

Supporting Information

Synthesis of Cyclic Dienamide Using Ruthenium-Catalyzed Ring-Closing Metathesis of Ene-Ynamide

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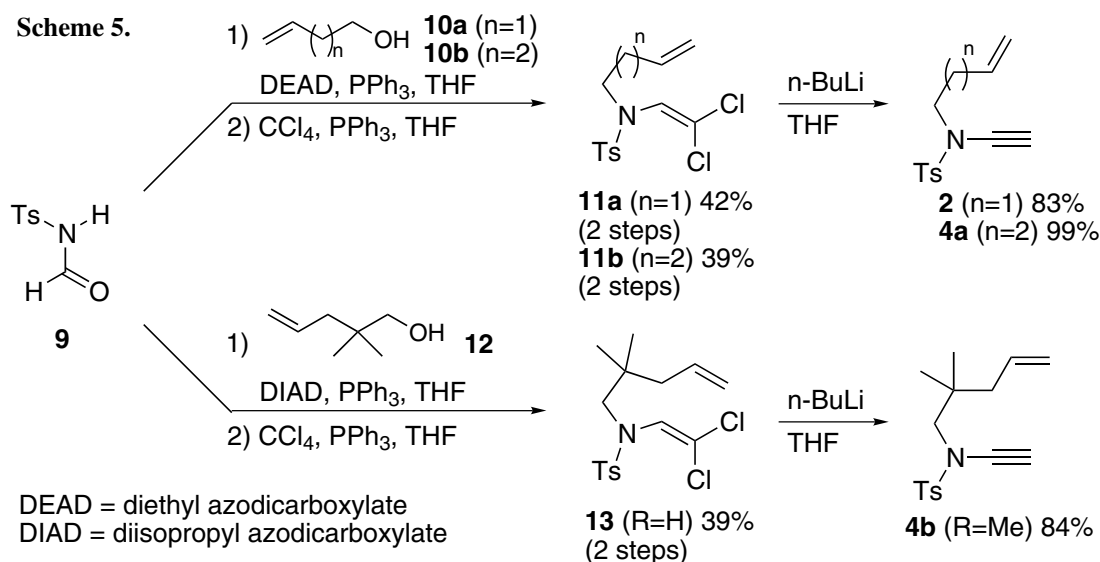
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General

The metathesis reactions were carried out under an ethylene atmosphere (1 atm) unless otherwise mentioned, and all the reaction solutions were degassed through freeze-pump-thaw cycle. Ethylene gas was purified by passing through the aqueous CuCl solution (2 g of CuCl in 180 ml of sat. NH_4Cl aq.) and conc. H_2SO_4 and then KOH tube. Solvents were distilled under an argon atmosphere from sodium benzophenone ketyl (toluene) or CaH_2 (CH_2Cl_2).

Procedure for the Synthesis of **2** and **4** (Scheme 5)

These compounds were prepared by Brückner's method (Brückner, D. *Synlett* **2000**, 1402.).



Ene-Enamide (11a). To a solution of **9** (2.9 g, 14 mmol) in THF (29 ml) were added PPh_3 (4.9 g, 19 mmol), **10a** (1.5 ml, 17 mmol) and DEAD (2.7 ml, 17 mmol) at 0 °C, and the mixture was stirred at rt for 14 h. After the solvent was evaporated, the residue was purified by short column chromatography on silica gel (hexane/ AcOEt =10/1) to give inseparable mixture of *N*-alkylated product and *O*-alkylated product (2.9 g, in the ratio of 1.3:1). To a solution of the above mixture (2.9 g) in THF (38 ml) were added PPh_3 (9.0 g, 35 mmol) and CCl_4 (11 ml, 115 mmol) at rt, and the mixture was stirred at 60 °C for 6 h. To the mixture was added saturated NaHCO_3 aq., and the aqueous layer was extracted with Et_2O . The organic layer was washed with saturated NaCl aq., dried over Na_2SO_4 , and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/ AcOEt =20/1) to give **11a** (1.9 g, 42 %, 2 steps) as a colorless solid. mp. 53~55 °C;

