 1 H, $J = 9.0, 9.0$ Hz), 5.38 (s, 2 H), 5.63 (dd, 1 H, $J = 7.5, 9.0$ Hz), 6.97-7.02 (m, 2 H), 7.25-7.37 (m, 8 H); ¹³C NMR (125 MHz, $CDCl_3$) δ 14.0, 22.4, 22.6, 27.5, 29.1, 31.3, 52.6, 61.4, 70.2, 126.9, 127.4, 128.3, 128.9, 129.0, 129.1, 132.7, 134.6, 137.5, 139.0, 155.7; mass spectrum (ESI): m/e (% relative intensity) 405.3 (340) ($M + H$)⁺, 427.3 (100) ($M + Na$)⁺; HRMS (ESI) calcd for $C_{24}H_{28}N_4O_2Na$ 427.2104, found 427.2101.



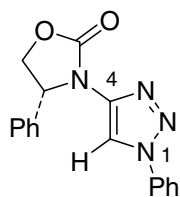
15a

$R_f = 0.18$ [33% EtOAc in hexanes]; $[\alpha]_D^{20} = -52.3$ (c 1.77, CHCl_3);
IR (film) cm^{-1} 3064(m), 3034(m), 2922(m), 1767(s), 1587(m), 1498(m), 1457(m), 1445(m), 1400(m), 1214(m), 1090(m), 1043(w), 1035(w); ^1H NMR (500 MHz, CDCl_3) δ 4.22 (dd, 1 H, $J = 8.5, 8.5$ Hz), 4.76 (dd, 1 H, $J = 8.5, 8.5$ Hz), 5.30 (d, 2 H, $J = 2.0$ Hz), 5.38 (dd, 1 H, $J = 8.5, 8.5$ Hz), 6.86-6.89 (m, 2 H), 6.99-7.03 (m, 4 H), 7.13 (dd, 2 H, $J = 7.5, 7.5$ Hz), 7.18-7.24 (m, 4 H), 7.35 (dd, 2 H, $J = 7.5, 7.5$ Hz), 7.45 (t, 1 H, $J = 7.5$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 52.5, 62.5, 70.3, 81.2, 125.3, 127.2, 127.3, 128.2, 128.7, 128.8, 128.9, 129.0, 129.8, 129.9, 134.8, 136.7, 138.7, 156.7; mass spectrum (ESI): m/e (% relative intensity) 397.3 (147) ($\text{M} + \text{H}$) $^+$, 419.3 (100) ($\text{M} + \text{Na}$) $^+$; HRMS (ESI) calcd for $\text{C}_{24}\text{H}_{20}\text{N}_4\text{O}_2\text{Na}$ 419.1478, found 419.1476.



16a

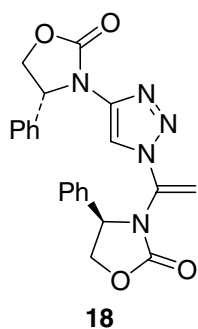
$R_f = 0.45$ [50% EtOAc in hexanes]; mp 151-153 $^\circ\text{C}$; $[\alpha]_D^{20} = -68.3$ (c 2.34, CHCl_3);
IR (film) cm^{-1} 3066(m), 3034(m), 2942(m), 2924(m), 1763(s), 1538(m), 1497(w), 1461(m), 1393(m), 1220(m), 1199(m), 1175(m), 1105(m), 1042(m); ^1H NMR (500 MHz, CDCl_3) δ 1.13-1.27 (m, 18 H), 1.40-1.55 (m, 3 H), 4.51-4.68 (br, 1 H), 4.70-4.96 (m, 3 H), 4.97-5.10 (br, 1 H), 6.91-7.00 (m, 2 H), 7.21-7.42 (m, 8 H); ^{13}C NMR (125 MHz, CDCl_3) δ 11.7, 18.8, 50.4, 63.3, 69.7, 105.3, 127.2, 127.9, 128.2, 128.4, 129.6, 129.9, 133.9, 137.0, 137.2, 155.0; mass spectrum (ESI): m/e (% relative intensity) 477.4 (1000) ($\text{M} + \text{H}$) $^+$, 499.4 (100) ($\text{M} + \text{Na}$) $^+$; HRMS (ESI) calcd for $\text{C}_{27}\text{H}_{37}\text{N}_4\text{O}_2$ 477.2680, found 477.2690.



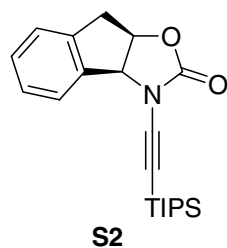
17

$R_f = 0.29$ [33% EtOAc in hexanes]; mp 133-134 $^\circ\text{C}$; $[\alpha]_D^{20} = -21.8$ (c 4.79, CHCl_3);

IR (film) cm^{-1} 3584(w), 3176(w), 3065(w), 3033(w), 3014(w), 2918(w), 1759(s), 1583(m), 1502(m), 1469(m), 1414(m), 1218(m), 1139(m), 1039(m); ^1H NMR (500 MHz, CDCl_3) δ 4.45 (dd, 1 H, $J = 4.0, 8.5$ Hz), 4.92 (dd, 1 H, $J = 8.5, 8.5$ Hz), 5.75 (dd, 1 H, $J = 4.0, 8.5$ Hz), 7.30-7.51 (m, 8 H), 7.71 (d, 2 H, $J = 7.5$ Hz), 8.37 (s, 1 H); ^{13}C NMR (125 MHz, CDCl_3) δ 58.9, 71.5, 111.0, 120.2, 126.5, 128.8, 129.2, 129.3, 129.7, 137.0, 138.7, 143.4, 154.9; mass spectrum (ESI): m/e (% relative intensity) 307.2 (91) ($\text{M} + \text{H}$) $^+$, 329.2 (100) ($\text{M} + \text{Na}$) $^+$; HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{14}\text{N}_4\text{O}_2\text{Na}$ 329.1009, found 329.1009.

