Efficient Construction of Cyclopenta[b]quinoline Core of Isoschizozygane Alkaloids via Intramolecular Formal Hetero Diels-Alder Reaction

Nabi Magomedov

Department of Chemistry, University of Rochester, Rochester, New York 14627-0216

magomedov@chem.rochester.edu

Supporting Information

General Information. All strong base reactions were carried out under an atmosphere of nitrogen in oven-dried glassware with magnetic stirring. Solvents and reagents were purified prior to use following the guidelines of Perrin and Armarego,¹ except for THF, toluene, acetonitrile, dichloromethane and ether that were dispensed using the Glass Contour solvent purification system. Air- and moisture-sensitive liquids and solutions were transferred via syringe or stainless steel cannula. Organic solutions were concentrated in vacuo below 45 °C at approximately 20 mm Hg. Purification of reaction products was carried out by flash chromatography using EM Reagent silica gel 60 (230-400 mesh). Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light and potassium permanganate solution or cerium ammonium molybdate followed by heating. Melting points were measured with a Unimelt Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin Elmer 1600 series FT-IR spectrometer. ¹H NMR spectra were recorded on a Bruker Avance-400 (400 MHz) or Bruker AMX-400 (400 MHz) spectrometer and are reported in ppm using solvent (CDCl₃ at 7.26 ppm) as an internal standard. Data are reported as (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet; coupling constant(s) in Hz; integration. Proton-decoupled ¹³C NMR spectra were recorded on a Bruker Avance-400 (100 MHz) spectrometer and are reported in ppm using solvent as the internal standard (CDCl₃ at 77.23 ppm). High resolution mass spectra were obtained on VG-7070 spectrometer in the UC Riverside Mass Spectrometry Facility.

2,2-Dimethyloct-5-enenitrile (7a): To a solution of 4.36 g (6.04 mL, 43.2 mmol) of *i*-Pr₂NH in 100 mL of dry THF, cooled to -78 °C, was added 27 mL of 1.59 M solution of *n*-BuLi (43.2 mmol) in hexanes dropwise over a period of 5 minutes. After 15 minutes at bath temperature, 2.99 g (3.88 mL, 43.2 mmol) of 2-methylpropionitrile was added dropwise over a period of 15 minutes. The red reaction mixture was stirred at -78 °C for 1 h and then a precooled (-78 °C) solution of hexe-3-enyl bromide (**6a**) in 10 mL of dry

¹ Books without Editors: Armarego, W. L. F; Perrin, D. D. *Purification of Laboratory Chemicals*; Butterworth-Heinemann: Bath, 2002.

THF was cannulated. The reaction mixture turned yellow and was stirred at bath temperature for 1 h, after which time TLC (silica gel, hexane) indicated complete consumption of the bromide. The reaction mixture was quenched with 20 mL of 1N HCl, concentrated in vacuo to an approximate volume of 50 mL and then partitioned between 150 mL of ether and 30 mL of water. The ethereal solution was dried (MgSO₄), concentrated in vacuo, and the residue was distilled at reduced pressure to provide 4.5 g (83%) of **7a** as a colorless liquid. Characterization data for **7a**: IR (neat) 2223, 1470, 1454, 1369 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 0.96 (t, *J* = 7.5 Hz, 3H), 1.34 (s, 6H), 1.54-1.59 (m, 2H), 1.96-2.03 (m, 2H), 2.14-2.20 (m, 2H), 5.34-5.41 (m, 1H), 5.48-5.55 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 13.8, 25.6, 26.7, 28.5, 32.2, 41.0, 125.0, 127.4, 133.2; HRMS (DCI): Exact mass calcd for C₁₀H₁₈N (MH⁺) 152.1439. Found 152.1439.

2,2-Dimethylocta-5,7-dienenitrile (7b). Prepared by similar procedure from 2-methylpropionitrile and hexa-3,5-dienyl bromide (**6b**) in 78% yield. Characterization data for **7b**: colorless liquid, IR (neat) 3079, 2234, 1652, 1603, 1471, 1454, 1370 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.34 (s, 6H), 1.59-1.63 (m, 2H), 2.22-2.30 (m, 2H), 4.99 (d, *J* = 10.2 Hz, 1H), 5.11 (d, *J* = 17.0 Hz, 1H), 5.67 (dt, *J* = 15.1 Hz, 6.8 Hz, 1H), 6.09 (dd, *J* = 15.1 Hz, 10.2 Hz, 1H), 6.28 (ddd, *J* = 17.0, 10.2, 10.2 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 26.8, 28.5, 32.3, 40.5, 115.9, 124.9, 132.1, 133.0, 138.4; HRMS (DEI): Exact mass calcd for C₁₀H₁₄N (M-H⁺) 148.1125. Found 148.1125.

