Supporting Information

Expeditious synthesis of the fused hexacycle of puberuline C *via* a radical-based cyclization/translocation/cyclization process

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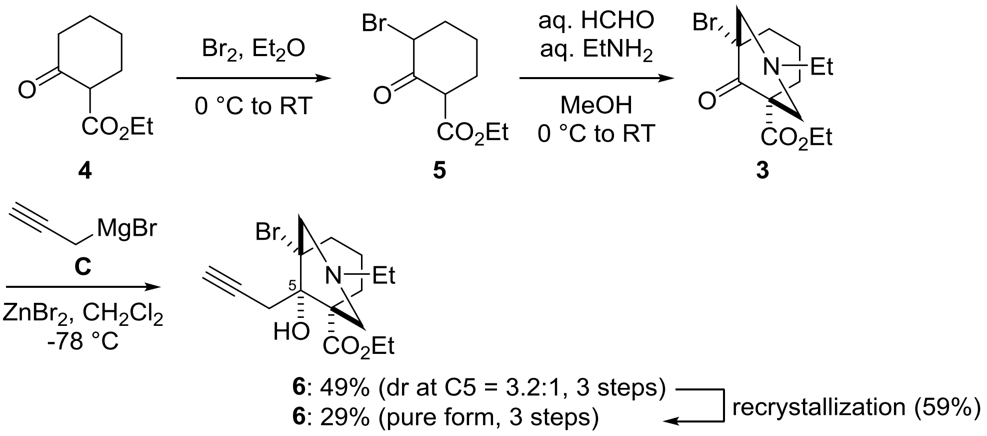
General Methods:

All reactions sensitive to air or moisture were carried out in dry solvents under argon atmosphere, unless otherwise noted. THF, CH_2Cl_2, toluene, and Et_2O were purified by Glass Contour solvent dispensing system (Nikko Hansen & Co., Ltd., Osaka, Japan). All other reagents were used as supplied unless otherwise noted. Analytical thin-layer chromatography (TLC) was performed using E. Merck Silica gel 60 F254 pre-coated plates (0.25 mm). Preparative thin-layer chromatography was performed using E. Merck Silica gel 60 F254 pre-coated plates (0.50 mm). Flash chromatography was performed using 40-50 μm Silica Gel 60N (Kanto Chemical Co., Inc.), 40-100 μm Silica Gel 60N (Kanto Chemical Co., Inc.), 100-210 μm Silica Gel 60N (Kanto Chemical Co., Inc.) or 32-53 μm Silica-gel BW-300 (Fuji Silysia Chemical Ltd.). Melting points were measured on Yanaco MP-J3 micro melting point apparatus, and are uncorrected. Infrared (IR) spectra were recorded as a thin film on a KBr disk using JASCO FT/IR-4100 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on JEOL JNM-ECX-500 or JNM-ECS-400 spectrometer at room temperature. Chemical shifts were reported in ppm on the δ scale relative to $CHCl_3$ ($\delta = 7.26$ for ^{1}H NMR), $CDCl_3$ ($\delta = 77.0$ for ^{13}C NMR), C_6HD_5 ($\delta = 7.16$ for ^{1}H NMR) and C_6D_6 ($\delta = 128.0$ for ^{13}C NMR) as internal references. Signal patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broaden peak. The numbering of compounds corresponds to that of the natural product. High resolution mass spectra were measured on JEOL JMS-T100LP instrument (ESI-TOF) or BRUKER DALTONICS microTOF II (ESI-TOF).



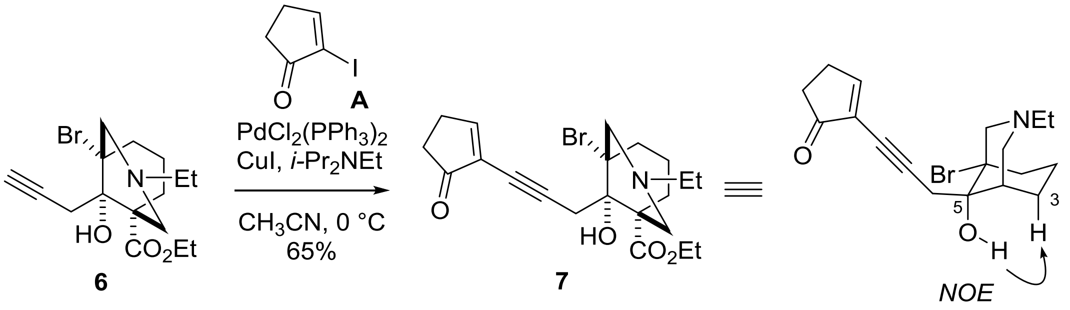
Alkyne 6. Bromine (20.0 g, 125 mmol) was added dropwise to a solution of **4** (19.4 g, 114 mmol) in Et_2O (71 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 3 h. After the reaction mixture was cooled to 0 °C,

saturated aqueous $NaHCO_3$ (250 mL) was added. The resultant mixture was extracted with Et_2O (200 mL x3), and the combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, filtered and concentrated to afford the crude **5**, which was used in the next reaction without further purification.

Aqueous HCHO (37%, 111 mL, 1.37 mol) and aqueous $EtNH_2$ (70%, 22.0 mL, 342 mmol) were added to a solution of the above crude **5** in MeOH (400 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h, warmed to room temperature, and stirred for 12 h. Then H_2O (1.0 L) was added. The resultant mixture was extracted with EtOAc (300 mL x3), and the combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography on silica gel (350 g, hexane/EtOAc 20/1 to 10/1) to afford the crude **3** (19.7 g), which was used in the next reaction without further purification.

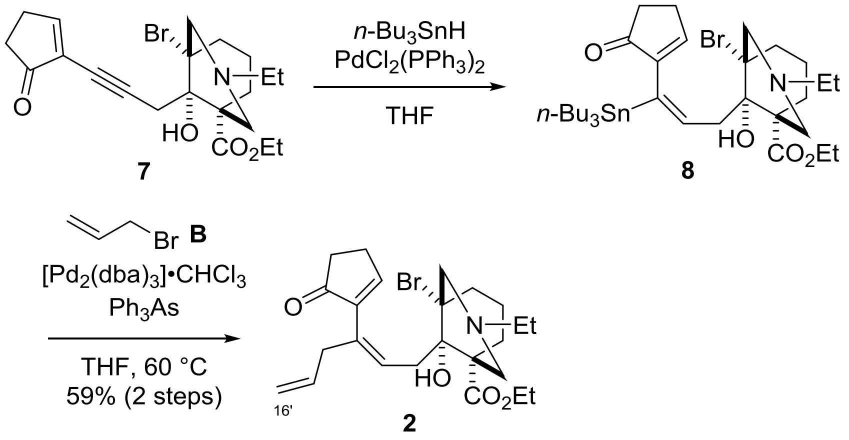
A mixture of magnesium turnings (10.3 g, 424 mmol) and $ZnBr_2$ (1.90 g, 8.44 mmol) was dried by a heat gun for 25 min under vacuum. After the mixture was cooled, the flask was filled with argon. Then, Et_2O (120 mL) was added. A part of a solution of 3-bromopropyne (15.9 mL, 184 mmol) in Et_2O (64.0 mL) was added to the mixture at room temperature. After the exothermic reaction occurred, the mixture was cooled to 0 °C. The remaining solution of the propargyl bromide was added at 0 °C over 1 h. The mixture was stirred at 0 °C for 1 h, and was warmed to room temperature. The concentration of propargyl magnesium bromide **C** was titrated to be 0.29 M by using (-)-menthol (141 mg, 0.902 mmol) and 1,10-phenanthroline (5.5 mg, 0.031 mmol) in THF (7 mL).[S1] The solution of propargyl magnesium bromide **C** (0.29 M in Et_2O, 160 mL, 46 mmol) was added to a solution of the above crude **3** (10.0 g) in CH_2Cl_2 (270 mL) at -78 °C over 20 min. The reaction mixture was stirred at -78 °C for 30 min, and then saturated aqueous NH_4Cl (150 mL) was added. The resultant mixture was extracted with EtOAc (200 mL x3), and the combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography on silica gel (200 g, hexane/EtOAc 20/1 to 10/1) to afford a 3.4:1 mixture of **6** and its C5-diastereomer (10.4 g, 29.0 mmol). The same procedure was repeated by using the rest of the above crude **3** (9.69 g) and propargyl magnesium bromide **C** (0.24 M in Et_2O, 170 mL, 41 mmol) in CH_2Cl_2 (300 mL). The residue was purified by flash column chromatography on silica gel (200 g, hexane/EtOAc 20/1 to 10/1) to afford a 2.9:1 mixture of **6** and its C5-diastereomer (9.69 g, 27.0 mmol). Consequently, **6** and its C5-diastereomer (20.09 g, 56.0 mmol) were obtained from **4** in 49% yield as 3.2:1 mixture. The mixture was combined and further purified by recrystallization from hexane/EtOAc to afford **6** (11.9 g, 33.2 mmol) in 29% yield over

3 steps: orange solid; m.p. 64.0-67.0 °C; IR (film) ν 3546, 3287, 2979, 2927, 1717, 1255 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.07 (3H, dd, *J* = 7.5, 7.5 Hz, NCH_2CH_3), 1.30 (3H, dd, *J* = 7.4, 7.4 Hz, OCH_2CH_3), 1.50-1.54 (1H, m, H2a), 1.65 (1H, dd, *J* = 13.8, 6.4 Hz, H3a), 2.08 (1H, dd, *J* = 2.9, 2.3 Hz, H8a), 2.23 (1H, dd, *J* = 13.2, 6.3 Hz, H1a), 2.34-2.42 (2H, m, NCH_2CH_3), 2.56 (1H, ddd, *J* = 13.8, 13.8, 7.5 Hz, H3b), 2.81 (1H, br d, *J* = 13.2 Hz, H19a). 2.81-2.90 (1H, m, H2b), 2.85 (1H, br d, *J* = 11.6 Hz, H17a), 2.97 (1H, dd, *J* = 17.8, 2.3 Hz, H6a), 3.02 (1H, ddd, *J* = 13.2, 13.2, 7.5 Hz, H1b), 3.10 (1H, br d, *J* = 13.2 Hz, H19b), 3.26 (1H, dd, *J* = 17.8, 2.9 Hz, H6b), 3.29 (1H, br d, *J* = 11.6 Hz, H17b), 4.09-4.21 (2H, m, OCH_2CH_3), 4.28 (1H, s, O*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.4, 13.8, 23.3, 26.9, 31.7, 39.4, 51.2, 51.4, 56.2, 61.2, 63.5, 72.7, 74.1, 74.3, 79.4, 173.9; HRMS (ESI) calcd for $C_{16}H_{25}BrNO_3$ 358.1012 and 360.0992 $[M+H]^+$, found 358.1024 and 360.1007.



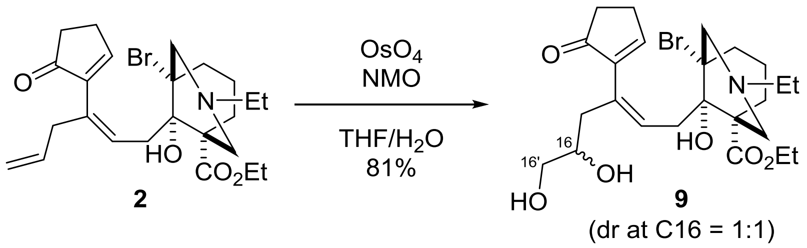
Enyne 7. A solution of alkyne **6** (8.71 g, 24.3 mmol), CuI (463 mg, 2.43 mmol), 2-iodo cyclopentenone **A** (10.1 g, 48.6 mmol) and $PdCl_2(PPh_3)_2$ (855 mg, 1.22 mmol) in CH_3CN (240 mL) was degassed by freeze-thaw procedure (x3). The degassed *i*-Pr_2NEt (13 mL, 73 mmol) by freeze-thaw procedure (x3) was added to the mixture at 0 °C. The reaction mixture was stirred at 0 °C for 12 h, and then H_2O (250 mL) was added. The resultant mixture was extracted with EtOAc (200 mL x2) and a 2:1 mixture of $CHCl_3$/EtOH (150 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography on silica gel (350 g, hexane/EtOAc 5/1 to 3/1) to afford **7** (6.93 g, 15.8 mmol) in 65% yield. The C5-configuration was determined by the NOE experiment: yellow solid; m.p. 109.0-111.0 °C; IR (film) ν 3540, 2973, 2925, 2802, 1714, 1255, 1098 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.00 (3H, t, *J* = 7.3 Hz, NCH_2CH_3), 1.18 (3H, dd, *J* = 7.3, 7.3 Hz, OCH_2CH_3), 1.46 (1H, ddd, *J* = 13.3, 6.9, 6.4 Hz, H2a), 1.57 (1H, dd, *J* = 13.7, 6.4 Hz, H3a), 2.16 (1H, dd, *J* = 12.8, 6.0 Hz, H1a), 2.32 (2H, q, *J* = 7.3 Hz, NCH_2CH_3), 2.34-2.38 (2H, m, H13ab), 2.48 (1H, ddd, *J* = 13.7, 13.3, 6.9 Hz, H3b), 2.62-2.65 (2H, m, H12ab), 2.71-2.84 (1H, m, H2b), 2.78 (1H, d, *J* = 12.8 Hz, H19a),

2.81 (1H, d, *J* = 11.4 Hz, H17a), 2.91-2.99 (1H, m, H1b), 3.03 (1H, d, *J* = 12.8 Hz, H19b), 3.12 (1H, d, *J* = 17.4 Hz, H6a), 3.22 (1H, d, *J* = 11.4 Hz, H17b), 3.38 (1H, d, *J* = 17.4 Hz, H6b), 3.99-4.08 (2H, m, OC*H*$_2$CH$_3$), 4.32 (1H, s, O*H*), 7.68 (1H, dd, *J* = 3.2, 1.8 Hz, H10); ^{13}C NMR (100 MHz, CDCl$_3$) δ 12.2, 13.6, 23.2, 27.0, 27.8, 31.6, 33.7, 39.2, 51.0, 51.2, 55.9, 61.2, 63.2, 74.2, 74.3, 75.5, 91.9, 129.9, 164.8, 173.8, 205.5; HRMS (ESI) calcd for $C_{21}H_{28}BrNO_4Na$ 460.1094 and 462.1073 [M+Na]$^+$, found 460.1076 and 462.1066.



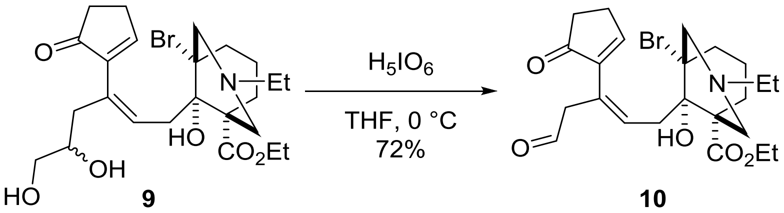
Triene 2. *n*-Bu$_3$SnH (8.5 mL, 32 mmol) was added to a solution of **7** (6.92 g, 15.8 mmol) and PdCl$_2$(PPh$_3$)$_2$ (555 mg, 0.791 mmol) in THF (150 mL) at room temperature. The reaction mixture was stirred at room temperature for 1.5 h, and then *n*-Bu$_3$SnH (1.3 mL, 0.48 mmol) was added. The reaction mixture was stirred at room temperature for 25 min, and then *n*-Bu$_3$SnH (0.85 mL, 0.32 mmol) was added. The reaction mixture was stirred at room temperature for 50 min and then concentrated. The residue was purified by flash column chromatography on silica gel (200 g, hexane to hexane/EtOAc 10/1) to afford the crude **8**, which was used in the next reaction without further purification.

A solution of Ph$_3$As (772 mg, 2.52 mmol) and [Pd$_2$(dba)$_3$]·CHCl$_3$ (650 mg, 0.628 mmol) in THF (60 mL), degassed by argon bubbling, was added to a solution of the above crude **8** and allylbromide **B** (6.5 mL, 75 mmol) in degassed THF (60 mL) at room temperature. The reaction mixture was warmed to 60 °C and stirred for 14 h. Then allylbromide **B** (6.5 mL, 75 mmol) was added. The reaction mixture was stirred at 60 °C for 11 h, and then allylbromide **B** (3.3 mL, 38 mmol) was added. The reaction mixture was stirred at 60 °C for further 13 h. After the mixture was cooled to room temperature, saturated aqueous KF (200 mL) was added. The resultant mixture was stirred at room temperature for 24 h, and was extracted with EtOAc (100 mL x3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography [a column consecutively packed with silica gel 225 g and 10% (w/w) KF contained silica gel 30 g, hexane/EtOAc 15/1 to 8/1] to afford **2** (4.45 g, 9.26 mmol) in 59% yield over 2 steps: yellow oil; IR (film) ν 3545, 3464, 2975, 2924, 2818, 1704, 1298, 1258, 1216, 1192 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.03 (3H, dd, *J* = 7.3, 7.3 Hz, NCH_2CH_3), 1.28 (3H, t, *J* = 7.3 Hz, OCH_2CH_3), 1.45-1.51 (1H, m, H2a), 1.58 (1H, dd, *J* = 13.3, 6.0 Hz, H3a), 2.18 (1H, dd, *J* = 12.8, 6.0 Hz, H1a), 2.30-2.35 (2H, m, NCH_2CH_3), 2.39-2.47 (3H, m, H3b and H13ab), 2.57-2.64 (1H, m, H6a), 2.64-2.67 (3H, m, H12ab and H19a), 2.75-3.02 (7H, m, H1b, H2b, H6b, H15ab, H17a and H19b), 3.21 (1H, d, *J* = 11.0 Hz, H17b), 4.12 (1H, s, O*H*), 4.13 (2H, q, *J* = 7.3 Hz, OCH_2CH_3), 4.96 (2H, m, H16'ab), 5.49 (1H, dd, *J* = 7.8, 7.8 Hz, H7), 5.63-5.73 (1H, m, H16), 7.50 (1H, dd, *J* = 2.7, 2.7 Hz, H10); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.2, 13.8, 23.4, 26.9, 32.0, 34.7, 34.9, 39.5, 41.3, 51.2, 51.4, 55.8, 61.3, 63.3, 75.4, 76.2, 116.4, 124.7, 134.5, 135.6, 144.4, 161.6, 175.1, 208.3; HRMS (ESI) calcd for $C_{24}H_{34}BrNO_4Na$ 502.1563 and 504.1543 $[M+Na]^+$, found 502.1558 and 504.1541.



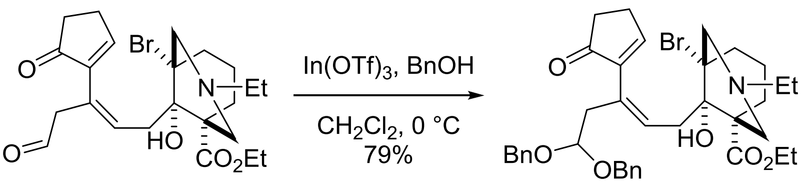
Triol 9. OsO_4 (0.16 M in H_2O, 3.2 mL, 0.51 mmol) was added to a solution of **2** (2.45 g, 5.10 mmol) and *N*-methylmorpholine *N*-oxide (NMO, 720 mg, 6.15 mmol) in a mixture of THF (50 mL) and H_2O (13 mL) at room temperature. The reaction mixture was stirred at room temperature for 2 h. After the mixture was cooled to 0 °C, saturated aqueous $NaHCO_3$ (50 mL) and saturated aqueous $Na_2S_2O_3$ (50 mL) were successively added. The resultant mixture was extracted with EtOAc (100 mL x5), and the combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography on silica gel (50 g, hexane/EtOAc 1/1 to EtOAc) to afford **9** (2.12 g, 4.12 mmol) as a 1:1 C16-diastereomixture in 81% yield: white amorphous; IR (film) ν 3438, 2971, 2926, 2860, 2818, 1699, 1298, 1258, 1096, 735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.04 (3H, dd, *J* = 7.4, 7.4 Hz, NCH_2CH_3), 1.29 (3H, dd, *J* = 7.3, 7.3 Hz, OCH_2CH_3), 1.49 (1H, ddd, *J* = 13.3, 6.8, 6.4 Hz), 1.58-1.63 (1H, m), 2.16-2.56 (10H, m), 2.64-2.74 (3H, m), 2.75-2.92 (3H, m), 2.94-3.06 (2H, m), 3.16-3.24 (2H, m), 3.41-3.47 (1H, m), 3.55-3.64

(2H, m), 4.11-4.21 (3H, m, OC*H*$_2$CH$_3$ and O*H*), 5.60 (1H, dd, *J* = 8.2, 7.8 Hz, H7), 7.58 (1H x1/2, t, *J* = 2.8 Hz, H10), 7.64 (1H x 1/2, t, *J* = 2.8 Hz, H10); ^{13}C NMR (100 MHz, CDCl$_3$) δ 12.22 (1C x1/2), 12.24 (1C x1/2), 13.9, 23.4, 27.3 (1C x1/2), 27.4 (1C x1/2), 31.98 (1C x1/2), 32.04 (1C x1/2), 34.5 (1C x1/2), 34.6 (1C x1/2), 35.0 (1C x1/2), 35.1 (1C x1/2), 39.5, 42.2 (1C x1/2), 42.3 (1C x1/2), 51.26 (1C x1/2), 51.31 (1C x1/2), 51.4 (1C x1/2), 51.7 (1C x1/2), 55.7 (1C x1/2), 55.8 (1C x1/2), 61.6, 63.25 (1C x1/2), 63.32 (1C x1/2), 66.1 (1C x1/2), 66.4 (1C x1/2), 69.6, 75.4 (1C x1/2), 75.5 (1C x1/2), 76.06 (1C x1/2), 76.15 (1C x1/2), 128.0 (1C x1/2), 128.2 (1C x1/2), 131.96 (1C x1/2), 132.02 (1C x1/2), 144.5 (1C x1/2), 144.8 (1C x1/2), 162.87 (1C x1/2), 162.91 (1C x1/2), 175.47 (1C x1/2), 175.54 (1C x1/2), 209.9; HRMS (ESI) calcd for $C_{24}H_{36}BrNO_6Na$ 536.1618 and 538.1598 [M+Na]$^+$, found 536.1609 and 538.1591.



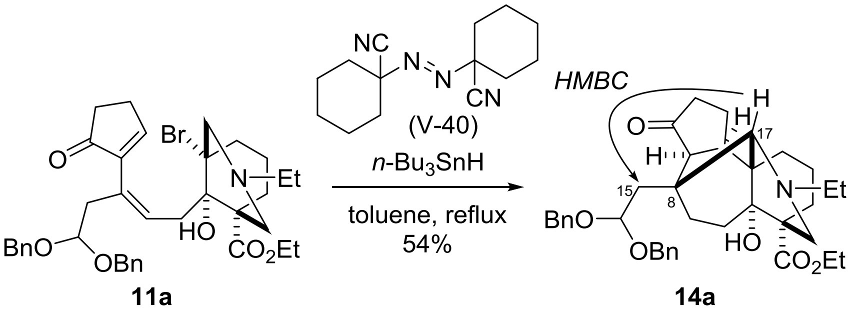
Aldehyde 10. H$_5$IO$_6$ (235 mg, 1.03 mmol) was added to a solution of **9** (1.05 g, 2.05 mmol) in THF (21 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min, and then H$_5$IO$_6$ (235 mg, 1.03 mmol) was added. The reaction mixture was stirred at 0 °C for 30 min, and then H$_5$IO$_6$ (94.0 mg, 0.412 mmol) was added. The mixture was stirred at 0 °C for 30 min, and then H$_5$IO$_6$ (94.0 mg, 0.412 mmol) was added. The reaction mixture was stirred at 0 °C for further 20 min, and then saturated aqueous NaHCO$_3$ (20 mL) and saturated aqueous Na$_2$S$_2$O$_3$ (20 mL) were successively added. The resultant mixture was extracted with EtOAc (40 mL x3), and the combined organic layers were dried over Na$_2$SO$_4$, filtered and concentrated. The residue was purified by flash column chromatography on silica gel (25 g, hexane/EtOAc 3/1 to 2/1) to afford **10** (715 mg, 1.48 mmol) in 72% yield: white amorphous; IR (film) ν 3450, 3278, 2974, 2930, 1704, 1443, 1391, 1369, 1260, 1210, 1096, 735 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.02 (3H, dd, *J* = 7.4, 7.4 Hz, NCH$_2$C*H*$_3$), 1.24 (3H, t, *J* = 7.3 Hz, OCH$_2$C*H*$_3$), 1.48 (1H, ddd, *J* = 12.8, 6.0, 6.0 Hz, H2a), 1.59 (1H, dd, *J* = 13.7, 6.4 Hz, H3a), 2.17 (1H, dd, *J* = 12.8, 6.0 Hz, H1a), 2.30-2.35 (2H, m, NC*H*$_2$CH$_3$), 2.37-2.43 (3H, m, H3b and H13ab), 2.58-2.67 (3H, m, H6a and H12ab), 2.60 (1H, d, *J* = 12.4 Hz, H19a), 2.79 (1H, ddddd, *J* = 12.8, 6.4, 6.4, 6.4, 6.0 Hz, H2b), 2.87 (1H, d, *J* = 11.5 Hz, H17a), 2.92-2.98 (2H, m, H1b and H6b), 3.03 (1H, d, *J* = 12.4 Hz, H19b), 3.22 (1H, d, *J* = 11.5 Hz, H17b), 3.23 (1H, d, *J* = 16.4 Hz, H15a), 3.39 (1H, d, *J* = 16.4 Hz, H15b), 4.08 (2H,

q, J = 7.3 Hz, OCH_2CH$_3$), 4.25 (1H, s, OH), 5.68 (1H, dd, J = 7.8, 7.8 Hz, H7), 7.63 (1H, dd, J = 2.7, 2.7 Hz, H10), 9.57 (1H, dd, J = 1.8, 1.8 Hz, H16); ^{13}C NMR (100 MHz, CDCl$_3$) δ 12.1, 13.8, 23.4, 27.0, 31.9, 34.6, 35.1, 39.3, 51.0, 51.2, 51.7, 55.6, 61.4, 63.3, 75.4, 75.5, 126.7, 130.5, 143.1, 162.5, 175.3, 199.6, 208.1; HRMS (ESI) calcd for $C_{24}H_{36}BrNO_6Na$ 536.1618 and 538.1598 [M+MeOH+Na]$^+$, found 536.1611 and 538.1606.



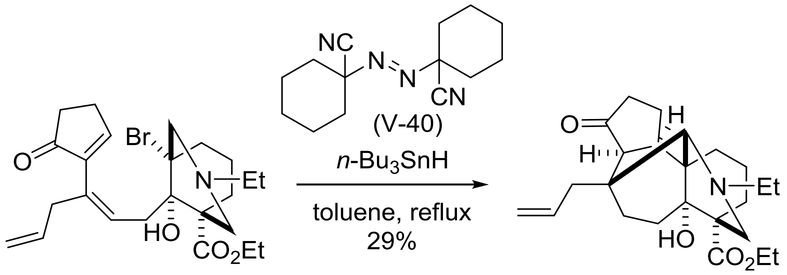
10 **11a**

Dibenzyl acetal 11a. BnOH (0.38 mL, 3.7 mmol) and In(OTf)$_3$ (515 mg, 0.916 mmol) were added to a solution of **10** (590 mg, 1.22 mmol) in CH$_2$Cl$_2$ (12 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1.5 h, and then pyridine (1.5 mL, 19 mmol) and Ac$_2$O (0.87 mL, 9.2 mmol) were added at 0 °C for conversion of excess BnOH to BnOAc. The resultant solution was warmed to room temperature and stirred for 40 min. After the mixture was cooled to 0 °C, saturated aqueous NaHCO$_3$ (10 mL) was added. The resultant mixture was extracted with EtOAc (15 mL x3), and the combined organic layers were dried over Na$_2$SO$_4$, filtered, and concentrated. The residue containing BnOAc was purified by flash column chromatography on silica gel (15 g, hexane/EtOAc 20/1 to 6/1) to afford **11a** (653 mg, 0.959 mmol) in 79% yield: yellow oil; IR (film) ν 3545, 3463, 3032, 2973, 2925, 2820, 1702, 1453, 1383, 1298, 1259, 1214, 1119, 1046, 737, 700 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.04 (3H, dd, J = 7.3, 7.3 Hz, NCH$_2$CH_3), 1.24 (3H, t, J = 7.3 Hz, OCH$_2$CH_3), 1.49 (1H, ddd, J = 12.8, 6.9, 6.9 Hz, H2a), 1.58 (1H, dd, J = 13.7, 6.4 Hz, H3a), 2.19 (1H, dd, J = 12.8, 5.9 Hz, H1a), 2.28 (2H, t, J = 5.0 Hz, H13ab), 2.30-2.36 (2H, m, NCH_2CH$_3$), 2.37-2.49 (3H, m, H3b and H12ab), 2.58-2.65 (3H, m, H6a, H15a and H19a), 2.80 (1H, ddddd, J = 12.8, 6.4, 6.4, 6.4, 5.9 Hz, H2b), 2.84-2.91 (3H, m, H6b, H15b and H17a), 2.96-3.05 (1H, m, H1b), 3.00 (1H, d, J = 12.8 Hz, H19b), 3.23 (1H, d, J = 11.4 Hz, H17b), 4.10 (2H, q, J = 7.3 Hz, OCH_2CH$_3$), 4.16 (1H, s, OH), 4.47 (1H, d, J = 11.9 Hz, OCH_AH$_B$Ph), 4.49 (1H, d, J = 11.9 Hz, OCH_CH$_D$Ph), 4.60 (1H, d, J = 11.9 Hz, OCH$_C$$H_D$Ph), 4.61 (1H, d, J = 11.9 Hz, OCH$_A$$H_B$Ph), 4.62 (1H, dd, J = 6.0, 6.0 Hz, H16), 5.61 (1H, dd, J = 8.2, 8.2 Hz, H7), 7.27-7.35 (11H, m, H10 and aromatic); ^{13}C NMR (100 MHz, CDCl$_3$) δ 12.2, 13.8, 23.5, 26.9, 32.0, 34.6, 34.8, 39.5, 41.1, 51.3, 51.5, 55.8, 61.4, 63.4, 67.3, 67.5, 75.5, 76.1, 101.1, 127.3, 127.51, 127.54, 127.8 (2C), 127.9 (2C), 128.29 (2C), 128.32 (2C), 131.7, 138.1, 138.2, 143.9, 161.5, 175.2, 208.2; HRMS (ESI) calcd for $C_{37}H_{46}BrNO_6Na$ 702.2401 and 704.2380 $[M+Na]^+$, found 702.2375 and 704.2356.



