Synthesis of Isoquinoline Derivatives Using ROM-RCM of Cyclobutene-Yne

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Supporting Information

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Experimental Section.

General Methods. Solvents were distilled under an argon atmosphere from sodium benzophenone (THF, Toluene) or CaH₂ (CH₂Cl₂). All other reagents were purified when necessary by standard procedure. All reactions were conducted under an argon atmosphere unless it was described. ¹H NMR spectra were recorded at 400 MHz or 270 MHz. ¹³C NMR spectra were recorded at 100 MHz or 67.8 MHz. ¹H NMR and ¹³C NMR shifts (ppm) were reported relative to internal tetramethylsilane (Me₄Si). For ¹³C NMR spectra, carbon type is defined as (CH₃), (CH₂), (CH), or (C) on the basis of DEPT experiments. Kieselgel 60 (Merck, 70-230 mesh) and Kieselgel 60 (Merck, 230-400 mesh) were used for column chromatography or flash column chromatography, respectively.

N-But-3-ynyl-*N*-cyclopent-1-enylmethyl-*p*-toluenesulfonamide (**2**).

To a solution of **11** (0.64 mL, 5 mmol) in CH₂Cl₂ (12.5 mL) was added DIBAL-H (13 mL, 12.5 mmol, 0.95 M in hexane), and the solution was stirred at -78 °C for 2 h. To this solution was added MeOH and saturated Rochelle salt solution at -78 °C and the aqueous layer was extracted with Et₂O. The organic layer was washed with brine, dried over Na₂SO₄ and carefully concentrated to give crude alcohol (500 mg). To a solution of crude alcohol (500 mg, ca. 5 mmol) in ether (5 mL) was added Et₃N (1.3 mL, 10 mmol), and MsCl (0.4 mL, 5 mmol) at -78 °C and the solution was stirred at 0 °C for 2 h. To this solution was added NaI (924 mg, 6.1 mmol) at 0 °C and the solution was stirred at rt for 3 h. The resulting solution (cyclopentenyl iodide in ether) was used for the next reaction without further purification. To a suspension of NaH (244 mg, 6 mmol, 60% oil

suspension) in DMF (5 mL) was added a solution of **13**¹ (1.1 g, 5 mmol) in DMF (5 mL) at 0 °C, and the solution was stirred for 30 min at 0 °C. To this solution was added cyclopentenyl iodide in ether. The whole solution was stirred at rt for 15 h. To this solution was added saturated NH₄Cl solution, and the aqueous layer was extracted with AcOEt. The organic layer was washed with brine, dried over Na₂SO₄, and concentrated. The residue was purified by column chromatography on silica gel (Hexane/AcOEt, 5:1) to yield **2** (800 mg, 53%, 4 steps) as colorless needles: mp 50-51 °C (Hexane); IR (nujol) 3282, 2924, 2851, 1654, 1598, 1326, 1153 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.85 (m, 2 H), 1.96 (t, *J* = 2.4 Hz, 1 H), 2.16 (m, 2 H), 2.30 (m, 2 H), 2.40-2.44 (m, 2 H), 2.43 (s, 3 H), 3.26 (m, 2 H), 3.87 (s, 2 H), 5.57 (s, 1 H), 7.30 (d, *J* = 8.0 Hz, 2 H), 7.70 (d, *J* = 8.0 Hz, 2 H); ¹³C NMR (100 MHz, CDCl₃) δ 18.9 (CH₂), 21.2 (CH₃), 23.2 (CH₂), 32.2 (CH₂), 32.9 (CH₂), 46.2 (CH₂), 48.7 (CH₂), 69.9 (CH), 80.8 (C), 126.7 (CH x 2), 129.3 (CH x 2), 129.5 (CH), 136.5 (C), 139.0 (C), 142.9 (C); LRMS *m/z* 303 (M⁺), 264, 184, 155, 148, 91, 81; Anal. calcd for C₁₇H₂₁NO₂S: C, 67.29; H, 6.98; N, 4.62; S, 10.57. Found: C, 67.12; H, 6.99; N, 4.48; S, 10.42.