IR (nujol) 1642, 1597, 1357, 1165 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 2.28 (dt, $J = 6.8, 7.3$ Hz, 2 H), 2.44 (s, 3 H), 3.41 (t, $J = 7.3$ Hz, 2 H), 5.05 (d, $J = 10.2$ Hz, 1 H), 5.08 (d, $J = 17.0$ Hz, 1 H), 5.70 (ddt, $J = 17.0, 10.2, 6.8$ Hz, 1 H), 6.31 (s, 1 H), 7.32 (d, $J = 8.1$ Hz, 2 H), 7.68 (d, $J = 8.1$ Hz, 2 H); ^{13}C NMR (100 MHz, CDCl_3) δ 21.6, 32.9, 48.5, 117.4, 124.1, 124.7, 127.1, 129.7, 133.9, 135.3, 144.0; EI-LRMS m/z 319 (M^+), 278, 223, 164, 155, 91; EI-HRMS calcd for $\text{C}_{13}\text{H}_{15}\text{NO}_2\text{S}^{35}\text{Cl}_2$ 319.0200, found 319.0190.

Ene-Ynamide (2). To a solution of **11a** (150 mg, 0.47 mmol) in THF (2.3 ml) was added BuLi (1.66 M solution in hexane, 0.62 ml, 1.0 mmol) at -78°C , and the mixture was warmed to -40°C over 1 h. To the mixture was added MeOH (95 μl), and the mixture was diluted with Et_2O . The organic layer was washed with saturated NaCl aq., dried over Na_2SO_4 , and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/ Et_2O / Et_3N =100/5/1) to give **2** (97 mg, 83 %) as a colorless oil. IR (nujol) 3260, 2150, 1374, 1167 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 2.40 (dt, $J = 7.3, 7.6$ Hz, 2 H), 2.46 (s, 3 H), 2.75 (s, 1 H), 3.38 (t, $J = 7.6$ Hz, 2 H), 5.05 (d, $J = 10.2$ Hz, 1 H), 5.10 (d, $J = 17.3$ Hz, 1 H), 5.71 (ddt, $J = 17.3, 10.2, 7.6$ Hz, 1 H), 7.35 (d, $J = 8.4$ Hz, 2 H), 7.81 (d, $J = 8.4$ Hz, 2 H); ^{13}C NMR (67.5 MHz, CDCl_3) δ 21.6, 32.0, 50.5, 59.4, 75.9, 117.8, 127.6, 129.8, 133.4, 134.6, 144.7; EI-LRMS m/z 248 (M^+-H), 184, 155, 96, 55; EI-HRMS calcd for $\text{C}_{13}\text{H}_{14}\text{O}_2\text{NS}$ (M^+-H) 248.0745, found 248.0736.