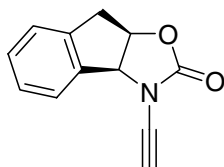


$R_f = 0.30$ [33% EtOAc in hexanes]; 195-196 $^{\circ}\text{C}$ $[\alpha]_{\text{D}}^{20} = -76.0$ (c 0.45, CHCl_3);
IR (film) cm^{-1} 2919(w), 1766(s), 1660(w), 1586(m), 1458(w), 1403(m), 1217(m), 1090(m), 1036(w), 1027(w); ^1H NMR (500 MHz, CDCl_3) δ 4.29 (dd, 1 H, $J = 4.5, 9.0$ Hz), 4.43 (dd, 1 H, $J = 4.5, 9.0$ Hz), 4.76 (dd, 1 H, $J = 9.0, 9.0$ Hz), 4.90 (dd, 1 H, $J = 9.0, 9.0$ Hz), 5.12-5.19 (m, 2 H), 5.34 (dd, 1 H, $J = 2.5, 5.5$ Hz), 5.66 (dd, 1 H, $J = 4.5, 9.0$ Hz), 7.16 (dd, 2 H, $J = 2.5, 7.0$ Hz), 7.24-7.44 (m, 8 H), 7.94 (s, 1 H); ^{13}C NMR (125 MHz, CDCl_3) δ 59.0, 60.7, 70.3, 71.4, 104.8, 105.0, 111.9, 126.1, 126.5, 127.0, 129.0, 129.2, 129.4, 129.6, 133.7, 136.1, 138.3, 142.8; mass spectrum (ESI): m/e (% relative intensity) 418.2 (66) ($\text{M} + \text{Na}$) $^+$, 440.2 (100) ($\text{M} + \text{Na}$) $^+$; HRMS (ESI) calcd for $\text{C}_{22}\text{H}_{19}\text{N}_5\text{O}_4\text{Na}$ 440.1329, found 440.1326.



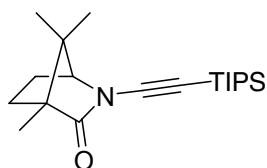
$R_f = 0.23$ [25% EtOAc in hexanes]; $[\alpha]_{\text{D}}^{20} = -13.8$ (c 10.9, CHCl_3);
IR (film) cm^{-1} 2943(m), 2865(m), 2179(m), 1774(s), 1384 (s); ^1H NMR (500 MHz, CDCl_3) δ 3.02 (s, 1 H), 3.31 (d, $J = 17.5$ Hz, 1 H), 3.45 (dd, 1 H, $J = 6.5, 17.5$ Hz), 5.38 (dd, 1 H, $J = 2.0, 13$ Hz), 5.42 (dd, 1 H, $J = 2.0$ Hz), 7.29-7.35 (m, 2 H), 7.39 (dd, 1 H, $J = 6.5, 7.5$ Hz), 7.61 (d, 1 H, $J = 8.0$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 33.5, 61.2, 65.1, 72.0, 78.9, 125.4, 125.5, 127.8, 130.3, 137.1, 140.0, 155.2; mass

spectrum (ESI): m/e (% relative intensity) 378.2 (79) ($M + Na$)⁺; HRMS (ESI) calcd for $C_{21}H_{29}NO_2SiNa$ 378.1865, found 378.1862.



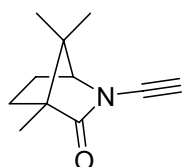
20

$R_f = 0.43$ [40% EtOAc in hexanes]; mp 64-65 °C; $[\alpha]_D^{20} = 72.6$ (c 9.50, $CHCl_3$); IR (film) cm^{-1} 3298(m), 2865(m), 2180(m), 2152(m), 1771(s), 1381 (s); 1H NMR (500 MHz, $CDCl_3$) δ 3.02 (s, 1 H), 3.31 (d, 1 H, $J = 17.5$ Hz), 3.45 (dd, 1 H, $J = 6.5, 17.5$ Hz), 5.38 (dd, 1 H, $J = 2.0, 13$ Hz), 5.42 (dd, 1 H, $J = 2.0$ Hz), 7.29-7.35 (m, 2 H), 7.39 (dd, 1 H, $J = 6.5, 7.5$ Hz), 7.61 (d, 1 H, $J = 8.0$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 33.5, 61.2, 65.1, 72.0, 78.9, 125.4, 125.5, 127.8, 130.3, 137.1, 140.0, 155.2; mass spectrum (ESI): m/e (% relative intensity) 222.1 (100) ($M + Na$)⁺; HRMS (ESI) calcd for $C_{12}H_9NO_2Na$ 222.0531, found 222.0527.



