A Convergent Total Synthesis of Ouabagenin

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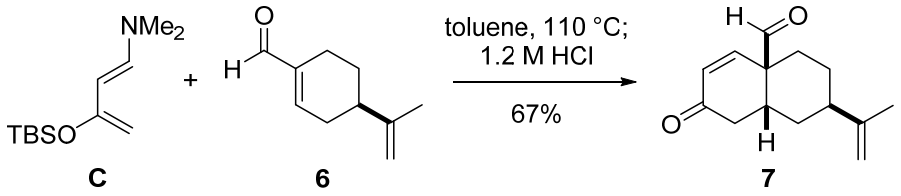
Supporting Information

58 pages

Contents: page

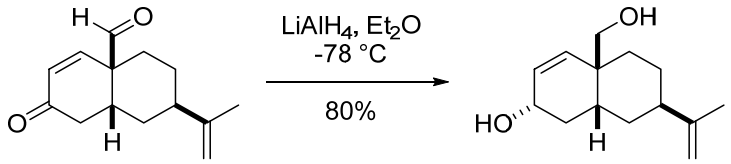
General Methods: All reactions sensitive to air or moisture were carried out under argon atmosphere under anhydrous conditions, unless otherwise noted. THF, CH_2Cl_2, toluene, DMF and Et_2O were purified by Glass Contour solvent dispensing system (Nikko Hansen & Co., Ltd., Osaka, Japan). All other reagents were used as supplied. Analytical thin-layer chromatography (TLC) was performed using E. Merck Silica gel 60 F254 pre-coated plates. Flash chromatography was performed using 40-50 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. Optical rotations were measured on JASCO DIP-1000 Digital Polarimeter at room temperature using the sodium D line. Infrared (IR) spectra were recorded as a thin film on a NaCl disk for synthetic intermediates and a KBr disk for ouabagenin (**1**) using JASCO FT/IR-4100 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on JEOL JNM-ECX-500, JNM-ECA-500, or JNM-ECS-400 spectrometer at room temperature. Chemical shifts were reported in ppm on the δ scale relative to $CHCl_3$ (δ = 7.26 for ^{1}H NMR), $CDCl_3$ (δ = 77.0 for ^{13}C NMR), CD_2HOD (δ =3.31 for ^{1}H NMR), CD_3OD (δ = 49.0 for ^{13}C NMR), C_6D_5H (δ = 7.16 for ^{1}H NMR), C_6D_6 (δ = 128.06 for ^{13}C NMR), $(CD_2H)CD_3SO$ (δ = 2.50 for ^{1}H NMR) and $(CD_3)_2SO$ (δ = 39.52 for ^{13}C NMR), as internal references. Signal patterns are indicated as s, singlet; d, doublet; m, multiplet; br, broaden peak. The numbering of compounds corresponds to that of **1**. High resolution mass spectra were measured on JEOL JMS-T100LP instrument (ESI-TOF) or BRUKER DALTONICS microTOF II (ESI-TOF).



C **6** **7**

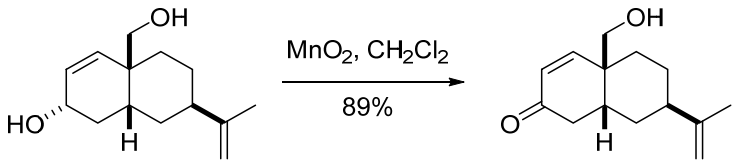
Aldehyde 7. Rawal's diene **C**[S1] (46.4 g, 204 mmol) was added to a solution of (*R*)-perillaldehyde **6**[S2] (15.9 g, 106 mmol) in refluxing toluene in five portions every three hours. After the consumption of **6** was confirmed by ^{1}H-NMR analysis of the reaction mixture, the mixture was cooled to room temperature and concentrated. THF (530 mL) and 1.2 M HCl (270 mL) were successively added to the resultant residue. The mixture was stirred at room temperature for 13 h, and then was concentrated to remove THF. After brine (200 mL) was added, the resultant mixture was extracted with EtOAc (600 mL x3). The combined organic layers were washed with brine (500 mL). The aqueous layers were re-extracted with EtOAc (500 mL). Then, the combined organic layers were

dried over Na_2SO_4, filtrated, and concentrated. The residue was purified by flash column chromatography on silica gel (800 g, hexane to hexane/EtOAc 5/1) to afford **7** (15.5 g, 71.0 mmol) in 67%: colorless oil; $[\alpha]_D^{25}$ -190 (*c* 1.8, $CHCl_3$). IR, ^1H and ^{13}C NMR data of **7** were identical to those of the antipode reported previously.[S3]