¹ a) Short, K. M.; Ziegler, C. B. Jr. *Tetrahedron Lett.* **1995**, 36, 355. b) Henry, J. R.; Marcin, L. R.; McIntosh, M. C.; Scola, P. M.; Harris, D. Jr.; Weinreb, S. M. *Tetrahedron Lett.* **1989**, 30, 5709.

***N*-But-3-ynyl-*N*-cyclobut-1-enylmethyl-*p*-toluenesulfonamide (**4a**).**

A mixture of **12** (2.0 mL, 12.35 mmol) and DBU (2.8 mL, 18.53 mmol) was stirred for 1 h at 90 °C. To the resulting mixture was added CH₂Cl₂ (10 mL). The organic phase was washed with 10% HCl solution and dried over MgSO₄. After filtration, volatiles were removed carefully under reduce pressure (360 mmHg, ~20 °C). The residue was dissolved in dry CH₂Cl₂ (15 mL) and cooled to –78 °C. DIBAL-H (39.5 mL, 37.06 mmol, 0.94 M in hexane) was added to a solution and the whole solution was stirred at the same temperature for 1.5 h. After the spot of the starting material had disappeared on TLC, HCO₂Me (1.0 mL) and saturated Rochelle salt solution (20 mL) were added to the solution. The resulting turbidity mixture was continuously stirred until turn to clear solution. The solution was extracted with Et₂O and the organic phase was dried over MgSO₄. After filtration, volatiles were removed carefully under reduce pressure (400 mmHg, ~30 °C). DEAD (3.1 mL, 6.80 mmol, 40% in Toluene) was added to the solution of the crude product, **13**¹ (1.38 g, 6.18 mmol) and PPh₃ (1.78 g, 6.80 mmol) in THF (30 mL) at 0 °C. The solution was stirred at rt for 14 h and then concentrated. The residue was purified by column chromatography on silica gel (Hexane/AcOEt, 3:1 and Hexane/Et₂O, 5:1) to afford **4a** (376.6 mg, 11% from **12**) as a colorless liquid and recovered **13** (0.98 g): IR (neat) 2120 (w), 1735 (m), 1598 (m), 1342 (s), 1158 (s) cm⁻¹; ¹H NMR (270 MHz, CDCl₃) δ 1.98 (dd, *J* = 2.4, 3.0 Hz, 1 H), 2.23-2.32 (m, 4 H), 2.42 (s, 3 H), 2.42-2.50 (m, 2 H), 3.33 (t, *J* = 7.6 Hz, 2 H), 3.81 (s, 2 H), 5.82 (s, 1 H), 7.29 (d, *J* = 8.5 Hz,

2 H), 7.70 (d, $J = 8.5$ Hz, 2 H); EI-LRMS m/z 289 (M^+), 250, 184, 155, 134, 91; ^{13}C NMR (67.8 MHz, CDCl_3) δ 19.2 (CH_2), 21.4 (CH_3), 26.7 (CH_2), 30.4 (CH_2), 46.4 (CH_2), 47.9 (CH_2), 70.1 (CH), 81.0 (C), 127.1 ($\text{CH} \times 2$), 129.5 ($\text{CH} \times 2$), 132.9 (CH), 136.9 (C), 143.3 (C), 143.6 (C); EI-HRMS m/z calcd for $\text{C}_{16}\text{H}_{19}\text{O}_2\text{NS}$ (M^+) 289.1137, found 289.1141.

Ethyl 2-[cyclobut-1-enylmethyl-(*p*-toluenesulfonyl)-amino]-pent-4-ynoate (4c).