S3

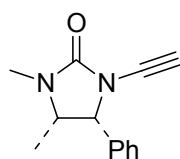
$R_f = 0.42$ [10% EtOAc in hexanes]; IR (film) cm^{-1} 2942(m), 2865(m), 2166(m), 1741(m), 1464, 1372 (m); 1H NMR (500 MHz, $CDCl_3$) δ 0.89 (s, 3 H), 0.99 (s, 3 H), 1.03 (s, 3 H), 1.04-1.08 (m, 21 H), 1.56 (dd, $J = 3.5, 9.5, 13.5$, 1 H), 1.72-1.82 (m, 2 H), 1.95 (ddd, 1 H, $J = 2.0, 3.5, 10$ Hz), 3.52 (d, 1 H, 1.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 9.3, 11.3, 17.8, 18.4, 18.6, 26.3, 30.3, 49.2, 53.8, 69.6, 71.3, 94.7, 179.5; mass spectrum (ESI): m/e (% relative intensity) 334.3 (24) ($M + 1$)⁺, 356.4 (100) ($M + Na$)⁺; HRMS (ESI) calcd for $C_{20}H_{35}NOSiNa$ 356.2386, found 356.2390.



21

$R_f = 0.60$ [40% EtOAc in hexanes]; mp 102-103 °C; $[\alpha]_D^{20} = -67.8$ (c 9.00, $CHCl_3$);

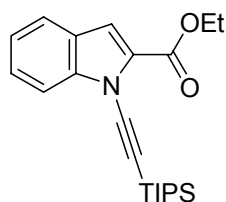
IR (film) cm^{-1} 3247(s), 2968 (m), 2134 (m), 1731(m), 1397, 1362 (m); ^1H NMR (500 MHz, CDCl_3) δ 0.85 (dd, 3H, $J = 2.5, 3.5$ Hz), 0.94 (dd, 3 H, $J = 3.0, 4.0$ Hz), 0.99 (t, 3 H, $J = 3.5$ Hz), 1.46-1.54 (m, 1 H), 1.68-1.78 (m, 2 H), 1.87-1.96 (m, 1 H), 2.83 (dd, 1 H, $J = 2.5, 3.0$ Hz), 3.51 (d, 1 H, $J = 2.5$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 9.3, 17.8, 18.4, 26.3, 30.3, 49.4, 53.8, 60.1, 70.8, 73.9, 180.0; mass spectrum (ESI): m/e (% relative intensity) 200.1 (100) ($\text{M} + \text{Na}$) $^+$; HRMS (ESI) calcd for $\text{C}_{11}\text{H}_{15}\text{NOSiNa}$ 200.1050, found 200.1051.



22

$R_f = 0.29$ [50% EtOAc in hexanes]; $[\alpha]_D^{20} = -212.7$ (c 1.59, CHCl_3);

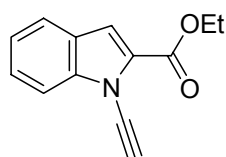
IR (film) cm^{-1} 3266(s), 3035(w), 3005(w), 2984 (w), 2944(w), 2895(m), 1711(s), 1424(m), 1390(m), 1338(m), 1262(m), 1208 (w), 1154(m); ^1H NMR (500 MHz, CDCl_3) δ 0.71 (d, 3 H, $J = 6.0$ Hz), 2.62 (s, 1 H), 2.77 (s, 3 H), 3.86 (dq, 1 H, $J = 6.0, 14.5$ Hz), 4.93 (d, 1 H, $J = 14.5$ Hz), 7.15-7.20 (m, 2 H), 7.28-7.35 (m, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 14.9, 28.9, 55.6, 59.6, 63.5, 75.2, 127.6, 128.0, 128.4, 134.4, 157.7; mass spectrum (ESI): m/e (% relative intensity) 237.2 (100) ($\text{M} + \text{Na}$) $^+$; HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{14}\text{N}_2\text{ONa}$ 237.0998, found 237.1001.



S4

$R_f = 0.63$ [20% EtOAc in hexanes];

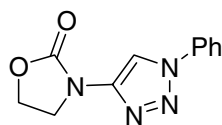
IR (film) cm^{-1} 2943(m), 2866(m), 2120(m), 1728(s), 1613(w), 1540(m), 1452(m), 1384(m), 1256(m), 1207(m), 1204(m), 1172(m), 1141(m), 1100(m); ^1H NMR (500 MHz, CDCl_3) δ 1.21-1.25 (m, 21 H), 1.42 (t, 3 H, $J = 7.0$ Hz), 4.44 (q, 2 H, $J = 7.0$ Hz), 7.26-7.30 (m, 1 H), 7.33 (s, 1 H), 7.45-7.50 (m, 1 H), 7.61-7.65 (m, 1 H), 7.67 (d, 1 H, $J = 7.5$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 11.5, 14.4, 18.8, 61.0, 72.0, 92.7, 112.3, 112.9, 122.7, 123.1, 126.0, 126.6, 129.6, 141.0, 160.0; mass spectrum (ESI): m/e (% relative intensity) 392.5 (100) ($\text{M} + \text{Na}$) $^+$; HRMS (ESI) calcd for $\text{C}_{22}\text{H}_{31}\text{NO}_2\text{Na}$ 392.2016, found 392.2021.