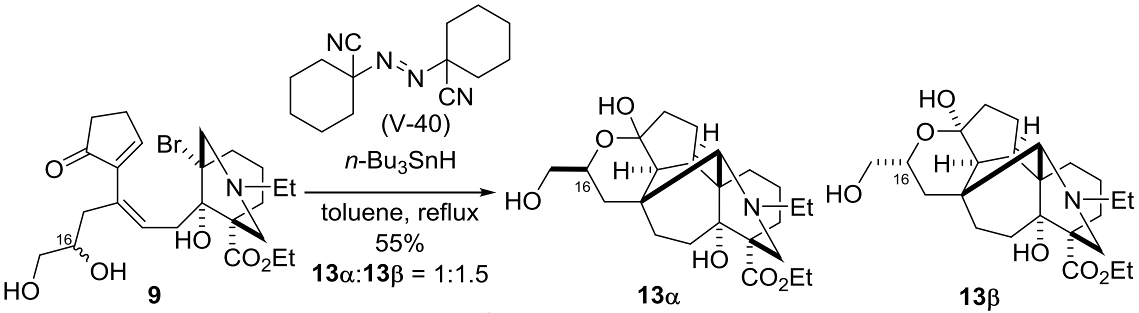
Pentacyclic compound 14a. A solution of dibenzyl acetal **11a** (67.7 mg, 99.5 μmol) and V-40 (5.0 mg, 20 μmol) in toluene (2.5 mL) was degassed by freeze-thaw procedure (x 3). The mixture was warmed to reflux temperature, and then a degassed solution of *n*-Bu_3SnH (135 μL, 0.502 mmol) and V-40 (4.9 mg, 20 μmol) in toluene (2.5 mL) by freeze-thaw procedure (x 3) was added over 3 h. After being cooled to room temperature, the mixture was concentrated. The residue was purified by flash column chromatography [consecutively packed with silica gel 3.5 g and 10% (w/w) KF contained silica gel 1.5 g, hexane/EtOAc 10/1 to 8/1] to afford the crude **14a**. The crude **14a** was further purified by preparative-TLC (hexane/EtOAc 3/1) to afford **14a** (32.1 mg, 53.3 μmol) in 54% yield. The C8-17 bond was confirmed by the HMBC experiment. The pentacyclic structure was confirmed by transformation of **14a** into aldehyde **15a** (see page S12): white amorphous; IR (film) ν 3479, 2964, 2928, 1727, 1698, 1640, 1455, 1371, 1261, 1117, 1088, 1029, 737, 699 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 0.83 (3H, dd, *J* = 7.3, 7.3 Hz, OCH_2CH_3), 0.89 (3H, dd, *J* = 7.3, 7.3 Hz, NCH_2CH_3), 1.16 (1H, dd, *J* = 12.8, 4.6 Hz, H1a), 1.36-1.44 (1H, m, H12a), 1.46-1.51 (1H, m, H2a), 1.55-1.64 (2H, m, H3a and H12b), 1.70-1.95 (6H, m, H6a, H7ab, H9 and H13ab), 2.00-2.04 (1H, m, H6b), 2.03 (1H, dd, *J* = 14.2, 1.4 Hz, H15a), 2.24 (1H, ddd, *J* = 12.8, 12.8, 6.0 Hz, H1b), 2.30 (1H, dd, *J* = 14.2, 8.7 Hz, H15b), 2.34-2.49 (2H, m, H2b and H3b), 2.42 (1H, s, H17), 2.53 (1H, dq, *J* = 14.6, 7.3 Hz, $NCH_AH_BCH_3$), 2.66 (1H, dq, *J* = 14.6, 7.3 Hz, $NCH_AH_BCH_3$), 3.02 (1H, ddd, *J* = 9.2, 9.2, 3.7 Hz, H10), 3.07 (1H, d, *J* = 12.8 Hz, H19a), 3.55 (1H, dd, *J* = 12.8, 2.3 Hz, H19b), 3.77 (1H, dq, *J* = 11.5, 7.3 Hz, $OCH_AH_BCH_3$), 3.85 (1H, dq, *J* = 11.5, 7.3 Hz, $OCH_AH_BCH_3$), 4.59 (1H, d, *J* = 11.9 Hz, OCH_AH_BPh), 4.62 (1H, s, OH), 4.79 (1H, d, *J* = 11.9 Hz, OCH_AH_BPh), 4.94 (1H, d, *J* = 11.9 Hz, OCH_CH_DPh), 5.00 (1H, d, *J* = 11.9 Hz, OCH_CH_DPh), 5.53 (1H, dd, *J* = 8.7, 1.4 Hz, H16), 7.05-7.14 (4H, m, aromatic), 7.22 (2H, dd, *J* = 7.8, 7.8 Hz, aromatic), 7.36 (2H, d, *J* = 6.9 Hz, aromatic), 7.60 (2H, d, *J* = 7.3 Hz, aromatic); ^{13}C

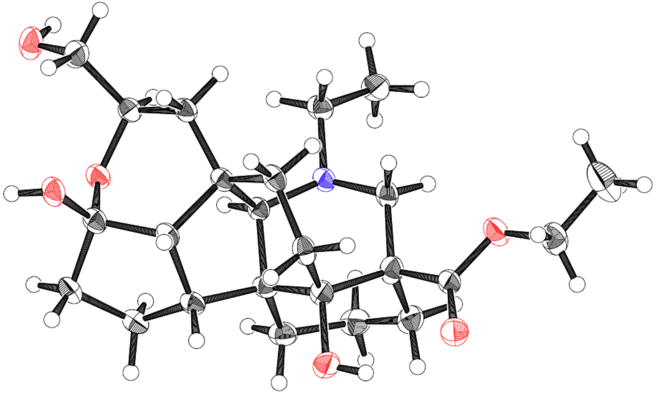
NMR (100 MHz, $CDCl_3$) δ 14.1, 14.6, 19.0, 22.6, 27.9, 32.0, 33.6, 33.9, 40.0, 40.1, 40.3, 45.1, 49.3, 50.8, 51.0, 52.0, 55.4, 61.0, 66.9, 68.5, 72.1, 75.4, 102,0, 127.38, 127.42, 127.9 (2C), 128.0 (2C), 128.28 (2C), 128.30 (2C), 138.4, 138.8, 177.7, 220.6; HRMS (ESI) calcd for $C_{37}H_{47}NO_6Na$ 624.3296 $[M+Na]^+$, found 624.3272.



2 **12**

Pentacyclic compound 12. According to the synthetic procedure of **14a**, **12** (13.0 mg, 32.4 μmol) was synthesized from **2** (53.7 mg, 112 μmol) in 29% yield by using V-40 (11.2 mg, 45.8 μmol) and *n*-Bu_3SnH (150 μL, 0.557 mmol) in toluene (5.6 mL). The crude was purified by flash column chromatography [consecutively packed with silica gel 3 g and 10% (w/w) KF contained silica gel 2 g, hexane/EtOAc 20/1 to 15/1] and preparative-TLC (hexane/EtOAc 3/1). The pentacyclic structure was confirmed by transformation of aldehyde **15a** into **12** (see page S14): colorless oil; IR (film) ν 3495, 2968, 2927, 2871, 1731, 1701, 1458, 1373, 1261, 1235, 1207, 1172, 1092, 1057, 1037 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.08 (3H, dd, J = 7.3, 7.3 Hz, NCH_2CH_3), 1.28 (3H, dd, J = 7.3, 7.3 Hz, OCH_2CH_3), 1.42 (1H, dd, J = 12.4, 6.4 Hz, H1a), 1.46-1.60 (4H, m, H2a, H3a and H7ab), 1.75-1.86 (3H, m, H6ab and H12a), 1.91-1.99 (1H, m, H12b), 2.03-2.25 (5H, m, H1b, H9, H13ab and H15a), 2.26-2.47 (3H, m, H2b, H3b and H15b), 2.67 (1H, s, H17), 2.79 (1H, dq, J = 13.3, 7.3 Hz, $NCH_AH_BCH_3$), 2.93 (1H, dq, J = 13.3, 7.3 Hz, $NCH_AH_BCH_3$), 3.02 (1H, ddd, J = 8.7, 8.7, 3.2 Hz, H10), 3.06 (1H, d, J = 12.8 Hz, H19a), 3.49 (1H, dd, J = 12.8, 2.7 Hz, H19b), 4.14-4.22 (2H, m, OCH_2CH_3), 4.34 (1H, s, O*H*), 4.98 (1H, d, J = 16.9 Hz, H16'a), 4.99 (1H, d, J = 10.5 Hz, H16'b), 6.10 (1H, dddd, J = 16.9, 10.5, 10.5, 6.0 Hz, H16); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 14.6, 19.0, 22.6, 28.0, 32.1, 33.7, 34.0, 39.8, 40.3, 41.1, 45.5, 49.4, 50.6, 51.6, 52.2, 55.2, 61.0, 72.4, 74.1, 116.4, 136.8, 177.7, 220.6; HRMS (ESI) calcd for $C_{24}H_{35}NO_4Na$ 424.2458 $[M+Na]^+$, found 424.2447.

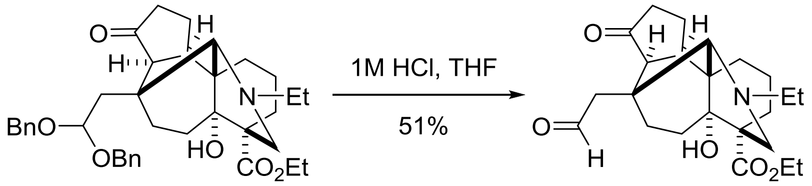




X-ray structure of **13**β (CCDC1452192)

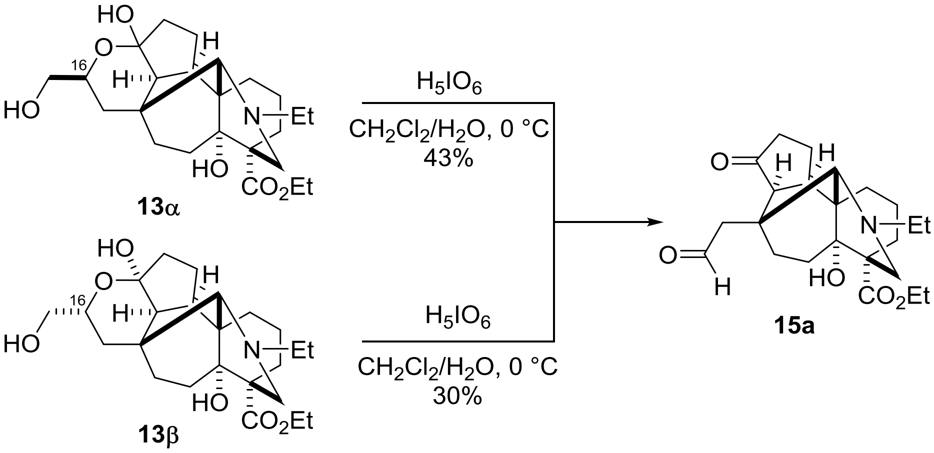
Pentacyclic compound 13. According to the synthetic procedure of **14a**, **13α** (9.2 mg, 21 μmol) and **13β** (13.8 mg, 31.7 μmol) were synthesized from **9** (49.3 mg, 95.8 μmol) in 22% and 33% yields, respectively, by using V-40 (9.4 mg, 38 μmol) and *n*-Bu_3SnH (130 μL, 0.482 mmol) in toluene (4.8 mL). The crude was purified by flash column chromatography [consecutively packed with silica gel 2.5 g and 10% (w/w) KF contained silica gel 1.3 g, hexane/EtOAc 2/1 to 1/2] and preparative-TLC (EtOAc). The structure of **13β** was confirmed by the X-ray crystallographic analysis. The diastereomeric relationship between **13α** and **13β** at the C16-position was confirmed by transformation of **13α** and **13β** into the same aldehyde **15a** (see page S13). Compound **13α** exists as a 4:1 mixture of the hemiacetal and ketone forms in C_6D_6: white solid; m.p. 78-83 °C; IR (film) ν 3418, 2962, 2929, 2868, 1699, 1458, 1369, 1299, 1260, 1244, 1093, 1051 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6) δ 0.85 (3H x4/5, dd, *J* = 7.3, 7.3 Hz, OCH$_2$C*H*$_3$), 0.89 (3H x1/5, dd, *J* = 7.3, 7.3 Hz, OCH$_2$C*H*$_3$), 0.92-0.97 (1H x1/5, m), 1.01 (3H, dd, *J* = 7.3, 7.3 Hz, NCH$_2$C*H*$_3$), 1.11 (1H x4/5, dd, *J* = 14.2, 7.0 Hz), 1.28-1.44 (3H, m), 1.45-1.78 (10H, m), 1.81-1.88 (2H, m), 1.93-2.02 (1H, m), 2.16-2.28 (2H, m), 2.30-2.41 (1H, m, NC*H*$_A$CH$_B$CH), 2.44-2.54 (1H, m), 2.55-2.64 (1H, m, NCH$_A$C*H*$_B$CH$_3$), 2.91 (1H x4/5, s, H17), 2.93-2.98 (3H x1/5, m), 3.07 (1H x4/5, d, *J* = 12.8 Hz, H19a), 3.10-3.18 (1H, m), 3.47-3.55 (2H x1/5 and 1H x4/5, m), 3.58-3.65 (1H x1/5 and 2H x4/5), 3.76-3.91 (2H, m, OC*H*$_2$CH$_3$), 4.02-4.09 (1H x4/5, m, H16), 4.26 (1H x4/5, s, O*H*), 4.56 (1H x1/5, s, O*H*), 4.57 (1H x4/5, s, O*H*), 5.03 (1H x 1/5, br d, *J* =

9.6 Hz, H16); ^{13}C NMR (100 MHz, C_6D_6) δ 14.0, 15.1 (1C x1/5), 15.2 (1C x4/5), 19.4 (1C x1/5), 19.7 (1C x4/5), 22.5 (1C x1/5), 25.7 (1C x4/5), 27.8 (1C x4/5), 28.0 (1C x1/5), 31.8 (1C x4/5), 32.2 (1C x1/5), 32.7 (1C x4/5), 32.9 (1C x1/5), 34.1 (1C x1/5), 34.5 (1C x4/5), 37.5 (1C x1/5), 37.7 (1C x4/5), 40.4 (1C x1/5), 40.6 (1C x1/5), 41.8 (1C x4/5), 43.6 (1C x4/5), 44.9 (1C x1/5), 45.4 (1C x4/5), 46.0 (1C x4/5), 49.6 (1C x1/5), 50.0 (1C x4/5), 50.6 (1C x1/5), 51.3 (1C x4/5), 51.8 (1C x1/5), 52.5 (1C x1/5), 53.2 (1C x4/5), 53.4 (1C x4/5), 56.2 (1C x1/5), 60.7 (1C x4/5), 60.8 (1C x1/5), 66.8 (1C x4/5), 69.1 (1C x1/5), 69.2 (1C x1/5), 69.4 (1C x4/5), 71.9 (1C x4/5), 72.2 (1C x1/5), 72.9 (1C x4/5), 75.5 (1C x1/5), 107.0 (1C x4/5), 177.6 (1C x1/5), 177.8 (1C x4/5), 225.4 (1C x1/5); HRMS (ESI), calcd for $C_{24}H_{37}NO_6Na$ 458.2513 [M+Na]$^+$, found 458.2506. **13β**: white solid; m.p. 154.5-156.0 °C; IR (film) ν 3382, 2936, 2866, 1699, 1459, 1262, 1244, 1066, 1046 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6) δ 0.87 (3H, dd, *J* = 7.3, 7.3 Hz, OCH$_2$C*H*$_3$), 0.95 (3H, dd, *J* = 7.3, 7.3 Hz, NCH$_2$C*H*$_3$), 0.98-1.02 (1H, m), 1.43-1.72 (8H, m), 1.70 (1H, d, *J* = 11.0 Hz), 1.77-1.83 (2H, m), 1.91-1.96 (2H, m), 2.17-2.26 (1H, m), 2.47-2.57 (2H, m), 2.62 (1H, dq, *J* = 13.7, 7.3 Hz, NC*H*$_A$CH$_B$CH$_3$), 2.72 (1H, dq, *J* = 13.7, 7.3 Hz, NCH$_A$C*H*$_B$CH$_3$), 2.79 (1H, br s, O*H*), 2.93-3.00 (1H, m), 3.11 (1H, s, H17), 3.21 (1H, d, *J* = 12.4 Hz, H19a), 3.44 (1H, dd, *J* = 11.4, 4.6 Hz, H16'a), 3.50 (1H, d, *J* = 12.4 Hz, H19b), 3.68 (1H, dd, *J* = 11.4, 2.8 Hz, H16'b), 3.83 (1H, dq, *J* = 11.0, 7.3 Hz, OC*H*$_A$H$_B$CH$_3$), 3.89 (1H, dq, *J* = 11.0, 7.3 Hz, OCH$_A$*H*$_B$CH$_3$), 4.08-4.15 (1H, m, H16), 4.57 (1H, s, O*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 14.7, 19.1, 26.1, 26.7, 29.3, 32.2, 34.2, 36.0, 41.2, 43.3, 44.4, 47.0, 49.3, 50.0, 52.6, 54.8, 60.9, 66.3, 66.7, 72.1, 72.2, 105.4, 177.8; HRMS (ESI), calcd for $C_{24}H_{37}NO_6Na$ 458.2513 [M+Na]$^+$, found 458.2522.



14a **15a**

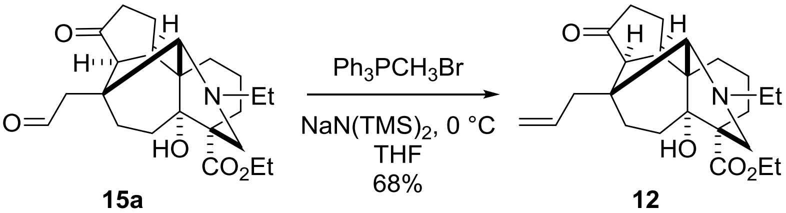
Synthesis of aldehyde 15a from 14a. This experiment was carried out for confirmation of the structure of **14a**. Aqueous 1.0 M HCl (35 μL, 35 μmol) was added to a solution of **14a** (5.3 mg, 8.8 μmol) in THF (0.40 mL) at room temperature. The reaction mixture was stirred at room temperature for 6 h. After the mixture was cooled to 0 °C, saturated aqueous $NaHCO_3$ (2 mL) was added. The resultant mixture was extracted with EtOAc (3 mL x3), and the combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography on silica gel (0.5 g, hexane/EtOAc 5/1 to 3/1) to afford the crude **15a**. The ^{1}H NMR signals of **15a** were identical with those of **15a**, which was derived from the fully characterized **13β**. The yield of **15a** was determined to be 51% by the analysis of ^{1}H NMR of the crude **15a** using CH_2Cl_2 as an internal standard.



Synthesis of aldehyde 15a from 13α and 13β. This experiment was carried out for confirmation of the structure of **13α**. H_5IO_6 (9.1 mg, 40 μmol) was added to a solution of **13β** (8.7 mg, 20 μmol) in a mixture of CH_2Cl_2 (0.40 mL) and H_2O (0.10 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min, and then H_5IO_6 (4.4 mg, 19 μmol) was added. The reaction mixture was stirred at 0 °C for 40 min, and then H_5IO_6 (5.2 mg, 23 μmol) was added. The reaction mixture was stirred at 0 °C for 50 min, and then H_5IO_6 (4.6 mg, 20 μmol) was added. The reaction mixture was stirred at 0 °C for further 2.5 h, and then saturated aqueous $NaHCO_3$ (1.5 mL) and saturated aqueous $Na_2S_2O_3$ (1.5 mL) were successively added. The resultant solution was extracted with EtOAc (3 mL x4), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (0.5 g, hexane/EtOAc 3/1 to 1/2) to afford **15a** (2.4 mg, 6.0 μmol) in 30% yield: colorless oil; IR (film) ν 3492, 2964, 2927, 2861, 1726, 1460, 1370, 1262, 1235, 1172, 1092, 1060, 1036 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (3H, dd, *J* = 7.3, 7.3 Hz, NCH_2CH_3), 1.28 (3H, dd, *J* = 7.3, 7.3 Hz, OCH_2CH_3), 1.45 (1H, dd, *J* = 13.2, 5.5 Hz, H1a), 1.51-1.67 (4H, m, H2a, H3a, H6a and H7a), 1.76-1.97 (4H, m, H6b, H7b and H12ab), 2.04-2.16 (2H, m, H1b and H13a), 2.20-2.40 (3H, m, H2b, H3b and H13b), 2.44 (1H, d, *J* = 10.1 Hz, H9), 2.56 (1H, dd, *J* = 17.4, 1.4 Hz, H15a), 2.71 (1H, d, *J* = 17.4 Hz, H15b), 2.73 (1H, dq, *J* = 13.3, 7.3 Hz, $NCH_AH_BCH_3$), 2.84 (1H, s, H17), 2.85 (1H, dq, *J* = 13.3, 7.3 Hz, $NCH_AH_BCH_3$), 3.03-3.10 (1H, m, H10), 3.07 (1H, d, *J* = 12.8 Hz, H19a), 3.47 (1H, dd, *J* = 12.8, 2.3 Hz, H19b), 4.15-4.22 (2H, m, OCH_2CH_3), 4.37

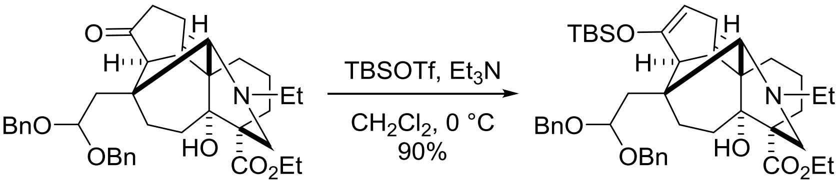
(1H, s, O*H*), 9.86 (1H, s, H16); ^{13}C NMR (100 MHz, CDCl$_3$) δ 14.1, 14.6, 18.9, 22.8, 27.2, 32.0, 33.8, 34.7, 39.9, 40.3, 45.6, 49.2, 49.4, 49.7, 50.3, 52.3, 53.9, 61.0, 71.7, 72.8, 177.5, 202.0, 220.5; HRMS (ESI) calcd for $C_{23}H_{33}NO_5Na$ 426.2251 [M+Na]$^+$, found 426.2247.

According to the above procedure, the same aldehyde **15a** (2.0 mg, 5.0 μmol) was synthesized from **13α** (5.0 mg, 12 μmol) in 43% yield by using H_5IO_6 (13.6 mg, 59.6 μmol) in a mixture of CH_2Cl_2 (0.30 mL) and H_2O (75 μL) at 0 °C. The crude was purified by flash column chromatography on silica gel (0.5 g, hexane/EtOAc 3/1).



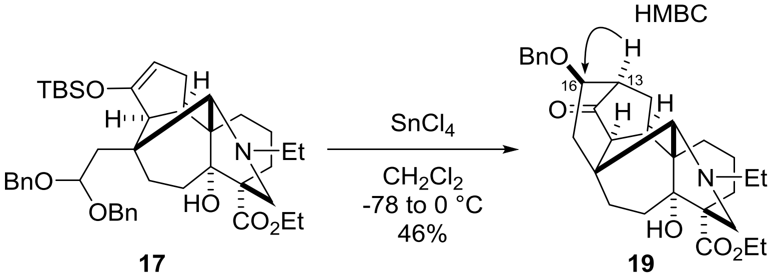
15a **12**

Synthesis of pentacyclic compound 12 from 15a. This experiment was carried out for confirmation of the structure of **12**. Ph_3PCH_3Br (17 mg, 49 μmol) was dried at 100 °C for 1 h under vacuum. After being cooled to room temperature, the flask was filled with argon. Then, THF (0.20 mL) was added. NaN(TMS)$_2$ (1.0 M in THF, 37 μL, 37 μmol) was added to the mixture at 0 °C. The mixture was stirred at 0 °C for 40 min, and then a solution of **15a** (3.0 mg, 7.4 μmol) in THF (0.25 mL) was added. The reaction mixture was stirred at 0 °C for 50 min, and then aqueous NH_4Cl (2 mL) was added. The resultant mixture was extracted with EtOAc (2 mL x3), and the combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography on silica gel (0.5 g, hexane/EtOAc 8/1 to 5/1) to afford **12** (2.0 mg, 5.0 μmol) in 68% yield. The ^{1}H NMR of **12** derived from the fully characterized **13β** was identical with that of **12**, which was synthesized from **2**.



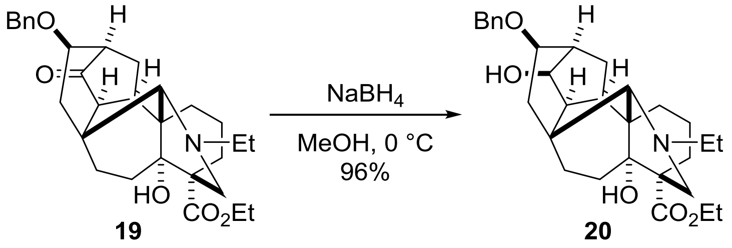
14a **17**

TBS enol ether 17. Et_3N (29 μL, 0.21 mmol) and TBSOTf (24 μL, 0.10 mmol) were successively added to a solution of **14a** (12.4 mg, 20.6 μmol) in CH_2Cl_2 (0.40 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 35 min, and then pH 7 phosphate buffer (1.5 mL) was added. The resultant mixture was extracted with EtOAc (3 mL x3), and the combined organic layers were dried over $\mathrm{Na_2SO_4}$, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (0.5 g, hexane to hexane/EtOAc 30/1) to afford **17** (13.3 mg, 18.6 μmol) in 90% yield: colorless oil; ^{1}H NMR (400 MHz, $\mathrm{C_6D_6}$) δ 0.23 (3H, s, $\mathrm{C}H_3$ of TBS), 0.24 (3H, s, $\mathrm{C}H_3$ of TBS), 0.85 (3H, dd, *J* = 7.3, 7.3 Hz, $\mathrm{OCH_2C}H_3$), 1.02 (3H, dd, *J* = 7.3, 7.3 Hz, $\mathrm{NCH_2C}H_3$), 1.02 (9H, s, *t*-Bu of TBS), 1.55-1.59 (3H, m), 1.71-1.75 (1H, m), 1.94-2.07 (3H, m), 2.23-2.34 (5H, m), 2.38-2.45 (1H, m), 2.53-2.61 (1H, m), 2.64 (1H, br d, *J* = 9.6 Hz), 2.72 (1H, dq, *J* = 14.2, 7.3 Hz, $\mathrm{NC}H_\mathrm{A}\mathrm{H_BCH_3}$), 2.88 (1H, s, H17), 2.93 (1H, dq, *J* = 14.2, 7.3 Hz, $\mathrm{NCH_A}H_\mathrm{B}\mathrm{CH_3}$), 3.07 (1H, d, *J* = 12.8 Hz, H19a), 3.30 (1H, ddd, *J* = 9.6, 9.6, 4.6 Hz), 3.76-3.91 (3H, m, H19b and $\mathrm{OC}H_2\mathrm{CH_3}$), 4.43 (1H, s, $\mathrm{O}H$), 4.57 (1H, d, *J* = 11.5 Hz, $\mathrm{OC}H_\mathrm{A}\mathrm{H_BPh}$), 4.70 (1H, d, *J* = 11.9 Hz, $\mathrm{OC}H_\mathrm{C}\mathrm{H_DPh}$), 4.73-4.74 (1H, m, H13), 4.75 (1H, d, *J* = 11.9 Hz, $\mathrm{OCH_C}H_\mathrm{D}\mathrm{Ph}$), 4.78 (1H, d, *J* = 11.5 Hz, $\mathrm{OCH_A}H_\mathrm{B}\mathrm{Ph}$), 5.41 (1H, dd, *J* = 5.0, 5.0 Hz, H16), 7.04-7.13 (4H, m, aromatic), 7.20 (2H, dd, *J* = 7.3, 7.3 Hz, aromatic), 7.35 (2H, d, *J* = 7.3 Hz, aromatic), 7.40 (2H, d, *J* = 7.3 Hz, aromatic); HRMS (ESI) calcd for $\mathrm{C_{43}H_{61}NO_6SiNa}$ 738.4160 $[\mathrm{M+Na}]^+$, found 738.4155.



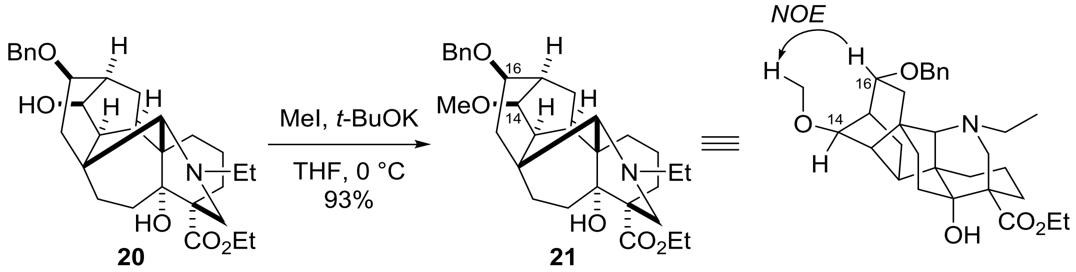
17 **19**

Hexacyclic compound 19. Freshly distilled $\mathrm{SnCl_4}$ (2.4 μL, 21 μmol) was added to a solution of **17** (11.8 mg, 16.5 μmol) in $\mathrm{CH_2Cl_2}$ (2.0 mL) at -78 °C. The reaction mixture was stirred at -78 °C for 20 min, and then $\mathrm{SnCl_4}$ (3.6 μL, 31 μmol) was added. The reaction mixture was stirred at -78 °C for 30 min, warmed to 0 °C, and stirred for further 2 h. Then saturated aqueous $\mathrm{NaHCO_3}$ (2 mL) was added. The resultant mixture was extracted with EtOAc (3 mL x3), and the combined organic layers were dried over $\mathrm{Na_2SO_4}$, filtered, and concentrated to afford the crude **19**. The procedure was repeated by using **17** (35.2 mg, 49.2 μmol) and $\mathrm{SnCl_4}$ (30.4 μL, 0.260 mmol) in $\mathrm{CH_2Cl_2}$ (6.3 mL). The obtained crude compounds were combined, and the mixture was purified by flash column chromatography on silica gel (2 g, hexane/EtOAc 7/1) to afford the crude **19**. The crude **19** was further purified by preparative-TLC (toluene/EtOAc 4/1) to afford **19** (15.0 mg, 30.4 μmol) in 46% yield. The C16-configuration was determined by the NOE experiment of compound **21**. The detail was shown below. The C13-16 bond was confirmed by the HMBC experiment: white solid; m.p. 127-128 °C; IR (film) ν 3477, 2956, 2862, 1740, 1699, 1454, 1374, 1255, 1208, 1076, 1040, 736, 698 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6) δ 0.83 (3H, dd, *J* = 7.3, 7.3 Hz, $\mathrm{OCH_2C}H_3$), 1.00 (3H, dd, *J* = 6.9, 6.9 Hz, $\mathrm{NCH_2C}H_3$), 1.24 (1H, dd, *J* = 12.4, 9.2 Hz, H7a), 1.39-1.46 (3H, m, H1a, H7b and H15a), 1.57-1.70 (3H, m, H2a, H3a and H12a), 1.74 (1H, d, *J* = 15.1 Hz, H15b), 1.81 (1H, dd, *J* = 15.6, 6.4 Hz, H6a), 1.88 (1H, dd, *J* = 14.6, 2.7 Hz, H12b), 2.09-2.25 (2H, m, H1b and H6b), 2.27-2.36 (2H, m, H2b and H3b), 2.46 (1H, dd, *J* = 7.3, 7.3 Hz, H13), 2.55 (1H, m, H10), 2.68 (1H, dq, *J* = 13.8, 6.9 Hz, $\mathrm{NC}H_\mathrm{A}\mathrm{H_BCH_3}$), 2.70 (1H, d, *J* = 6.9 Hz, H9), 3.14 (1H, dq, *J* = 13.8, 6.9 Hz, $\mathrm{NCH_A}H_\mathrm{B}\mathrm{CH_3}$), 3.14 (1H, d, *J* = 11.9 Hz, H19a), 3.37 (1H, d, *J* = 11.9 Hz, H19b), 3.78 (1H, dq, *J* = 11.0, 7.3 Hz, $\mathrm{OC}H_\mathrm{A}\mathrm{H_BCH_3}$), 3.86 (1H, dq, *J* = 11.0, 7.3 Hz, $\mathrm{OCH_A}H_\mathrm{B}\mathrm{CH_3}$), 3.96 (1H, d, *J* = 12.4 Hz, $\mathrm{OC}H_\mathrm{A}\mathrm{H_BPh}$), 4.01 (1H, dd, *J* = 7.3, 7.3 Hz, H16), 4.18 (1H, d, *J* = 12.4 Hz, $\mathrm{OCH_A}H_\mathrm{B}\mathrm{Ph}$), 4.24 (1H, s, H17), 5.09 (1H, s, O*H*), 7.08 (1H, m, aromatic), 7.10-7.20 (4H, m, aromatic); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 14.3, 19.0, 23.6, 25.8, 33.3, 33.6, 35.6, 36.8, 40.0, 46.7, 48.6, 51.4, 51.7, 52.1, 57.0, 60.6, 61.0, 67.2, 70.9, 74.1, 81.6, 127.0 (2C), 127.6, 128.4 (2C), 138.1, 178.3, 220.3; HRMS (ESI) calcd for $C_{30}H_{39}NO_5Na$ 516.2720 [M+Na]$^+$, found 516.2702.

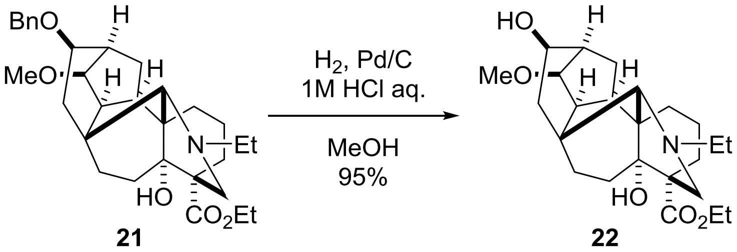


Diol 20. $NaBH_4$ (19.3 mg, 0.510 mmol) was added to a solution of **19** (79.0 mg, 0.160 mmol) in MeOH (2.6 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 40 min, and then saturated aqueous NH_4Cl (4 mL) was added. The resultant mixture was extracted with EtOAc (5 mL x3), and the combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography on silica gel (4.5 g, hexane/EtOAc 3/1 to 2/1) to afford **20** (76.1 mg, 0.154 mmol) in 96% yield: white amorphous; IR (film) ν 3470, 2932, 2861, 1697, 1454, 1370, 1256, 1211, 1074, 736, 697 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6) δ 0.86 (3H, dd, *J* = 7.3, 7.3 Hz, $\mathrm{OCH_2C}H_3$), 1.10 (3H, dd, *J* = 7.3, 7.3 Hz, $\mathrm{NCH_2C}H_3$), 1.39-1.47 (2H, m, H2a and H7a), 1.54 (1H, ddd, *J* = 14.7, 9.2, 6.8 Hz, H12a), 1.62-1.73 (3H, m, H1a, H3a and H7b), 1.88 (1H, dd, *J* = 14.7, 2.8 Hz, H12b), 1.90 (1H, d, *J* = 13.7 Hz, H15a), 2.00 (1H, dd, *J* = 15,1, 6.9 Hz, H6a), 2.16-2.21 (1H, m, H1b), 2.23-2.38 (6H, m, H2b, H3b,

H9, H10, H13 and H15b), 2.50 (1H, ddd, *J* = 15.1, 8.7, 6.4 Hz, H6b), 2.90 (1H, dq, *J* = 14.6, 7.3 Hz, NC*H*$_A$H$_B$CH$_3$), 3.17 (1H, d, *J* = 12.4 Hz, H19a), 3.28 (1H, dq, *J* = 14.6, 7.3 Hz, NCH$_A$*H*$_B$CH$_3$), 3.58 (1H, d, *J* = 12.4 Hz, H19b), 3.63 (1H, dd, *J* = 4.1, 4.1 Hz, H14), 3.82 (1H, dq, *J* = 11.0, 7.3 Hz, OC*H*$_A$H$_B$CH$_3$), 3.90 (1H, dq, *J* = 11.0, 7.3 Hz, OCH$_A$*H*$_B$CH$_3$), 3.98 (1H, s, H17), 4.15 (1H, dd, *J* = 7.4, 7.4 Hz, H16), 4.35, (1H, d, *J* = 12.4 Hz, OC*H*$_A$H$_B$Ph), 4.41 (1H, d, *J* = 12.4 Hz, OCH$_A$*H*$_B$Ph), 5.22 (1H, s, O*H*), 7.08 (1H, dd, *J* = 7.3, 7.3 Hz, aromatic), 7.18 (2H, dd, *J* = 7.3, 7.3 Hz, aromatic), 7.33 (2H, d, *J* = 7.3 Hz, aromatic); ^{13}C NMR (100 MHz, CDCl$_3$) δ 14.1, 14.6, 19.3, 26.4, 26.6, 33.4, 33.8, 34.2, 37.0, 39.6, 42.6, 49.1, 49.5, 50.3, 50.6, 51.8, 52.4, 60.8, 69.0, 70.3, 74.5, 75.8, 78.2, 127.0 (2C), 127.1, 128.2 (2C), 139.3, 178.8; HRMS (ESI) calcd for $C_{30}H_{41}NO_5Na$ 518.2877 [M+Na]$^+$, found 518.2855.