Ene-Enamide (11b). A crude product, which was obtained from **9** (3.0 g, 14 mmol), PPh_3 (5.1 g, 20 mmol), **10b** (2.0 ml, 19 mmol) and DEAD (2.8 ml, 18 mmol), was purified by short column chromatography on silica gel (hexane/ AcOEt =10/1) to give inseparable mixture of *N*-alkylated product and *O*-alkylated product (3.0 g, in the ratio of 1.8:1). To a solution of the above mixture (3.0 g) in THF (38 ml) were added PPh_3 (8.9 g, 34 mmol) and CCl_4 (11 ml, 115 mmol) at rt, and the mixture was stirred at 60°C for 22 h. To the mixture was added saturated NaHCO_3 aq., and the aqueous layer was extracted with Et_2O . The organic layer was washed with saturated NaCl aq., dried over Na_2SO_4 , and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/ AcOEt =20/1) to give **11b** (2.0 g, 39 %, 2 steps) as a colorless solid. mp. $73\sim 75^\circ\text{C}$; IR (nujol) 1638, 1597, 1351, 1161 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.62 (tt, $J = 7.4, 7.4$ Hz, 2 H), 2.08 (dt, $J = 6.8, 7.4$ Hz, 2 H), 2.44 (s, 3 H), 3.32 (t, $J = 7.4$ Hz, 2 H), 4.99 (d, $J = 10.2$ Hz, 1 H), 5.02 (d, $J = 16.9$ Hz, 1 H), 5.75 (ddt, $J = 16.9, 10.2, 6.8$ Hz, 1 H), 6.26 (s, 3 H), 7.32 (d, $J = 8.1$ Hz, 2 H), 7.68 (d, $J = 8.1$ Hz, 2 H); ^{13}C NMR (100 MHz, CDCl_3) δ 21.5, 27.5, 30.5, 48.6, 115.3, 124.6, 124.7, 127.0, 129.7, 135.0, 136.9, 144.0; EI-LRMS m/z 333 (M^+), 318, 298, 278, 237, 178, 91; EI-HRMS calcd for $\text{C}_{14}\text{H}_{17}\text{NO}_2\text{S}^{35}\text{Cl}_2$ 333.0357, found 333.0354.

Ene-Ynamide (4a). In a similar manner to that for the synthesis of **2** from **11a**, **4a** (262 mg, 99%) was synthesized from **11b** (347 mg, 1.0 mmol) and BuLi (1.66 M solution in hexane, 1.4 ml, 2.3 mmol). IR (neat) 3297, 2132, 1641, 1597, 1364, 1169 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.75 (tt, $J = 7.2, 7.2$ Hz, 2 H), 2.09 (dt, $J = 6.6, 7.2$ Hz, 2 H), 2.45 (s, 3 H), 2.73 (s, 1 H), 3.31 (t, $J = 7.2$ Hz, 2 H), 4.99 (d, $J = 10.1$ Hz, 1 H), 5.02 (d, $J = 16.9$ Hz, 1 H), 5.75 (ddt, $J = 16.9, 10.1, 6.6$ Hz, 1 H), 7.35 (d, $J = 8.3$ Hz, 2 H), 7.80 (d, $J = 8.3$ Hz, 2 H); ^{13}C NMR (100 MHz, CDCl_3) δ 21.6, 26.8, 30.2, 50.6, 59.1, 75.9, 115.5, 127.4, 129.6, 134.3, 136.8, 144.6; FAB-LRMS m/z 264 (M^++H), 237, 198, 155, 108, 91; FAB-HRMS calcd for $\text{C}_{14}\text{H}_{18}\text{NO}_2\text{S}$ 264.1058 (M^++H), found 264.1034.

Ene-Ynamide (13). To a solution of **9** (1.6 g, 8.0 mmol) in THF (26 ml) were added PPh_3 (2.5 g, 20 mmol), **12** (1.1 g, 9.6 mmol) and DIAD (1.9 ml, 9.7 mmol) at 0°C , and the mixture was stirred at 50°C for 16 h. After the solvent was evaporated, the residue was purified by short column chromatography on silica gel (hexane/ AcOEt =10/1) to give inseparable mixture of *N*-alkylated product and *O*-alkylated product (1.5 g, in the ratio of 1:1.4). To a solution of the above mixture (1.5 g) in THF (17 ml) were added PPh_3 (1.0 g, 15 mmol) and CCl_4 (4.9 ml, 51 mmol) at rt, and the mixture was stirred at 60°C for 24 h. To the mixture was added saturated NaHCO_3 aq., and the aqueous layer was extracted with Et_2O . The organic layer was washed with saturated NaCl aq., dried over Na_2SO_4 , and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/ AcOEt =20/1) to give **13** (675 mg, 23 %, 2 steps) as a colorless oil. IR (nujol) 1638, 1598, 1358, 1168 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 0.94 (s, 6 H), 2.03 (d, $J = 7.3$ Hz, 2 H), 2.44 (s, 3 H), 3.02 (s, 2 H), 5.02 (d, $J = 16.9$ Hz, 1 H), 5.05 (d, $J = 9.2$ Hz, 1 H), 5.77 (ddt, $J = 16.9, 9.2, 7.3$ Hz, 1 H), 7.32 (d, $J = 8.1$ Hz, 2 H), 7.65 (d, $J = 8.1$ Hz, 2 H); ^{13}C NMR (100 MHz, CDCl_3) δ 21.5, 25.3, 35.4, 44.6, 59.8, 117.7, 127.2, 127.3, 127.7, 129.7, 134.1, 135.1, 143.9.