In a similar manner to that for the synthesis of **4a** from **12**, **4c** (176.6 mg, 8%*d*) was synthesized from **12** (1.0 mL, 6.18 mmol) and **7**² (359.3 mg, 1.22 mmol): IR (neat) 2124 (w), 1732 (s), 1598 (m), 1337 (s), 1164 (s) cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.18 (t, $J = 7.2$ Hz, 3 H), 2.01 (t, $J = 2.6$ Hz, 1 H), 2.25-2.40 (m, 4 H), 2.42 (s, 3 H), 2.72 (ddd, $J = 2.6, 8.2, 17.0$ Hz, 1 H), 2.88 (ddd, $J = 2.6, 6.5, 17.0$ Hz, 1 H), 3.77 (d, $J = 17.0$ Hz, 1 H), 3.91 (d, $J = 17.0$ Hz, 1 H), 4.00-4.13 (m, 2 H), 4.72 (dd, $J = 6.5, 8.2$ Hz, 1 H), 5.89 (s, 1 H), 7.27 (d, $J = 8.2$ Hz, 2 H), 7.76 (d, $J = 8.2$ Hz, 2 H); ^{13}C NMR (100 MHz, CDCl_3) δ 14.0 (CH_3), 21.2 (CH_2), 21.6 (CH_3), 26.7 (CH_2), 30.5 (CH_2), 45.6 (CH_2), 58.7 (CH), 61.6 (CH_2), 71.2 (CH), 79.6 (C), 127.6 ($\text{CH} \times 2$), 129.2 ($\text{CH} \times 2$), 132.6 (CH), 137.2 (C), 143.3 (C), 144.5 (C), 169.1 (C); EI-LRMS m/z 362 ($M^+ + 1$), 322, 288, 256, 222, 206, 155, 105, 91; EI-HRMS m/z calcd for $\text{C}_{19}\text{H}_{23}\text{O}_4\text{NS}$ (M^+) 361.1348, found 361.1373.

² a) Kotha, S.; Sreenivasachary, N. *Chem. Commun.* **2000**, 503. b) Kotha, S.; Sreenivasachary, N. *Eur. J. Org. Chem.* **2001**, 3375.

Methyl 5-[Cyclobut-1-enylmethyl-(*p*-toluenesulfonyl)-amino]-pent-2-ynoate (14**).**

To a solution of **4a** (320.2 mg, 1.11 mmol) in THF (11 mL) was added BuLi (0.83 mL, 1.33 mmol, 1.60 M in hexane) at $-78\text{ }^{\circ}\text{C}$. After stirring at the same temperature for 0.5 h, freshly distilled ClCO₂Me (0.17 mL, 2.21 mmol) was added and the solution was stirred for 1 h. Saturated NH₄Cl solution was added and the aqueous layer was extracted with AcOEt. The organic phase was washed with brine, dried over MgSO₄ and concentrated. The residue was purified by column chromatography on silica gel (Hexane/Et₂O, 5:1) to afford **14** (260.1 mg, 68%) as a colorless liquid and recovered **4a** (38.0 mg, 12%): IR (neat) 2242 (s), 1717 (s), 1598 (m), 1345 (s), 1260 (s), 1159 (s) cm⁻¹; ¹H NMR (270 MHz, CDCl₃) δ 2.24-2.28 (m, 2 H), 2.28-2.33 (m, 2 H), 2.43 (s, 3 H), 2.64 (t, $J = 7.5$ Hz, 2 H), 3.36 (t, $J = 7.5$ Hz, 2 H), 3.76 (s, 3 H), 3.81 (br, 2 H), 5.84 (br, 1 H), 7.30 (d, $J = 8.4$ Hz, 2 H), 7.70 (d, $J = 8.4$ Hz, 2 H); ¹³C NMR (67.8 MHz, CDCl₃) δ 19.3 (CH₂), 21.1 (CH₃), 26.5 (CH₂), 30.1 (CH₂), 45.2 (CH₂), 47.9 (CH₂), 52.3 (CH₃), 73.9 (C), 85.6 (C), 126.9 (CH x 2), 129.4 (CH x 2), 132.9 (CH), 136.3 (C), 143.1 (C), 143.2 (C), 153.4 (C); EI-LRMS m/z 347 (M⁺), 316, 294, 250, 192, 184, 155, 91; EI-HRMS m/z calcd for C₁₈H₂₁O₄NS (M⁺) 347.1191, found 347.1197.

