SYNTHETIC STUDIES ON KERAMAPHIDIN B: FORMATION OF A MACROCYCLIC RING BY INTRAMOLECULAR DIELS-ALDER REACTION

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Supporting Information

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**General Information**

$^1$H and $^{13}$C-NMR spectra were recorded on JEOL ECZ500R and Bruker AVANCE 600 spectrometers. Chemical shifts are reported in ppm with the residual solvent resonance as internal standard (CDCl$_3$ $^1$H, $\delta = 7.26$ ppm, $^{13}$C, $\delta = 77.16$ ppm). The following abbreviations were used to explain the multiplicities: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad. IR spectra were recorded on a JASCO FT/IR-8300. Mass spectra analyses were provided at the Materials Characterization Central Laboratory, Waseda University. All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. All reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent, and phosphomolybdic acid, basic potassium permanganate, $p$-anisaldehyde and heat as developing agents. Kanto Chemical Silica Gel 60N (spherical, neutral, 63-210 μm or 40-50 μm partial size) was used for flash column chromatography. Preparative thin-layer chromatography (PTLC) separations were carried out on self-made 0.3 mm E. Merck silica gel plates (60F-254). TLC $R_f$s of purified compounds were included.

**Materials.**

THF and Et$_2$O were distilled from sodium/benzophenone ketyl, and CH$_2$Cl$_2$, benzene, and MeCN from calcium hydride. Toluene was distilled from sodium. MeOH was distilled from magnesium and I$_2$. All reagents were purchased from Aldrich, TCI, Merck, or Kanto Chemical Co. Ltd.
1,1-dibromo-5-methylenehepta-1,6-diene (11)

To a stirred solution of CBr₄ (13.2 g, 39.9 mmol, 2.0 equiv.) and PPh₃ (20.9 g, 79.8 mmol, 4.0 equiv) dissolved in CH₂Cl₂ (200 mL) at 0 °C was added 10 (2.20 g, 20.0 mmol) in CH₂Cl₂ (20 mL) via a cannula (5 mL×2) and the reaction mixture was stirred at 0 °C for 10 min before quenching with sat. NaHCO₃ aq. (40mL) and H₂O (40 mL). The aqueous layer was extracted with CH₂Cl₂ (20 mL×3). The combined organic layer was dried over Na₂SO₄. After filtration, the solution was filtered through a celite pad. The filtrate was evaporated and the residue was purified by flash silica gel column chromatography (hexane) to afford the product 24 (3.96 g, 75%) as a colorless oil: \( R_f = 0.71 \) (hexane); \( ^1H \) NMR (500 MHz, CDCl₃) \( \delta \) 6.42 (t, \( J = 6.4 \) Hz, 1H), 6.38 (dd, \( J = 10.9, 17.8 \) Hz, 1H), 5.24 (d, \( J = 17.8 \) Hz, 1H), 5.10 (d, \( J = 10.9, 1H \)), 5.08 (s, 1H), 5.02 (s, 1H), 2.38-2.27 (m, 4H); \( ^13C \) NMR (125 MHz, CDCl₃) \( \delta \) 144.8, 138.5, 138.2, 116.7, 113.7, 89.3, 31.7, 29.4; IR (ATR) \( \nu_{\text{max}} \) 3087, 2932, 1630, 1594, 1439, 1270, 990, 896, 793, 753 cm⁻¹; HRMS (DART) [M+NH₄]⁺ calculated for C₈H₁₄Br₂N: 281.9488, found: 281.9482.

2-((9-methyleneundec-10-en-5-yn-1-yl)oxy)tetrahydro-2H-pyran (13)