Ene-Ynamide (4b): In a similar manner to that for the synthesis of **2** from **11a**, **4b** (247 mg, 84%)

was synthesized from **13** (366 mg, 1.0 mmol) and BuLi (1.66 M solution in hexane, 1.4 ml, 2.3 mmol). IR (neat) 3302, 2134, 1638, 1597, 1367, 1170 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.01 (s, 6 H), 2.10 (d, $J = 7.5$ Hz, 2 H), 2.23 (s, 3 H), 2.68 (s, 1 H), 3.13 (s, 2 H), 5.03 (d, $J = 10.3$ Hz, 1 H), 5.04 (d, $J = 16.9$ Hz, 1 H), 5.81 (ddt, $J = 16.9, 10.3, 7.5$ Hz, 1 H), 7.35 (d, $J = 8.2$ Hz, 2 H), 7.79 (d, $J = 8.2$ Hz, 2 H); ^{13}C NMR (100 MHz, CDCl_3) δ 21.7, 25.1, 35.9, 44.4, 58.3, 61.6, 78.6, 117.9, 127.6, 129.5, 135.1, 134.2, 144.6; EI-LRMS m/z 291 (M^+), 290, 276, 262, 250, 155, 136, 91; EI-HRMS calcd for $\text{C}_{16}\text{H}_{21}\text{NO}_2\text{S}$ 291.1293, found 291.1287.

Typical Procedure for the RCM of **2** in the presence of **1b** under Ethylene Gas (Table 1, run 3).

A solution of **2** (91.5 mg, 0.37 mmol) and **1b** (15.6 mg, 0.018 mmol) in degassed-toluene was refluxed for 15 min under ethylene gas (1 atm). After the reaction mixture was cooled to room temperature, a few drops of ethyl vinyl ether was added to the mixture. After the solvent was removed under reduced pressure, the residue was purified by flash column chromatography on silica gel (hexane/ Et_2O / Et_3N =100/5/1) to give **3** (76.2 mg, 83% yield) as a colorless oil.

Spectral Data of RCM products

3: IR (neat) 1647, 1589, 1343, 1147 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 2.10 (ddd, $J = 8.4, 8.4, 3.0$ Hz, 2 H), 2.40 (s, 3 H), 3.77 (dd, $J = 8.4, 8.4$ Hz, 2 H), 5.20 (d, $J = 10.8$ Hz, 1 H), 5.35 (dd, $J = 3.0, 3.0$ Hz, 1 H), 5.53 (d, $J = 17.6$ Hz, 1 H), 6.60 (dd, $J = 17.6, 10.8$ Hz, 1 H), 7.26 (d, $J = 8.4$ Hz, 2 H), 7.64 (d, $J = 8.4$ Hz, 2 H); ^{13}C NMR (67.5 MHz, CDCl_3) δ 21.5, 27.5, 50.5, 103.9, 113.5, 117.0, 127.9, 128.8, 129.5, 133.9, 143.6; EI-LRMS m/z 249 (M^+), 184, 155, 91, 55; EI-HRMS calcd for $\text{C}_{13}\text{H}_{15}\text{NO}_2\text{S}$ 249.0823, found 149.0831.