***N*-Cyclobut-1-enylmethyl-*N*-(5-hydroxy-pent-3-ynyl)-*p*-toluenesulfonamide (**15**).**

To a solution of **14** (334.3 mg, 0.96 mmol) in toluene (10 mL) was added DIBAL-H (4.2 mL, 4.23 mmol, 1.01 M in toluene) at $-25\text{ }^{\circ}\text{C}$. The solution was stirred at the same temperature for 1.5 h. AcOEt (5.0 mL) and saturated Rochelle salt solution (20 mL) were added to this solution. The resulting turbidity mixture was continuously stirred until turn to clear solution. The solution was extracted with AcOEt and the organic phase was washed with brine, dried over MgSO_4 and concentrated. The residue was purified by column chromatography on silica gel (Hexane/AcOEt, 3:2) to afford **15** (300.0 mg, 98%) as a colorless liquid: IR (neat) 3515 (m), 2226 (w), 1598 (m), 1341 (s), 1158 (s) cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 2.16 (br, 1 H), 2.21-2.31 (m, 4 H), 2.42 (s, 3 H), 2.44-2.53 (m, 2 H), 3.32 (t, $J = 7.5\text{ Hz}$, 2 H), 3.80 (br, 2 H), 4.21 (t, $J = 2.1\text{ Hz}$, 2 H), 5.81 (br, 1 H), 7.29 (d, $J = 8.2\text{ Hz}$, 2 H), 7.70 (d, $J = 8.2\text{ Hz}$, 2 H); ^{13}C NMR (67.8 MHz, CDCl_3) δ 19.3 (CH_2), 21.4 (CH_3), 26.7 (CH_2), 30.3 (CH_2), 46.3 (CH_2), 47.6 (CH_2), 50.9 (CH_2), 80.3 (C), 82.4 (C), 127.0 ($\text{CH} \times 2$), 129.5 ($\text{CH} \times 2$), 132.8 (CH), 136.8 (C), 143.2 (C), 143.5 (C); EI-LRMS m/z 319 (M^+), 250, 184, 155, 91; EI-HRMS m/z calcd for $\text{C}_{17}\text{H}_{21}\text{O}_3\text{NS}$ (M^+) 319.1242, found 319.1233.

5-[Cyclobut-1-enylmethyl-(*p*-toluenesulfonyl)-amino]-pent-2-ynyl acetate (4b**).**

To a solution of **15** (110.7 mg, 0.35 mmol) and pyridine (0.28 mL, 3.47 mmol) in CH_2Cl_2 (4 mL) was added Ac_2O (0.16 mL, 1.73 mmol) at $0\text{ }^{\circ}\text{C}$. The solution was stirred at $0\text{ }^{\circ}\text{C}$ for 0.5 h and at rt for 2 h. The solution was poured onto ice, and the aqueous layer was extracted with AcOEt. The organic phase was washed with brine, dried over MgSO_4 and concentrated. The residue was purified by column chromatography on silica gel (Hexane/AcOEt, 2:1) to afford **4b** (108.4 mg, 87%) as a colorless liquid: IR (neat) 2240 (w), 1748 (s), 1598 (w), 1344 (s), 1227 (s), 1159 (s) cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 2.09 (s, 3 H), 2.23-2.32 (m, 4 H), 2.42 (s, 3 H), 2.47-2.55 (m, 2 H), 3.31 (t, $J = 7.6\text{ Hz}$, 2 H), 3.80 (br, 2 H), 4.62 (t, $J = 2.1\text{ Hz}$, 2 H), 5.81 (br, 1 H), 7.29 (d, $J = 8.2\text{ Hz}$, 2 H), 7.70 (d, $J = 8.2\text{ Hz}$, 2 H); ^{13}C NMR (67.8 MHz, CDCl_3) δ 19.4 (CH_2), 20.6 (CH_3), 21.3 (CH_3), 26.6 (CH_2), 30.2 (CH_2), 46.2 (CH_2), 47.8 (CH_2), 52.3 (CH_2), 75.7 (C), 83.8 (C), 127.0 ($\text{CH} \times 2$), 129.5 ($\text{CH} \times 2$), 132.7 (CH), 136.9 (C), 143.2 (C), 143.5 (C), 170.1 (C); EI-LRMS m/z 361

(M⁺), 302, 250, 184, 155, 91; EI-HRMS *m/z* calcd for C₁₉H₂₃O₄NS (M⁺) 361.1348, found 361.1350.