2-Methylocta-5,7-dienenitrile (7c): Prepared by similar procedure from propionitrile and hexa-3,5-dienyl bromide (**6b**) in 69% yield. Characterization data for **7c**: colorless liquid, IR (CH₂Cl₂) 3088, 3038, 2984, 2942, 2240, 1652, 1602, 1456 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.31 (d, *J* = 7.0 Hz, 3H), 1.57-1.66 (m, 1H), 1.69-1.78 (m, 1H), 2.18-2.36 (m, 2H), 2.57-2.66 (m, 1H), 5.00 (d, *J* = 10.2 Hz, 1H), 5.13 (d, *J* = 17.0 Hz, 1H), 5.62 (dt, *J* = 15.1 Hz, 7.0 Hz, 1H), 6.11 (dd, *J* = 15.1 Hz, 10.2 Hz, 1H), 6.29 (ddd, *J* = 17.0, 10.2, 10.2 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 18.0, 24.9, 29.9, 33.5, 116.1, 122.8, 132.3, 132.7, 136.7; HRMS (DEI): Exact mass calcd for C₉H₁₂N (M-H⁺) 134.0970. Found 134.0967.

2,2-Dimethyloct-5-enal (8a): To a solution of 3.73 g (24.7 mmol) of **7a** in 100 mL of toluene, cooled to -78 °C, was added a solution of 4.91 g (34.6 mmol) of DIBAL-H in 20 mL of toluene via a cannula. The reaction mixture was stirred at bath temperature for 1 h and warmed to -20 °C for 20 min. TLC (silica gel, hehane) indicated complete consumption of starting nitrile. The reaction mixture was quenched 20 mL of 3N aqueous HCl and then partitioned between 150 mL of ether and 30 mL of 3N HCl. The organic solution was separated, dried (MgSO₄), and concentrated in vacuo to give a light yellow liquid. The liquid was distilled under reduced pressure to give 3.35 g (88%) of **8a** as a colorless liquid. Characterization data for **8a**: IR (neat) 2963, 2932, 2693, 1728, 1470, 1462 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 0.94 (t, *J* = 7.4 Hz, 3H), 1.04 (s, 6H), 1.51-1.54 (m, 2H), 1.87-2.01 (m, 4H), 5.29-5.36 (m, 1H), 5.41-5.48 (m, 1H), 9.44

(s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 13.9, 21.4, 25.6, 27.6, 37.4, 45.8, 128.5, 132.8, 206.2; HRMS (DCI): Exact mass calcd for $\text{C}_{10}\text{H}_{19}\text{O}$ (MH^+) 155.1436. Found 155.1443.

2,2-Dimethylocta-5,7-dienal (8b): Prepared by similar procedure in 81% yield. Characterization data for **8b**: colorless liquid, IR (neat) 3085, 2965, 2931, 2699, 1727, 1652, 1470 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.06 (s, 6H), 1.55-1.60 (m, 2H), 1.98-2.04 (m, 2H), 4.98 (d, $J = 10.3$ Hz, 1H), 5.10 (d, $J = 16.9$ Hz, 1H), 5.65 (dt, $J = 15.2$ Hz, 6.8 Hz, 1H), 6.05 (dd, $J = 15.2$ Hz, 10.3 Hz, 1H), 6.29 (ddd, $J = 16.9$, 10.3, 10.3 Hz, 1H), 9.45 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 21.4, 27.5, 36.7, 45.8, 115.5, 131.6, 134.3, 137.1, 206.1; HRMS (DCI): Exact mass calcd for $\text{C}_{10}\text{H}_{16}\text{O}$ (M^+) 152.1201. Found 152.1203.