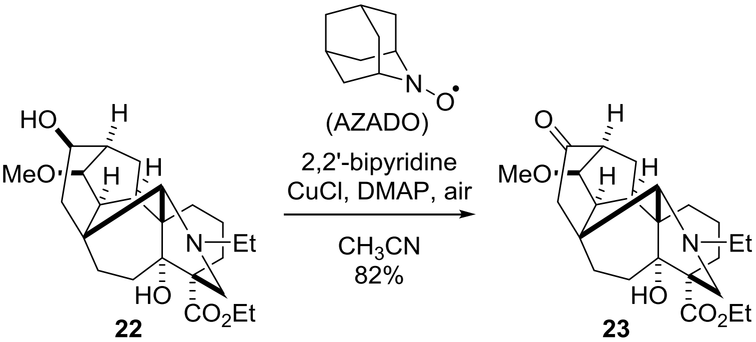


Methyl ether 21. *t*-BuOK (0.20 M in THF, 2.1 mL, 0.42 mmol) was added to a solution of **20** (71.0 mg, 0.142 mmol) and MeI (89 μL, 1.4 mmol) in THF (1.2 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1.5 h, and then *t*-BuOK (0.20 M in THF, 0.35 mL, 0.070 mmol) was added. The reaction mixture was stirred at 0 °C for further 40 min, and then aqueous NH$_4$Cl (5 mL) was added. The resultant mixture was extracted with EtOAc (5 mL x3), and the combined organic layers were dried over Na$_2$SO$_4$, filtered and concentrated. The residue was purified by flash column chromatography on silica gel (3.5 g, hexane/EtOAc 5/1 to 2/1) to afford **21** (67.3 mg, 0.132 mmol) in 93% yield. The C14- and C16-configurations were confirmed by the NOE experiment: colorless oil; IR (film) ν 3482, 2931, 2861, 1700, 1457, 1380, 1259, 1207, 1086, 735, 697 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.06 (3H, dd, *J* = 7.4, 7.4 Hz, NCH$_2$C*H*$_3$), 1.28 (3H, dd, *J* = 7.3, 7.3 Hz, OCH$_2$C*H*$_3$), 1.34 (1H, dd, *J* = 11.9, 9.2 Hz, H7a), 1.39-1.44 (1H, m, H2a), 1.51-1.57 (3H, m, H1a, H3a and H7b), 1.63 (1H, ddd, *J* = 16.0, 9.6, 6.4 Hz, H12a), 1.71-1.85 (4H, m, H1b, H6a, H12b and H15a), 1.88 (1H, dd, *J* = 14.2, 7.3 Hz, H15b), 2.01-2.10 (2H, m, H3b and H10), 2.14-2.28 (2H, m, H2b and H6b), 2.50 (1H, dd, *J* = 3.7, 3.7 Hz, H9), 2.59 (1H, ddd, *J* = 7.3, 6.4, 5.0 Hz, H13), 2.82 (1H, dq, *J* = 13.8, 7.4 Hz, NC*H*$_A$H$_B$CH$_3$), 3.00 (1H, d, *J* = 11.9 Hz, H19a), 3.14 (1H, dq, *J* = 13.8, 7.4 Hz, NCH$_A$*H*$_B$CH$_3$), 3.28 (3H, s, OC*H*$_3$), 3.35 (1H, dd, *J* = 11.9, 2.3 Hz, H19b), 3.53 (1H, dd, *J* = 5.0, 3.7 Hz, H14), 3.76 (1H, s, H17), 4.02 (1H, dd, *J* = 7.3, 7.3 Hz, H16), 4.11-4.24 (2H, m, OCH_2CH_3), 4.52 (1H, d, *J* = 12.4 Hz, OCH_AH_BPh), 4.57 (1H, d, *J* = 12.4 Hz, OCH_AH_BPh), 4.86 (1H, s, O*H*), 7.26-7.29 (1H, m, aromatic), 7.34-7.35 (4H, m, aromatic); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 14.5, 19.3, 26.0, 26.6, 33.4, 33.7, 33.8, 37.1, 37.3, 42.4, 46.7, 49.2, 49.4, 50.5, 51.8, 52.4, 57.2, 60.8, 68.9, 70.3, 74.5, 78.2, 84.5, 126.9 (x2), 127.1, 128.2 (x2), 139.3, 178.7; HRMS (ESI) calcd for $C_{31}H_{43}NO_5Na$ 532.3033 $[M+Na]^+$, found 532.3028.

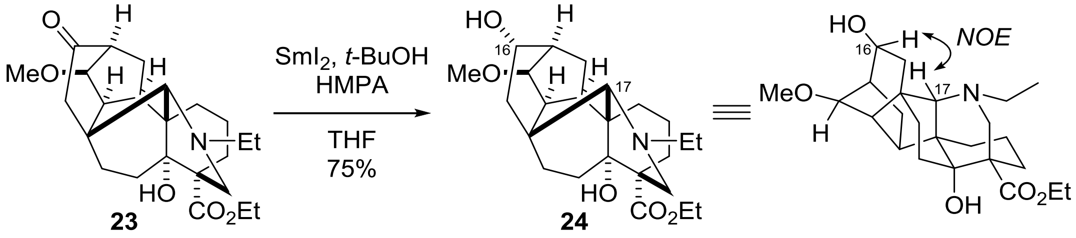


Diol 22. A suspension of **21** (67.3 mg, 0.132 mmol) and Pd/C (10 wt% Pd on carbon, 21.5 mg) in MeOH (5.0 mL) and aqueous 1.0 M HCl (ca. 20 μL) was exposed to H_2 atmosphere (1 atm) at room temperature. The reaction mixture was stirred at room temperature for 2 h, and then aqueous 1.0 M HCl (ca. 20 μL) was added. The reaction mixture was stirred for further 4 h under H_2 atmosphere (1 atm), and was filtered through a pad of Celite with EtOAc (10 mL) and MeOH (10 mL). The filtrate was cooled to 0 °C, and then saturated aqueous $NaHCO_3$ (4 mL) was added. The resultant mixture was extracted with EtOAc (7 mL x3), and the combined organic layers were washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography on silica gel (2.5 g, hexane/EtOAc 3/1 to 2/1) to afford **22** (53.0 mg, 0.126 mmol) in 95% yield: white solid; m.p. 69.0-71.0 °C; IR (film) ν 3471, 2932, 2861, 1697, 1459, 1377, 1259, 1206, 1118, 1073, 735 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10 (3H, dd, *J* = 7.3, 7.3 Hz, NCH_2CH_3), 1.28 (3H, dd, *J* = 7.3, 7.3 Hz, OCH_2CH_3), 1.34 (1H, dd, *J* = 11.9, 8.2 Hz, H7a), 1.39-1.45 (1H, m, H2a), 1.50-1.65 (4H, m, H1a, H3a, H7b and H12a), 1.56 (1H, d, *J* = 14.2 Hz, H15a), 1.70-1.79 (2H, m, H6a and H12b), 1.82 (1H, ddd, *J* = 10.0, 10.0, 5.5 Hz, H1b), 1.95 (1H, dd, *J* = 14.2, 7.3 Hz, H15b), 2.02-2.10 (2H, m, H3b and H10), 2.15-2.28 (2H, m, H2b and H6b), 2.45-2.50 (2H, m, H9 and H13), 2.85 (1H, dq, *J* = 14.2, 7.3 Hz, $NCH_AH_BCH_3$), 3.01 (1H, d, *J* = 11.9 Hz, H19a), 3.12 (1H, dq, *J* = 14.2, 7.3 Hz, $NCH_AH_BCH_3$), 3.30 (3H, s, OCH_3), 3.33 (1H, dd, *J* = 11.9, 1.8 Hz, H19b), 3.52 (1H, dd, *J* = 4.6, 4.6 Hz, H14), 3.64 (1H, s, H17), 4.09-4.24 (2H, m, OCH_2CH_3), 4.40 (1H, dd, *J* = 7.3, 7.3 Hz, H16), 4.86 (1H, s, O*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 14.6, 19.3,

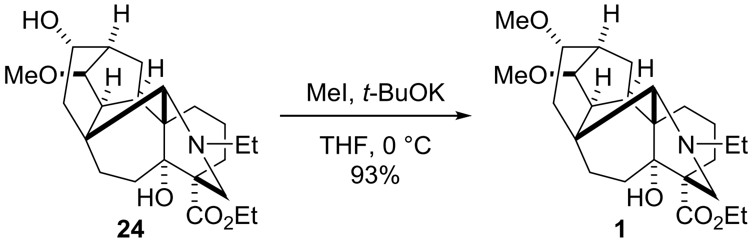
25.5, 26.6, 33.7, 33.8, 36.4, 37.1, 39.6, 42.1, 46.6, 49.2, 49.5, 50.8, 51.8, 52.3, 57.2, 60.8, 69.0, 70.9, 74.5, 84.7, 178.7; HRMS (ESI) calcd for $C_{24}H_{37}NO_5Na$ 442.2564 $[M+Na]^+$, found 442.2559.



Ketone 23. 2,2'-Bipyridine (3.5 mg, 22 μmol), DMAP (5.4 mg, 44 μmol), AZADO (3.4 mg, 22 μmol) and CuCl (2.2 mg, 22 μmol) were successively added to a solution of diol **22** (61.5 mg, 0.147 mmol) in CH_3CN (2.0 mL) at room temperature. The reaction mixture was stirred at room temperature for 45 min under air. After the mixture was cooled to 0 °C, saturated aqueous $NaHCO_3$ (2 mL) and saturated aqueous $Na_2S_2O_3$ (2 mL) were successively added. The resultant mixture was extracted with EtOAc (3 mL x3), and the combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography on silica gel (2.5 g, hexane/EtOAc 5/1) to afford a mixture of **23** and 2,2'-bipyridine. The mixture was further purified by flash column chromatography on silica gel (2 g, CH_2Cl_2/EtOAc 9/1) to afford ketone **23** (50.1 mg, 0.120 mmol) in 82% yield: white solid; m.p. 122-123 °C; IR (film) ν 3476, 2933, 2864, 1707, 1459, 1377, 1297, 1260, 1170, 1104, 1020 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.06 (3H, dd, J = 7.3, 7.3 Hz, NCH_2CH_3), 1.26 (3H, dd, J = 7.3, 7.3 Hz, OCH_2CH_3), 1.36-1.44 (2H, m), 1.52-1.57 (2H, m), 1.60-1.67 (2H, m), 1.77-1.85 (2H, m), 2.00-2.11 (2H, m), 2.14 (1H, m), 2.21-2.28 (2H, m), 2.27 (1H, d, J = 15.6 Hz, H15a), 2.53 (1H, s, H17), 2.69-2.76 (3H, m, H9, H13 and $NCH_AH_BCH_3$), 2.85 (1H, d, J = 15.6 Hz, H15b), 2.91 (1H, dq, J = 14.7, 7.3 Hz, $NCH_AH_BCH_3$), 3.00 (1H, d, J = 12.4 Hz, H19a), 3.27 (3H, s, OCH_3), 3.30 (1H, dd, J = 12.4, 2.3 Hz, H19b), 3.65 (1H, dd, J = 3.7, 3.7 Hz, H14), 4.16-4.24 (2H, m, OCH_2CH_3), 4.88 (1H, s, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 14.1, 19.0, 26.5, 32.2, 32.7, 33.5, 36.8, 42.5, 46.5, 46.9, 47.2, 48.6, 49.1, 51.3, 51.5, 52.5, 57.2, 61.0, 72.2, 74.6, 83.4, 178.3, 216.4; HRMS (ESI) calcd for $C_{24}H_{35}NO_5Na$ 440.2407 $[M+Na]^+$, found 440.2402.



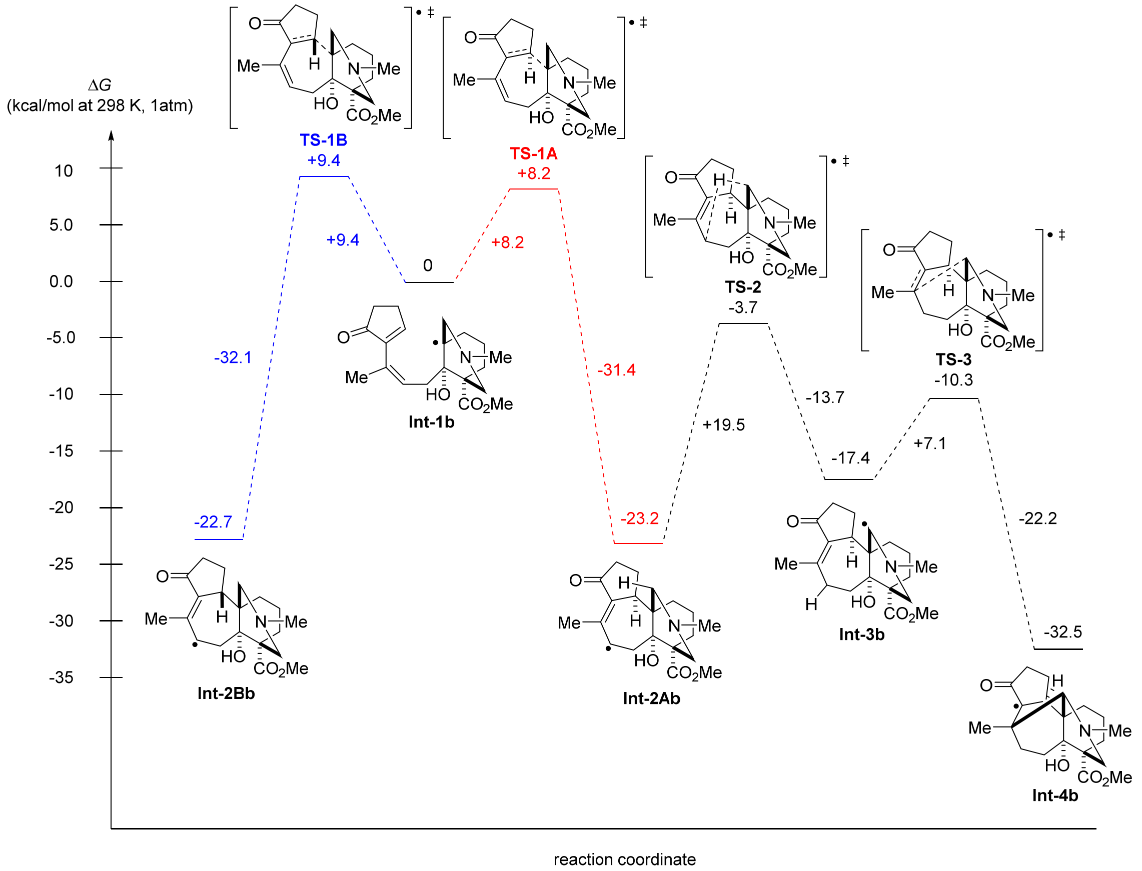
Diol 24. SmI$_2$ (0.10 M in THF, 10 mL, 1.0 mmol), *t*-BuOH (0.39 mL, 4.1 mmol) and HMPA (0.36 mL, 2.0 mmol) were successively added to **23** (42.6 mg, 0.102 mmol) at room temperature. The reaction mixture was stirred at room temperature for 2.5 h. After the mixture was cooled to 0 °C, saturated aqueous NaHCO$_3$ (10 mL) was added. The resultant mixture was extracted with EtOAc (10 mL x3), and the combined organic layers were dried over Na$_2$SO$_4$, filtered and concentrated. The residue was purified by flash column chromatography on silica gel (3 g, hexane/EtOAc 6/1 to 5/1) to afford a 8:1 mixture of **24** and **22**. The mixture was further purified by preparative-TLC (hexane/EtOAc 1/1) to afford **24** (32.1 mg, 76.5 μmol) in 75% yield. The C16-configuration was confirmed by the NOE experiment: colorless oil; IR (film) ν 3476, 2936, 2864, 1698, 1460, 1379, 1254, 1209, 1180, 1115, 1090, 1035 cm^{-1}; ^{1}H NMR (400 MHz, C$_6$D$_6$) δ 0.86 (3H, dd, *J* = 7.3, 7.3 Hz, OCH$_2$C*H*$_3$), 1.00 (3H, dd, *J* = 6.9, 6.9 Hz, NCH$_2$C*H*$_3$), 1.16 (1H, dd, *J* = 15.1, 3.2 Hz, H12a), 1.34-1.44 (3H, m, H1a, H2a and H7a), 1.54-1.65 (3H, m, H3a, H7b and H12b), 1.80 (1H, dd, *J* = 12.8, 7.8 Hz, H15a), 1.92 (1H, dd, *J* = 15.1, 6.9 Hz, H6a), 2.09 (1H, ddd, *J* = 13.3, 13.3, 4.6 Hz, H1b), 2.21-2.30 (5H, m, H2b, H3b, H10, H13 and H15b), 2.41 (1H, ddd, *J* = 15.1, 10.5, 10.5 Hz, H6b), 2.52 (1H, br s, H9), 2.64 (1H, dq, *J* = 13.7, 6.9 Hz, NC*H*$_A$H$_B$CH$_3$), 2.80 (1H, s, H17), 2.86 (1H, dq, *J* = 13.7, 6.9 Hz, NCH$_A$*H*$_B$CH$_3$), 2.98 (3H, s, OC*H*$_3$), 3.11 (1H, d, *J* = 11.9 Hz, H19a), 3.27 (1H, dd, *J* = 3.2, 3.2 Hz, H14), 3.41 (1H, d, *J* = 11.9 Hz, H19b), 3.81 (1H, dq, *J* = 11.0, 7.3 Hz, OC*H*$_A$H$_B$CH$_3$), 3.90 (1H, dq, *J* = 11.0, 7.3 Hz, OCH$_A$*H*$_B$CH$_3$), 4.07 (1H, dd, *J* = 7.8, 7.8 Hz, H16), 5.16 (1H, s, O*H*); ^{13}C NMR (100 MHz, C$_6$D$_6$) δ 13.9, 14.6, 19.8, 26.9, 30.8, 34.2, 34.4, 37.5, 38.4, 43.4, 44.9, 46.6, 49.0, 49.2, 49.5, 52.1, 53.2, 56.8, 60.8, 68.6, 74.5, 75.0, 85.7, 178.6; HRMS (ESI) calcd for C$_{24}$H$_{37}$NO$_5$Na 442.2564 [M+Na]$^+$, found 442.2570.



Compound 1. *t*-BuOK (0.20 M in THF, 0.94 mL, 0.19 mmol) was added to a solution of **24** (26.3 mg, 62.7 μmol) and MeI (39 μL, 0.63 mmol) in THF (0.60 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 50 min, and then aqueous NH_4Cl (2.5 mL) was added. The resultant mixture was extracted with EtOAc (3 mL x3), and the combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography on silica gel (1.5 g, hexane/EtOAc 3/1) to afford **1** (25.2 mg, 58.1 μmol) in 93% yield: colorless oil; IR (film) ν 3476, 2936, 2864, 1697, 1645, 1459, 1376, 1297, 1253, 1209, 1095 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 0.86 (3H, dd, J = 7.3, 7.3 Hz, OCH_2CH_3), 1.03 (3H, dd, J = 7.3, 7.3 Hz, NCH_2CH_3), 1.19 (1H, dd, J = 15.1, 3.2 Hz, H12a), 1.44-1.55 (3H, m, H1a, H2a and H7a), 1.57-1.65 (2H, m, H3a and H7b), 1.66-1.73 (1H, m, H12b), 1.89 (1H, dd, J = 15.1, 6.0 Hz, H6a), 2.06 (1H, dd, J = 12.4, 7.8 Hz, H15a), 2.12-2.21 (1H, m, H1b), 2.26 (1H, ddd, J = 5.0, 5.0, 3.2 Hz, H10), 2.29-2.39 (4H, m, H2b, H3b, H13 and H15b), 2.45 (1H, ddd, J = 15.1, 9.2, 6.0 Hz, H6b), 2.64-2.73 (2H, m, H9 and $NCH_AH_BCH_3$), 2.91 (1H, dq, J = 14.6, 7.3 Hz, $NCH_AH_BCH_3$), 2.92 (1H, s, H17), 3.15 (1H, d, J = 11.9 Hz, H19a), 3.22 (3H, s, OCH_3), 3.29 (3H, s, OCH_3), 3.33 (1H, dd, J = 2.3, 2.3 Hz, H14), 3.42 (1H, dd, J = 11.9, 1.8 Hz, H19b), 3.55 (1H, dd, J = 7.8, 7.8 Hz, H16), 3.81 (1H, dq, J = 11.0, 7.3 Hz, $OCH_AH_BCH_3$), 3.87 (1H, dq, J = 11.0, 7.3 Hz, $OCH_AH_BCH_3$), 5.12 (1H, s, OH); ^{13}C NMR (100 MHz, C_6D_6) δ 13.9, 14.6, 19.9, 27.1, 31.8, 33.3, 34.2, 34.6, 37.7, 38.4, 43.0, 49.0, 49.1, 49.2, 49.7, 52.2, 53.5, 56.3, 56.9, 60.7, 67.9, 75.0, 84.1, 84.7, 178.5; HRMS (ESI) calcd for $C_{25}H_{39}NO_5Na$ 456.2720 $[M+Na]^+$, found 456.2715.

Energy diagram of the radical cascade reaction

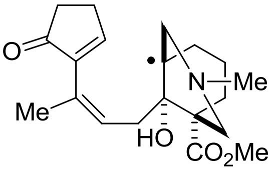
The energy diagram of the radical cascade reaction was created by comparison of the calculated Gibbs free energies of the lowest energy conformers of the radical intermediates (**Int-1b**, **Int-2Ab**, **Int-2Bb**, **Int-3b** and **Int-4b)** and the transition states (**TS-1A**, **TS-1B**, **TS-2** and **TS-3**) at UM06-2X/6-31G(d) level of theory. The relative Gibbs energies (Δ*G*, 298 K, 1 atm), which are computed for the gas phase, is given in kcal/mol. The nature of the stationary points as transition structures was confirmed by the vibration analyses and the intrinsic reaction coordinate (IRC) method at the same level with the optimization. For the global analyses of the conformational isomers of **Int-1b**, **TS-1A**, **TS-1B**, **TS-2** and **TS-3**, the structures were created by the conformational search using molecular mechanics simulations, geometry-optimized using the semiempirical method, and subjected to the DFT calculations. The molecular mechanics simulations were carried out by MacroModel ver. 10.4[S2] and the semiempirical and DFT methods were by Gaussian 09 program.[S3] A part of the computational research was conducted using the HITACHI SR16000 System (yayoi) in the Information Technology Center, The University of Tokyo.



Optimization of the structure of Int-1b

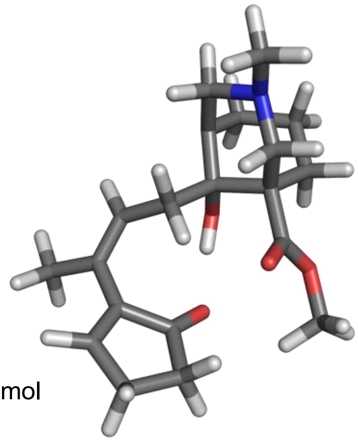
The conformational search of the C11-hydrogenated form of **Int-1b** was first conducted by molecular mechanics simulation instead of radical **Int-1b**. The calculation was performed using a 10000-step of Monte Carlo-based torsional sampling (MCMM) and PRCG energy minimization with MM2* force field (gas phase) to afford 41 conformational isomers within 5.0 kcal/mol. All of the structures were transferred into Gaussian program and changed into the corresponding C11-radical species. Then the geometry optimizations and frequency calculations of the 41 structures were performed at UPM6 semiempirical method (298 K, 1 atm, gas phase) to afford 31 conformational isomers, each of which has no imaginary frequencies. The geometry optimizations and frequency calculations of the 31 structures were performed at UM06-2X/6-31G(d) level of theory (298 K, 1 atm, gas phase) to afford 28 conformational isomers, each of which has no imaginary frequencies, as the optimized structures of **Int-1b**. Among them, the lowest energy structure was defined as **Int-1b**.

Energy, structure and Cartesian coordinate of **Int-1b**:



Int-1b

Gibbs free energy (298 K) = -711388.8856 kcal/mol



C	-3.648749	0.241149	-1.475777
C	-3.043097	-1.162938	-1.728924
C	-2.145354	-1.489257	-0.574587
C	-0.935661	-0.591376	-0.489755
C	-1.574184	0.769104	0.030772
C	-2.579147	1.256696	-1.043055
H	-4.419898	0.158585	-0.707443
H	-4.127013	0.606859	-2.391993
H	-2.463705	-1.155925	-2.655787
H	-3.846284	-1.902233	-1.826102
C	-2.818895	-1.760411	0.740942
C	0.160519	-1.145146	0.452038
O	-0.421899	-0.404871	-1.787627
C	-2.211910	0.511977	1.411334
C	-0.469275	1.805130	0.239311
H	-1.992274	1.535796	-1.919166

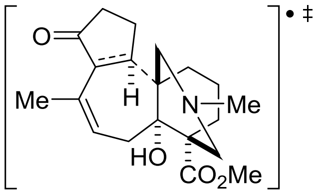
H	-3.063761	2.170971	-0.678287
N	-3.257573	-0.501909	1.366526
O	0.243540	1.859965	1.221800
O	-0.349432	2.663824	-0.777370
C	0.674274	3.647166	-0.639703
C	1.029923	-2.145915	-0.248635
C	2.362421	-2.075326	-0.348230
C	3.102919	-0.904582	0.176198
C	4.148110	-0.875666	1.019689
C	4.667590	0.508473	1.313779
C	3.702692	1.429777	0.555308
C	2.827359	0.493903	-0.258821
O	2.040251	0.847365	-1.116643
C	3.189015	-3.153086	-1.001014
C	-3.802900	-0.742157	2.685771
H	-2.162407	-2.330779	1.425783
H	-3.714205	-2.374684	0.581214
H	-0.304490	-1.628932	1.316887
H	0.757580	-0.329763	0.863610
H	0.473958	-0.025275	-1.709796
H	-2.668045	1.443724	1.771758
H	-1.413700	0.256640	2.131972
H	0.526436	4.341212	-1.466150
H	0.580300	4.160803	0.319505
H	1.651784	3.167874	-0.712498
H	0.517833	-3.001857	-0.688996
H	4.592550	-1.758803	1.471674
H	5.700676	0.614344	0.962271
H	4.682765	0.701276	2.391454
H	4.192032	2.158639	-0.095601
H	3.030003	1.977883	1.226297
H	3.760805	-2.751921	-1.845114
H	3.913723	-3.576351	-0.295030
H	2.555328	-3.965245	-1.365721
H	-4.200644	0.190037	3.098801
H	-4.621377	-1.465771	2.617767
H	-3.048551	-1.139094	3.391885

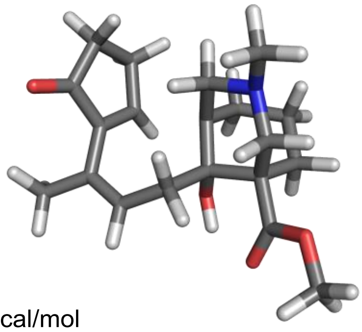
Optimization of the structures of TS-1A and TS-1B

The conformational search of the C11-anion species of **Int-1b** was first conducted by molecular mechanics simulation instead of radical **Int-1b**. The C10-11 distance was constrained as 2.1 Å (force constant: 119.5 kcal/mol・Å^2), and the calculation was performed using a 10000-step of MCMM and PRCG energy minimization with MM2* force field (gas phase) to afford 51 conformational isomers having ca. 2.3 Å of the C10-11 distance within 119.5 kcal/mol. All of the structures were transferred into Gaussian program and changed into the corresponding C11-radical species. Then, the geometry optimizations and frequency calculations of the 51 structures were performed at UPM6 semiempirical method (298 K, 1 atm, gas phase) to afford 22 conformational isomers, each of which has a single imaginary frequency. To reduce the number of the structures for the next DFT calculation, the rotational isomers of the two bonds of the

O-H and C5-18 were not taken into account as conformational isomers. Therefore, the lowest energy 12 structures, which have the different geometries except for the above two bonds, were selected from the 22 structures for the DFT calculations. The geometry optimizations and frequency calculations of the 12 structures were performed at UM06-2X/6-31G(d) level of theory (298 K, 1 atm, gas phase) to afford 7 conformational isomers, each of which has a single imaginary frequency, as the optimized structures of **TS-1A** and 5 conformational isomers, each of which has a single imaginary frequency, as the optimized structures of **TS-1B**. Among them, each of the lowest energy structures was defined as **TS-1A** or **TS-1B**. The IRC method at the same level of theory confirmed the built structure of **TS-1A** and **TS-1B** as the transition states.