23

$R_f = 0.69$ [20% EtOAc in hexanes];

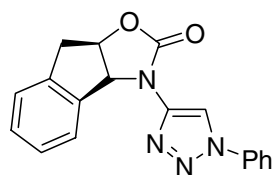
IR (film) cm^{-1} 3300(s), 2982(m), 2151(m), 1721(s), 1613(w), 1542(m), 1450(m), 1399(m), 1386(m), 1255(m), 1205(m), 1172(m), 1167(m), 1096(m); ^1H NMR (500 MHz, CDCl_3) δ 1.42 (t, 3 H, $J = 7.0$ Hz), 3.33 (s, 1 H), 4.43 (q, 2 H, $J = 7.0$ Hz), 7.25-7.29 (m, 1 H), 7.31 (s, 1 H), 7.46 (dd, 1 H, $J = 7.5, 7.5$ Hz), 7.62-7.67 (m, 2 H); ^{13}C NMR (125 MHz, CDCl_3) δ 14.3, 61.2, 61.6, 72.5, 112.1, 113.1, 122.8, 123.3, 126.0, 126.8, 129.2, 140.8, 160.2; mass spectrum (ESI): m/e (% relative intensity) 236.1 (100) ($\text{M} + \text{Na}$) $^+$; HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{11}\text{NO}_2\text{Na}$ 236.0682, found 236.0686.



25

$R_f = 0.25$ [50% EtOAc in hexanes]; mp 179-180 °C;

IR (film) cm^{-1} 1778(s), 1703(w), 1248(m), 1235(m), 1045(m); ^1H NMR (500 MHz, CDCl_3) δ 4.33 (t, 2 H, $J = 8.0$ Hz), 4.62 (t, 2 H, $J = 8.0$ Hz), 7.45 (d, 1 H, $J = 7.5$ Hz), 7.52 (dd, 2 H, $J = 7.5, 7.5$ Hz), 7.76 (d, 2 H, $J = 7.5$ Hz), 8.36 (s, 1 H); ^{13}C NMR (125 MHz, CDCl_3) δ 43.7, 63.5, 109.9, 120.4, 129.0, 129.8, 137.0, 144.3, 154.9; mass spectrum (ESI): m/e (% relative intensity) 253.3 (100) ($\text{M} + \text{Na}$) $^+$; HRMS (ESI) calcd for $\text{C}_{11}\text{H}_{10}\text{N}_4\text{O}_2\text{Na}$ 253.0696, found 253.0690

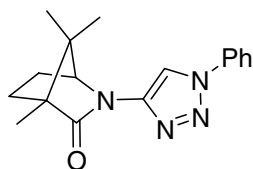


26

$R_f = 0.43$ [40% EtOAc in hexanes]; $[\alpha]_D^{20} = -174.5$ (c 7.3, CHCl_3);

IR (film) cm^{-1} 2964 (m), 2924 (w), 2360(s), 2339(m), 2239(m), 1788(s), 1701(s), 1456(w), 1422(w), 1386(w), 1262(m), 1194(s), 1097(s), 1024(s); ^1H NMR (500 MHz, CDCl_3) δ 1.24 (t, 3H, $J = 7.5$ Hz), 4.16 (dq, 2 H, $J = 2.5, 7.5$ Hz); 4.33 (dt, 1 H, $J = 2.5, 9.0$ Hz), 4.80 (t, 1 H, $J = 9.0$ Hz), 5.16 (dt, 1 H, $J = 2.5, 9.0$ Hz), 7.32-7.35 (m, 2H), 7.43-7.48 (m, 3 H); ^{13}C NMR (75 MHz, CDCl_3) δ 38.7, 64.2, 79.7, 110.8, 120.5, 125.5, 127.4, 128.1, 129.1, 130.0, 130.1, 137.3, 138.7 140.2, 144.3, 154.2 (ESI): m/e (%)

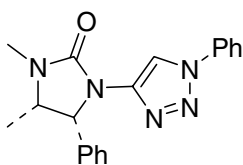
relative intensity) 282.1 (100) ($M + Na$)⁺, 346.1 (2200) ($M + Na + 2MeOH$)⁺; HRMS (ESI) calcd for $C_{14}H_{17}NO_4Na$ 282.0737, found 282.0728.



27

$R_f = 0.58$ [40% EtOAc in hexanes]; $[\alpha]_D^{20} = 204.0$ (c 0.558, $CHCl_3$);

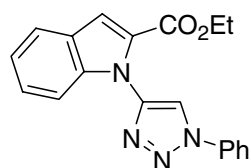
IR (film) cm^{-1} 2969 (m), 1701 (s), 1576 (s), 1409 (m); 1H NMR (500 MHz, $CDCl_3$) δ 0.99 (s, 3 H), 1.00 (s, 3 H), 1.12 (s, 3 H), 1.51-1.58 (m, 2 H), 1.76 (ddd, 1 H, $J = 4.0, 9.0, 13.5$ Hz), 1.86 (ddd, 1 H, $J = 4.0, 10.5, 13.5$ Hz), 2.04-2.11 (m, 1 H), 4.49 (s, 1 H), 7.41 (t, 1 H, $J = 7.5$ Hz), 7.49 (d, 1 H, $J = 8.0$ Hz), 7.51 (d, 1 H, $J = 8.0$ Hz), 7.73 (d, 2 H, $J = 7.5$ Hz), 8.40 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.3, 17.9, 18.5, 26.7, 30.9, 49.8, 55.3, 66.0, 110.6, 120.4, 128.7, 129.7, 137.2, 143.9, 177.0; mass spectrum (ESI): m/e (% relative intensity) 297.2 (21) ($M + H$)⁺, 319.2 (100) ($M + Na$)⁺; HRMS (ESI) calcd for $C_{17}H_{20}N_4ONa$ 319.1535, found 319.1533.