7 **8**

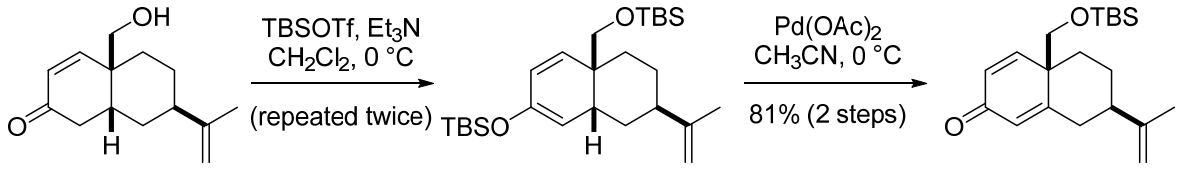
Alcohol 8. $LiAlH_4$ (6.7 g, 180 mmol) was added to a solution of **7** (15.5 g, 71.0 mmol) in Et_2O (710 mL) at -78 ºC. The reaction mixture was stirred at -78 ºC for 7 h, and then H_2O (7 mL), aqueous 15 wt% NaOH (7 mL) and H_2O (21 mL) were successively added at -78 ºC. The mixture was warmed to room temperature, and was filtered through a pad of Celite with EtOAc (300 mL). The filtrate was concentrated, and the residue was purified by flash column chromatography on silica gel (430 g, CH_2Cl_2 to CH_2Cl_2/EtOAc 2/1) to afford diol **8** (12.6 g, 56.7 mmol) in 80% yield: white crystal; m.p. 97-98 ºC; $[\alpha]_D^{25}$ -32 (*c* 2.6, $CHCl_3$); IR (neat) ν 3345, 2931, 2862, 1644, 1456, 1052, 1032 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.21-1.32 (1H, m, $H8_a$), 1.27-1.35 (1H, m, O*H*) 1.45-1.51 (1H, m, $H6_a$), 1.52-1.62 (3H, m, $H8_b$ and 9), 1.71 (3H, s, CCH_3), 1.73 (1H, ddd, *J* = 13.8, 13.8, 5.2 Hz, $H6_b$), 1.79-1.84 (2H, m, H4), 2.02-2.08 (1H, m, H5), 2.08 (1H, m, H7), 3.49 (1H, d, *J* = 10.9 Hz, $H19_a$), 3.71 (1H, dd, *J* = 10.9, 4.6 Hz, $H19_b$), 4.36 (1H, m, H3), 4.67-4.71 (2H, m, CCH_3=CH_2), 5.51 (1H, dd, *J* = 10.3, 2.3 Hz, H2), 5.76 (1H, dd, *J* = 10.3, 1.7 Hz, H1); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.9, 27.3, 30.3, 31.5, 33.4, 35.6, 39.3, 40.4, 66.7, 68.7, 108.5, 132.6, 136.0, 150.1; HRMS (ESI) calcd for $C_{14}H_{22}O_2Na$ $[M+Na]^+$ 245.1512, found 245.1512.



8 **9**

Enone 9. MnO_2 (90% purity, 50.4 g, 522 mmol) was added to a solution of diol **8** (7.74 g, 34.8 mmol) in CH_2Cl_2 (120 mL) at room temperature. The reaction mixture was stirred at room temperature for 7 h, and then was filtered through a pad of Celite with CH_2Cl_2 (300 mL), MeOH (500 mL) and a 3 : 1 mixture of $CHCl_3$ and MeOH (500 mL). The filtrate was concentrated, and the residue was purified by flash column chromatography on silica gel (100 g, hexane to hexane/Et_2O 1/2) to afford enone **9** (6.86 g, 31.1 mmol) in 89% yield:

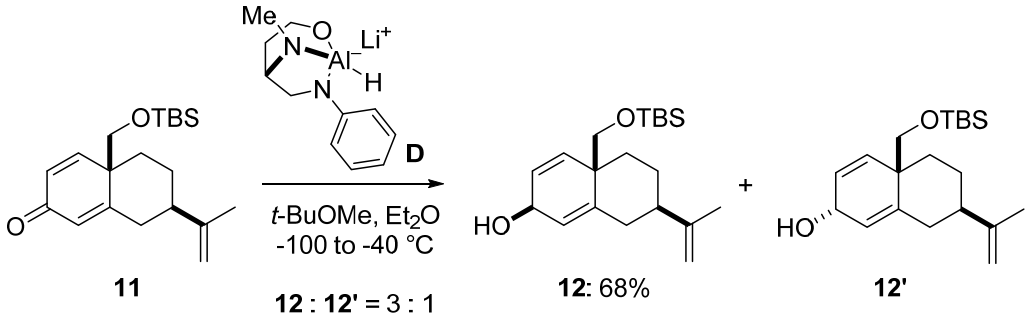
crystal; m.p. 83-84 ºC; $[\alpha]_D^{25}$ -2.1 (*c* 1.2, $CHCl_3$). IR, ^1H and ^{13}C NMR data of **9** were identical to those reported previously.[S4]



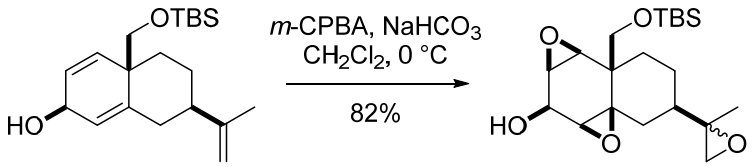
9 **10** **11**

Dienone 11. TBSOTf (36 mL, 160 mmol) was added to a solution of enone **9** (6.84 g, 31.0 mmol) and Et_3N (43 mL, 310 mmol) in CH_2Cl_2 (310 mL) at 0 ºC. The reaction mixture was stirred at 0 ºC for 2 h, and then saturated aqueous $NaHCO_3$ (50 mL) was added. After H_2O (50 mL) was added, the resultant solution was extracted with EtOAc (300 mL x3). The combined organic layers were washed with brine (300 mL), dried over Na_2SO_4, filtrated, and concentrated. The residue was purified by flash column chromatography on silica gel (200g, hexane/Et_3N 100/1 to EtOAc/Et_3N 100/1) to afford **10** and the desilylated enone (3.3 g). According to the above procedure, the desilylated enone was silylated again by using TBSOTf (8.0 mL, 35 mmol) and Et_3N (9.7 mL, 70 mmol) in CH_2Cl_2 (91 mL).

$Pd(OAc)_2$ (4.0 g, 1.8 mmol) was added to a solution of the above combined crude TBS-enol ether **10** in CH_3CN (310 mL) at 0 ºC. The reaction mixture was stirred at 0 ºC for 3 h, and then $Pd(OAc)_2$ (0.5-1.0 g, 0.16-0.32 mmol) was added every 3 h. Total 7.0 g of $Pd(OAc)_2$ was added until **10** disappeared on TLC. The reaction mixture was filtered through a pad of Al_2O_3 (400 g) with EtOAc, and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (200 g, hexane to hexane/EtOAc 15/1) to afford dienone **11** (8.25 g, 24.8 mmol) in 81% yield over 2 steps: colorless oil; $[\alpha]_D^{26}$ -160 (*c* 1.1, $CHCl_3$); IR (neat) ν 2951, 2931, 2857, 1666, 1469, 1442, 1396, 1254, 1100, 841 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ -0.04 (3H, s, C*H*$_3$ of TBS), -0.03 (3H, s, C*H*$_3$ of TBS), 0.80 (9H, s, *t*-Bu of TBS), 1.24 (1H, ddd, *J* = 13.7, 13.7, 4.0 Hz, H9$_a$), 1.55 (1H, dddd, *J* = 13.7, 13.7, 13.7, 4.0 Hz, H8$_a$), 1.70-1.74 (1H, m, H8$_b$), 1.71 (3H, s, CC*H*$_3$), 2.02 (1H, dddd, *J* = 13.7, 12.6, 4.0, 4.0 Hz, H7$_a$), 2.19 (1H, ddd, *J* = 13.7, 4.0, 2.9 Hz, H9$_b$), 2.29 (1H, ddd, *J* = 12.6, 12.6, 1.8 Hz, H6$_a$), 2.36 (1H, ddd, *J* = 12.6, 4.0, 1.8 Hz, H6$_b$), 3.53 (1H, d, *J* = 9.8 Hz, H19$_a$), 3.80 (1H, d, *J* = 9.8 Hz, H19$_b$), 4.72 (1H, s, CCH_3=C*H*$_A$H$_B$), 4.74 (1H, s, CCH_3=CH$_A$*H*$_B$), 6.14 (1H, dd, *J* = 1.8, 1.8 Hz, H4), 6.21 (1H, dd, *J* = 9.8, 1.7 Hz, H2), 6.87 (1H, d, *J* = 9.8 Hz, H1); ^{13}C NMR (125 MHz, $CDCl_3$) δ -5.73, -5.68, 18.0, 20.6, 25.6, 26.1, 32.1, 37.8, 46.3, 46.8, 65.5, 109.6, 126.9, 128.3, 147.8, 154.6, 163.4, 186.7; HRMS (ESI) calcd for $C_{20}H_{32}O_2SiNa$ $[M+Na]^+$ 355.2064, found 355.2067.