Energy, structure and Cartesian coordinate of **TS-1A**:





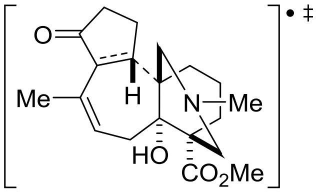
TS-1A

Gibbs free energy (298 K) = -711380.6596 kcal/mol

C	-1.593313	-2.097291	-1.854678
C	-0.114136	-1.651848	-1.913773
C	0.242259	-0.915369	-0.650665
C	-0.538307	0.371374	-0.482817
C	-1.984893	-0.172141	-0.158574
C	-2.514461	-0.963218	-1.387882
H	-1.683434	-2.941681	-1.169873
H	-1.916018	-2.431190	-2.847310
H	0.031301	-0.992843	-2.774886
H	0.525622	-2.532792	-2.042748
C	0.335893	-1.745016	0.598401
C	-0.039336	1.300426	0.661745
O	-0.530878	1.044621	-1.722295
C	-1.939861	-1.012806	1.132489
C	-2.942712	0.999378	0.003571
H	-2.642847	-0.242667	-2.202148
H	-3.506138	-1.363030	-1.142939
N	-1.009691	-2.132053	1.044456
C	-0.956549	-2.861381	2.295567
C	1.018641	2.321558	0.312948
C	2.301512	2.056141	0.052017
C	2.770072	0.667182	-0.106094
C	2.421169	-0.184003	-1.112450
C	3.222051	-1.471349	-1.067800

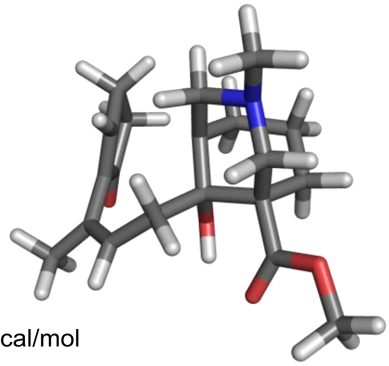
C	3.918991	-1.429446	0.300593
C	3.748447	0.013983	0.785122
O	4.324489	0.517375	1.728478
O	-2.847737	2.052618	-0.593396
O	-3.954281	0.743257	0.839035
C	-4.914703	1.794280	0.977499
C	3.350609	3.126118	-0.096030
H	0.890049	-1.210604	1.393397
H	0.889219	-2.671250	0.392379
H	0.324645	0.690012	1.493504
H	-0.901383	1.849329	1.056097
H	-1.153250	1.787483	-1.632704
H	-2.936901	-1.422477	1.325557
H	-1.703037	-0.349589	1.987787
H	-0.567182	-2.246960	3.128734
H	-1.958887	-3.208759	2.563994
H	-0.308209	-3.735726	2.182374
H	0.715083	3.365981	0.367536
H	1.901172	0.150834	-2.005609
H	3.952492	-1.467188	-1.885779
H	2.602710	-2.362014	-1.210368
H	4.977845	-1.697073	0.272926
H	3.434444	-2.092645	1.026623
H	-4.432084	2.699522	1.351102
H	-5.379085	2.009506	0.013154
H	-5.651556	1.426554	1.689179
H	2.925561	4.122295	0.052612
H	4.141308	2.962871	0.644244
H	3.815399	3.086066	-1.087725

Energy, structure and Cartesian coordinate of **TS-1B**:



TS-1B

Gibbs free energy (298 K)= -711379.5301 kcal/mol



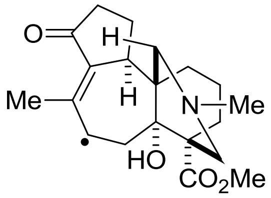
C	-1.111010	1.796264	2.031565
C	0.312024	1.706692	1.424222
C	0.216864	1.181656	0.019409
C	-0.317842	-0.232524	-0.021203
C	-1.844316	-0.019350	0.306344
C	-1.960372	0.545394	1.752094
H	-1.613242	2.670570	1.615362
H	-1.036617	1.936012	3.115968
H	0.927198	1.029440	2.023020
H	0.770058	2.702871	1.444224
C	-0.395430	2.110397	-0.995308
C	-0.121294	-0.952145	-1.392423
O	0.286570	-0.948224	1.030815

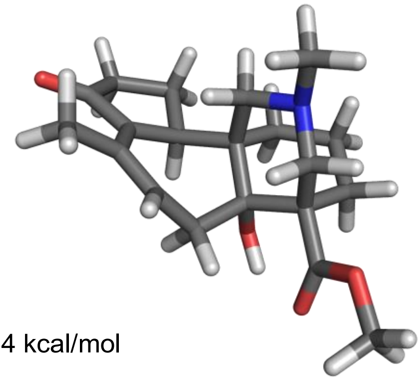
C	-2.485309	0.897790	-0.750649
C	-2.555695	-1.364564	0.343259
H	-1.651113	-0.254036	2.432634
H	-3.015972	0.761300	1.954847
N	-1.847894	2.205718	-0.800831
C	-2.453993	3.039859	-1.819179
C	1.072827	-1.873210	-1.485768
C	2.323313	-1.658744	-1.050744
C	2.743872	-0.380639	-0.459890
C	2.400893	0.866366	-0.889278
C	3.169423	1.960752	-0.180678
C	3.806349	1.240076	1.014412
C	3.642340	-0.253237	0.712117
O	4.175460	-1.148288	1.334301
O	-2.015824	-2.433287	0.536596
O	-3.882420	-1.250883	0.199191
C	-4.613960	-2.473833	0.312794
C	3.378808	-2.732349	-1.147889
H	-0.168662	1.790533	-2.031540
H	0.025533	3.117728	-0.877302
H	-0.090268	-0.207619	-2.196392
H	-1.008126	-1.558079	-1.603560
H	-0.066539	-1.852538	0.986168
H	-3.541956	1.045359	-0.506210
H	-2.455072	0.392285	-1.738494
H	-3.524766	3.146760	-1.621391
H	-1.998806	4.034762	-1.797300
H	-2.328509	2.623555	-2.836663
H	0.869457	-2.842211	-1.939129
H	1.909932	1.047390	-1.841391
H	2.535371	2.805068	0.106280
H	3.933464	2.358111	-0.860005
H	3.282637	1.459617	1.950638
H	4.862368	1.474506	1.168590
H	-4.278958	-3.186261	-0.443666
H	-4.466235	-2.911115	1.302304
H	-5.658421	-2.208327	0.158938
H	4.248362	-2.374597	-1.711106
H	3.735356	-3.001590	-0.150408
H	2.983544	-3.621980	-1.645065

Optimization of the structure of Int-2Ab

The geometry optimization and frequency calculation were performed at UM06-2X/6-31G(d) level of theory (298 K, 1 atm, gas phase) for the terminal structure of the IRC calculation of **TS-2** to afford **Int-2Ab** having no imaginary frequencies.

Energy, structure and Cartesian coordinate of **Int-2Ab**:





Int-2Ab
Gibbs free energy (298 K) = -711412.0564 kcal/mol

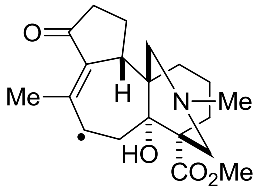
C	1.328953	2.794462	0.129740
C	-0.078991	2.424399	-0.364005
C	-0.466158	0.948255	-0.105913
C	0.617357	0.079282	-0.802867
C	1.943260	0.266478	-0.009471
C	2.407042	1.742758	-0.176146
H	1.297713	2.962946	1.205729
H	1.629439	3.738550	-0.339579
H	-0.162122	2.614193	-1.437654
H	-0.801139	3.076358	0.139405
C	-1.843577	0.650927	-0.769427
C	-0.527935	0.698792	1.419236
C	0.201991	-1.412726	-1.004852
O	0.778746	0.616465	-2.108960
C	1.736299	-0.117387	1.458354
C	3.048763	-0.563814	-0.644834
H	2.740521	1.859046	-1.211224
H	3.278935	1.905853	0.469276
N	0.771697	0.767287	2.081161
C	0.633211	0.473785	3.493506
C	-2.051010	-1.822832	0.117838
C	-2.590768	-0.593792	-0.317062
C	-2.898797	1.771061	-0.575208
C	-4.239266	1.098811	-0.857254
C	-4.035677	-0.321160	-0.345921
H	-1.639574	0.582223	-1.851244
O	-4.936205	-1.088575	-0.044657
O	3.156288	-0.766770	-1.838668
O	3.950523	-1.012830	0.232246
C	5.049557	-1.731341	-0.334255
H	-1.005354	-0.264096	1.646250
H	-1.164711	1.477758	1.860930
H	1.106941	-2.013104	-1.139855
H	-0.293676	-1.403296	-1.984037

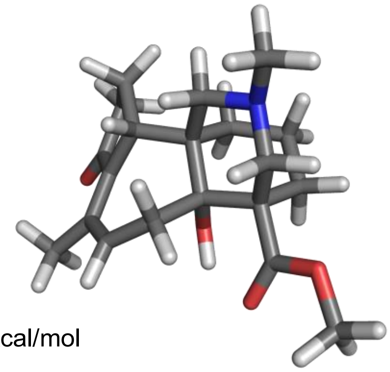
H	1.531503	0.140271	-2.502747
H	2.685319	-0.028054	1.995474
H	1.426806	-1.183065	1.524411
H	1.603826	0.574014	3.988458
H	-0.061996	1.185055	3.949608
H	0.250658	-0.547977	3.678187
C	-2.924864	-2.825408	0.840232
H	-2.702089	2.632952	-1.216117
H	-2.878922	2.117742	0.465487
H	-4.436180	1.048778	-1.936481
H	-5.103034	1.566930	-0.380598
H	5.677302	-2.018268	0.507282
H	4.689268	-2.612741	-0.868439
H	5.598558	-1.093337	-1.029653
H	-3.487862	-2.358319	1.651575
H	-3.667050	-3.254011	0.162655
H	-2.308035	-3.631604	1.246506
C	-0.718487	-2.125394	-0.063284
H	-0.347156	-3.043062	0.388146

Optimization of the structure of Int-2Bb

The geometry optimization and frequency calculation were performed at UM06-2X/6-31G(d) level of theory (298 K, 1 atm, gas phase) for the terminal structure of the IRC calculation of **TS-1B** to afford **Int-2Bb** having no imaginary frequencies.

Energy, structure and Cartesian coordinate of **Int-2Bb**:





Int-2Bb

Gibbs free energy (298 K) = -711411.6096 kcal/mol

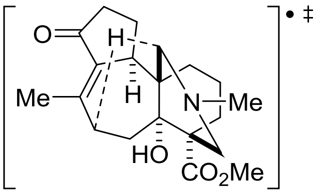
C	-0.926753	1.698422	2.028340
C	0.471657	1.511249	1.416469
C	0.435463	1.015290	-0.042302
C	-0.335787	-0.331608	-0.045202
C	-1.826705	-0.003956	0.273040
C	-1.903558	0.549799	1.727266
H	-1.354404	2.631638	1.661853
H	-0.827051	1.788053	3.116185
H	1.039492	0.782878	2.002413
H	1.004279	2.467071	1.470945
C	-0.264572	2.035360	-0.969302
C	-0.152369	-1.085744	-1.397383
O	0.178672	-1.101794	1.023459
C	-2.407411	0.985578	-0.743487
C	-2.643239	-1.288307	0.295891

H	-1.692790	-0.284436	2.402445
H	-2.932839	0.876401	1.917141
N	-1.677936	2.238920	-0.701018
C	-2.242460	3.202617	-1.624418
C	1.072024	-1.964147	-1.445076
C	2.288363	-1.721572	-0.875274
C	2.591472	-0.451024	-0.305312
C	1.861168	0.817564	-0.655976
C	2.889470	1.929404	-0.303091
C	3.761010	1.348568	0.814256
C	3.740240	-0.156241	0.546213
O	4.555287	-0.955378	0.984924
O	-2.195288	-2.398226	0.500992
O	-3.953259	-1.072783	0.130714
C	-4.780571	-2.233780	0.239834
C	3.323132	-2.822197	-0.828029
H	-0.124684	1.726350	-2.025901
H	0.244462	3.002823	-0.863918
H	-0.146711	-0.363742	-2.225230
H	-1.020108	-1.727815	-1.580115
H	-0.295172	-1.951484	0.998674
H	-3.455431	1.184229	-0.500739
H	-2.391356	0.536629	-1.760011
H	-3.297944	3.366066	-1.387896
H	-1.715794	4.156946	-1.529475
H	-2.169359	2.870281	-2.677569
H	0.927415	-2.939184	-1.906512
H	1.710716	0.808915	-1.743737
H	2.419565	2.880153	-0.038343
H	3.512026	2.115722	-1.184179
H	3.332835	1.534448	1.806621
H	4.788548	1.719470	0.822956
H	-4.507602	-2.965293	-0.523451
H	-4.663856	-2.688349	1.225510
H	-5.800390	-1.882861	0.092586
H	4.289818	-2.481203	-1.207631
H	3.495032	-3.141837	0.202739
H	2.990110	-3.680516	-1.417686

Optimization of the structure of TS-2

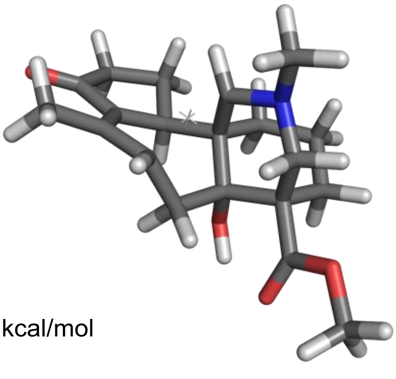
The conformational search of the C7-anion species of **Int-2Ab** was first conducted by molecular mechanics simulation instead of radical **Int-2Ab**. The C7-H17 distance was constrained as 0.1 Å (force constant: 239 kcal/mol・Å^2), and the calculation was performed using a 10000-step of MCMM and PRCG energy minimization with OPLS_2005 force field (gas phase) to afford 22 conformational isomers having ca. 1.8 Å of the C7-H17 distance within 119.5 kcal/mol. All of the structures were transferred into Gaussian program and changed into the corresponding C7-radical species. The C7-H17 distance of each of the 22 structures was set as 1.45 Å, and then the geometry optimizations and frequency calculations were performed at UPM6 semiempirical method (298 K, 1 atm, gas phase) to afford 10 conformational isomers, each of which has a single imaginary frequency. The geometry optimizations and frequency calculations of the 10 structures were performed at UM06-2X/6-31G(d) level of theory (298 K, 1 atm, gas phase) to afford 8 conformational isomers, each of which has a single imaginary frequency, as the optimized structures of **TS-2**. Among them, the lowest energy structure was defined as **TS-2**. The IRC method at the same level of theory confirmed the built structure of **TS-2** as the transition state.

Energy, structure and Cartesian coordinate of **TS-2**:



TS-2

Gibbs free energy (298 K) = -711392.5409 kcal/mol



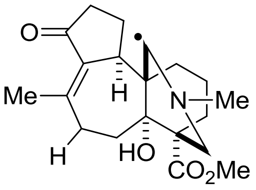
C	1.391635	2.757130	0.158752
C	-0.040718	2.403405	-0.253782
C	-0.443447	0.920050	-0.041474
C	0.597067	0.019676	-0.759052
C	1.979839	0.276842	-0.078419
C	2.415911	1.740062	-0.346419
H	1.456879	2.830652	1.246057
H	1.644301	3.743425	-0.247307
H	-0.176987	2.620336	-1.319891
H	-0.733784	3.043673	0.301422
C	-1.848406	0.696410	-0.679851
C	-0.415997	0.520370	1.425807
C	0.163465	-1.476315	-0.701519
O	0.652526	0.439018	-2.108980
C	1.913940	-0.037104	1.424493
C	3.045262	-0.584106	-0.740752
H	2.542946	1.852937	-1.427445
H	3.392001	1.911187	0.123606
N	0.823254	0.662205	2.090909
C	0.764836	0.327051	3.501442
C	-2.206951	-1.715973	0.221150
C	-2.658559	-0.540612	-0.291057
C	-2.865991	1.835364	-0.419415
C	-4.210661	1.243093	-0.840480
C	-4.093089	-0.229989	-0.463859
H	-1.668080	0.676788	-1.765584
O	-5.035021	-0.989806	-0.333313
O	3.025750	-0.942277	-1.900719
O	4.068882	-0.865480	0.072738
C	5.135645	-1.609430	-0.522320
H	-0.601859	-0.851362	1.278333
H	-1.259168	0.877169	2.022743

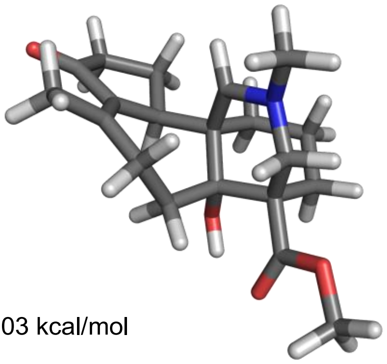
H	1.050619	-2.119275	-0.687527
H	-0.342103	-1.664643	-1.655087
H	1.349830	-0.094232	-2.528989
H	2.856064	0.249146	1.902016
H	1.799748	-1.130747	1.565516
H	1.723469	0.560136	3.973278
H	-0.015886	0.918333	3.986420
H	0.545590	-0.743454	3.660082
C	-3.133790	-2.808384	0.691644
H	-2.617100	2.749977	-0.961804
H	-2.886831	2.075028	0.652380
H	-4.337877	1.304697	-1.929769
H	-5.088031	1.698717	-0.376178
H	5.873489	-1.748178	0.265686
H	4.768147	-2.571444	-0.884469
H	5.561558	-1.053314	-1.359806
H	-3.950126	-2.415790	1.301765
H	-3.610873	-3.300664	-0.161904
H	-2.577709	-3.559560	1.258945
C	-0.768837	-1.876074	0.438765
H	-0.485008	-2.795423	0.951414

Optimization of the structure of Int-3b

The geometry optimization and frequency calculation were performed at UM06-2X/6-31G(d) level of theory (298 K, 1 atm, gas phase) for the terminal structure of the IRC calculation of **TS-3** to afford **Int-3b** having no imaginary frequencies.

Energy, structure and Cartesian coordinate of **Int-3b**:





Int-3b

Gibbs free energy (298 K) = -711406.3203 kcal/mol

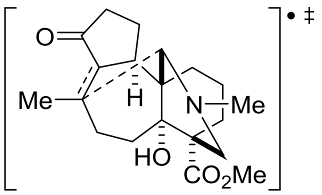
C	1.331279	2.710243	0.624034
C	-0.046423	2.466946	0.003893
C	-0.457074	0.965760	0.025350
C	0.613951	0.176243	-0.774817
C	1.955205	0.286815	0.019023
C	2.401424	1.773901	0.059241
H	1.271232	2.584194	1.707996
H	1.637693	3.745935	0.437942
H	-0.061742	2.818948	-1.033684
H	-0.787548	3.044761	0.564790
C	-1.835307	0.792816	-0.668361
C	-0.511355	0.453779	1.438581
C	0.193661	-1.281753	-1.083442

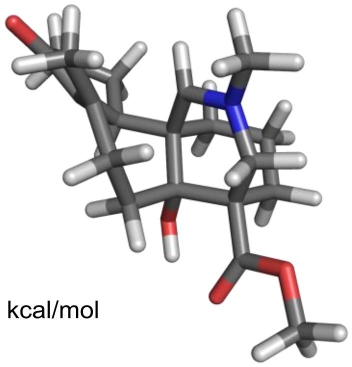
O	0.759306	0.844425	-2.020235
C	1.805958	-0.314152	1.422545
C	3.071973	-0.426240	-0.730485
H	2.636671	2.072008	-0.967058
H	3.324996	1.846690	0.646711
N	0.673445	0.239804	2.144543
C	0.523634	-0.330655	3.467516
C	-2.128698	-1.713656	-0.042375
C	-2.599488	-0.492537	-0.360585
C	-2.868860	1.890500	-0.309763
C	-4.215775	1.298533	-0.714569
C	-4.059531	-0.186765	-0.418062
O	-4.981994	-0.965651	-0.288717
H	-1.650208	0.867460	-1.750310
C	-3.026487	-2.846160	0.393270
O	3.143243	-0.531463	-1.938227
O	4.037016	-0.878260	0.077909
C	5.157842	-1.473986	-0.581185
H	1.095401	-1.862824	-1.311385
H	-0.363619	-1.223327	-2.025343
H	1.486549	0.395473	-2.486075
H	2.712771	-0.113652	2.003103
H	1.722816	-1.414015	1.342443
H	1.464599	-0.233560	4.017053
H	-0.255620	0.209694	4.010715
H	0.246773	-1.397719	3.429924
H	-2.651141	2.838785	-0.805863
H	-2.859128	2.070859	0.772930
H	-4.381196	1.406822	-1.795069
H	-5.085737	1.712707	-0.200474
H	-3.835945	-2.509715	1.040348
H	-3.502702	-3.316085	-0.475287
H	-2.436002	-3.609776	0.909304
H	5.841159	-1.771378	0.212214
H	4.837651	-2.340717	-1.162726
H	5.629045	-0.751140	-1.250045
H	-1.349020	0.756994	2.062378
C	-0.667366	-2.087982	-0.107582
H	-0.628301	-3.134982	-0.439504
H	-0.265521	-2.093387	0.913966

Optimization of the structure of TS-3

The conformational search of the C17-anion species of **Int-3b** was first conducted by molecular mechanics simulation instead of radical **Int-3b**. The C8-17 distance was constrained as 0.5 Å (force constant: 239 kcal/mol･Å^2), and the calculation was performed using a 10000-step of MCMM and PRCG energy minimization with OPLS_2005 force field (gas phase) to afford 52 conformational isomers having ca. 2.2 Å of the C8-17 distance within 29 kcal/mol. All of the structures were transferred into Gaussian program and changed into the corresponding C17-radical species. Then the geometry optimizations and frequency calculations of the 52 structures were performed at UPM6 semiempirical method (298 K, 1 atm, gas phase) to afford 17 conformational isomers, each of which has a single imaginary frequency. The geometry optimizations and frequency calculations of the 17 structures were performed at UM06-2X/6-31G(d) level of theory (298 K, 1 atm, gas phase) to afford 7 conformational isomers, each of which has a single imaginary frequency, as the optimized structures of **TS-3**. Among them, the lowest energy structure was defined as **TS-3**. The IRC method at the same level of theory confirmed the built structure of **TS-3** as the transition state.

Energy, structure and Cartesian coordinate of **TS-3**:





TS-3

Gibbs free energy (298 K) = -711399.1956 kcal/mol

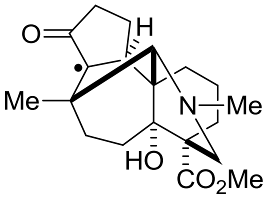
C	1.147177	1.990951	1.924904
C	-0.160973	2.141290	1.145559
C	-0.519240	0.881706	0.318476
C	0.645794	0.587785	-0.662047
C	1.911684	0.271484	0.194740
C	2.291227	1.526044	1.024371
H	1.010447	1.278359	2.745189
H	1.418308	2.950014	2.379888
H	-0.087163	2.988196	0.453604
H	-0.971725	2.357487	1.847552
C	-1.827780	1.092308	-0.502403
C	-0.713411	-0.327088	1.203970
C	0.275092	-0.528162	-1.662278
O	0.866478	1.780621	-1.395345
C	1.682199	-0.954308	1.093154
C	3.112767	0.020852	-0.705744
H	2.547898	2.324401	0.321395
H	3.185686	1.298705	1.616937
N	0.386305	-0.950273	1.753588
C	0.154741	-2.110412	2.588840
C	-1.869202	-1.439260	-0.537510
C	-2.532234	-0.239934	-0.667218
C	-2.918044	1.958418	0.178897
C	-4.231633	1.445401	-0.411911
C	-3.976466	-0.057317	-0.539906
O	-4.848174	-0.915108	-0.554117
H	-1.550556	1.579400	-1.446621
C	-2.620453	-2.694302	-0.163127
O	3.278305	0.514231	-1.802148
O	4.033715	-0.760984	-0.130621
C	5.226046	-0.965248	-0.894372
H	1.185373	-0.877600	-2.164416

H	-0.325466	-0.038729	-2.436351
H	1.634581	1.610432	-1.968254
H	2.456824	-0.982608	1.870017
H	1.809608	-1.877185	0.505898
H	0.985372	-2.232204	3.291192
H	-0.769429	-1.972304	3.154544
H	0.064062	-3.031519	1.992465
H	-2.751601	3.029744	0.034489
H	-2.925864	1.764191	1.258495
H	-4.402399	1.862502	-1.413199
H	-5.118953	1.644511	0.193024
H	-3.388926	-2.503531	0.586606
H	-3.136196	-3.106472	-1.038904
H	-1.923522	-3.455170	0.205436
H	5.860696	-1.604013	-0.282979
H	4.987775	-1.449061	-1.843599
H	5.713309	-0.008905	-1.093494
H	-1.578901	-0.321288	1.865862
C	-0.515764	-1.731909	-1.153775
H	-0.711449	-2.380788	-2.023240
H	0.066324	-2.354531	-0.464526

Optimization of the structure of Int-4b

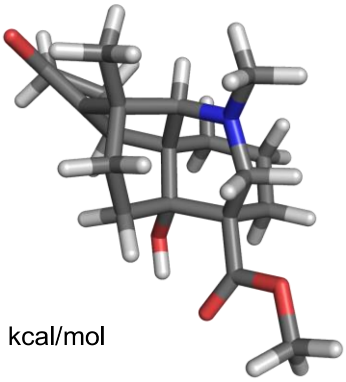
The geometry optimization and frequency calculation were performed at UM06-2X/6-31G(d) level of theory (298 K, 1 atm, gas phase) for the terminal structure of the IRC calculation of **TS-3** to afford **Int-4b** having no imaginary frequencies.

Energy, structure and Cartesian coordinate of **Int-4b**:



Int-4b

Gibbs free energy (298 K) = -711421.4352 kcal/mol



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C	0.212574	-1.733495	1.652124
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C	-0.614169	-0.744815	-0.532256
C	-1.870957	-0.228351	0.227334
C	-2.236195	-1.214035	1.367248
H	-0.973359	-0.482742	2.958362
H	-1.354155	-2.202293	3.062532
H	0.149400	-2.748625	1.242266
H	1.038155	-1.725397	2.373138
C	1.846496	-1.207972	-0.250180

C	0.836629	0.676807	0.896058
C	-0.245226	0.129195	-1.760479
O	-0.820954	-2.077056	-0.966904
C	-1.626580	1.195051	0.755478
C	-3.081717	-0.231841	-0.693661
H	-2.473584	-2.180618	0.909590
H	-3.140138	-0.849831	1.869463
N	-0.341397	1.345398	1.411657
C	-0.160561	2.675741	1.947636
C	1.580423	1.258580	-0.370259
C	2.472694	0.092609	-0.650979
C	3.008518	-1.898567	0.505901
C	4.244898	-1.472340	-0.305231
C	3.914965	-0.030011	-0.717393
O	4.727223	0.836944	-1.013585
H	1.585920	-1.843411	-1.109187
C	2.346851	2.556436	-0.132181
O	-3.233603	-0.961824	-1.652562
O	-4.030404	0.622242	-0.295055
C	-5.235375	0.601800	-1.064631
H	-1.149536	0.344911	-2.340985
H	0.369492	-0.514967	-2.397495
H	-1.605237	-2.056070	-1.543215
H	-2.404193	1.432276	1.494141
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H	-5.883592	1.352852	-0.616836
H	-5.022029	0.844247	-2.107403
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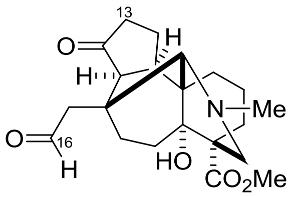
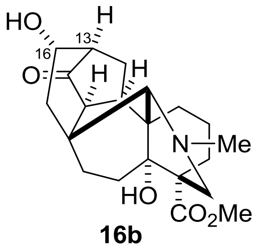
H	1.572577	0.674117	1.716758
C	0.532506	1.425227	-1.485502
H	1.032867	1.743227	-2.407730
H	-0.131390	2.247586	-1.197822

The thermal stability of aldehyde 15b and aldol 16b

The thermal stability of aldehyde **15b** and aldol **16b** was evaluated by comparison of the calculated Gibbs free energies of the lowest energy conformers of aldehyde **15b** and aldol **16b** at M06-2X/6-31G(d) level of theory. For the global analyses of the conformational isomers of aldehyde **15b** and aldol **16b**, the structures were created by the conformational search using molecular mechanics simulations, geometry- optimized using the semiempirical method, and subjected to the DFT calculations. The relative Gibbs energies (Δ*G*, 298 K, 1 atm), which are computed for the gas phase, are given.



15b
0 kcal/mol

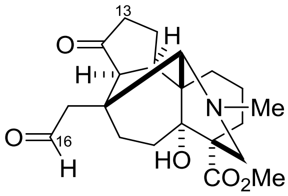


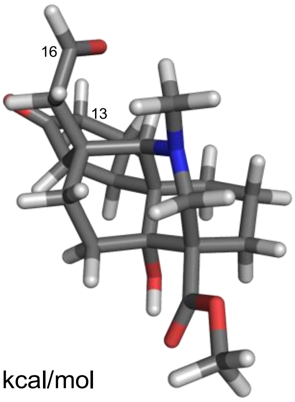
16b
+17.6 kcal/mol

Optimization of the structures of 15b and 16b

The conformational search of **15b** was first performed by molecular mechanics simulation using a 10000-step of MCMM and PRCG energy minimization with MM2* force field (gas phase) to afford 22 conformational isomers whthin 5.3 kcal/mol. All of the structures were transferred into Gaussian program. Then the geometry optimizations and frequency calculations of the 22 structures were performed at PM6 semiempirical method (298 K, 1 atm, gas phase) to afford 12 conformational isomers, each of which has no imaginary frequencies. The geometry optimizations and frequency calculations of the 12 structures were performed at M06-2X/6-31G(d) level of theory (298 K, 1 atm, gas phase) to afford 11 conformational isomers, each of which has no imaginary frequencies, as the optimized structures of **15b**. Among them, the lowest energy structure was defined as **15b**. The optimized structure and the potential energy of **16b** were obtained by the same procedure as above.

Energy, structure and Cartesian coordinate of **15b**:





15b

Gibbs free energy (298 K) = -782898.7584 kcal/mol

C	-1.370696	-1.108782	2.503828
C	-0.160739	-1.682793	1.766771
C	0.217295	-0.937237	0.476276
C	-1.008999	-0.874184	-0.476563
C	-2.150847	-0.134506	0.286987
C	-2.549692	-0.932893	1.552606
H	-1.111830	-0.146254	2.953161
H	-1.659309	-1.784411	3.317079
H	-0.366587	-2.724851	1.492075
H	0.698846	-1.690022	2.443702
C	1.437383	-1.593740	-0.210353
C	0.694754	0.512962	0.672795
C	-0.665478	-0.165328	-1.813041
O	-1.384581	-2.211926	-0.746650
C	-1.715701	1.303362	0.625422
C	-3.416162	-0.099494	-0.556580
H	-2.909629	-1.916037	1.229217
H	-3.380418	-0.417294	2.048578
N	-0.367872	1.383803	1.154050
C	0.006706	2.734848	1.494176
O	-3.715278	-0.906613	-1.413573
O	-4.238408	0.895205	-0.203318
C	-5.492122	0.926690	-0.889224
C	0.257491	1.063011	-1.721676
C	1.381073	0.834475	-0.700881
C	2.073013	-0.504555	-1.101514
C	2.578635	-1.994990	0.766090
C	3.875687	-1.811421	-0.020708
C	3.584469	-0.638053	-0.940013
O	4.400760	0.037150	-1.522428
H	1.118595	-2.468196	-0.787560
H	1.903717	-0.669941	-2.172435
C	2.330131	2.033935	-0.702776
C	3.387254	2.077244	0.371044
O	3.616953	1.200354	1.171572
H	1.462637	0.521963	1.451665
H	-1.590040	0.093468	-2.341128
H	-0.181326	-0.932367	-2.426594
H	-2.206786	-2.164770	-1.265500
H	-2.396569	1.703634	1.389287
H	-1.863331	1.946524	-0.261512
H	-0.690433	3.135708	2.240431

H	1.011248	2.738230	1.930645
H	-0.002957	3.430343	0.634255
H	-6.031994	-0.009067	-0.731421
H	-6.038876	1.766434	-0.463756
H	-5.333917	1.070118	-1.960071
H	-0.296244	1.968069	-1.452590
H	0.695020	1.252344	-2.710770
H	2.448513	-3.006874	1.157757
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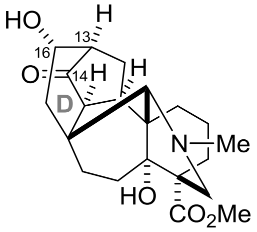
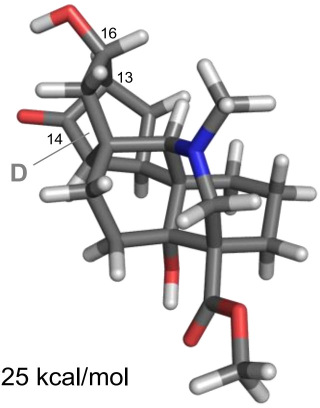
Energy, structure and Cartesian coordinate of **16b**:





16b

Gibbs free energy (298 K) = -782881.1725 kcal/mol

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C	0.115734	-0.246849	1.060241
C	-1.057429	-0.923038	0.277617
C	-2.215903	0.128357	0.222438
C	-2.678071	0.543271	1.637581
H	-1.248752	2.128896	1.976979
H	-1.866523	1.386144	3.446975
H	-0.637151	-0.688522	3.010883
H	0.480931	0.672210	2.984636
C	1.398285	-1.103939	1.194173
C	0.618137	0.834857	0.109603
C	-0.712078	-1.343027	-1.194820
O	-1.435163	-2.058046	1.027556
C	-1.764492	1.347511	-0.619151
C	-3.458597	-0.490184	-0.402416
H	-3.025601	-0.356007	2.160152
H	-3.527177	1.230456	1.546885
N	-0.372371	1.730577	-0.452601
C	-0.138115	3.151636	-0.356438
O	-3.741153	-1.671340	-0.401062
O	-4.284871	0.435125	-0.903489
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H	3.110460	0.204790	-2.257564
H	2.271552	1.716647	-1.913835
H	5.183498	0.446845	-1.270998

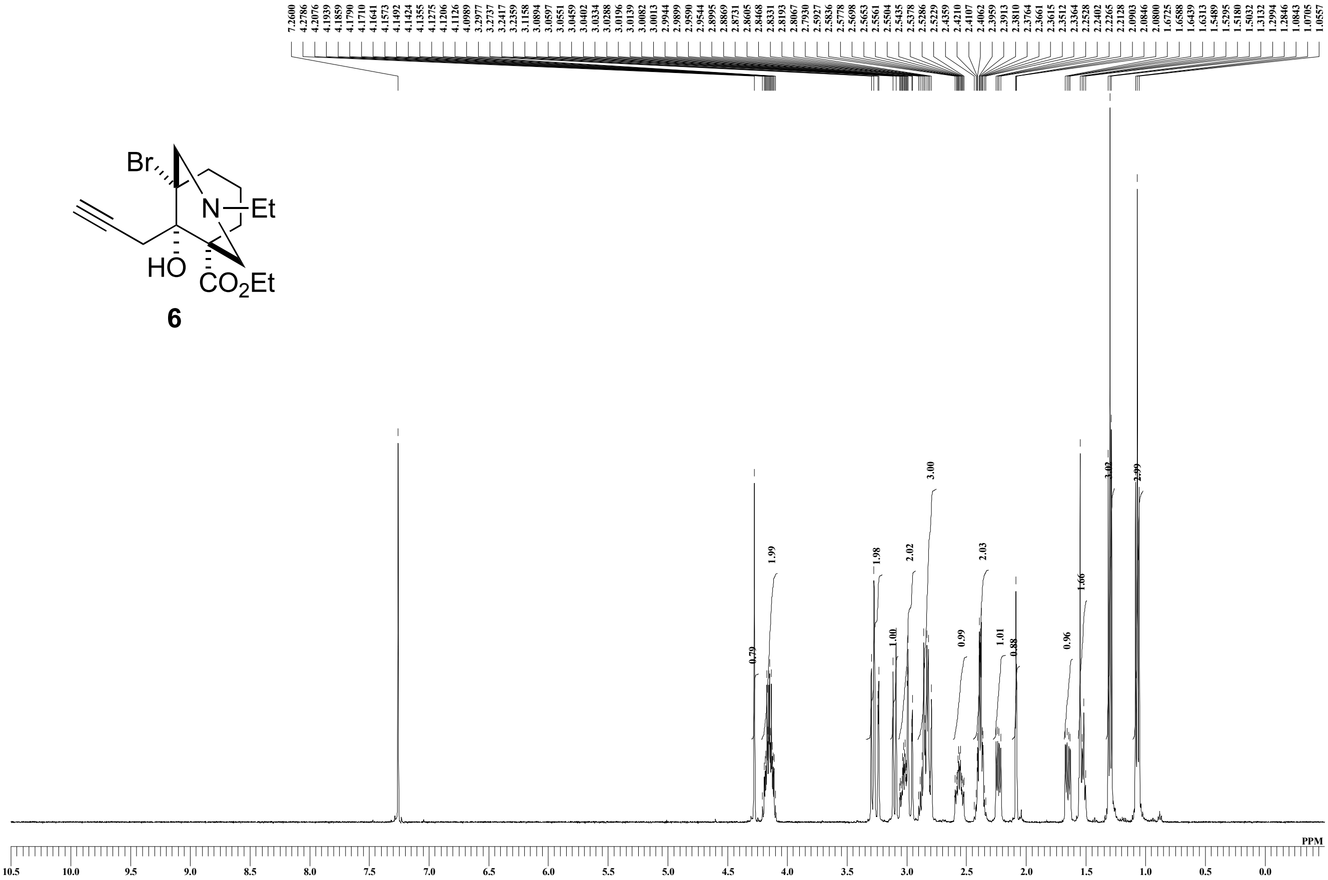
References

S1 H.-S. Lin and L. A. Paquette, *Synth. Commun.*, 1994, **24**, 2503.