***N*-Benzyl-*N*-(but-3-ynyl)-1-cyclobutene-1-carboxamide (**8a**).**

To a solution of KOH (1.46 g, 25.94 mmol) in toluene (25 mL) was added **11** (1.0 mL, 6.18 mL) and the solution was refluxed for 45 min. After cooling, water was added and an aqueous layer was washed with petroleum ether. An aqueous layer was acidified by addition of 10% HCl. The acidic phase was extracted with ether and the organic phase was washed with brine, dried over MgSO₄ and concentrated to afford crude 1-cyclobutenecarboxylic acid. To a solution of crude 1-cyclobutenecarboxylic acid (6.18 mmol) in CH₂Cl₂ (21 mL) was added Et₃N (1.7 mL, 12.35 mmol) and ClPO(OEt)₂ (1.1 mL, 7.41 mmol) at 0 °C. After stirring for 1 h at the same temperature, **17a**³ (1.28 g, 8.03 mmol) in CH₂Cl₂ (10 mL) was added. The resulting solution was stirred at rt for 2 h. Saturated NaHCO₃ solution was added, and the aqueous phase was extracted with AcOEt. The combined organic phase was washed with saturated NH₄Cl solution and brine, dried over MgSO₄, filtered, and concentrated. The residue was purified by column chromatography on silica

³ Mengelberg, M. *Chem. Ber.* **1956**, 89, 1185.

gel (Hexane/AcOEt, 2:1) to afford **8a** (853.4 mg, 58%, 2 steps) as a pale yellow liquid: IR (neat) 2119 (w), 1696 (s), 1631 (s), 1422 (s), 1243 (s) cm^{-1} ; ^1H NMR (270 MHz, DMSO, 100 $^\circ\text{C}$) δ 2.38-2.44 (m, 4 H), 2.65 (t, $J = 2.5$ Hz, 1 H), 2.74 (m, 2 H), 3.48 (t, $J = 7.1$ Hz, 2 H), 4.69 (s, 2 H), 6.40 (br, 1 H), 7.22-7.37 (m, 5 H); EI-LRMS m/z 239 (M^+), 200, 142, 91; EI-HRMS m/z calcd for $\text{C}_{16}\text{H}_{17}\text{ON}$ (M^+) 239.1310, found 239.1302.

***N*-Benzyl-*N*-(pent-3-ynyl)-1-cyclobutene-1-carboxamide (**8b**).**

In a similar manner to that for the synthesis of **8a** from **12**, **8b** (448.9 mg, 57%, 2 steps) was synthesized from **12** (0.5 mL, 3.09 mmol) and **17b**⁴ (695.6 mg, 4.01 mmol): IR (neat) 1627 (s), 1586 (s), 1422 (m) cm^{-1} ; ^1H NMR (270 MHz, DMSO, 100 $^\circ\text{C}$) δ 1.71 (t, $J = 2.6$ Hz, 3 H), 2.33 (tq, $J = 7.1, 2.6$ Hz, 2 H), 2.39-2.43 (m, 2 H), 2.75 (t, $J = 3.2$ Hz, 2 H), 3.44 (t, $J = 7.1$ Hz, 2 H), 4.67 (s, 2 H), 6.40 (brs, 1 H), 7.21-7.37 (m, 5 H); EI-LRMS m/z 253 (M^+), 238, 200, 156, 120, 91; EI-HRMS m/z calcd for $\text{C}_{17}\text{H}_{19}\text{ON}$ (M^+) 253.1467, found 253.1486.