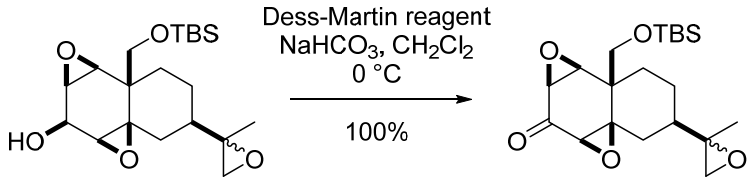


Allylic alcohol 12. $LiAlH_4$ (1.0 M in Et_2O, 140 mL, 140 mmol) was added to a solution of (*S*)-4-anilino-3-methylamino-1-butanol (27.2 g, 140 mmol) in *t*-BuOMe (100 mL) at 0 ºC over 40 min. The mixture was warmed to room temperature, and stirred for 3 h. After the mixture was cooled to -100 ºC, a solution of dienone **11** (7.76 g, 23.2 mmol) in *t*-BuOMe (17 mL) was added over 10 min. The reaction mixture was stirred at -100 ºC for 4 h and -40 ºC for 20 h, and then MeOH (5 mL) and H_2O (30 mL) were successively added. After being warmed at room temperature, the resultant solution was filtered through a pad of Celite with Et_2O (1 L). The filtrate was washed with brine (200 mL), dried over Na_2SO_4, and filtrated. Hexane (1 L) and Et_3N (10 mL) were added to the solution, and the combined solution was filtered through a pad of silica gel (50 g, hexane/Et_2O/Et_3N 100/100/1) to remove (*S*)-4-anilino-3-methylamino-1-butanol. The filtrate was concentrated to afford a 3 : 1 diastereomeric mixture of allyllic alcohol **12** and **12'**. The residue was purified by flash column chromatography on silica gel (250 g, hexane/Et_3N 100/1 to hexane/EtOAc/Et_3N 150/10/1) to afford **12** (5.27 g, 15.8 mmol) in 68% yield and impure **12'** (2.0 g): colorless oil; $[\alpha]_D^{26}$ -22 (*c* 1.2, $CHCl_3$); IR (neat) ν 3348, 2930, 2857, 1644, 1470, 1442, 1255, 1092, 839 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.035 (3H, s, C*H*$_3$ of TBS), 0.041 (3H, s, C*H*$_3$ of TBS), 0.88 (9H, s, *t*-Bu of TBS), 1.29 (1H, ddd, *J* = 13.7, 13.7, 4.6 Hz, H9$_a$), 1.42-1.52 (1H, m, H8$_a$), 1.47 (1H, d, *J* = 10.9 Hz, O*H*), 1.64-1.71 (1H, m, H8$_b$), 1.74 (3H, s, CC*H*$_3$=CH$_2$), 1.81 (1H, ddd, *J* = 13.7, 3.5, 3.5 Hz, H9$_b$), 1.97 (1H, dddd, *J* = 12.6, 12.6, 3.5, 3.5 Hz, H7), 2.12 (1H, d, *J* = 13.8, 12.6, 1.2 Hz, H6$_a$), 2.22 (1H, ddd, *J* = 13.8, 3.5, 2.3 Hz, H6$_b$), 3.48 (1H, d, *J* = 9.8 Hz, H19$_a$), 3.72 (1H, d, *J* = 9.8 Hz, H19$_b$), 4.39 (1H, ddd, *J* = 10.9, 5.2, 4.6 Hz, H3), 4.71-4.74 (2H, m, CCH$_3$=C*H*$_2$), 5.68 (1H, d, *J* = 9.8 Hz, H1), 5.82-5.85 (1H, m, H4), 5.97 (1H, ddd, *J* = 9.8, 4.6, 1.7 Hz, H2); ^{13}C NMR (125 MHz, $CDCl_3$) δ -5.5, -5.4, 18.6, 20.8, 26.0, 27.1, 34.1, 37.3, 42.4, 46.6, 62.6, 65.5, 108.8, 124.1, 127.0, 137.1, 142.7, 149.3; HRMS (ESI) calcd for $C_{20}H_{34}O_2SiNa$ $[M+Na]^+$ 357.2220, found 357.2222.