5a: IR (neat) 1654, 1343, 1161 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.20-1.30 (m, 2 H), 1.90-1.97 (m, 2 H), 2.42 (s, 3 H), 3.58-3.63 (m, 2 H), 5.04 (d, $J = 10.7$ Hz, 1 H), 5.39 (d, $J = 17.2$ Hz, 1 H), 5.50 (dd, $J = 4.0, 4.0$ Hz, 1 H), 6.51 (dd, $J = 17.2, 10.6$ Hz, 1 H), 7.27 (d, $J = 8.5$ Hz, 2 H), 7.63 (d, $J = 8.5$ Hz, 2 H); ^{13}C NMR (100 MHz, CDCl_3) δ 19.9, 21.6, 22.8, 46.4, 112.8, 116.0, 127.2, 129.4, 136.4, 136.5, 137.6, 143.3; EI-LRMS m/z 263 (M^+), 198, 155, 108, 91; EI-HRMS calcd for $\text{C}_{14}\text{H}_{17}\text{NO}_2\text{S}$ 263.0980, found 263.0965.

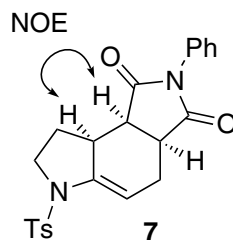
5b: IR (neat) 1635, 1598, 1349, 1163 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 0.93 (s, 6 H), 1.83 (d, $J = 3.8$ Hz, 2 H), 2.41 (s, 3 H), 3.34 (s, 2 H), 4.98 (d, $J = 10.6$ Hz, 1 H), 5.13 (t, $J = 3.8$ Hz, 1 H), 5.32 (d, $J = 16.9$ Hz, 1 H), 6.47 (dd, $J = 16.9, 10.6$ Hz, 1 H), 7.26 (d, $J = 8.0$ Hz, 2 H), 7.68 (d, $J = 8.0$ Hz, 2 H); ^{13}C NMR (100 MHz, CDCl_3) δ 21.5, 26.4, 29.5, 37.5, 56.9, 110.0, 114.3, 127.0, 129.4, 134.3, 136.4, 138.2, 143.0; EI-LRMS m/z 291 (M^+), 276, 262, 248, 155, 136, 91; EI-HRMS calcd for $\text{C}_{16}\text{H}_{21}\text{NO}_2\text{S}$ 291.1293, found 291.1289.

Spectral Data of Diels-Alder Products

6a: IR (neat) 1733, 1646, 1597, 1359, 1163 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.65 (dddd, $J = 11.8, 11.8, 11.3, 8.2$ Hz, 1 H), 2.15 (ddd, $J = 11.8, 6.0, 6.0$ Hz, 1 H), 2.43 (s, 3 H), 2.94 (m, 1 H), 3.08 (ddd, $J = 22.5, 11.3, 2.2$ Hz, 1 H), 3.24 (ddd, $J = 22.5, 7.0, 5.6$ Hz, 1 H), 3.35 (ddd, $J = 10.0, 6.0, 6.0$ Hz, 1 H), 3.75 (s, 3 H), 3.76 (s, 3 H), 3.79 (dd, $J = 9.9, 8.2$ Hz, 1 H), 5.79 (dd, $J = 5.1, 2.5, 2.5$ Hz, 1 H), 7.29 (d, $J = 8.2$ Hz, 2 H), 7.69 (d, $J = 8.2$ Hz, 2 H); ^{13}C NMR (67.5 Hz, CDCl_3) δ 21.6, 27.3, 28.8, 39.5, 48.9, 52.3, 52.4, 101.4, 127.2, 133.4, 134.3, 134.7, 136.4, 144.1, 167.3, 167.4; EI-LRMS m/z 391, 236, 159, 91; EI-HRMS calcd for $\text{C}_{19}\text{H}_{21}\text{NO}_6\text{S}$ 391.1080, found 391.1089.