S2 (a) *MacroModel version 10.4*; Schrodinger, LLC, New York, NY; (b) F. Mohamadi, N. G. J. Richards, W. C. Guida, R. Liskamp, M. Lipton, C. Caufield, G. Chang, T. Hendrickson and W. C. Still, *J. Comput. Chem.*, 1990, **11**, 440.

S3 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J.

Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski and D. J. Fox, Gaussian 09 (Revision D.01), Gaussian, Inc., Wallingford CT, 2013.



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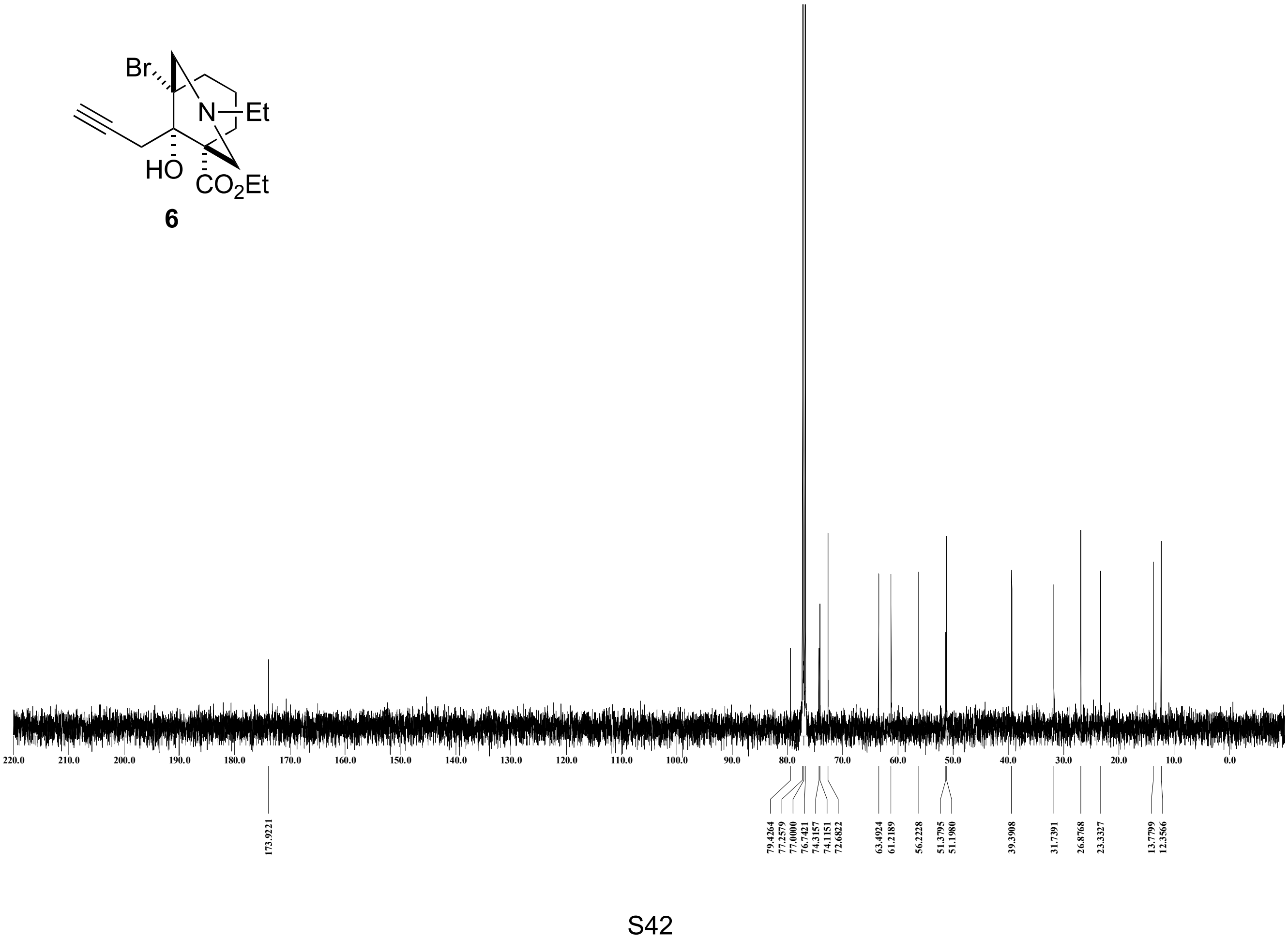