12 13

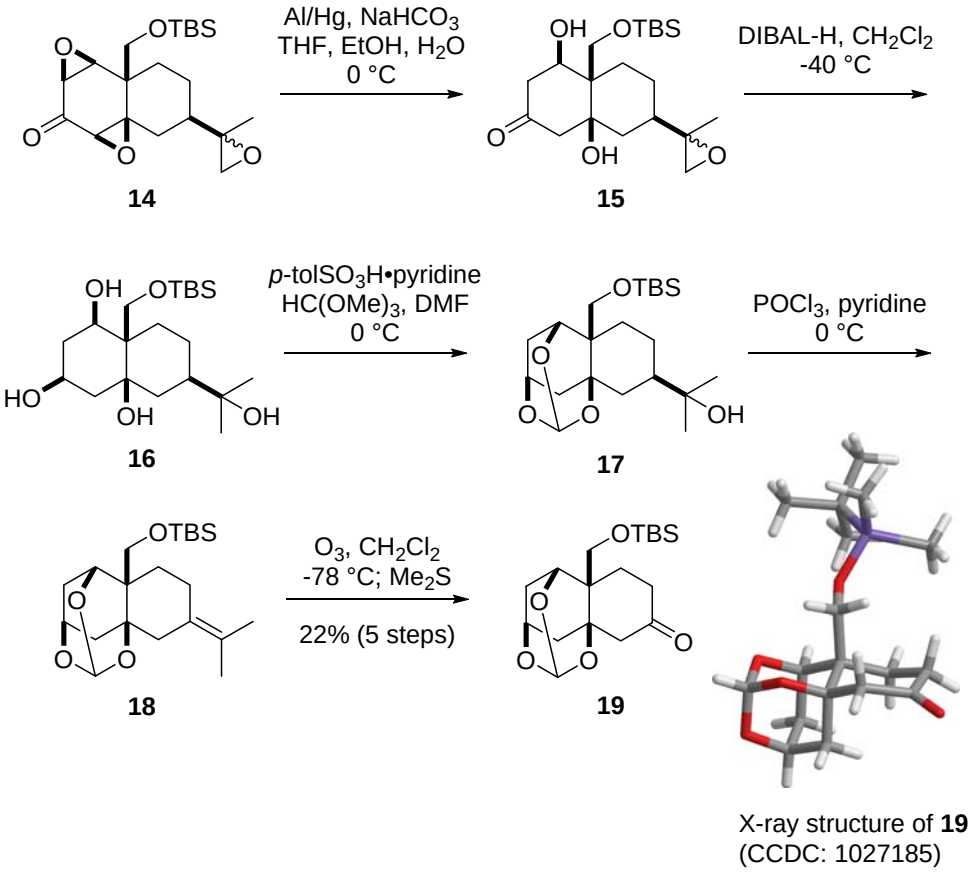
Tris-epoxide 13. *m*-CPBA (77% purity, 12.4 g, 55.2 mmol) was added to a mixture of allylic alcohol **12** (5.27 g, 15.8 mmol) and $NaHCO_3$ (5.3 g, 63 mmol) in CH_2Cl_2 (160 mL) at 0 ºC. The reaction mixture was stirred at 0 ºC for 3 h, and then saturated aqueous $Na_2S_2O_3$ (20 mL) was added. After saturated aqueous $NaHCO_3$ (40 mL) was added, the resultant solution was extracted with EtOAc (150 mL x3). The combined organic layers were washed with $NaHCO_3$ (100 mL x3) and brine (200 mL), dried over Na_2SO_4, filtrated, and concentrated. The residue was purified by flash column chromatography on silica gel (100 g, hexane to EtOAc) to afford a 1 : 1 diastereomeric mixture of tris-epoxide **13** (4.93 g, 12.9 mmol) in 82% yield: white solid; m.p. 116-117 ºC; $[\alpha]_D^{27}$ -9.9 (*c* 1.0, $CHCl_3$); IR (neat) ν 3414, 2935, 2860, 1645, 1467, 1254, 1095, 1034, 841 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.09 (3H, s, C*H*$_3$ of TBS), 0.10 (3H, s, C*H*$_3$ of TBS), 0.91 (9H, s, *t*-Bu of TBS), 1.01-1.13 (2H, m), 1.26 (3/2H, s, C*H*$_3$), 1.27 (3/2H, s, C*H*$_3$), 1.38-1.48 (2H, m), 1.65-1.78 (1H, m), 1.78-1.92 (1H, m), 2.22-2.28 (1H, m), 2.42-2.52 (1H, m), 2.54 (1H, dd, *J* = 4.5, 4.5 Hz), 2.62 (1H, d, *J* = 4.5 Hz), 2.98-3.03 (1H, m), 3.18-3.20 (1H, m), 3.35 (1H, m), 3.81-3.84 (1H, m), 3.98-4.00 (1H, m), 4.21-4.27 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ -5.60, -5.59, 18.21, 18.25, 18.35, 22.3, 22.7, 25.8, 28.58, 28.61, 34.0, 34.4, 37.5, 37.6, 43.3, 52.9, 53.1, 54.2, 58.36, 58.39, 60.82, 60.84, 60.95, 61.13, 61.16, 65.1, 65.4, 65.5, some of ^{13}C peaks were not observed due to overlap with other peaks; HRMS (ESI) calcd for $C_{20}H_{34}O_5SiNa$ $[M+Na]^+$ 405.2068, found 405.2064.