***N*-Benzyl-*N*-(4-phenyl-but-3-ynyl)-1-cyclobutene-1-carboxamide (**8c**).**

To a suspension of $\text{Pd}(\text{PPh}_3)_4$ (45.2 mg, 39.15 μmol) and CuI (7.5 mg, 39.15 μmol) in Et_3N (2 mL) was added PhI (0.09 mL, 0.82 mmol) at rt. After stirred for 10 min, **8a** (187.4 mg, 0.78 mmol) in benzene (1 mL) was added to this solution, and the resulting solution was stirred at rt for 16 h and concentrated. The residue was purified by column chromatography on silica gel (Hexane/AcOEt, 2:1) to afford **8c** (226.1 mg, 92%) as a pale yellow liquid: IR (neat) 1713 (s), 1628 (s), 1586 (s), 1492 (m), 1421 (s) cm^{-1} ; ^1H NMR (270 MHz, DMSO, 100 $^\circ\text{C}$) δ 2.38-2.42 (br, 2 H), 2.48 (t, $J = 6.9$ Hz, 2 H), 2.74-2.78 (br, 2 H), 3.60 (t, $J = 6.9$ Hz, 2 H), 4.74 (s, 2 H), 6.44 (brs, 1 H), 7.23-7.38 (m, 10 H); EI-LRMS m/z 315 (M^+), 200, 91; EI-HRMS m/z calcd for $\text{C}_{22}\text{H}_{21}\text{ON}$ (M^+) 315.1623, found 315.1624.

⁴ Van Houten, K. A.; Kim, J.-M.; Bogdan, M. A.; Ferri, D. C.; Mariano, P. S. *J. Am. Chem. Soc.* **1998**, *120*, 5864.

Ethyl 4-{4-[benzyl-(cyclobut-1-enecarbonyl)-amino]-but-1-ynyl}-benzoate (8d).

In a similar manner to that for the synthesis of **8c** from **8a**, **8d** (203.0 mg, 81%) was synthesized from **8a** (154.7 mg, 0.65 mmol) and Ethyl 4-iodobenzoate (0.11 mL, 0.68 mmol): IR (neat) 2231 (w), 1716 (s), 1627 (s), 1607 (s), 1584 (m), 1274 (s), 755 (s) cm^{-1} ; ^1H NMR (270 MHz, DMSO, 100 °C) δ 1.33 (t, $J = 7.1$ Hz, 3 H), 2.38-2.42 (m, 2 H), 2.71 (t, $J = 6.9$ Hz, 2 H), 2.76 (t, $J = 3.2$ Hz, 2 H), 3.61 (t, $J = 6.9$ Hz, 2 H), 4.33 (q, $J = 7.1$ Hz, 2 H), 4.74 (s, 2 H), 6.44 (br, 1 H), 7.24-7.38 (m, 5 H), 7.47 (d, $J = 8.6$ Hz, 2 H), 7.91 (d, $J = 8.6$ Hz, 2 H); EI-LRMS m/z 387 (M^+), 342, 200, 91; EI-HRMS m/z calcd for $\text{C}_{25}\text{H}_{25}\text{O}_3\text{N}$ (M^+) 387.1834, found 387.1826.

N-Benzyl-N-(4-naphthalen-1-yl-but-3-ynyl)-1-cyclobut-1-enecarboxamide (8e).

In a similar manner to that for the synthesis of **8c** from **8a**, **8e** (213.3 mg, 81%) was synthesized from **8a** (172.0 mg, 0.72 mmol) and 1-Iodonaphthalene (0.11 mL, 0.75 mmol): IR (neat) 2224 (w), 1718 (w), 1625 (s), 1585 (m), 1421 (s), 755 (s) cm^{-1} ; ^1H NMR (270 MHz, DMSO, 100 °C) δ 2.39 (br, 2 H), 2.77 (br, 2 H), 2.85 (t, $J = 6.8$ Hz, 2 H), 3.65-3.75 (m, 2 H), 4.79 (s, 2 H), 6.46 (br, 1 H), 7.25-8.25 (m, 12 H); EI-LRMS m/z 364 (M^+-1), 200, 178, 165, 91; EI-HRMS m/z calcd for $\text{C}_{26}\text{H}_{23}\text{ON}$ (M^+) 365.1779, found 365.1770.