To a stirred solution of 11 (3.94 g, 14.8 mmol) in THF (150 mL) was added n-BuLi (1.60 M in hexane, 18.5 mL, 29.6 mmol, 2.0 equiv) at –78 °C. After stirring for 1 h, HMPA (38 mL) and TMEDA (4.4 mL, 29.6 mmol, 2.0 equiv) were added at –78 °C and stirred for 40 min. To the reaction mixture was added 12 (4.20 g, 14.8 mmol, 1.0 equiv) in THF (20 mL) at –78 °C via a cannula (5 mL×2). The mixture was warmed to room temperature and stirred for 4 h, then warmed to 50 °C and stirred for additional 1.5 h before quenching with sat. NH₄Cl aq. (20 mL) and water (40 mL). The resulting mixture was evaporated and then, the aqueous layer was extracted with hexane (30 mL×3). The combined organic layer was dried over Na₂SO₄, filtered, and evaporated. The residue was purified by flash silica gel column chromatography (hexane→hexane/AcOEt = 30/1→hexane/AcOEt = 20/1) to afford a mixture of the product 13 and 12 (3.44 g). The mixture was used in the next step without further purification: \( R_f = 0.69 \) (hexane/ethyl acetate = 4/1).
To a stirred solution of the mixture of 13 and 12 (3.44 g) in MeOH (130 mL) was added TsOH·H2O (49.9 mg, 0.26 mmol, 2 mol%) at room temperature. After stirring at room temperature for 3 h, additional TsOH-H2O (49.5 mg, 0.26 mmol, 2 mol%) was added. After stirring at room temperature for 2.5 h, the reaction mixture was quenched with sat. NaHCO₃ aq. (20 mL) and water (10 mL). The mixture was evaporated and the aqueous layer was then extracted by diethyl ether (30 mL×3). The combined organic layer was dried over Na₂SO₄, filtered, and evaporated. The residue was purified by flash silica gel column chromatography (hexane/ethyl acetate = 6/1) to afford 14 (1.23 g, 48%, 2 steps) as a pale yellow oil: Rf = 0.23 (hexane/ethyl acetate = 4/1); ¹H NMR (500 MHz, CDCl₃) δ 6.35 (dd, J = 10.9, 17.8 Hz, 1H), 5.22 (d, J = 17.8 Hz, 1H), 5.09-5.02 (m, 3H), 3.66 (t, J = 6.3 Hz, 2H), 2.44-2.38 (m, 2H), 2.37-2.30 (m, 2H), 2.19 (tt, J = 2.3, 6.9 Hz, 2H), 1.71-1.62 (m, 2H), 1.60-1.52 (m, 2H); 1.46 (brs, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 144.9, 138.6, 116.4, 113.4, 80.5, 80.2, 62.6, 32.0, 31.2, 25.4, 18.6, 18.0; IR (ATR) νmax 3333, 3088, 2937, 2864, 1595, 1434, 1335, 1056, 990, 896 cm⁻¹; HRMS (DART) [M+NH₄]⁺ calculated for C₁₂H₂₂NO: 196.1696, found: 196.1694.

5,6-dihydro-3-iodo-1-(9-methyleneundec-10-en-5-ynyl)pyridin-2(1H)-one (15)

To a stirred solution of 6 (422.4 mg, 2.37 mmol) in CH₂Cl₂ (24 mL) were added 2,6-lutidine (0.55 mL, 4.74 mmol, 2.0 equiv.) and Tf₂O (0.58 mL, 3.56 mmol, 1.5 equiv.) at −78 °C. The reaction mixture was stirred at −78 °C for 45 min before quenching with 10 mL of 0.5 N H₂SO₄ aq. at −78 °C. The solution was diluted with hexane (20 mL) and the organic layer was washed by water (5 mL×3). The organic layer was dried over Na₂SO₄, filtered, and evaporated. The crude product 7c (741.9 mg) was dried under vacuum and diluted with dry diethyl ether (1.5 mL) and used for the next step.

To a stirred solution of 8 (535.2 mg, 2.40 mmol, 1.0 equiv) in THF (24mL) was added KHMDS in toluene (4.7 mL, 2.40 mmol, 1.0 equiv) at −78 °C. After the reaction mixture was stirred at −78 °C for 1 h, the crude triflate 7c (741.9 mg) in diethyl ether (1.5 mL) was added at −78 °C via cannula (1.5 mL×2). The reaction mixture was stirred at −78 °C for 2 h before quenching with sat. NH₄Cl aq. (10 mL) and water (10 mL). The aqueous layer was extracted
with diethyl ether (20 mL×3). The combined organic layer was dried over Na2SO4, filtered, and evaporated. The residue was purified by flash silica gel column chromatography (benzene/ethyl acetate = 50/1→40/1) to afford 15 (795.0 mg, 88%) as a yellow oil: Rf = 0.50 (hexane/ethyl acetate = 2/1); 1H NMR (500 MHz, CDCl3) δ 7.24-7.28 (m, 1 H), 6.36 (dd, J = 10.9, 17.2 Hz, 1H), 5.23 (d, J = 17.2 Hz, 1H), 5.10-5.02 (m, 3H), 3.49-3.44 (m, 4H), 2.44-2.31 (m, 6H), 2.19 (tt, J = 2.3, 6.9 Hz, 2H), 1.70-1.62 (m, 2H), 1.53-1.46 (m, 2H); 13C NMR (125 MHz, CDCl3) δ 160.1, 148.2, 144.9, 138.6, 116.5, 113.5, 97.8, 80.31, 80.28, 48.3, 45.8, 31.2, 28.2, 26.9, 26.3, 18.6, 18.0; IR (ATR) νmax 3086, 2931, 2860, 1722, 1647, 1596, 1477, 1205, 1136, 901 cm–1; HRMS (DART) [M+NH4]+ calculated for C17H26IN2O: 401.1084, found: 401.1077.