28

$R_f = 0.73$ [EtOAc]; mp 197-198 °C; $[\alpha]_D^{20} = 28.9$ (c 1.21, $CHCl_3$);

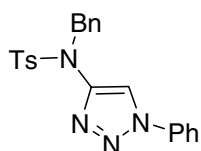
IR (film) cm^{-1} 3161(w), 3138(w), 3028 (w), 2975(m), 2959(m), 2336(m), 1699(s), 1580(m), 1500(m), 1435(m), 1403(m), 1230(w), 1123(m); 1H NMR (500 MHz, $CDCl_3$) δ 0.88 (d, 3 H, $J = 6.5$ Hz), 2.87 (s, 3 H), 4.03-4.10 (m, 1 H), 5.58 (d, 1 H, $J = 8.0$ Hz), 7.21-7.32 (m, 5 H), 7.37 (t, 1 H, $J = 8.0$ Hz), 7.46 (dd, 2 H, $J = 8.0, 8.0$ Hz), 7.70 (d, 2 H, $J = 8.0$ Hz), 8.40 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.0, 28.6, 56.3, 60.9, 109.6, 120.0, 127.7, 128.1, 128.4, 128.5, 129.6, 136.2, 137.3, 145.0, 157.8; mass spectrum (ESI): m/e (% relative intensity) 334.2 (840) ($M + H$)⁺, 356.2 (100) ($M + Na$)⁺; HRMS (ESI) calcd for $C_{19}H_{20}N_5O$ 334.1662, found 334.1659.



29

$R_f = 0.33$ [20% EtOAc in hexanes]; mp 112-114 °C;

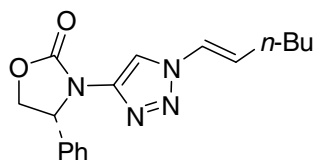
IR (film) cm^{-1} 3131(w), 3059(w), 2983(m), 1717(s), 1580(m), 1506(m), 1449(m), 1300(m), 1250(m), 1204(m), 1149(m); ^1H NMR (500 MHz, CDCl_3) δ 1.31 (t, 3 H, $J = 7.0$ Hz), 4.28 (q, 2 H, $J = 7.0$ Hz), 7.22-7.27 (m, 1 H), 7.32-7.38 (m, 2 H), 7.48-7.53 (m, 2 H), 7.55-7.61 (m, 2 H), 7.72-7.76 (m, 1 H), 7.85 (d, 2 H, $J = 8.0$ Hz), 8.20 (s, 1 H); ^{13}C NMR (125 MHz, CDCl_3) δ 14.2, 60.8, 111.8, 113.1, 118.7, 120.5, 122.0, 122.5, 126.2, 126.5, 129.0, 129.1, 129.9, 137.0, 140.7, 143.2, 161.0; mass spectrum (ESI): m/e (% relative intensity) 333.1 (40) ($\text{M} + \text{H}$) $^+$, 355.1 (100) ($\text{M} + \text{Na}$) $^+$; HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{16}\text{N}_4\text{O}_2\text{Na}$ 355.1165, found 355.1174.



30

$R_f = 0.50$ [33% EtOAc in hexanes]; mp 179-181 °C;

IR (film) cm^{-1} 3583(w), 1598(m), 1558(m), 1506(m), 1355(m), 1166(m), 1091(w); ^1H NMR (500 MHz, CDCl_3) δ 2.42 (s, 3 H), 4.97 (s, 2 H), 7.22-7.30 (m, 6 H), 7.40-7.45 (m, 2 H), 7.50 (dd, 2 H, $J = 8.0, 8.0$ Hz), 7.62 (d, 2 H, $J = 8.0$ Hz), 7.69 (d, 2 H, $J = 8.0$ Hz), 8.02 (s, 1 H); ^{13}C NMR (125 MHz, CDCl_3) δ 21.6, 52.5, 111.7, 117.8, 120.1, 127.4, 127.8, 128.4, 128.8, 128.9, 129.7, 130.0, 135.2, 135.8, 136.8, 144.2; mass spectrum (ESI): m/e (% relative intensity) 405.2 (89) ($\text{M} + \text{H}$) $^+$, 427.2 (100) ($\text{M} + \text{Na}$) $^+$; HRMS (ESI) calcd for $\text{C}_{22}\text{H}_{20}\text{N}_4\text{O}_2\text{SNa}$ 427.1199, found 427.1210.