2-Methylocta-5,7-dienal (8c): Prepared by similar procedure in 76% yield. Characterization data for **8c**: colorless liquid, IR (CH_2Cl_2) 3087, 2973, 2933, 2719, 1722, 1652, 1602, 1458 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.09 (d, $J = 7.0$ Hz, 3H), 1.44 (dddd, $J = 13.8$, 8.2, 6.9, 6.9 Hz, 1H), 1.83 (dddd, $J = 13.8$, 8.8, 6.6, 6.6 Hz, 1H), 2.06-2.20 (m, 2H), 2.32-2.40 (m, 1H), 4.97 (d, $J = 10.1$ Hz, 1H), 5.09 (d, $J = 16.9$ Hz, 1H), 5.64 (dt, $J = 15.1$ Hz, 7.0 Hz, 1H), 6.05 (dd, $J = 15.1$ Hz, 10.4 Hz, 1H), 6.29 (ddd, $J = 16.9$, 10.4, 10.1 Hz, 1H), 9.60 (d, $J = 1.5$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 13.3, 29.8, 29.9, 45.6, 115.5, 132.0, 133.7, 137.0, 204.7; HRMS (DEI): Exact mass calcd for $\text{C}_9\text{H}_{14}\text{O}$ (M^+) 138.1045. Found 138.1050.

Compound 9a: To a solution of 152 mg (1.0 mmol) of **8b** in 40 mL of benzene was added 128 mg (1.0 mmol) of *m*-anisidine followed by addition of 10 mg (5 mol%) of *p*-toluenesulfonic acid. The reaction mixture was refluxed with a Dean-Stark trap for 1 h, after which time TLC (silica gel, CH_2Cl_2) indicated complete consumption of starting aldehyde. The reaction mixture was cooled down to room temperature and then passed through a 2-cm pad of basic alumina. The alumina cake was washed with 50 mL of ether and concentrated in vacuo to give an off-white solid. The solid was flash chromatographed over 20 g of silica gel (CH_2Cl_2) to provide 26 mg (10%) of **9b** and 192 mg (75%) of the more polar **9a**. Characterization data for **9a**: thin white needles, mp 169-170 $^\circ\text{C}$ (CH_2Cl_2 /hexane); IR (CH_2Cl_2) 3054, 2986, 1612, 1462, 1421, 1270 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 0.94 (s, 3H), 1.11 (s, 3H), 1.23-1.33 (m, 1H), 1.59-1.63 (m, 2H), 1.82-1.98 (m, 2H), 2.80 (d, $J = 10.6$ Hz, 1H), 3.17 (dd, $J = 10.8$, 9.2 Hz, 1H), 3.74 (s, 3H), 3.82 (bs, 1H), 5.14 (dd, $J = 9.9$, 2.0 Hz, 1H), 5.17 (dd, $J = 17.0$, 2.0 Hz, 1H), 5.62 (ddd, $J = 17.0$, 9.9, 9.2 Hz, 1H), 6.16 (d, $J = 2.5$ Hz, 1H), 6.27 (dd, $J = 8.4$, 2.5 Hz, 1H), 6.97 (d, $J = 8.4$, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 23.0, 25.9, 28.6, 38.6, 39.8, 44.1, 50.5, 55.3, 66.2, 100.6, 104.1, 116.3, 117.3, 130.3, 141.6, 147.0, 159.3; HRMS (DEI): Exact mass calcd for $\text{C}_{17}\text{H}_{23}\text{NO}$ (M^+) 257.1780. Found 257.1770.

Compound **10** was prepared in 71% yield. Characterization data for **10**: thin white needles, mp 99-100 °C; IR (CH₂Cl₂) 3054, 2986, 1519, 1462, 1439, 1421, 1260 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 0.95 (s, 3H), 1.11 (s, 3H), 1.23-1.34 (m, 1H), 1.56-1.62 (m, 2H), 1.84-1.96 (m, 2H), 2.76 (d, *J* = 10.5 Hz, 1H), 3.19 (dd, *J* = 10.5, 8.9 Hz, 1H), 3.63 (bs, 1H), 3.77 (s, 3H), 3.82 (s, 3H), 5.15 (dd, *J* = 10.1, 1.8 Hz, 1H), 5.19 (dd, *J* = 17.1, 1.8 Hz, 1H), 5.63 (ddd, *J* = 17.1, 10.1, 8.9 Hz, 1H), 6.23 (s, 1H), 6.64 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 23.0, 25.9, 28.5, 38.5, 39.7, 44.0, 50.8, 55.8, 56.7, 66.6, 100.5, 113.5, 115.8, 116.3, 139.9, 141.6, 141.7, 148.5; HRMS (DCI): Exact mass calcd for C₁₈H₂₆NO₂ (MH⁺) 288.1964. Found 288.1960.