7: IR (nujol) 1707, 1348, 1162 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 2.18 (m, 1 H), 2.26 (m, 1 H), 2.35 (s, 3 H), 2.60 (m, 1 H), 2.82 (m, 1 H), 2.89 (ddd, $J = 15.6, 7.8, 1.5$ Hz, 1 H), 3.20 (ddd, $J = 10.7, 7.3, 1.5$ Hz, 1 H), 3.29 (dd, $J = 9.3, 7.3$ Hz, 1 H), 3.61-3.71 (m, 2 H), 5.65 (ddd, $J = 7.8, 2.0, 2.0$ Hz, 1 H), 6.95 (d, $J = 8.3$ Hz, 2 H), 7.21 (br d, $J = 8.3$ Hz, 2 H), 7.34-7.42 (m, 3 H), 7.68 (br d, $J = 8.3$ Hz, 2 H); ^{13}C NMR (67.5 Hz, CDCl_3) δ 21.3, 21.5, 21.6, 29.4, 39.5, 42.1, 49.0, 115.1, 126.2, 127.3, 128.6, 129.1, 129.9, 131.6, 134.2, 138.8, 143.9, 174.5, 177.1; EI-LRMS m/z 422 (M^+), 267, 155, 120, 91; EI-HRMS calcd for $\text{C}_{23}\text{H}_{22}\text{N}_2\text{O}_4\text{S}$ 422.1300, found 422.1301.

The stereochemistry of **7** was determined by NOE experiment.



8a: mp. 129 °C (decomp.); IR (nujol) 1724, 1594, 1346, 1156 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.30-1.55 (m, 2 H), 1.75 (br d, $J = 13.3$ Hz, 1 H), 1.87 m, 1 H), 2.43 (s, 3 H), 2.77 (m, 1 H), 3.03 (m, 1 H), 3.05 (ddd, $J = 23.7, 8.3, 3.7$ Hz, 1 H), 3.20 (ddd, $J = 23.7, 8.1, 3.8$ Hz, 1 H), 3.75 (s, 6 H), 4.17 (br d, $J = 13.4$ Hz, 1 H), 5.83 (ddd, $J = 3.6, 3.6, 1.4$ Hz, 1 H), 7.29 (d, $J = 8.4$ Hz, 2 H), 7.71 (d, $J = 8.4$ Hz, 2 H); ^{13}C NMR (400 MHz, CDCl_3) δ 21.5, 24.0, 27.7, 30.5, 36.6, 47.8, 52.1, 52.3, 119.5, 126.9, 127.8, 129.6, 133.2, 137.8, 138.4, 143.4, 166.6, 168.0; EI-LRMS m/z 405 (M^+), 374, 282, 218, 131, 91; EI-HRMS calcd for $\text{C}_{20}\text{H}_{23}\text{NO}_6\text{S}$ 405.1246, found 405.1226.

8b: IR (neat) 1734, 1708, 1635, 1596, 1343, 1162 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.45-1.54 (m, 2 H), 1.96-2.02 (m, 2 H), 2.44 (s, 3 H), 2.48-2.55 (m, 2 H), 2.75-2.85 (m, 2 H), 3.63-3.68 (m, 2 H), 3.78 (s, 3 H), 3.81 (s, 3 H), 7.31 (d, $J = 8.3$ Hz, 2 H), 7.65 (d, $J = 8.3$ Hz, 2 H); ^{13}C NMR (100 MHz, CDCl_3) δ 20.8, 21.6, 22.8 (2C), 26.6, 46.5, 52.0, 52.3, 115.3, 120.8, 128.9, 129.8, 136.7, 139.2, 142.0, 144.0, 166.0, 168.8; EI-LRMS m/z 405 (M^+), 374, 250, 218, 190, 158; EI-HRMS calcd for $\text{C}_{20}\text{H}_{23}\text{NO}_6\text{S}$ 405.1246, found 405.1234.