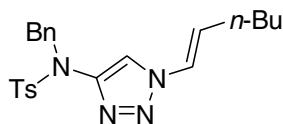


32

$R_f = 0.50$ [33% EtOAc in hexanes]; mp 88-91 °C; $[\alpha]_D^{20} = 3.64$ (c 1.54, CHCl_3);

IR (film) cm^{-1} 2957(w), 2928(w), 2858(w), 2366(m), 1759(s), 1583(m), 1458(w), 1416(m), 1217(m), 1114(m), 1037(m); ^1H NMR (500 MHz, CDCl_3) δ 0.84 (t, 3 H, $J = 7.0$ Hz), 1.23-1.32 (m, 2 H), 1.33-1.41 (m, 2 H), 2.11 (dt, 2 H, $J = 7.0, 7.0$ Hz), 4.32 (dd, 1 H, $J = 4.5, 9.0$ Hz), 4.80 (dd, 1 H, $J = 9.0, 9.0$ Hz), 5.61 (dd, 1 H, $J = 4.5, 9.0$ Hz), 6.09 (td, 1 H, $J = 7.0, 14.0$ Hz), 6.92 (d, 1 H, $J = 14.0$ Hz), 7.21-

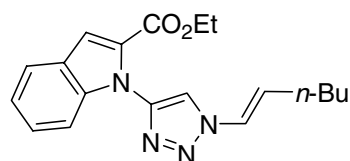
7.30 (m, 5 H), 8.01 (s, 1 H); ^{13}C NMR (125 MHz, CDCl_3) δ 13.8, 22.1, 29.2, 31.0, 58.8, 71.4, 110.0, 123.7, 124.2, 126.5, 128.8, 129.1, 138.7, 142.7, 154.9; mass spectrum (ESI): m/e (% relative intensity) 335.2 (100) ($\text{M} + \text{Na}$) $^+$; HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{20}\text{N}_4\text{O}_2\text{Na}$ 335.1478, found 335.1482.



33

R_f = 0.55 [33% EtOAc in hexanes]; mp 83-84 $^\circ\text{C}$;

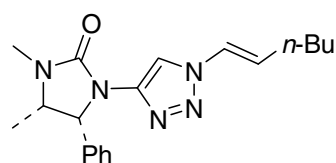
IR (film) cm^{-1} 3153(m), 3032(m), 2956(m), 2929(m), 2871(m), 2859(m), 1674(w), 1598(m), 1557(m), 1456(m), 1358(m), 1167(m); ^1H NMR (300 MHz, CDCl_3) δ 0.95 (t, 3 H, J = 7.2 Hz), 1.34-1.54 (m, 4 H), 2.22 (dt, 2 H, J = 7.2, 7.2 Hz), 2.44 (s, 3 H), 4.94 (s, 2 H), 6.20 (dt, 1 H, J = 7.2, 14.4 Hz), 7.00 (d, 1 H, J = 14.4 Hz), 7.24-7.33 (m, 5 H), 7.41 (d, 2 H, J = 8.4 Hz), 7.61 (d, 2 H, J = 8.4 Hz), 7.78 (s, 1 H); ^{13}C NMR (75 MHz, CDCl_3) δ 13.6, 21.4, 21.9, 29.1, 30.7, 52.2, 116.7, 123.8, 123.9, 127.3, 127.6, 128.3, 128.6, 129.7, 135.0, 135.6, 143.8, 144.1; mass spectrum (ESI): m/e (% relative intensity) 411.2 (18) ($\text{M} + \text{H}$) $^+$, 433.2 (100) ($\text{M} + \text{Na}$) $^+$; HRMS (ESI) calcd for $\text{C}_{22}\text{H}_{26}\text{N}_4\text{O}_2\text{SNa}$ 433.1669, found 433.1669.



34

R_f = 0.49 [20% EtOAc in hexanes]; mp 52-54 $^\circ\text{C}$;

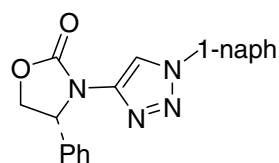
IR (film) cm^{-1} 3131(w), 3078(w), 2958(m), 2930(m), 2872(m), 2859(m), 1717(s), 1581(m), 1538(m), 1464(m), 1297(m), 1205(s), 1145(m); ^1H NMR (300 MHz, CDCl_3) δ 0.99 (t, 3 H, J = 7.2 Hz), 1.26-1.38 (m, 3 H), 1.40-1.64 (m, 4 H), 2.31 (dt, 2 H, J = 7.2, 7.2 Hz), 4.30 (q, 2 H, J = 7.2 Hz), 6.37 (dt, 1 H, J = 7.2, 14.4 Hz), 7.17-7.40 (m, 4 H), 7.51 (s, 1 H), 7.75 (d, 1 H, J = 8.1 Hz), 7.95 (s, 1 H); ^{13}C NMR (75 MHz, CDCl_3) δ 13.8, 14.2, 22.2, 29.3, 31.0, 60.8, 81.2, 111.8, 112.9, 117.6, 122.0, 122.5, 124.3, 124.4, 126.1, 126.4, 128.9, 140.7, 161.0; mass spectrum (ESI): m/e (% relative intensity) 339.1 (22) ($\text{M} + \text{H}$) $^+$, 361.1 (100) ($\text{M} + \text{Na}$) $^+$; HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{22}\text{N}_4\text{O}_2\text{Na}$ 361.1635, found 361.1632.