Compound **11** was prepared in 60% yield. In this particular case, the reaction was conducted in refluxing toluene for 24 h. Characterization data for **11**: thin white needles, mp 143-145 °C (CH₂Cl₂/hexane); IR (CH₂Cl₂) 3054, 2986, 1614, 1512, 1461, 1422, 1264 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 0.80 (t, *J* = 7.4 Hz, 3H), 0.95 (s, 3H), 1.10 (s, 3H), 1.24-1.33 (m, 1H), 1.60-1.66 (m, 2H), 1.73-1.83 (m, 1H), 1.89-2.04 (m, 3H), 2.72-2.75 (m, 1H), 2.77 (d, *J* = 10.4 Hz, 1H), 3.75 (s, 3H), 3.75 (bs, 1H), 6.16 (d, *J* = 2.5 Hz, 1H), 6.30 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.04 (d, *J* = 8.5, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 8.9, 23.1, 24.0, 26.2, 28.6, 38.9, 39.6, 41.9, 43.6, 55.3, 67.0, 100.8, 104.3, 118.2, 128.6, 148.3, 158.6; HRMS (DCI): Exact mass calcd for C₁₇H₂₆NO (MH⁺) 260.2014. Found 260.2002.

Compound **13** was prepared in 79% yield. Characterization data for **13**: thick colorless oil, hydrochloride mp > 250 °C (decom.); IR (CH₂Cl₂) 3054, 2986, 1511, 1422, 1270 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.08 (d, *J* = 6.6 Hz, 3H), 1.14 (s, 3H), 1.27 (s, 3H), 1.37-1.45 (m, 1H), 1.47-1.58 (m, 1H), 1.70-1.88 (m, 3H), 1.97-2.07 (m, 1H), 2.68 (dd, *J* = 10.5, 9.8 Hz, 1H), 3.79 (s, 3H), 3.82 (s, 3H), 3.82 (bs, 1H), 6.15 (s, 1H), 6.77 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 18.1, 21.2, 26.8, 28.7, 30.5, 35.2, 40.0, 52.1, 55.6, 56.9, 60.1, 99.8, 111.6, 124.0, 138.5, 141.8, 148.1; HRMS (DCI): Exact mass calcd for C₁₇H₂₆NO₂ (MH⁺) 276.1964. Found 276.1959.

Compound **14** was prepared in 76% yield. Characterization data for **14**: thin white needles, mp 153-154 °C (CH₂Cl₂/hexane); IR (CH₂Cl₂) 3054, 2986, 1612, 1510, 1459, 1422, 1266 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.09 (d, *J* = 6.5 Hz, 3H), 1.28-1.36 (m, 2H), 1.74-1.90 (m, 3H), 1.99-2.03 (m, 1H), 2.63 (dd, *J* = 10.1, 10.1 Hz, 1H), 3.17 (dd, *J* = 10.9, 9.3 Hz, 1H), 3.74 (s, 3H), 4.10 (bs, 1H), 5.15 (dd, *J* = 9.8, 1.9 Hz, 1H), 5.16 (dd, *J* = 17.0, 1.9 Hz, 1H), 5.61 (ddd, *J* = 17.0, 9.8, 9.3 Hz, 1H), 6.15 (d, *J* = 2.5 Hz, 1H), 6.29 (dd, *J* = 8.4, 2.5 Hz, 1H), 6.98 (d, *J* = 8.4, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 18.2, 26.7, 30.5, 39.5,

47.2, 49.9, 55.3, 64.3, 100.6, 104.2, 116.3, 117.5, 130.4, 141.5, 146.7, 159.3; HRMS (DCI): Exact mass calcd for $\text{C}_{16}\text{H}_{22}\text{NO}$ (MH^+) 244.1701. Found 244.1693.

7a

CDCl₃, 100 MHz

7b

CDCl₃, 100 MHz

7c

CDCl₃, 100 MHz

CDCl₃, 400 MHz

8c

CDCl₃, 100 MHz

ppm

CDCl₃, 100 MHz

159.267
147.049
141.585
130.340
117.269
116.301
104.050
100.593
77.543
77.226
76.908
66.242
55.283
50.497
44.050
39.761
38.583
28.507
25.855
23.022

ppm

CDCl₃, 100 MHz

11

CDCl₃, 100 MHz

13

CDCl₃, 100 MHz

14

CDCl₃, 100 MHz