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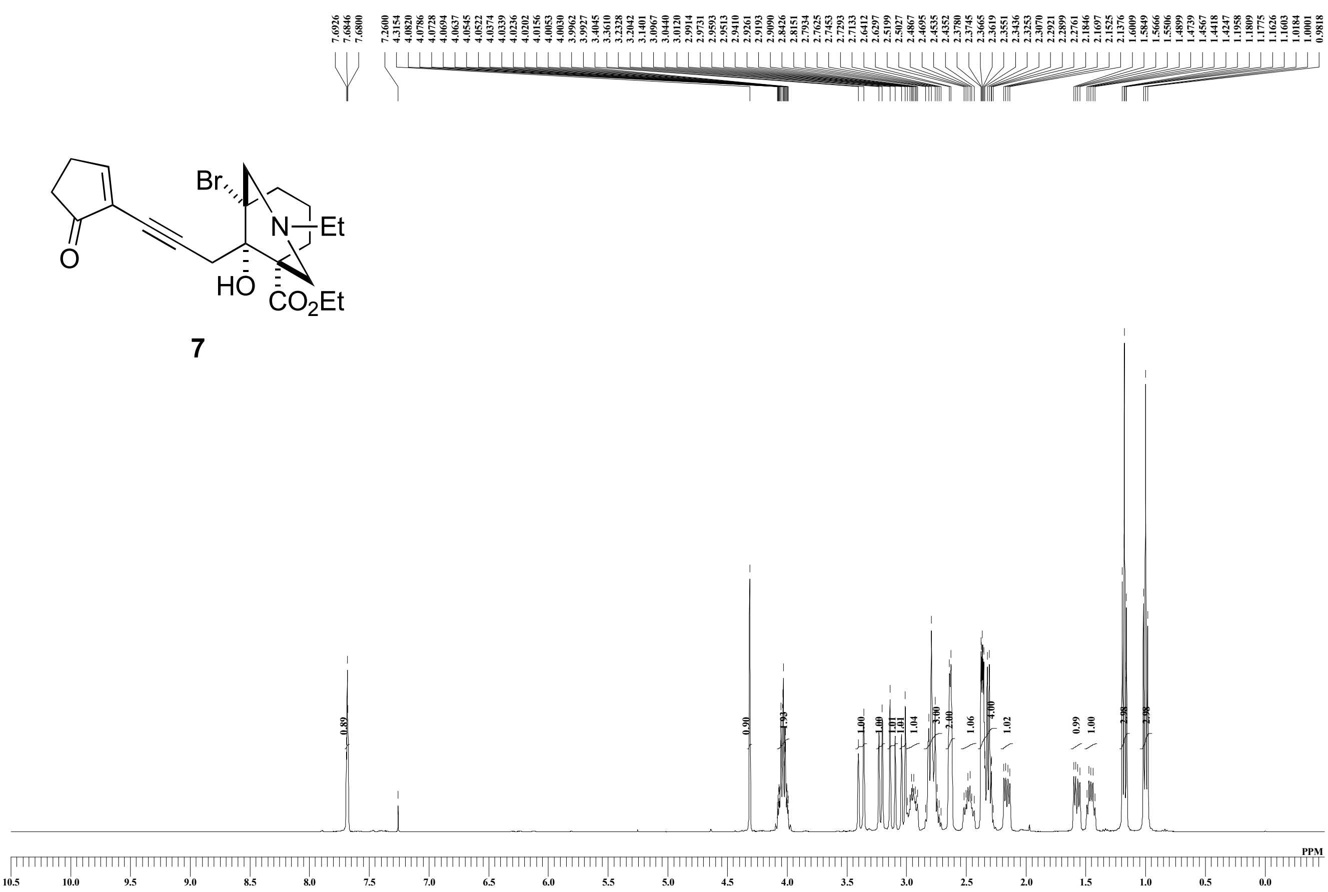
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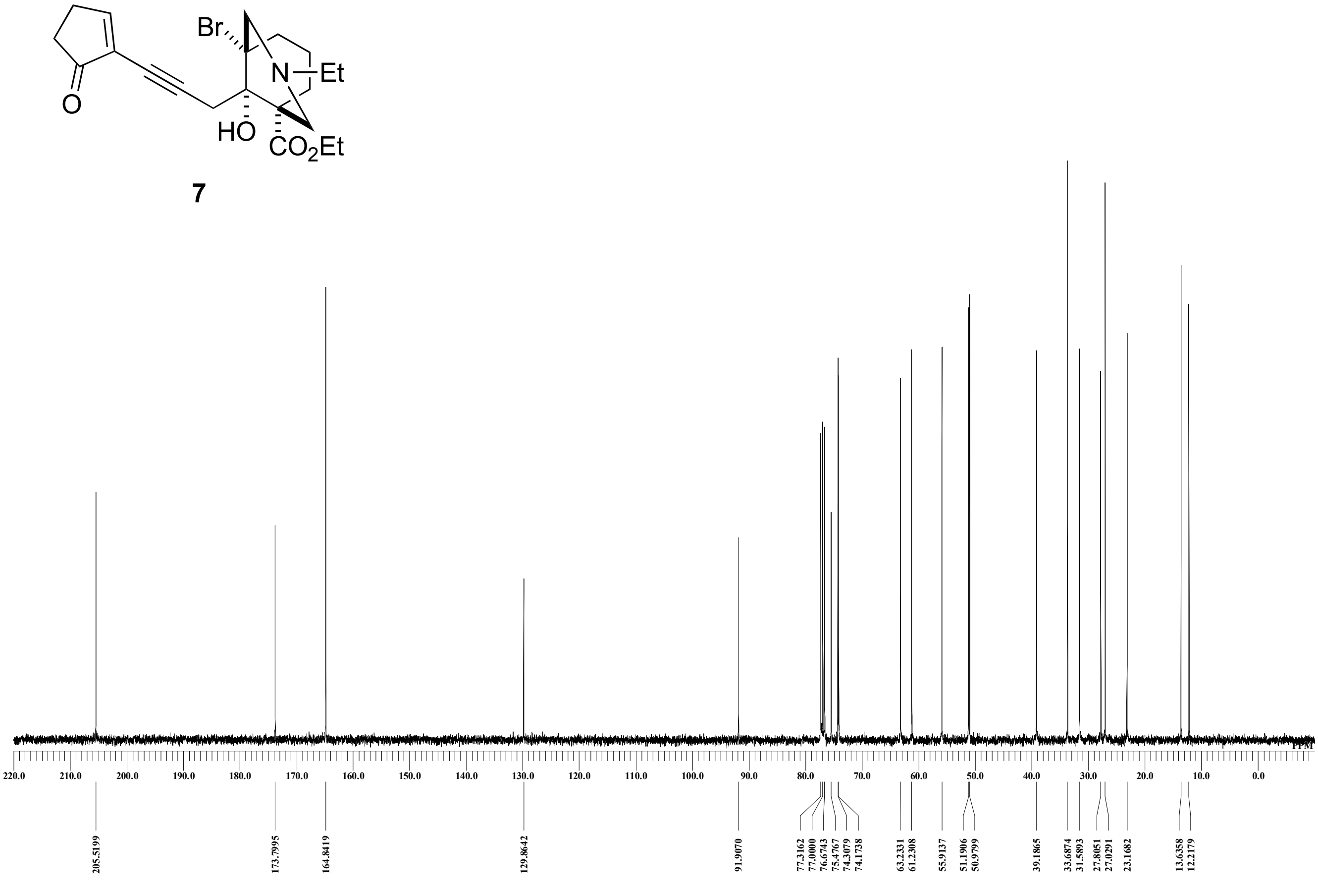
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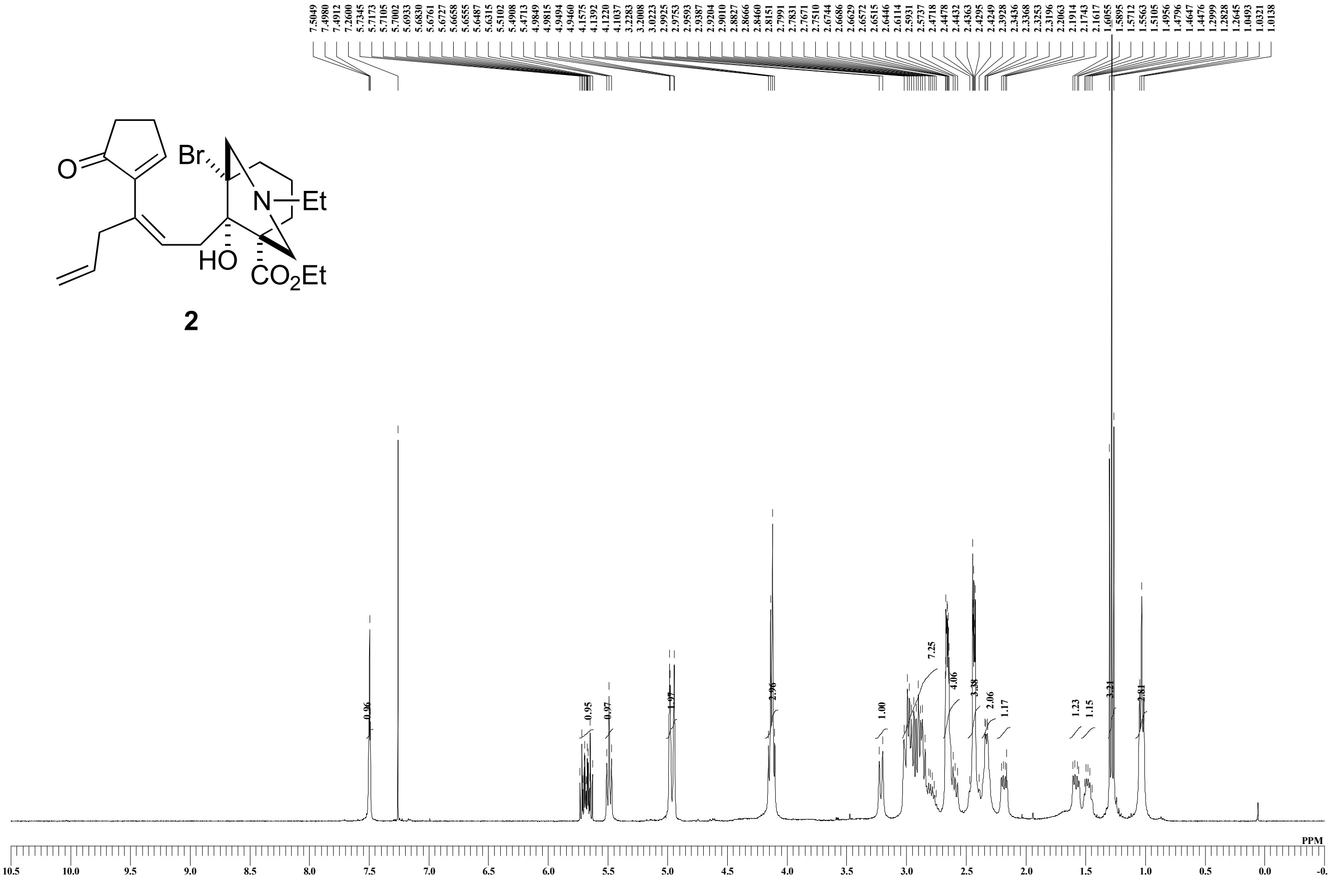
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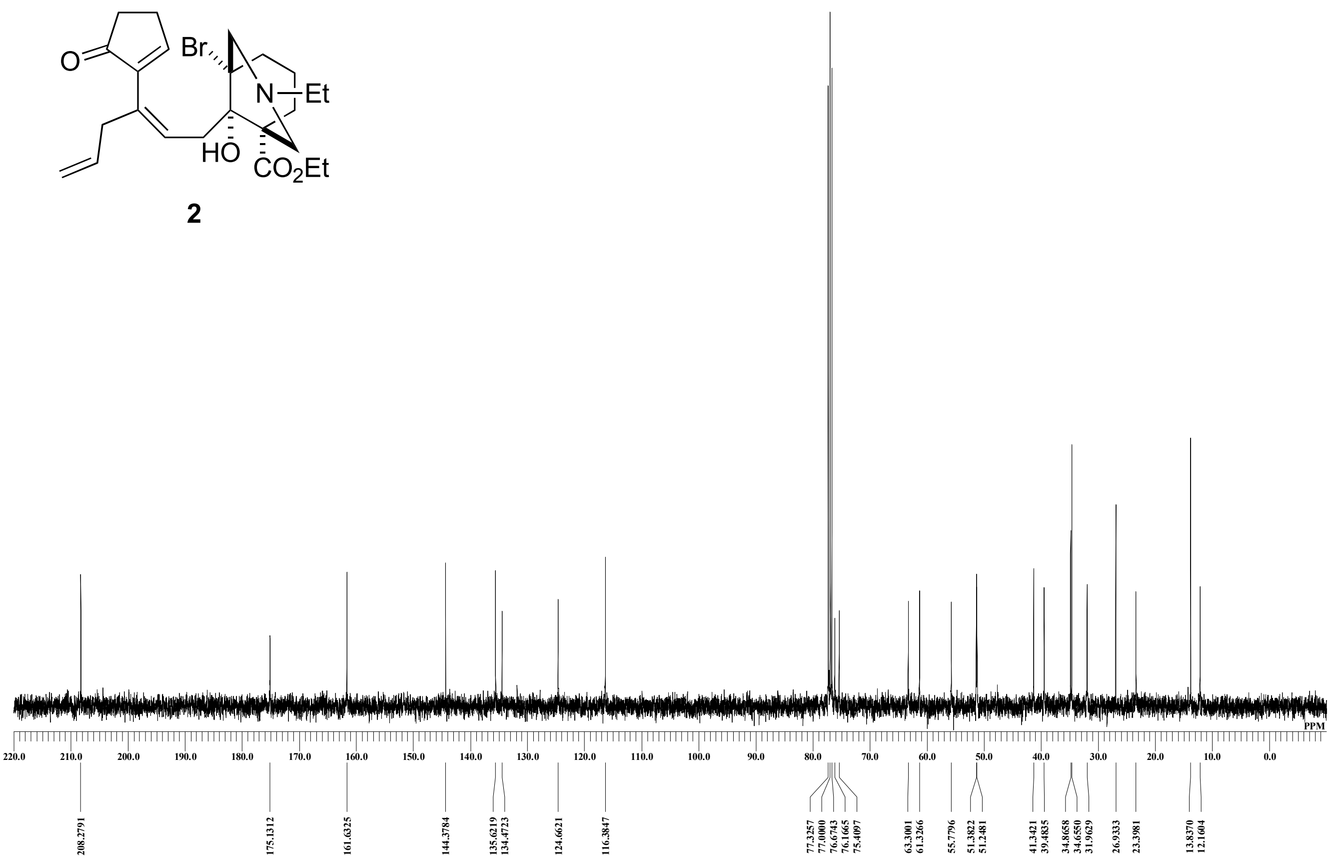
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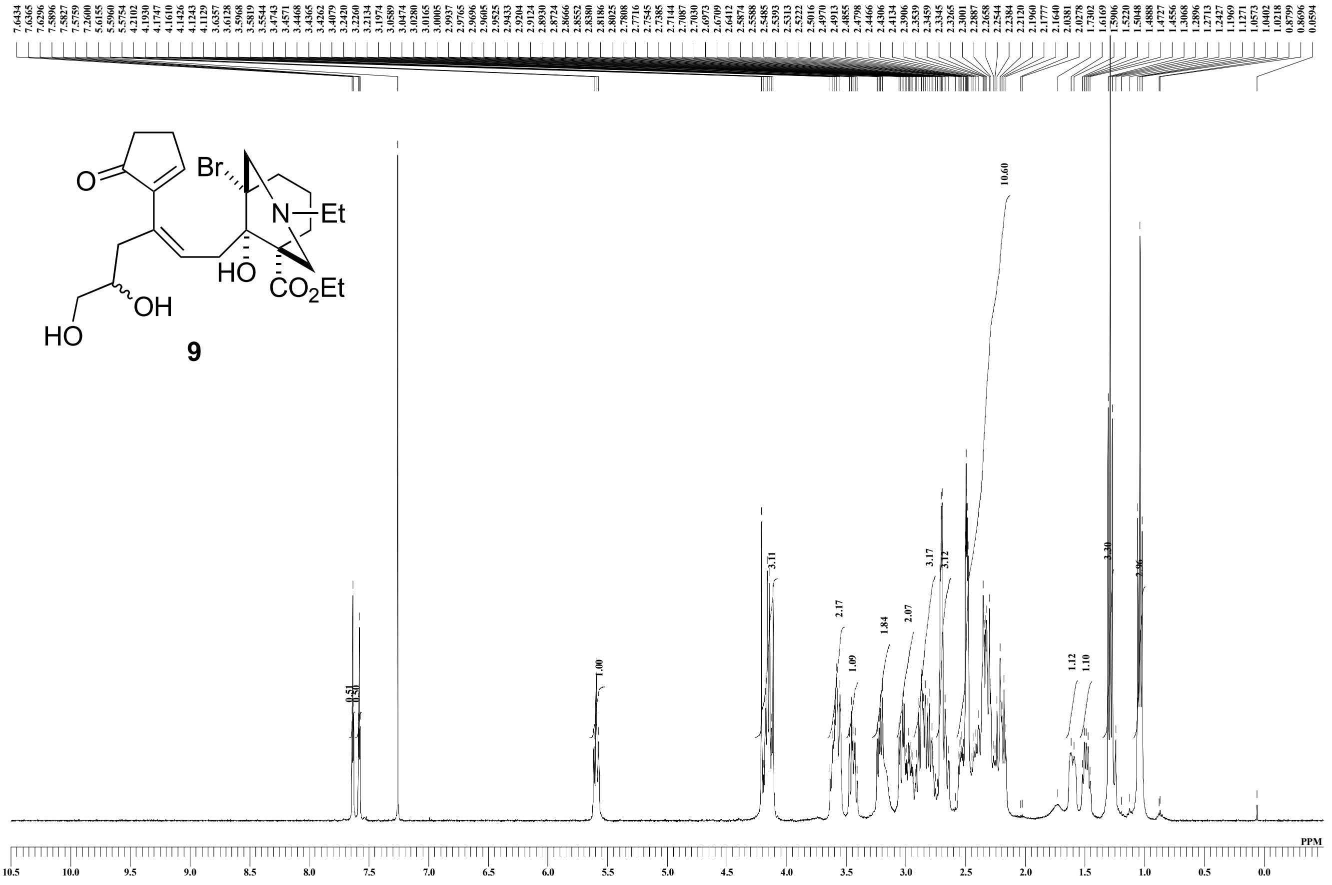
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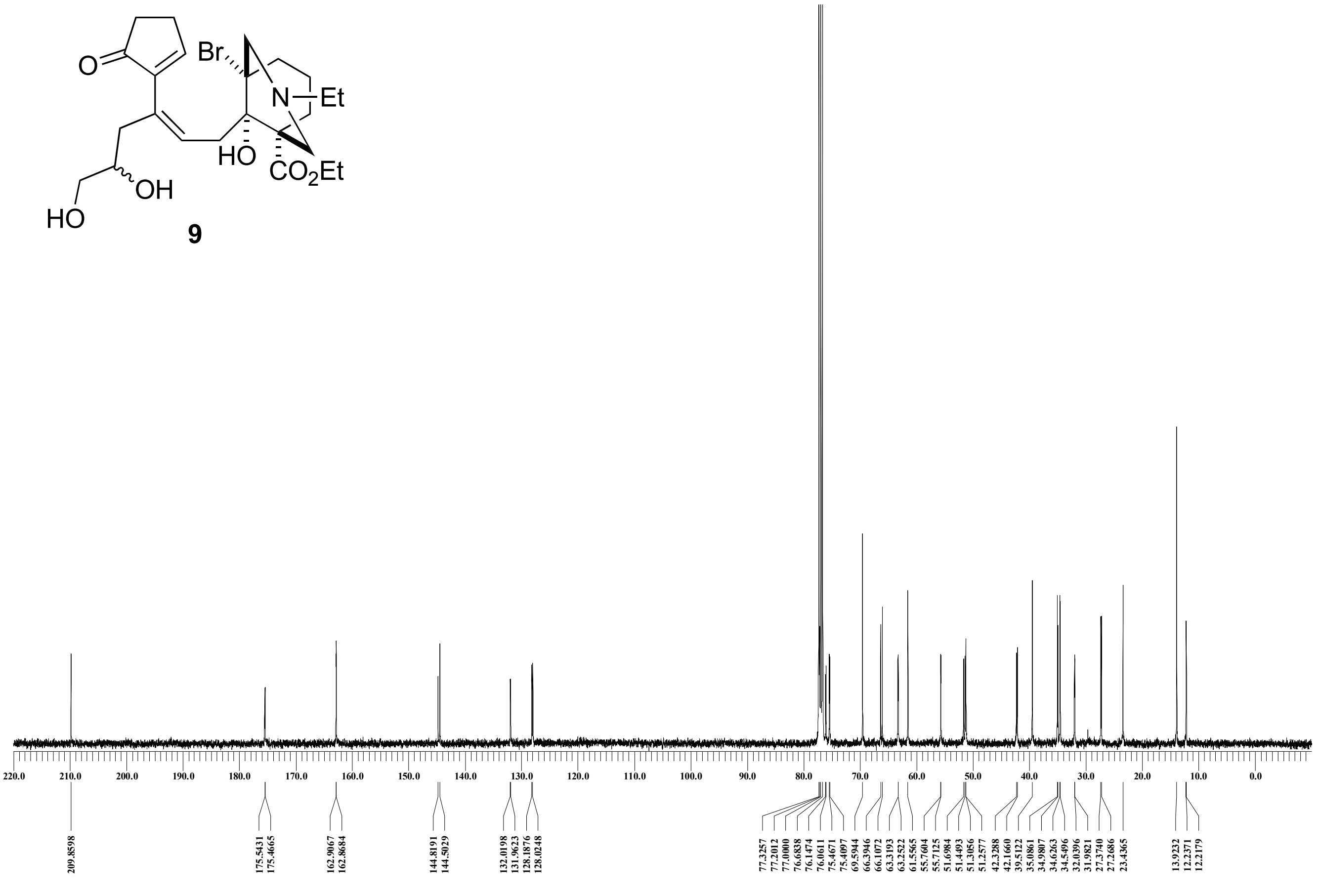
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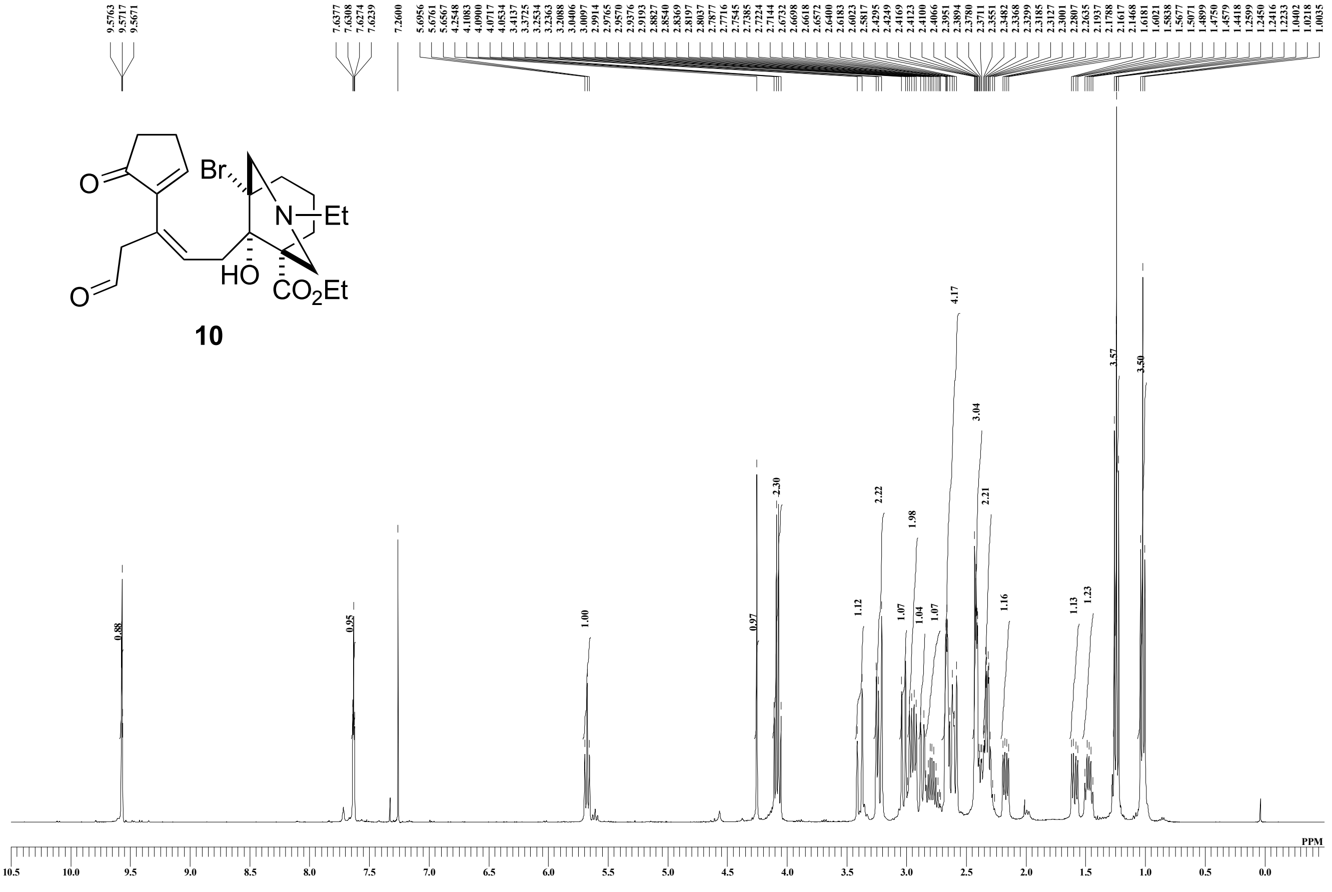
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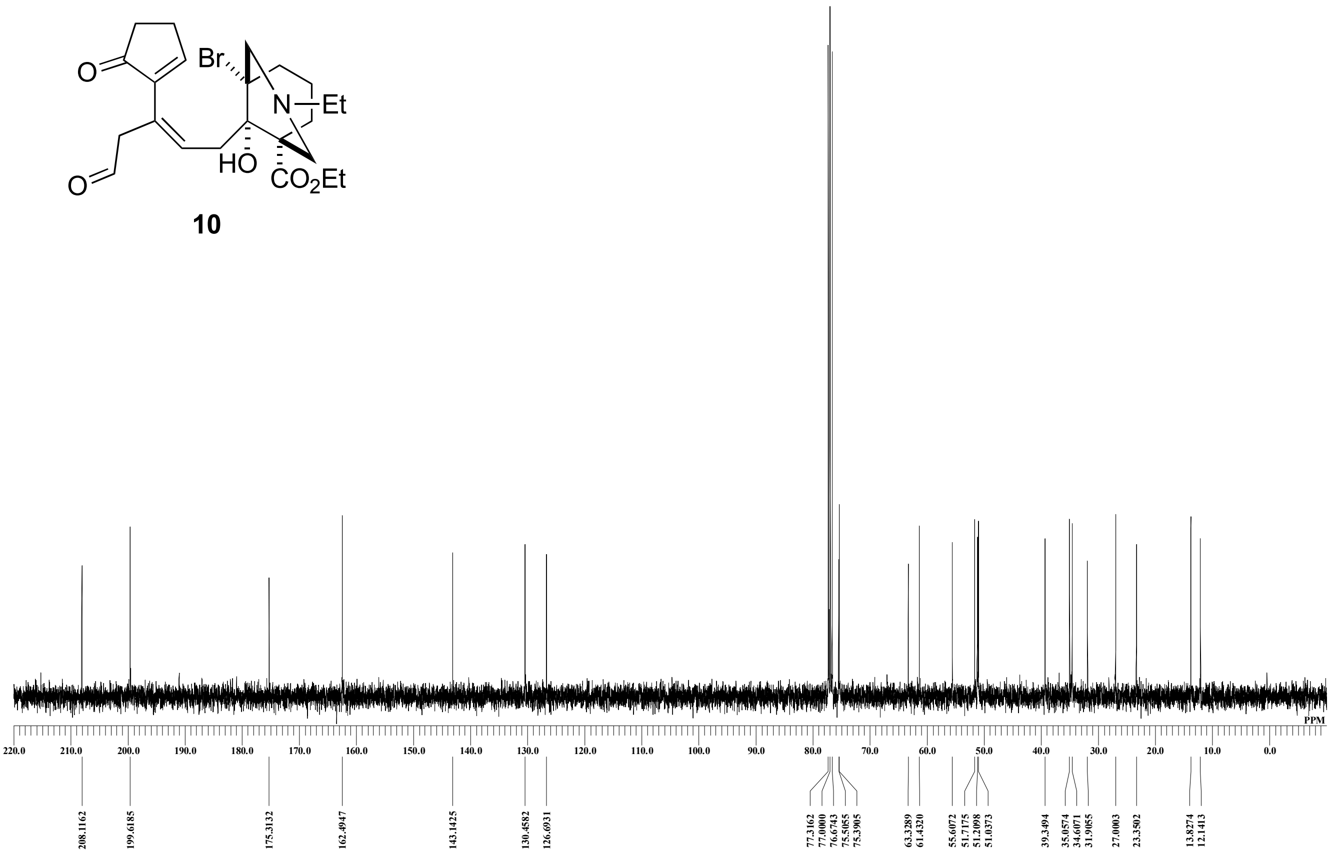
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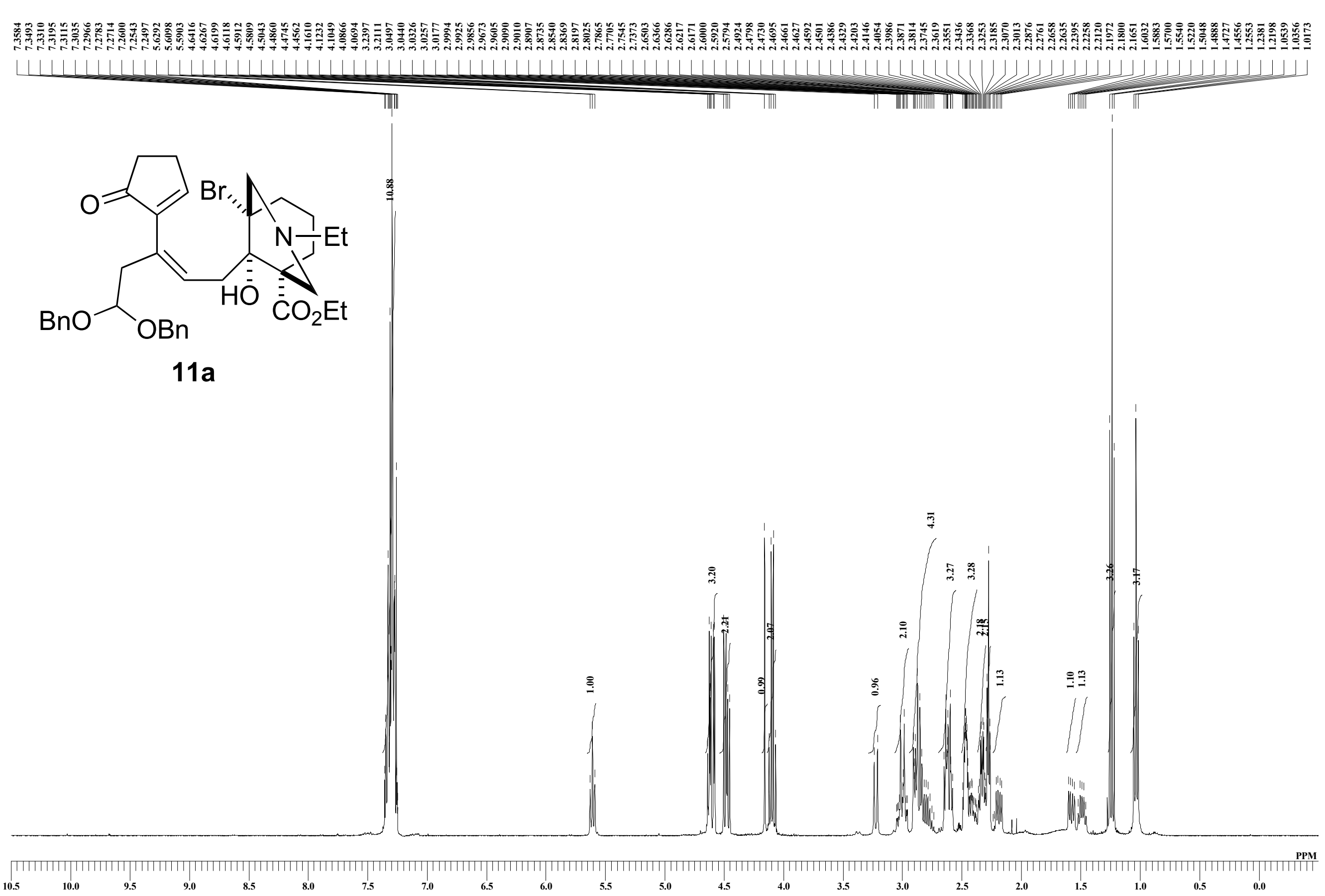
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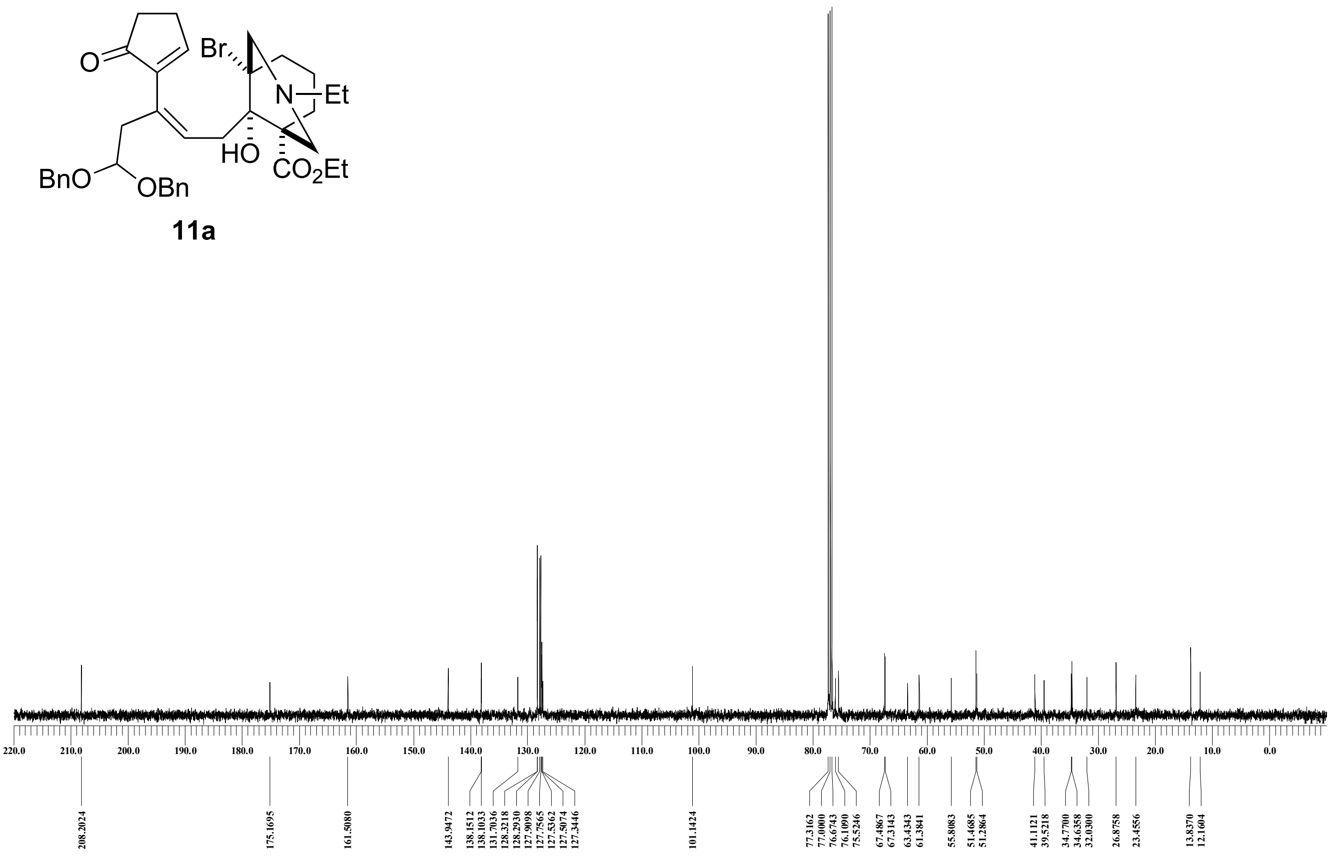
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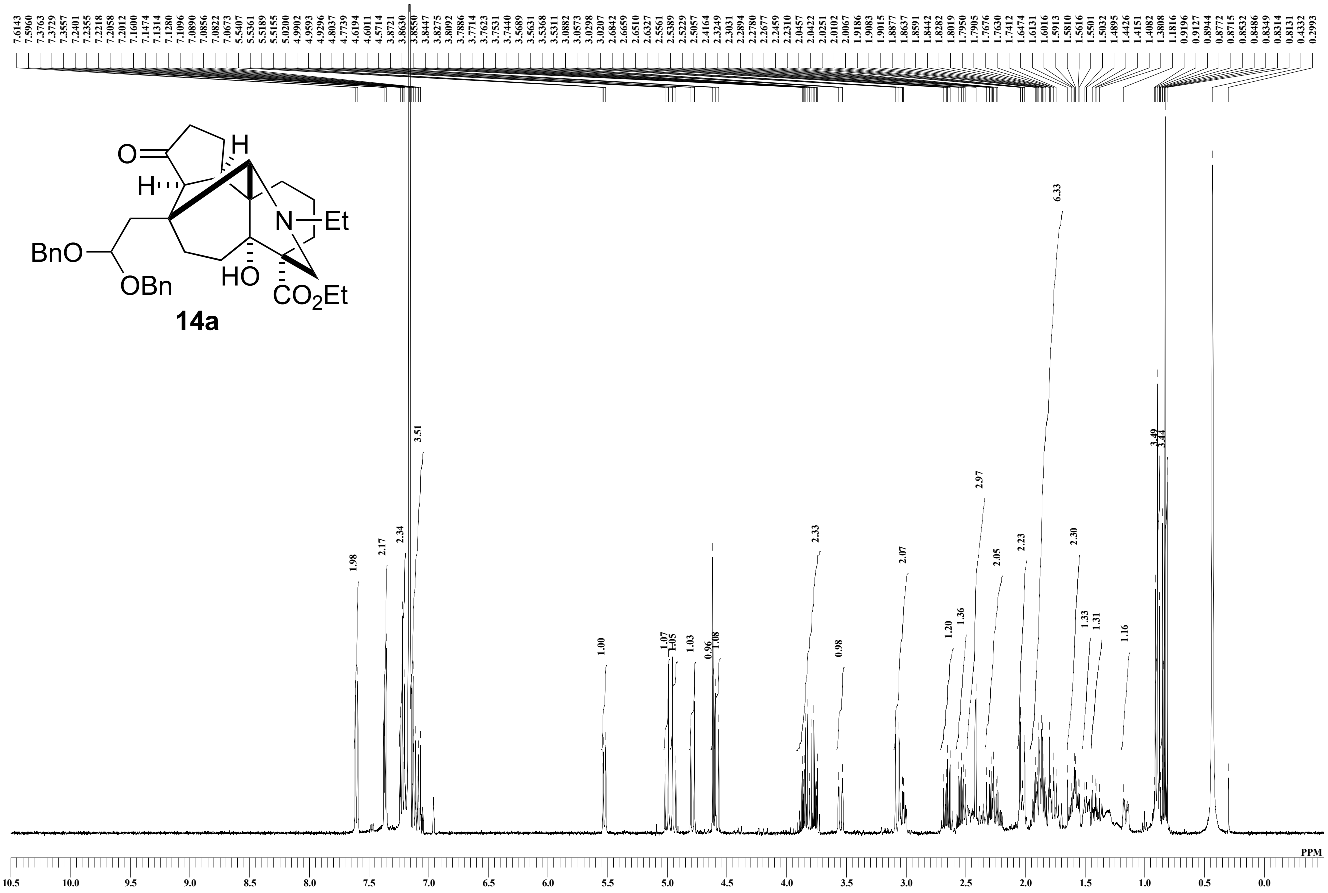