35

$R_f = 0.58$ [EtOAc]; mp 170-173 °C; $[\alpha]_D^{20} = 53.8$ (c 3.65, CHCl₃);

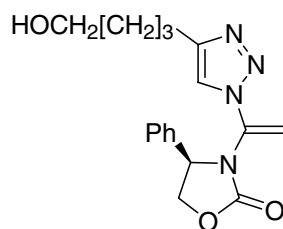
IR (film) cm⁻¹ 3138(w), 3028 (w), 2964(m), 2926(m), 2857(m), 1699(s), 1587(m), 1404(m), 1285(w), 1229(w), 1215(w), 1107(m); ¹H NMR (300 MHz, CDCl₃) δ 0.84-0.94 (m, 6 H), 1.28-1.52 (m, 4 H), 2.18 (dt, 2 H, $J = 7.2, 7.2$ Hz), 2.86 (s, 3 H), 4.00-4.10 (m, 1 H), 5.54 (d, 1 H, $J = 8.7$ Hz), 6.13 (td, 1 H, $J = 7.2, 14.4$ Hz), 7.01 (d, 1 H, $J = 14.4$ Hz), 7.19-7.32 (m, 5 H), 8.15 (s, 1 H); ¹³C NMR (75 MHz, CDCl₃) δ 13.6, 14.8, 21.9, 28.4, 29.0, 30.8, 56.0, 60.6, 108.4, 122.5, 124.4, 127.5, 127.9, 128.3, 136.1, 144.1, 157.6; mass spectrum (ESI): m/e (% relative intensity) 340.2 (85) (M + H)⁺, 362.2 (100) (M + Na)⁺; HRMS (ESI) calcd for C₁₉H₂₅N₅ONa 362.1951, found 362.1954.



36

$R_f = 0.47$ [50% EtOAc in hexanes]; mp 177-180 °C; $[\alpha]_D^{20} = -0.52$ (c 0.383, CHCl₃);

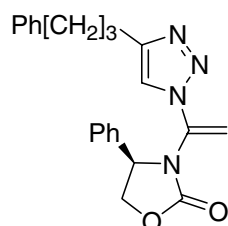
IR (film) cm⁻¹ 3582(w), 3175(w), 3067(w), 2924(w), 2338(m), 1760(s), 1582(m), 1500(m), 1418(m), 1214(m), 1100(w), 1035(m); ¹H NMR (500 MHz, CDCl₃) δ 4.48 (dd, 1 H, $J = 4.5, 8.5$ Hz), 4.95 (dd, 1 H, $J = 8.5, 8.5$ Hz), 5.81 (dd, 1 H, $J = 4.5, 8.5$ Hz), 7.35-7.63 (m, 10 H), 7.95 (d, 1 H, $J = 8.5$ Hz), 7.95-8.02 (m, 1 H), 8.30 (s, 1 H); ¹³C NMR (125 MHz, CDCl₃) δ 59.1, 71.5, 108.4, 112.1, 115.8, 122.3, 123.5, 126.6, 127.1, 127.9, 128.3, 128.9, 129.3, 130.5, 133.6, 134.1, 135.3, 138.8, 142.8; mass spectrum (ESI): m/e (% relative intensity) 379.2 (100) (M + Na)⁺; HRMS (ESI) calcd for C₂₁H₁₆N₄O₂Na 379.1165, found 379.1158.



38a

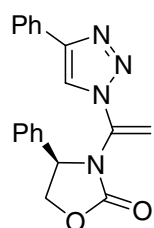
$R_f = 0.27$ [EtOAc]; $[\alpha]_D^{20} = -70.7$ (c 0.574, CHCl₃);

IR (film) cm^{-1} 3583(w), 2937(m), 28865(w), 1771(s), 1661(m), 1457(w), 1397(m), 1215(m), 1047(m); ^1H NMR (500 MHz, CDCl_3) δ 1.56-1.65 (m, 2 H), 1.69-1.78 (m, 2 H), 1.86-2.04 (br, 1 H), 2.72 (t, 2 H, $J = 7.0$ Hz), 3.67 (t, 2 H, $J = 6.5$ Hz), 4.28 (dd, 1 H, $J = 7.0, 9.0$ Hz), 4.79 (dd, 1 H, $J = 9.0, 9.0$ Hz), 5.18-5.25 (m, 2 H), 5.28 (d, 1 H, $J = 2.0$ Hz), 7.14-7.19 (m, 2 H), 7.24-7.28 (m, 1 H) 7.32-7.38 (m, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 25.0, 25.4, 32.0, 60.5, 62.4, 70.3, 104.1, 111.7, 120.6, 127.0, 129.3, 129.4, 133.9, 136.5, 155.4; mass spectrum (ESI): m/e (% relative intensity) 351.2 (100) ($\text{M} + \text{Na}$) $^+$; HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{20}\text{N}_4\text{O}_3\text{Na}$ 351.1428, found 351.1438.