methyl 1,2,5,6-tetrahydro-1-(9-methyleneundec-10-en-5-ynyl)-2-oxopyridine-3-carboxylate (5)

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\begin{align*}
\text{CO}_2\text{Me} \quad \text{N} \quad \text{N}
\end{align*}
\]

To a stirred solution of 15 (263.0 mg, 0.686 mmol) in MeCN (14 mL) and MeOH (2.7 mL) were added triethylamine (0.58 mL, 4.12 mmol, 6.0 equiv) and PdCl2(dppf)·CH2Cl2 (43.0 mg, 0.055 mmol, 0.08 equiv). The reaction mixture was stirred at room temperature for 2 h before quenching with sat. NH4Cl aq. (5 mL) and water (5 mL). The solution was evaporated and then the aqueous layer was extracted with ethyl acetate (10 mL×3). The combined organic layer was dried over Na2SO4, filtered, and evaporated. The residue was purified by flash silica gel column chromatography (hexane/ethyl acetate = 2/1) to afford 5 (128.5 mg, 59%) as an orange oil: Rf = 0.41 (hexane/ethyl acetate = 1/2); 1H NMR (500 MHz, CDCl3) δ 7.32 (t, J = 4.6 Hz, 1H), 6.37 (dd, J = 10.9, 17.8 Hz, 1H), 5.23 (d, J = 17.8 Hz, 1H), 5.10-5.02 (m, 3H), 3.82 (s, 3H), 3.49-3.40 (m, 4H), 2.48 (dt, J = 4.6, 6.9 Hz, 2H), 2.44-2.38 (m, 2H), 2.37-2.30 (m, 2H), 2.24-2.15 (m, 2H), 1.74-1.62 (m, 2H), 1.55-1.44 (m, 2H); 13C NMR (125 MHz, CDCl3) δ 165.5, 160.9, 145.7, 144.9, 138.6, 130.0, 116.5, 113.5, 80.30, 80.28, 52.5, 46.4, 44.9, 31.2, 27.0, 26.4, 24.5, 18.6, 18.0; IR (ATR) νmax 3468, 2929, 2859, 1737, 1656, 1621, 1595, 1483, 1434, 1276, 1209, 1123, 899 cm–1; HRMS (ESI) [M+H]+ calculated for C19H26NO3: 316.1907, found: 316.1909.

methyl (4aR,8aS)-6,2-oct[3]ynyl-1-oxo-2,3,4,4a,5,8-hexahydroisoquinoline-8a(1H)-carboxylate (19)
To a stirred solution of 5 (77.8 mg, 0.247 mmol) in degassed (CH$_2$Cl)$_2$ (250 mL, 0.001 M) was added SnCl$_4$ (0.085 mL, 0.074 mmol, 0.3 equiv). The reaction mixture was stirred at 80 °C for 17 h before quenching with 0.5 N HCl aq. (2 mL), sat. NH$_4$Cl aq. (5 mL) and water (50 mL). The aqueous layer was extracted with ethyl acetate (30 mL×3). The combined organic layer was dried over Na$_2$SO$_4$, filtered, and evaporated. The residue was purified by flash silica gel column chromatography (hexane/ethyl acetate = 1.5/1→1/1.5) to afford **19** (24.7 mg, 32%) as a colorless glassy oil: $R_f = 0.41$ (hexane/ethyl acetate = 1/2); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.47 (d, $J = 5.2$ Hz, 1H), 4.29 (dd, $J = 5.7$, 13.8 Hz, 1H), 3.72 (s, 3H), 3.62 (ddd, $J = 8.3$, 9.7, 12.6 Hz, 1H), 3.29 (ddd, $J = 1.7$, 8.0, 12.6 Hz, 1H), 3.19 (dd, $J = 5.2$, 16.3 Hz, 1H), 2.62-2.54 (m, 1H), 2.50-2.32 (m, 4H), 2.31-2.10 (m, 3H), 2.07-1.90 (m, 4H), 1.89-1.66 (m, 3H), 1.63-1.51 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 175.0, 167.6, 134.2, 120.5, 81.6, 79.5, 53.4, 52.8, 48.0, 45.5, 35.5, 32.7, 31.2, 30.1, 28.1, 27.5, 24.2, 18.7, 17.8; IR (ATR) $\nu_{\text{max}}$ 2932, 2239, 1727, 1636, 1496, 1430, 1356, 1263, 1232, 1218, 911, 724 cm$^{-1}$; HRMS (ESI) [M+Na]$^+$ calculated for C$_{19}$H$_{25}$NO$_3$Na: 338.1727, found: 338.1724.
X : parts per Million : Carbon13
H-H COSY of 19
H-H COSY of 19
HMBC of 19
NOESY of 19
NOESY of 19