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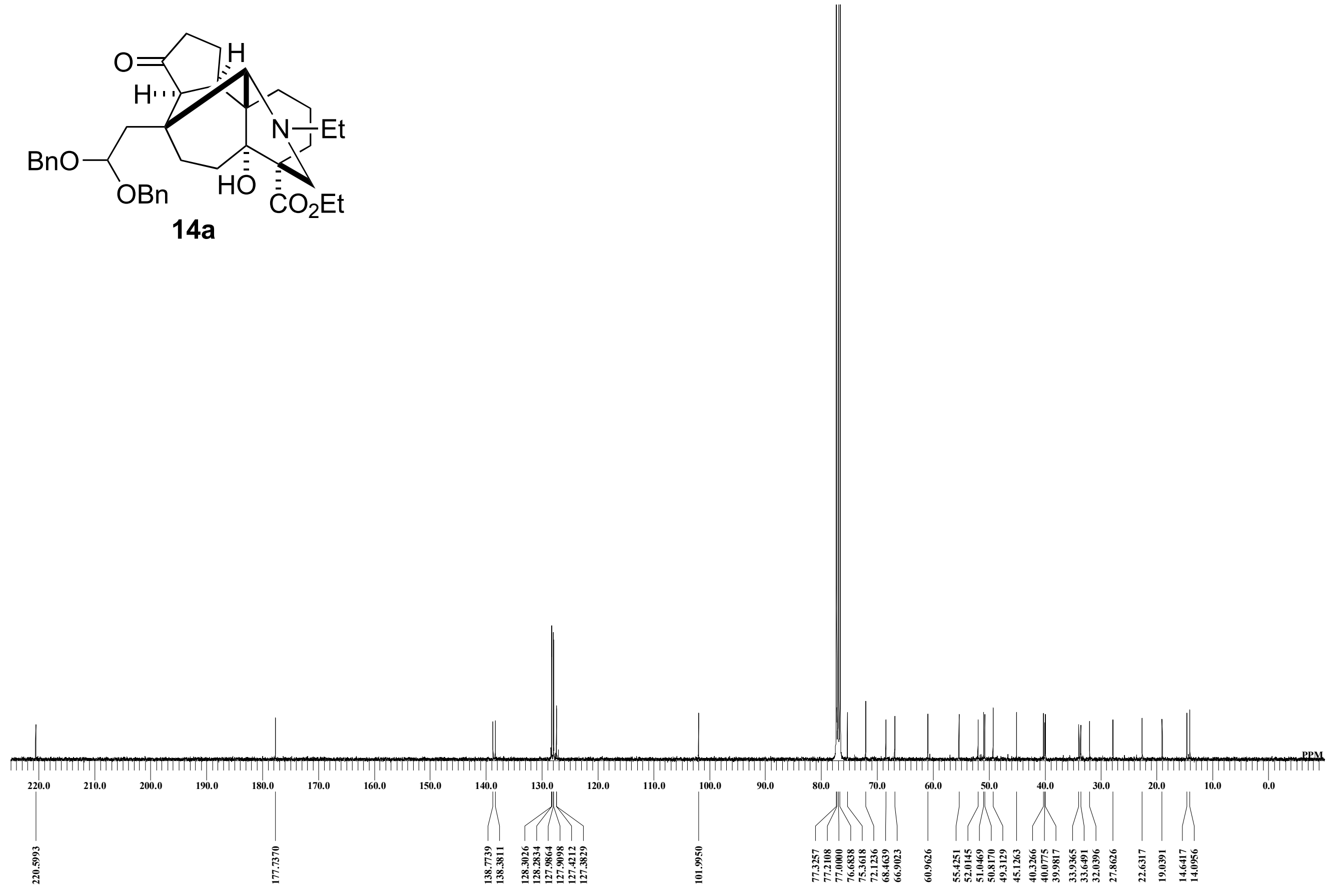
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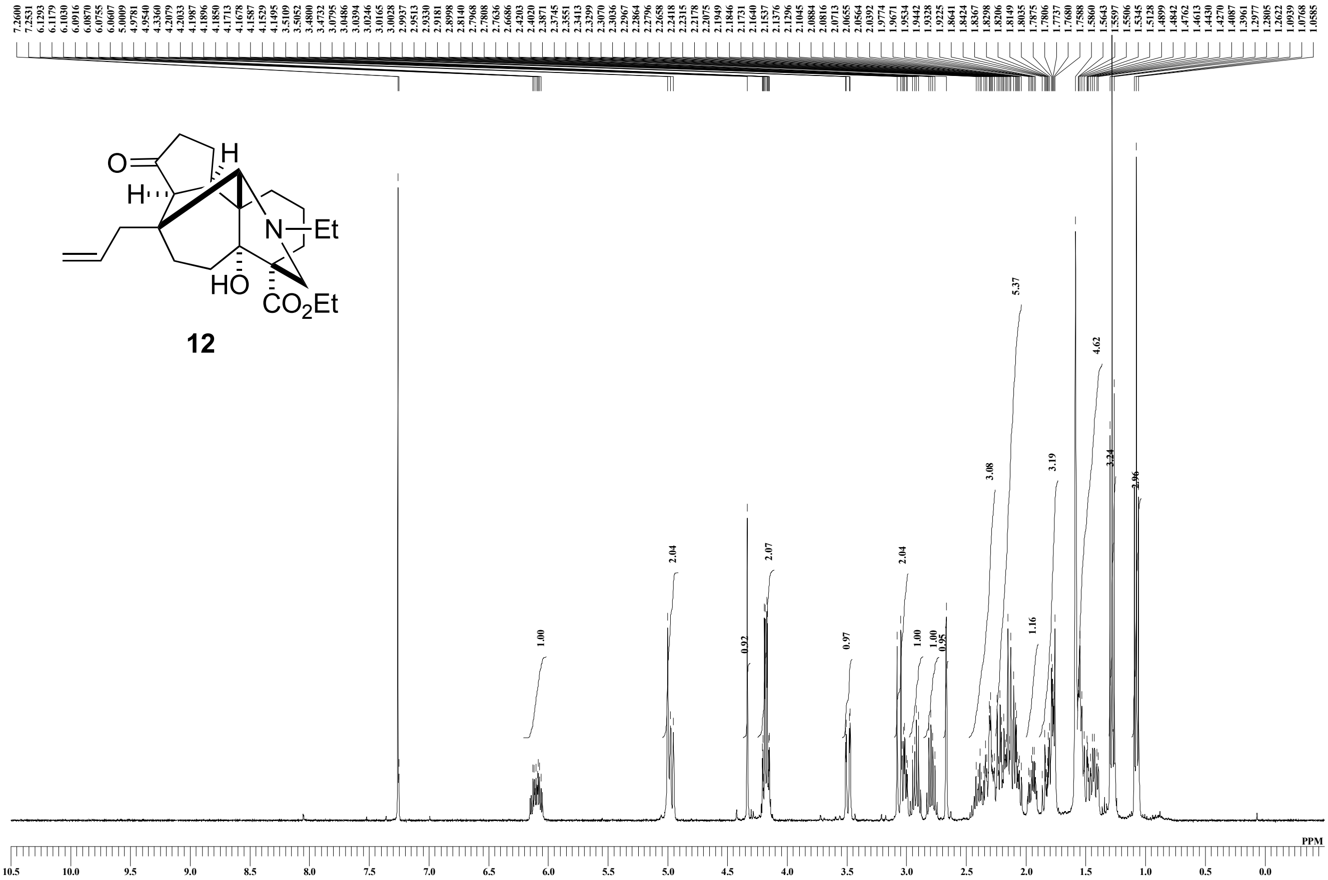
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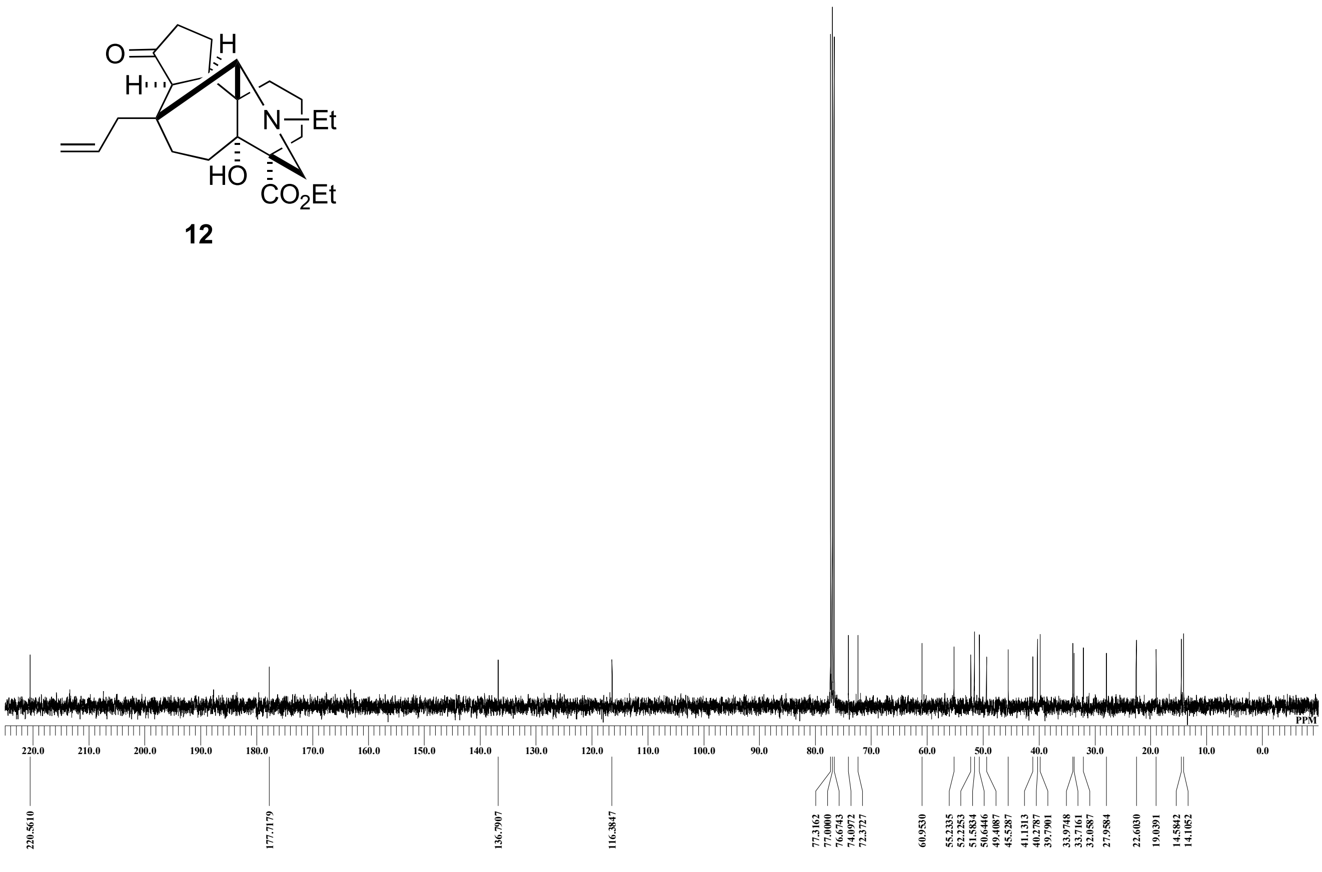
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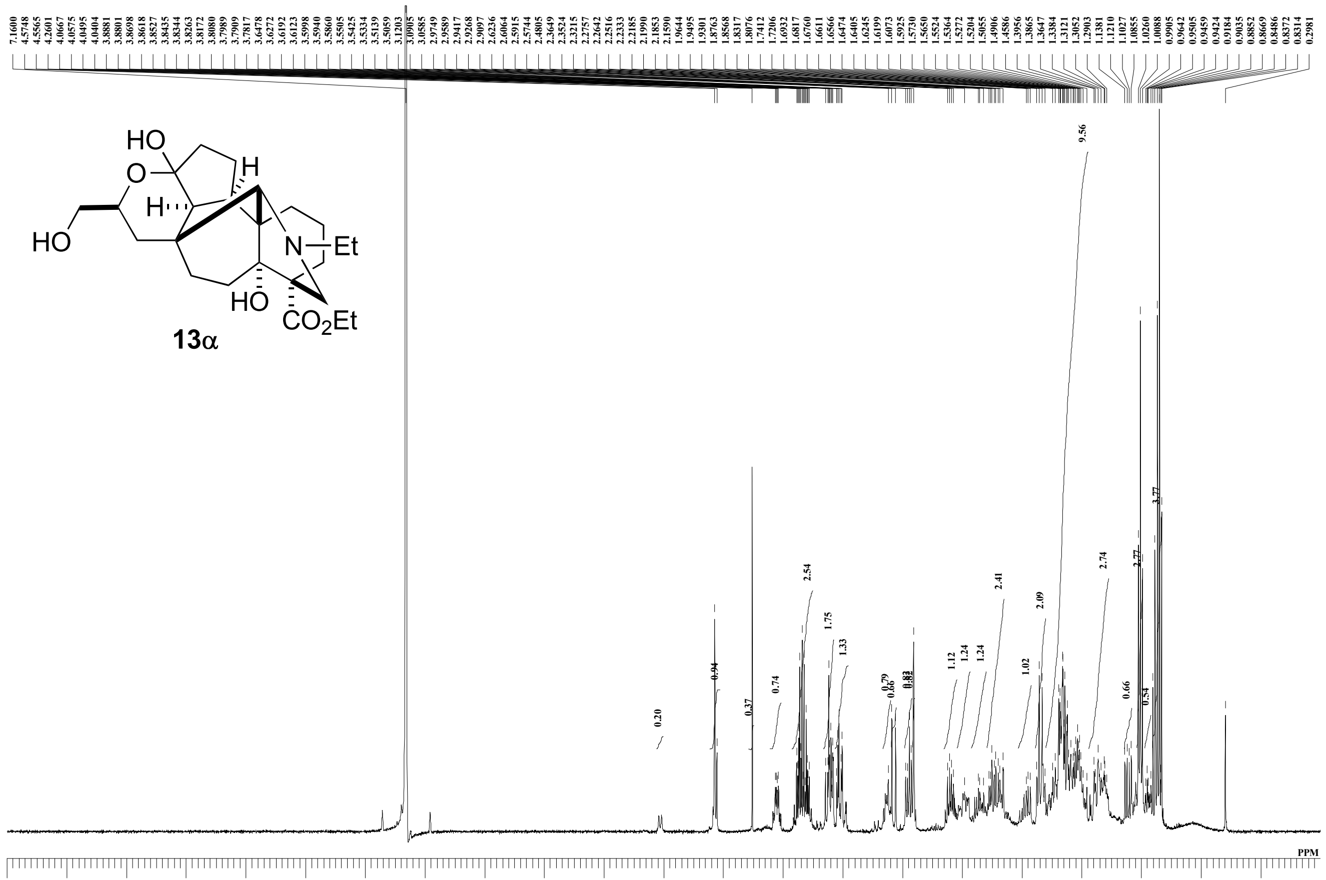
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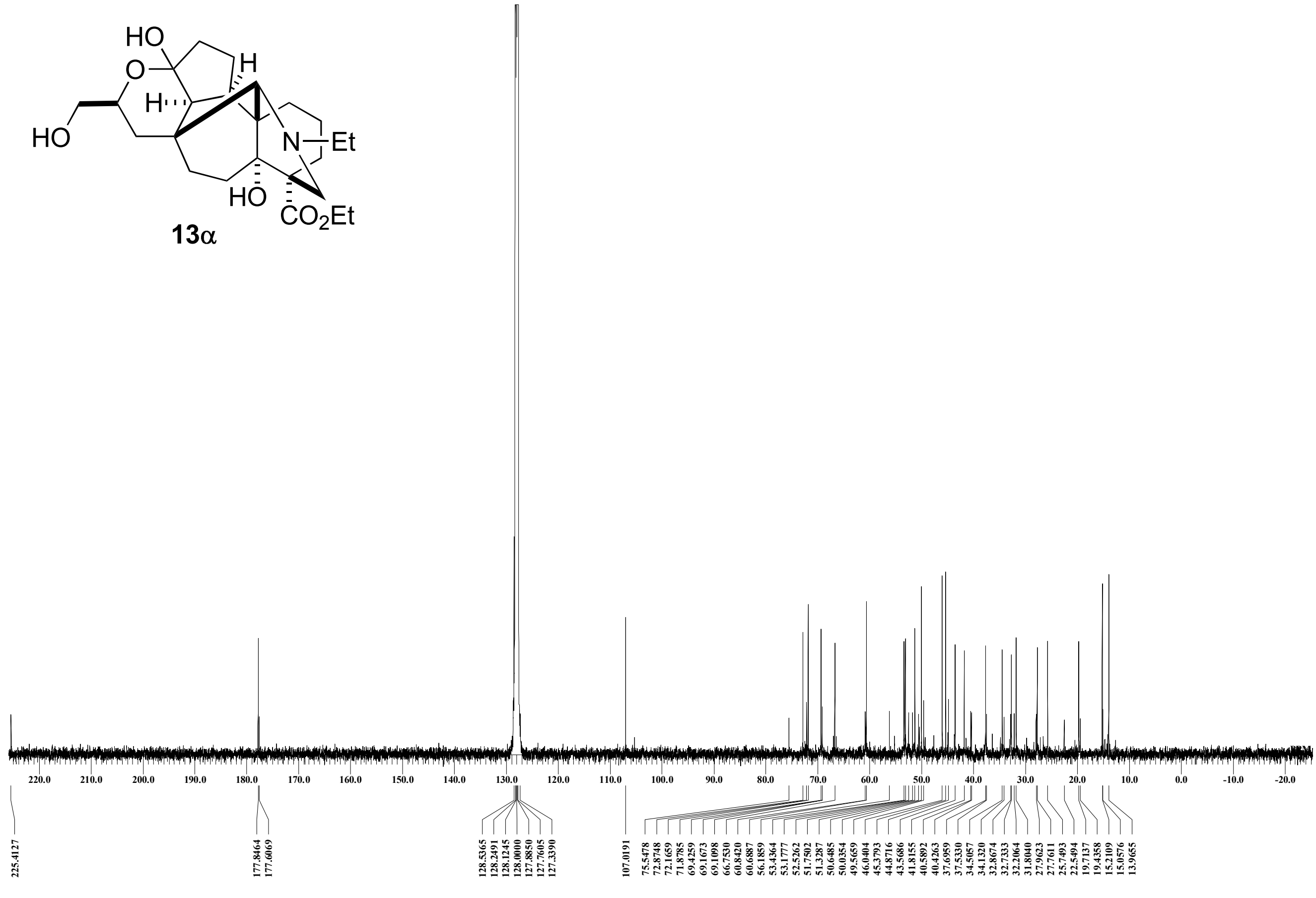
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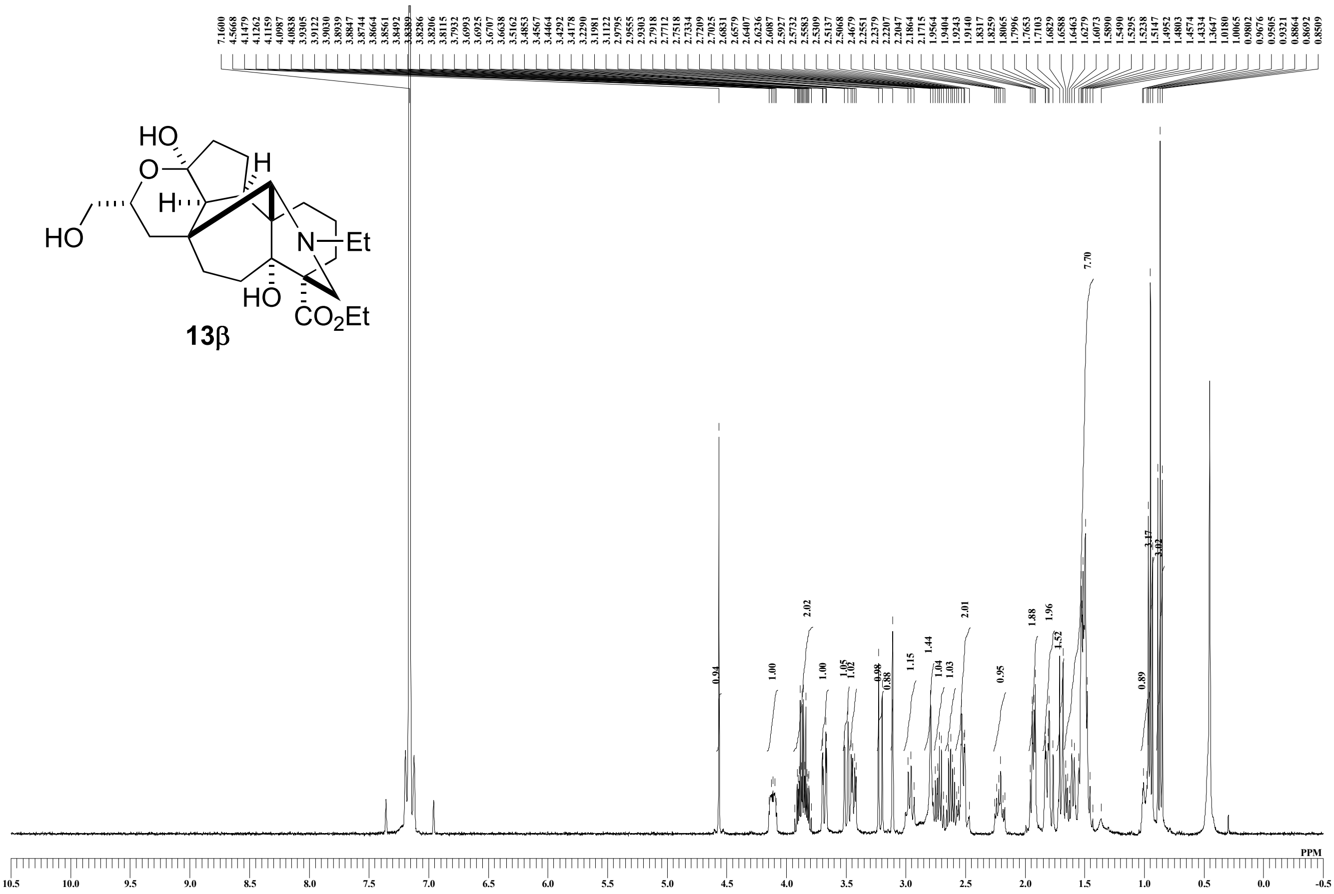
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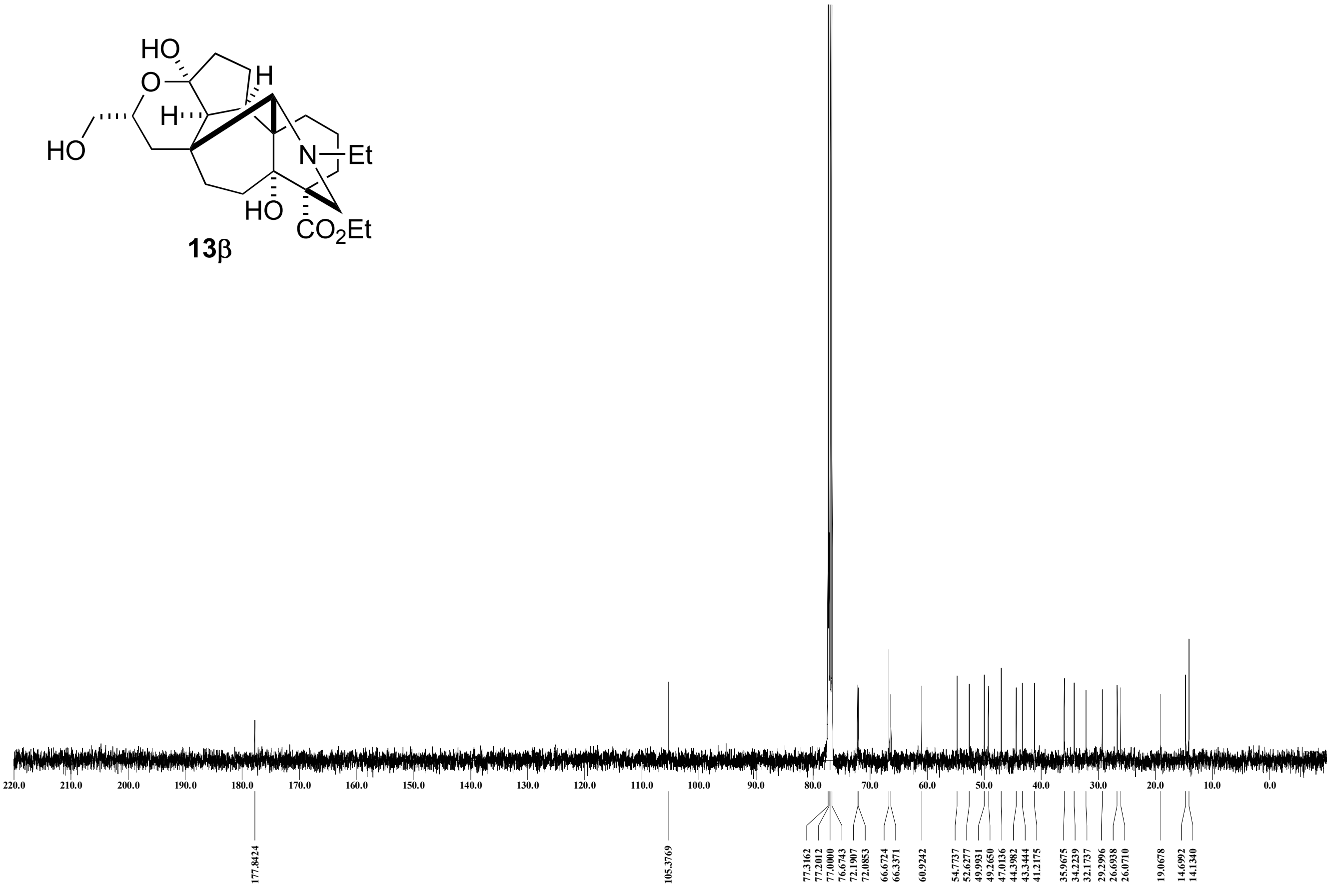
13β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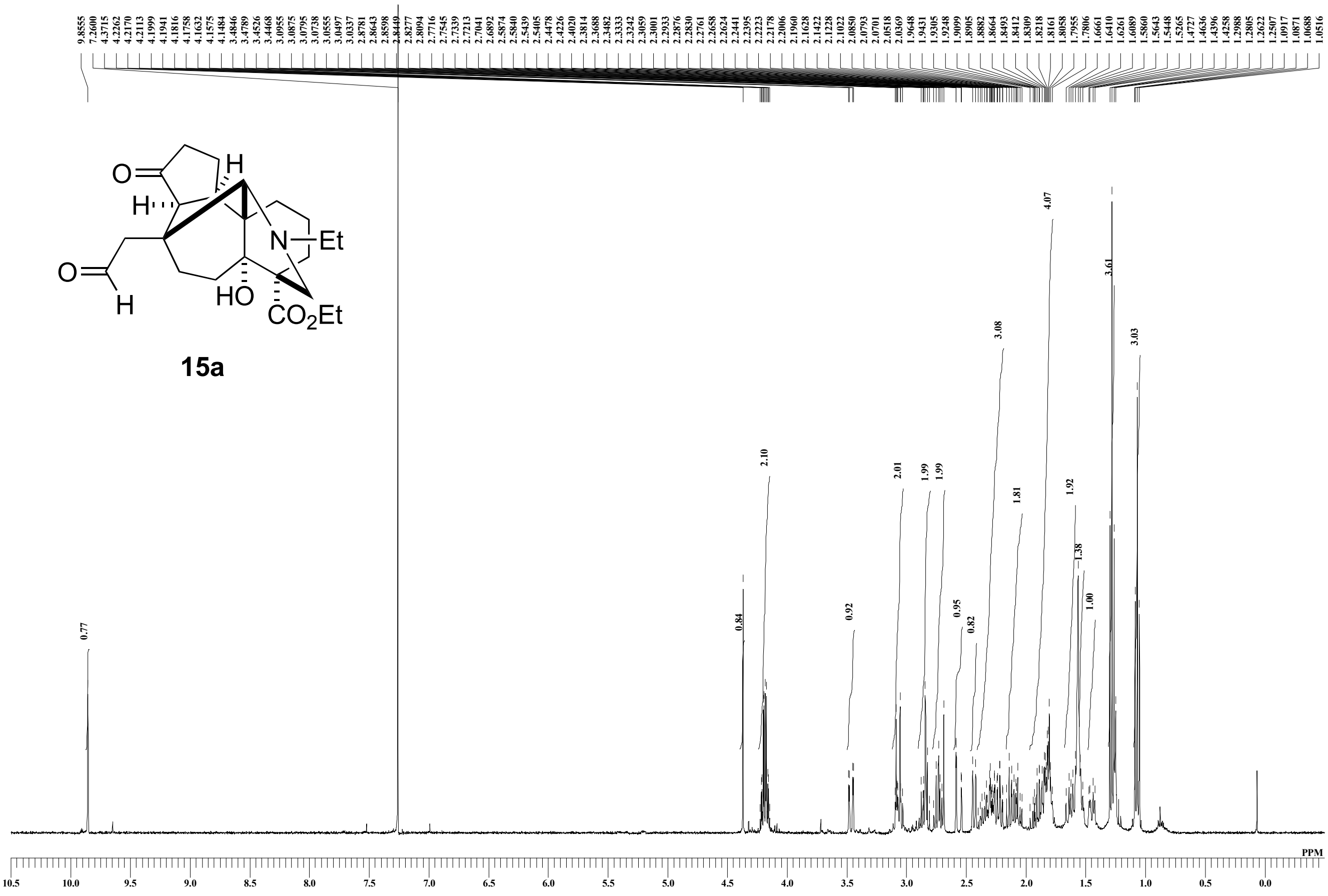
13β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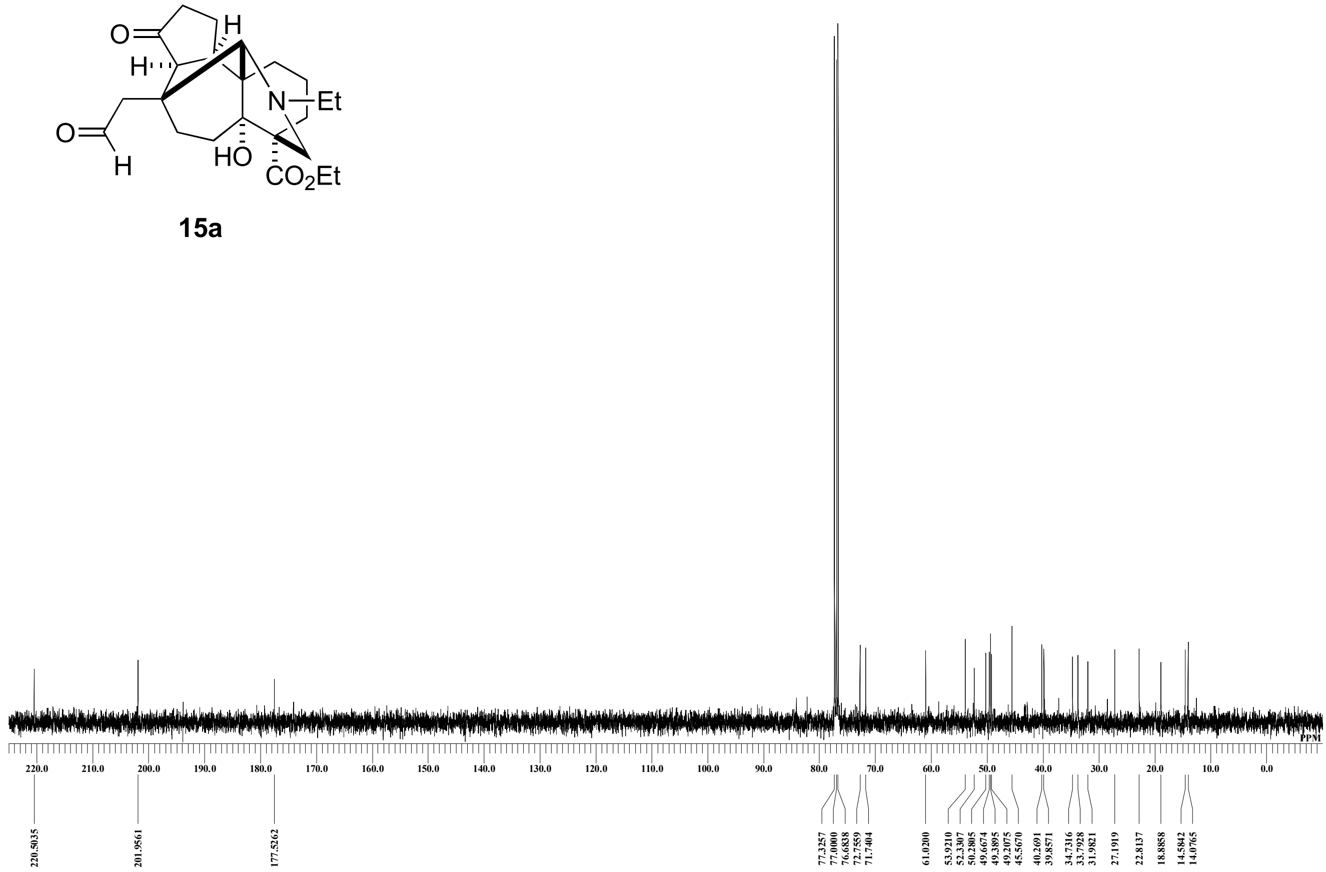
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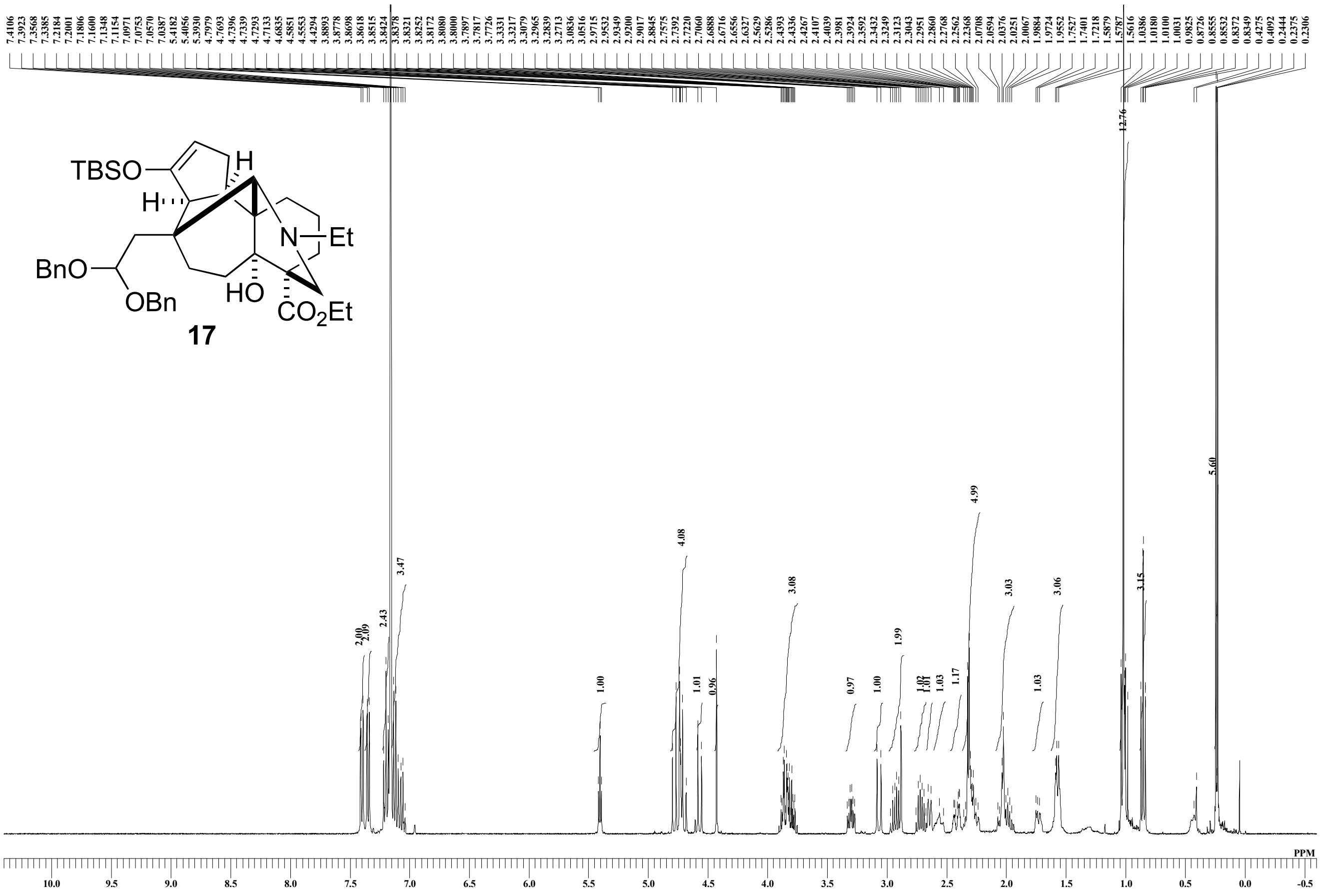