38b

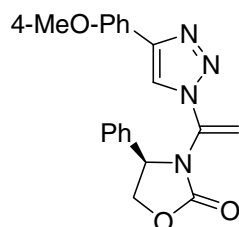
$R_f = 0.46$ [50% EtOAc in hexanes]; $[\alpha]_D^{20} = -77.4$ (c 0.773, CHCl_3); IR (film) cm^{-1} 3584(w), 3140(w), 3061(w), 3026(w), 2926(m), 2858(w), 1771(s), 1660(m), 1451(w), 1395(m), 1216(m), 1043(m); ^1H NMR (500 MHz, CDCl_3) δ 1.97 (tt, 2 H, $J = 7.5, 7.5$ Hz), 2.64-2.74 (m, 4 H), 4.28 (dd, 1 H, $J = 7.0, 9.0$ Hz), 4.78 (dd, 1 H, $J = 9.0, 9.0$ Hz), 5.21 (dd, 1 H, $J = 7.0, 9.0$ Hz), 5.23 (d, 1 H, $J = 2.5$ Hz), 5.27 (d, 1 H, $J = 2.5$ Hz), 7.13-7.22 (m, 6 H), 7.24-7.35 (m, 5 H); ^{13}C NMR (125 MHz, CDCl_3) δ 24.9, 30.8, 35.2, 60.5, 70.3, 104.0, 120.5, 126.0, 127.0, 128.4, 128.5, 129.3, 129.4, 133.9, 136.5, 141.7, 147.9, 155.4; mass spectrum (ESI): m/e (% relative intensity) 375.2 (151) ($\text{M} + \text{Na}$) $^+$, 397.2 (100) ($\text{M} + \text{Na}$) $^+$; HRMS (ESI) calcd for $\text{C}_{22}\text{H}_{22}\text{N}_4\text{O}_2\text{Na}$ 397.1635, found 397.1637.



38c

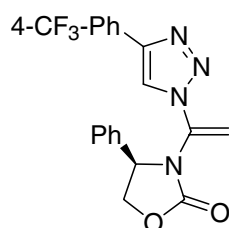
$R_f = 0.45$ [50% EtOAc in hexanes]; mp 154-155 $^\circ\text{C}$; $[\alpha]_D^{20} = -84.4$ (c 0.289, CHCl_3); IR (film) cm^{-1} 3583(w), 3138(w), 3066(w), 3036(w), 2912(w), 1772(s), 1654(w), 1458(m), 1395(m), 1234(m), 1071(m), 1019(m); ^1H NMR (500 MHz, CDCl_3) δ 4.33 (dd, 1 H, $J = 7.0, 9.0$ Hz), 4.82 (dd, 1 H, $J = 9.0, 9.0$ Hz), 5.23 (dd, 1 H, $J = 7.0, 9.0$ Hz), 5.29-5.31 (m, 1 H), 5.38-5.40 (m, 1 H), 7.17-7.21 (m, 2 H), 7.33-7.39 (m, 4 H), 7.43-7.46 (m, 2 H), 7.67 (s, 1 H), 7.79 (dd, 1 H, $J = 1.5, 6.5$ Hz); ^{13}C

NMR (125 MHz, CDCl₃) δ 60.5, 70.3, 104.7, 119.1, 125.9, 127.0, 128.7, 128.9, 129.4, 129.5, 129.6, 133.9, 136.5, 143.8, 155.3; mass spectrum (ESI): m/e (% relative intensity) 333.4 (69) (M + Na)⁺, 355.4 (100) (M + Na)⁺; HRMS (ESI) calcd for C₁₉H₁₆N₄O₂Na 355.1165, found 355.1165.



38d

R_f = 0.55 [50% EtOAc in hexanes]; [α]_D²⁰ = - 123.0 (*c* 1.30, CHCl₃);
¹H NMR (400 MHz, CDCl₃) δ 3.84 (s, 3 H), 4.32 (dd, 1 H, *J* = 6.8, 8.8 Hz), 4.80 (dd, 1 H, *J* = 8.8, 8.8 Hz), 5.23 (dd, 1 H, *J* = 6.8, 8.8 Hz), 5.23 (dd, 1 H, *J* = 2.4 Hz), 5.37 (dd, 1 H, *J* = 2.4 Hz), 6.95 (td, 2 H, *J* = 2.0, 8.4 Hz), 7.17-7.20 (m, 2 H), 7.32-7.36 (m, 3 H), 7.60 (s, 1 H), 7.71 (td, 2 H, *J* = 2.0, 8.4 Hz);
¹³C NMR (100 MHz, CDCl₃) δ 55.6, 60.8, 70.5, 104.8, 114.6, 118.4, 122.5, 127.3, 127.4, 129.4, 129.6, 134.1, 136.7, 147.8, 155.6, 160.2; mass spectrum (MALDI): m/e (% relative intensity) 401.1 (100) (M + H)⁺; HRMS (MALDI) calcd for C₂₀H₁₉N₄O₃ 363.1452, found 363.1431.



38e

R_f = 0.50 [50% EtOAc in hexanes]; [α]_D²⁰ = - 84.0 (*c* 1.95, CHCl₃);
¹H NMR (400 MHz, CDCl₃) δ 4.34 (dd, 1 H, *J* = 7.2, 8.8 Hz), 4.82 (dd, 1 H, *J* = 8.8, 8.8 Hz), 5.23 (dd, 1 H, *J* = 7.2, 8.8 Hz), 5.28 (d, 1 H, *J* = 3.2 Hz), 5.41 (d, 1 H, *J* = 3.2 Hz), 7.21-7.24 (m, 2 H), 7.33-7.36 (m, 3 H), 7.67 (d, 2 H, *J* = 8.0 Hz), 7.82 (s, 1 H), 7.90 (d, 2 H, *J* = 8.0 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 61.1, 70.7, 105.3, 120.3, 126.2, 126.3, 127.3, 129.7, 129.8, 130.5, 130.8, 133.4, 134.1, 136.5, 146.5, 155.6; mass spectrum (MALDI): m/e (% relative intensity) 401.1 (100) (M + H)⁺; HRMS (MALDI) calcd for C₂₀H₁₆F₃N₄O₂ 401.1220, found 401.1205.