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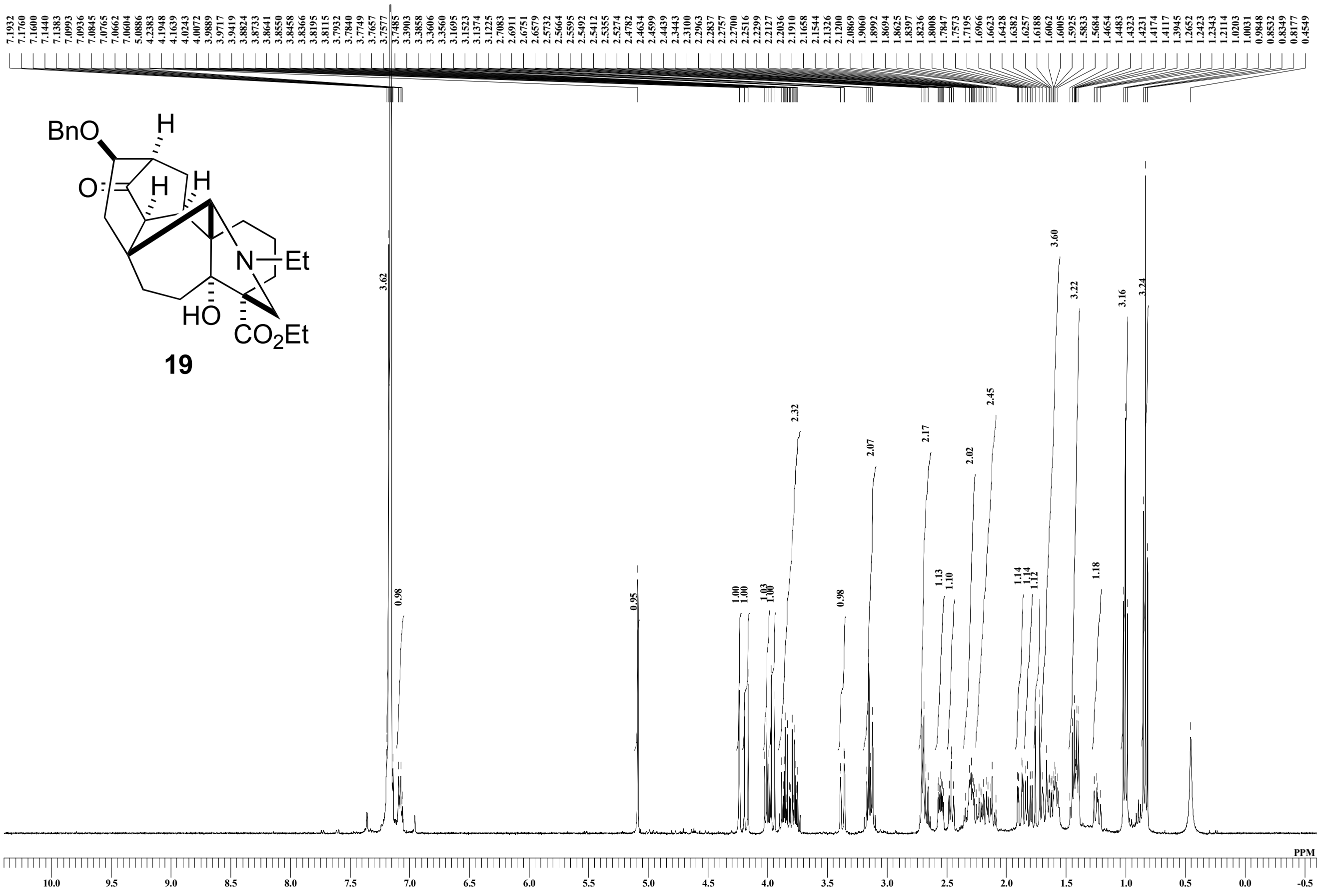
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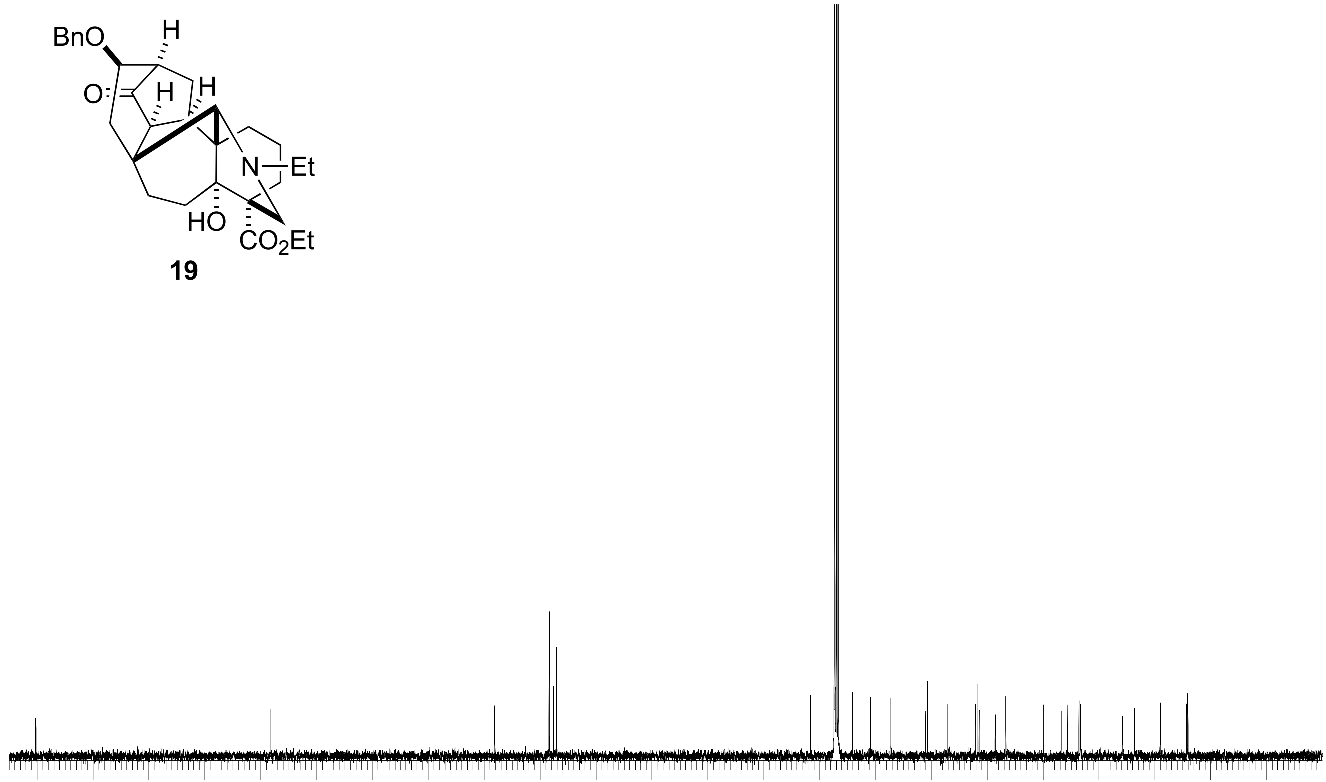
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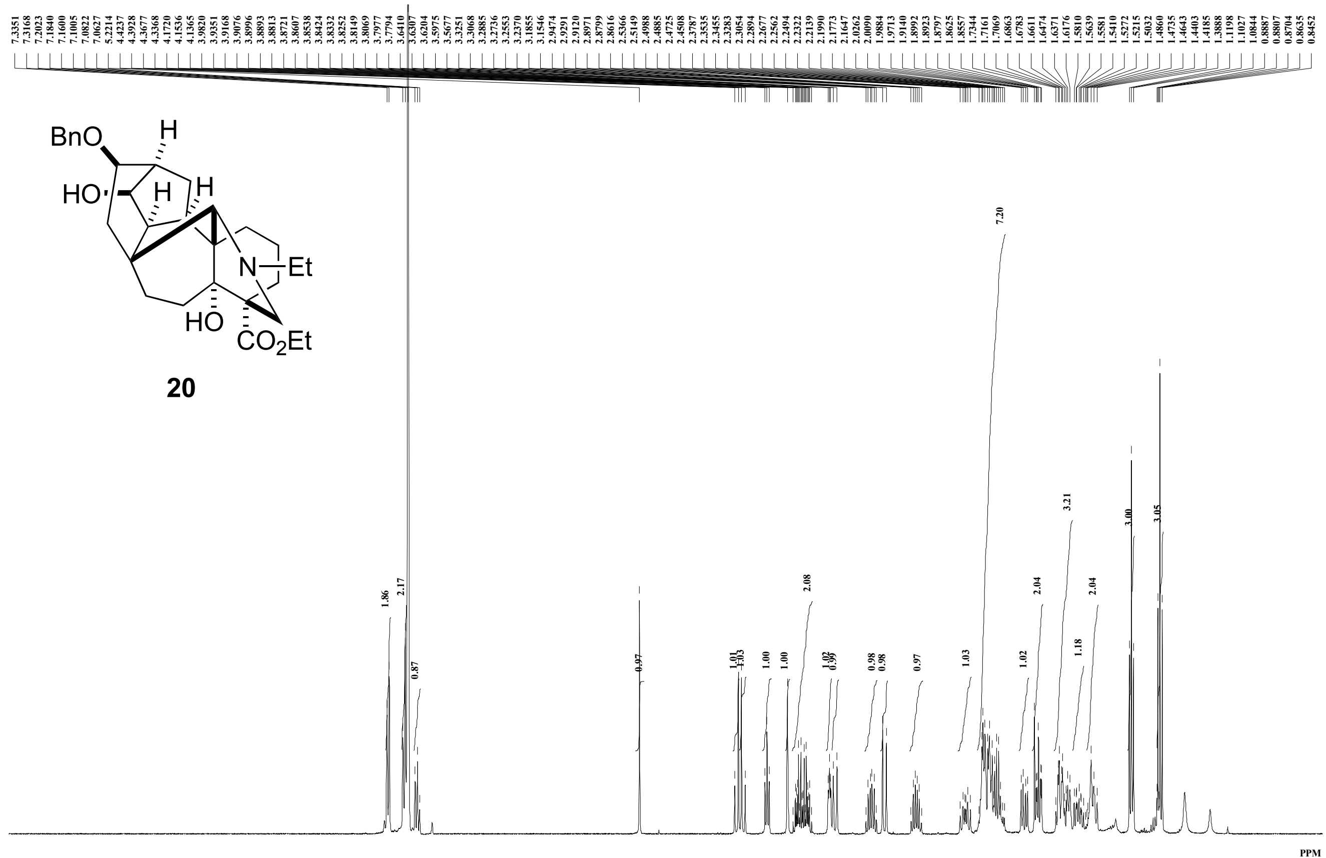
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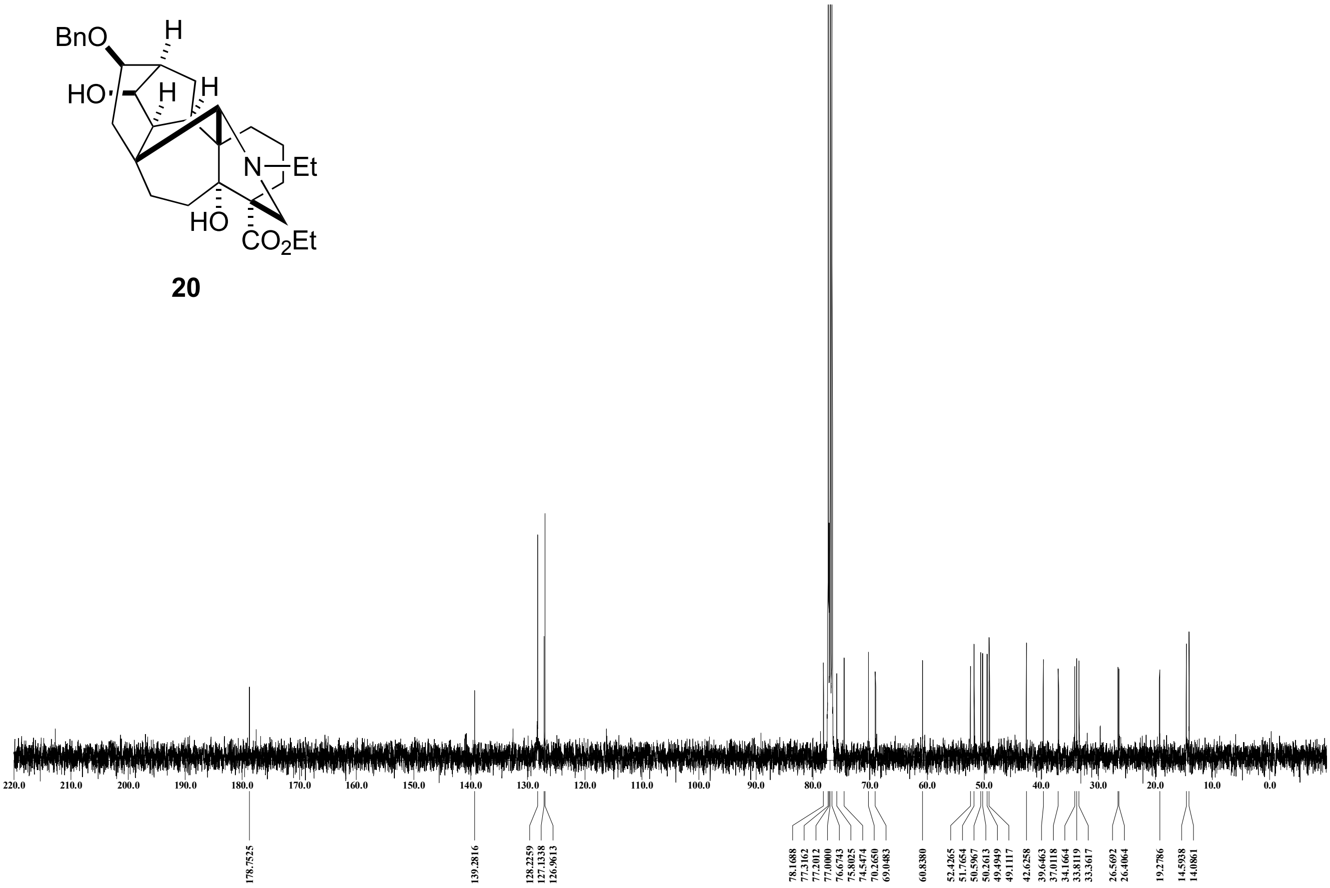
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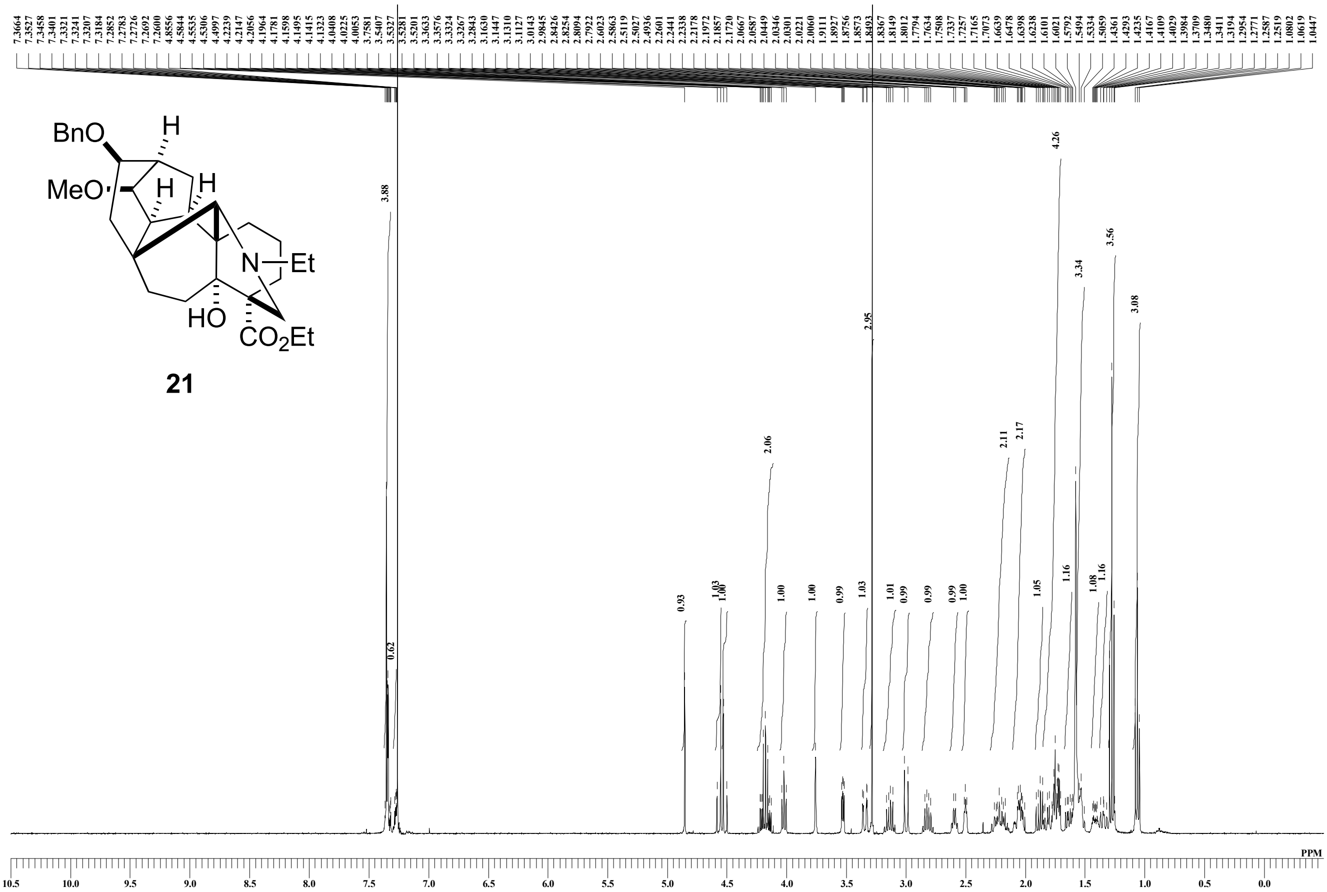
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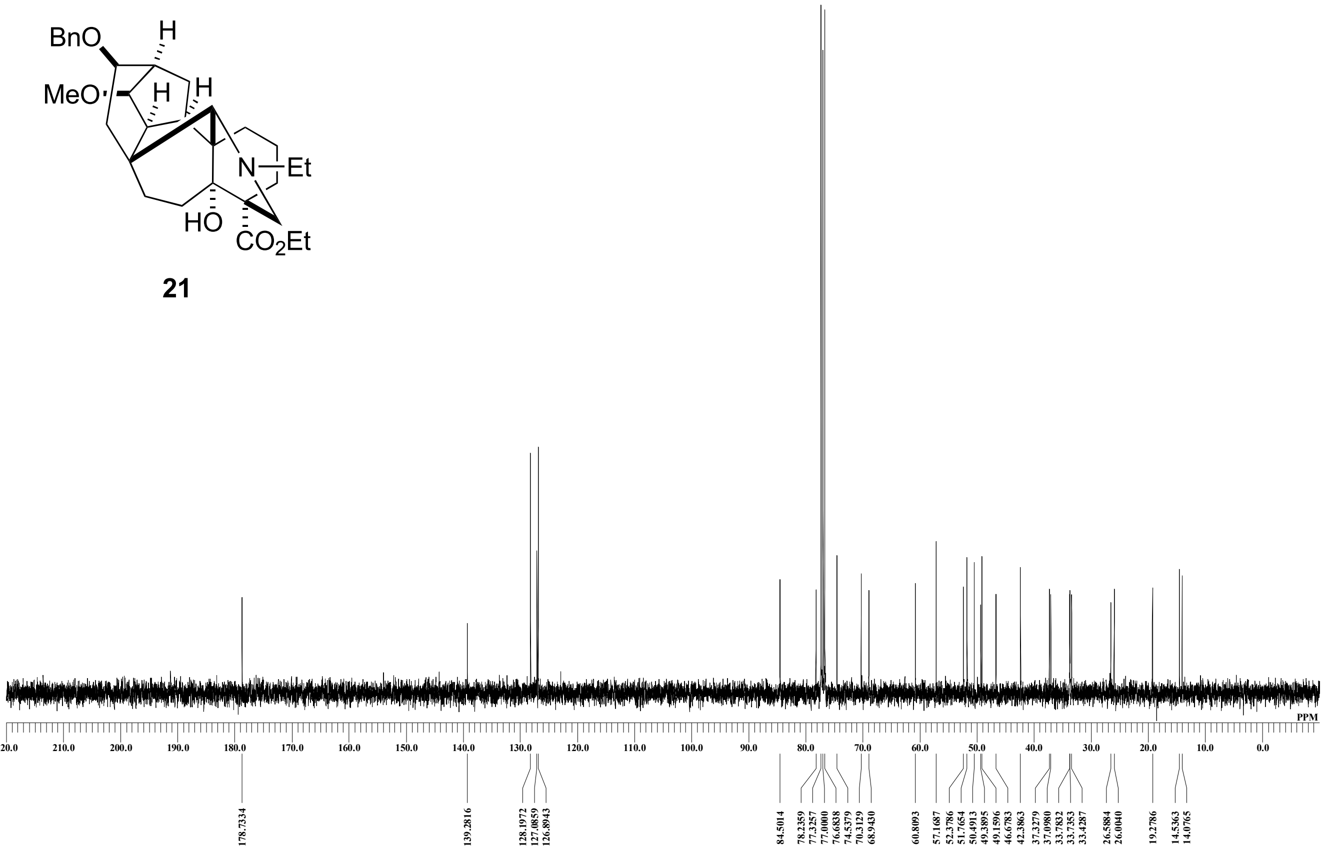
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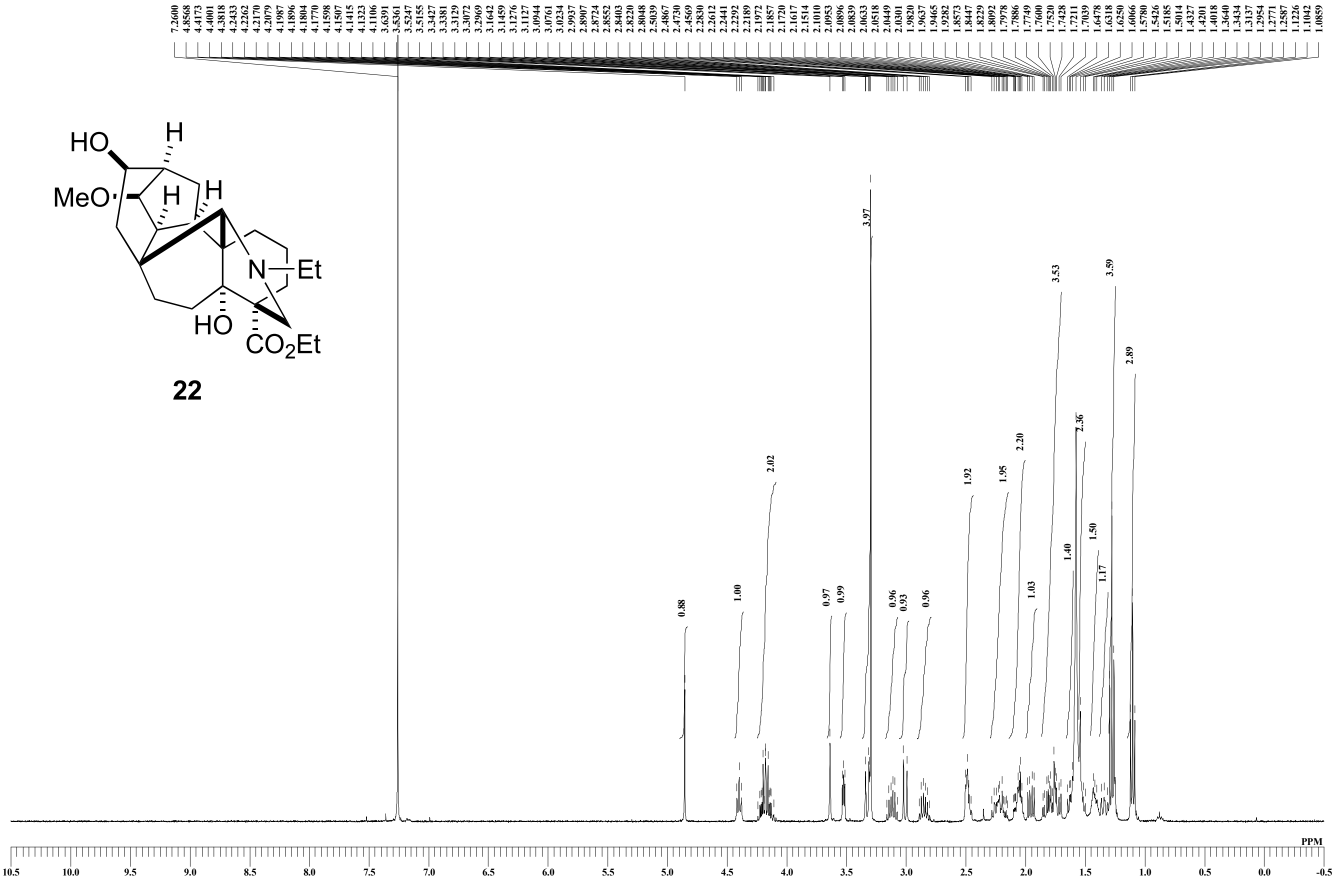
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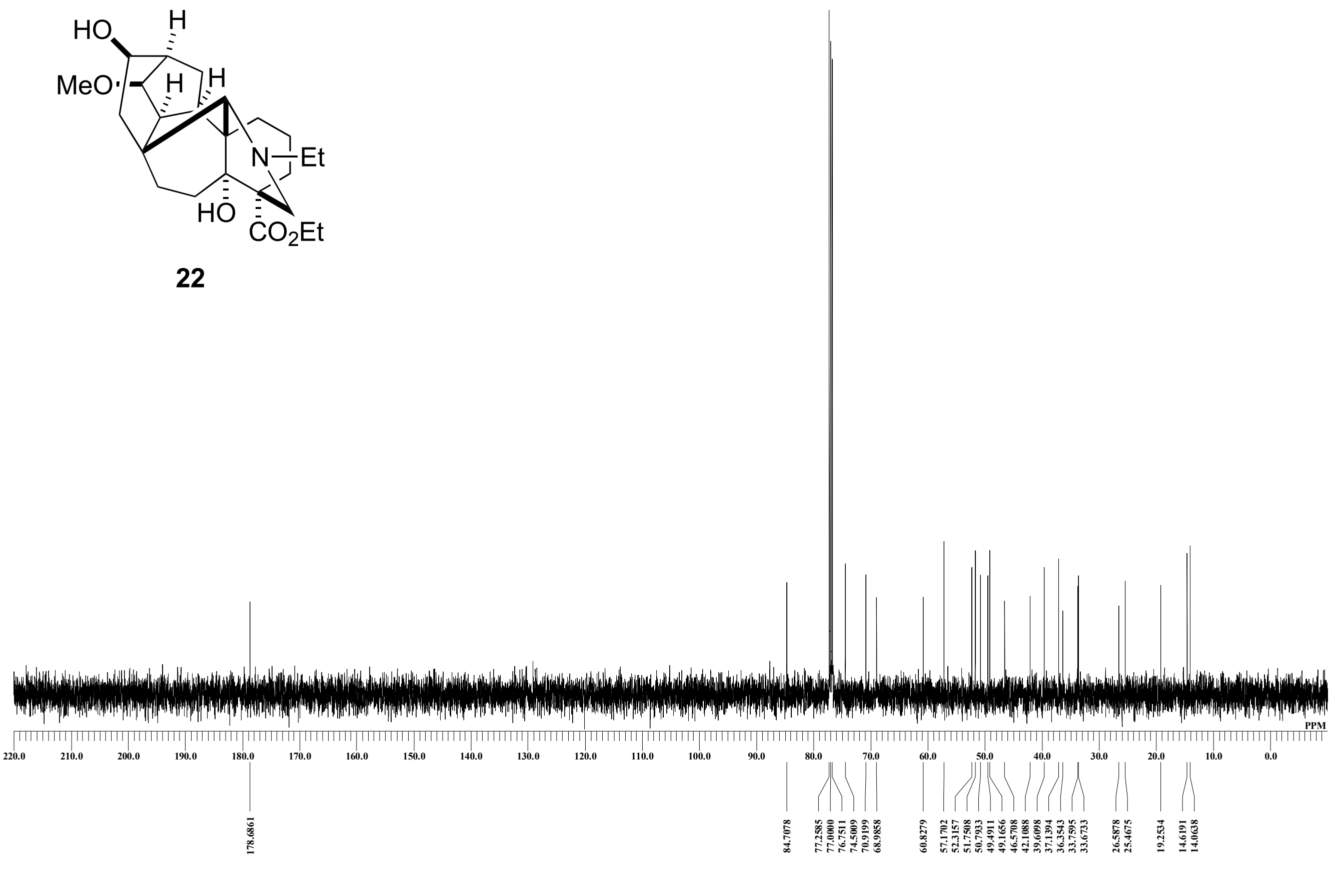
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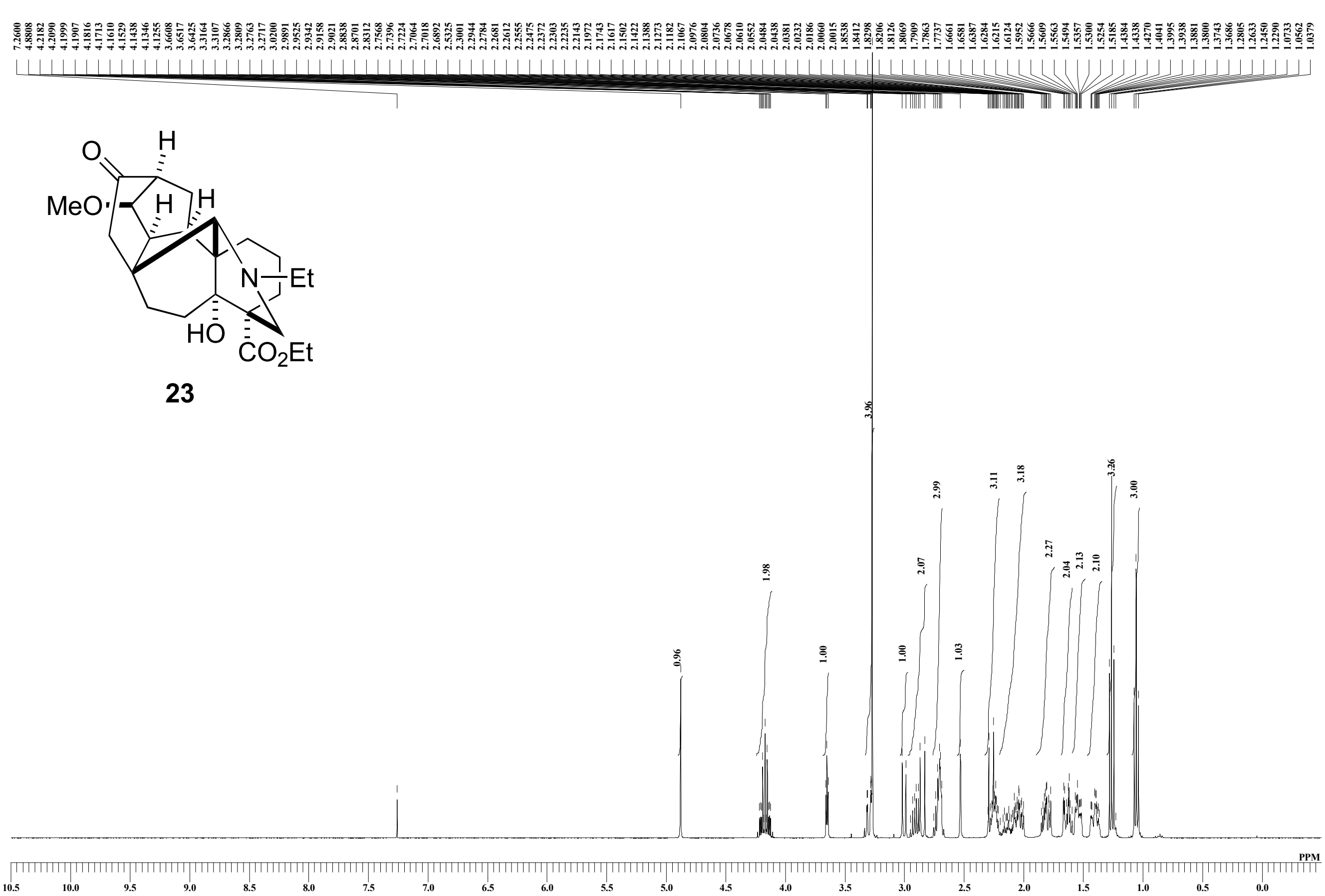
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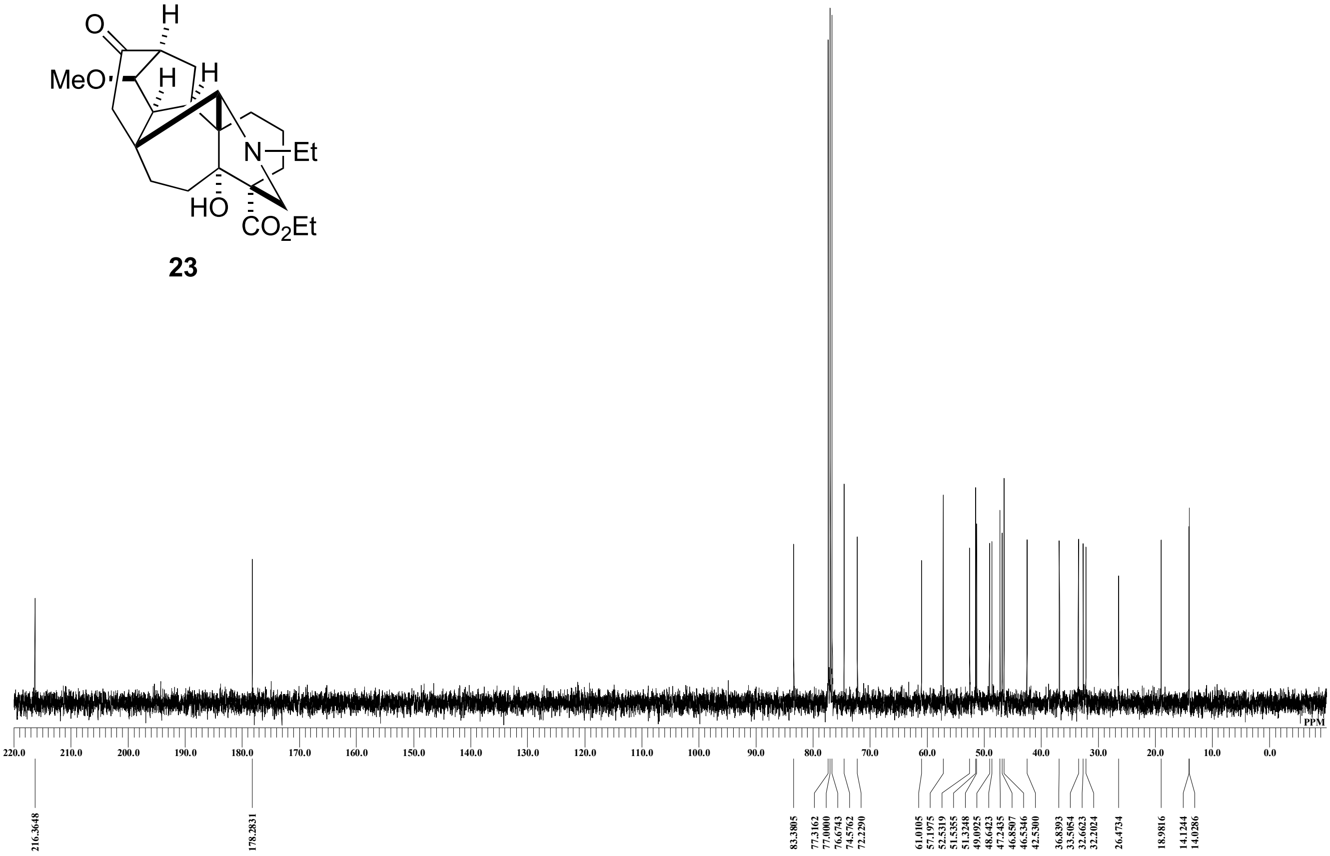
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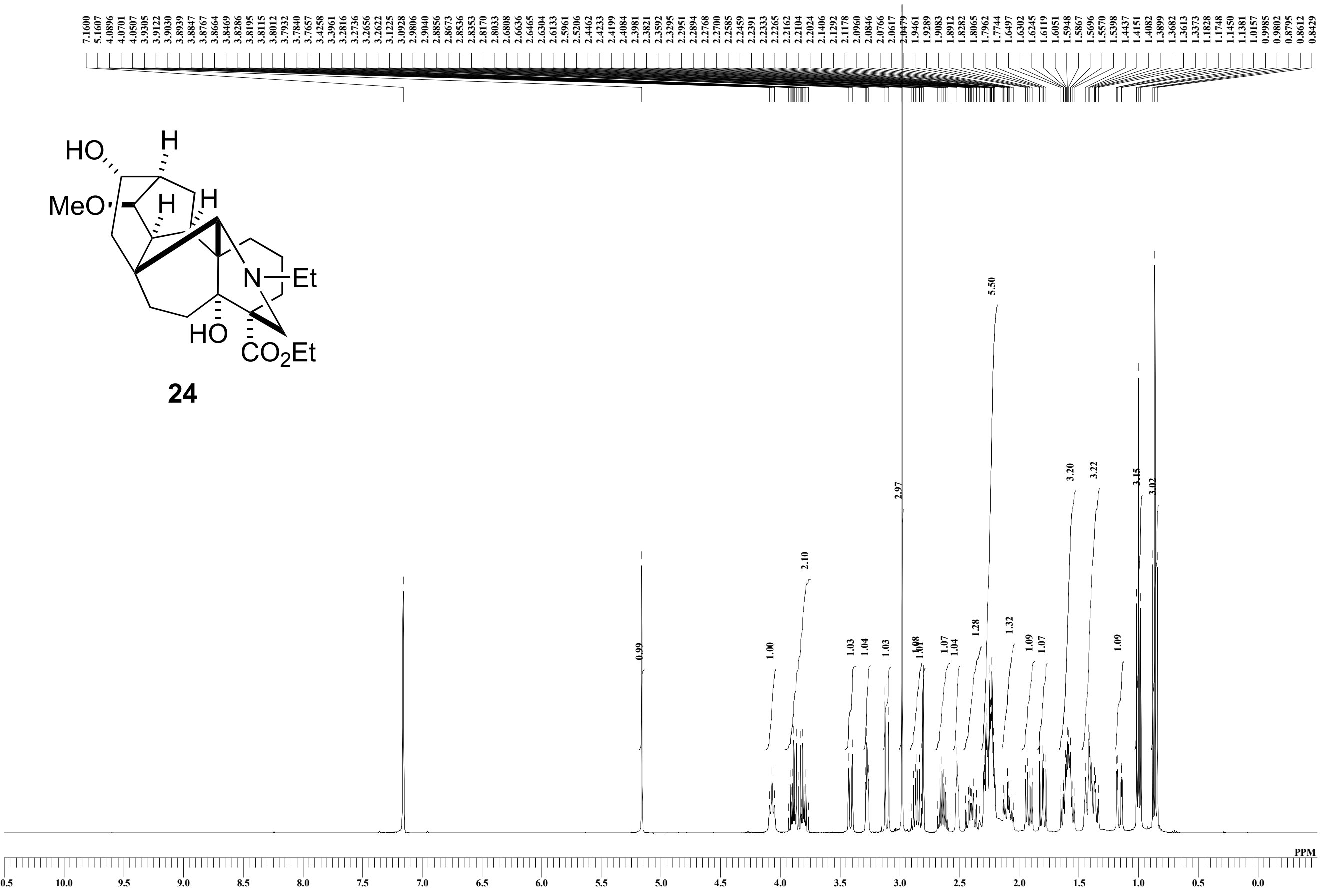
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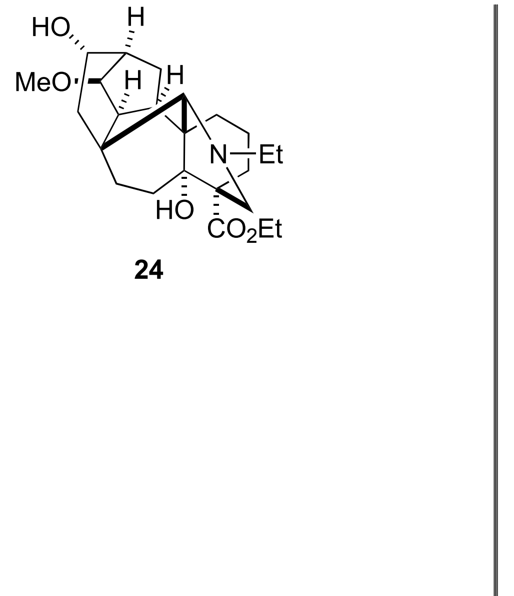
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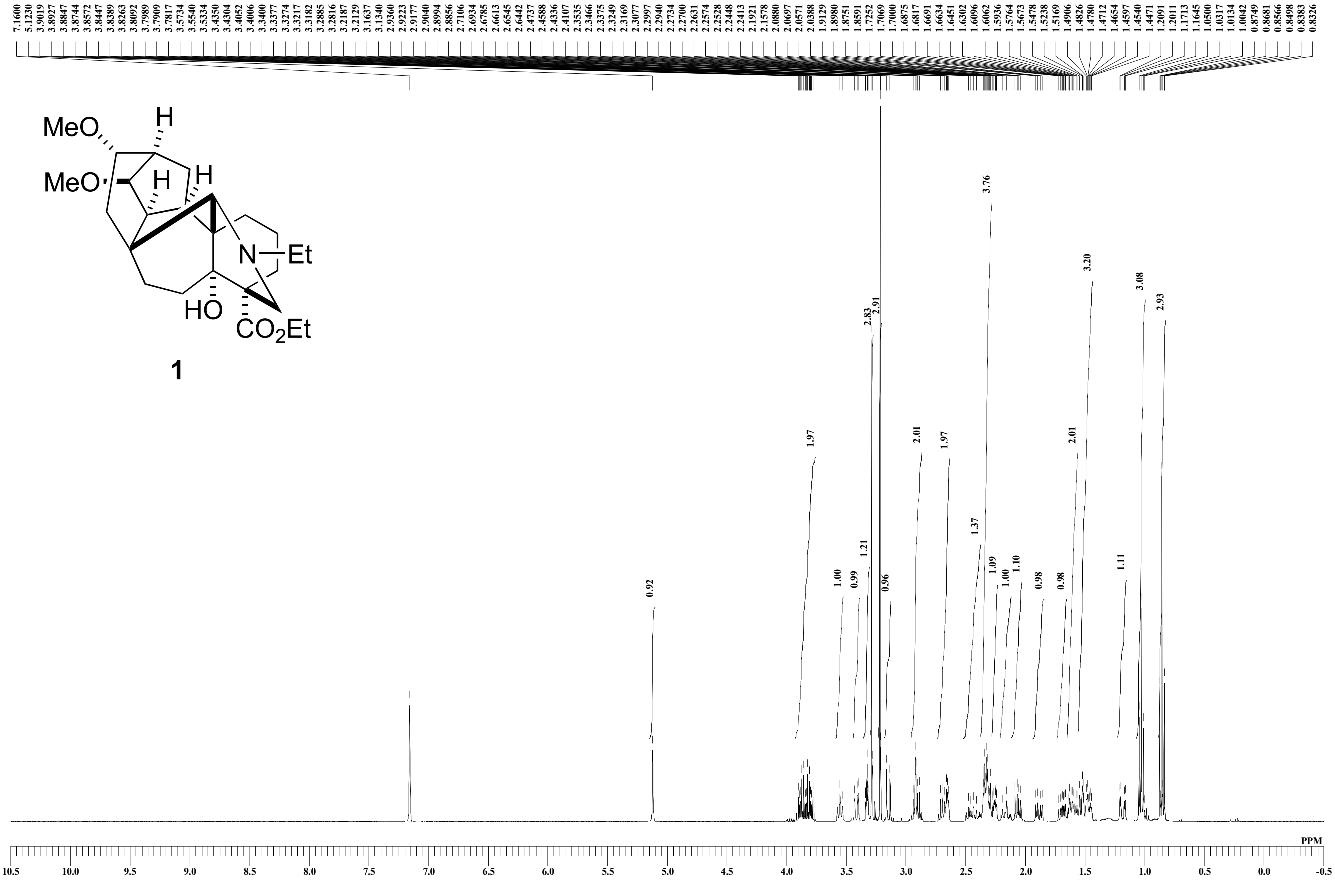
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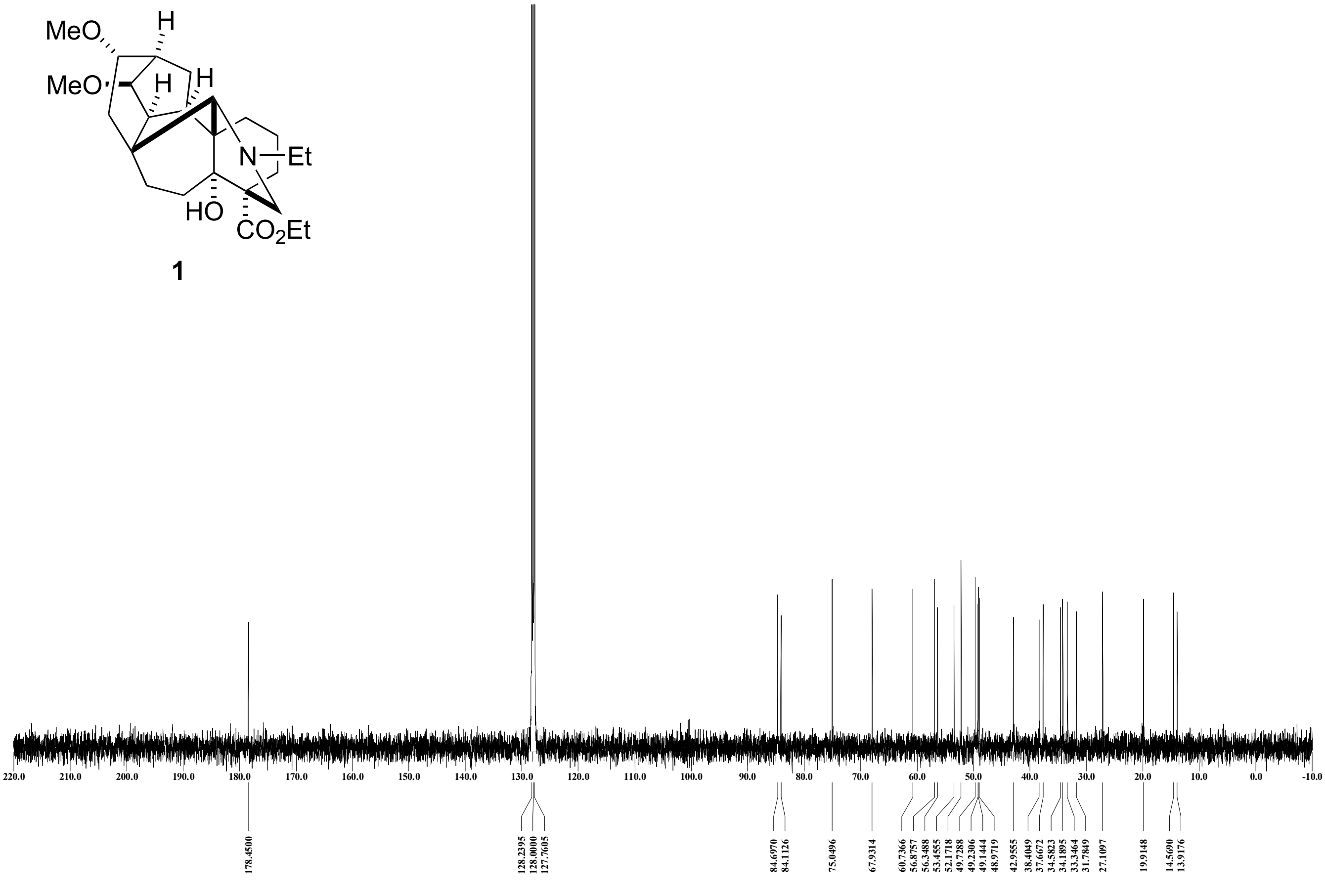
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