13 14

Ketone 14. Dess-Martin periodinane (11.2 g, 26.4 mmol) was added to a 1 : 1 diastereomeric mixture of tris-epoxide **13** (6.71 g, 17.5 mmol) and $NaHCO_3$ (4.4 g, 52 mmol) in CH_2Cl_2 (180 mL) at 0 ºC. The reaction mixture was stirred at room temperature for 5 h, and then saturated aqueous $Na_2S_2O_3$ (20 mL) was added. After saturated aqueous $NaHCO_3$ (20 mL) was added, the resultant solution was extracted with EtOAc (150 mL x3). The combined organic layers were washed with brine (150 mL), dried over Na_2SO_4, filtrated, and concentrated. The residue was purified by flash column chromatography on

silica gel (200 g, hexane to hexane/EtOAc 4/1) to afford a 1 : 1 diastereomeric mixture of ketone **14** (6.67 g, 17.5 mmol) in 100 % yield: colorless oil; $[\alpha]_D^{25}$ -10 (*c* 2.0, $CHCl_3$); IR (neat) ν 2932, 2884, 2857, 1705, 1468, 1445, 1388, 1254, 1102, 942, 840 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.12 (3H, s, C*H*$_3$ of TBS), 0.13 (3H, s, C*H*$_3$ of TBS), 0.92 (9H, s, *t*-Bu of TBS), 1.01-1.08 (1H, m), 1.16 (1H, ddd, *J* = 13.8, 13.8, 4.6 Hz), 1.27 (3H, s, C*H*$_3$), 1.38-1.57 (2H, m), 1.72-1.80 (1H, m), 1.88 (1/2H, dd, *J* = 13.8 Hz, H7), 1.94 (1/2H, dd, *J* = 13.8 Hz, H7), 2.28-2.34 (1H, m), 2.54-2.57 (1H, m), 2.60-2.64 (1H, m), 3.07-3.10 (1H, m), 3.41-3.43 (1H, m), 3.48 (1H, d, *J* = 4.0 Hz), 4.01-4.05 (1H, m), 4.06-4.10 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ -5.6, 14.1, 18.2, 18.3, 18.6, 21.9, 22.2, 22.6, 25.8, 27.8, 27.9, 31.6, 33.7, 34.0, 39.50, 39.54, 42.9, 43.0, 52.7, 53.1, 55.9, 58.08, 58.11, 61.38, 61.40, 61.44, 64.6, 64.7, 64.6, 64.7, 70.30, 70.34, 200.7, some of ^{13}C peaks were not observed due to overlap with other peaks; HRMS (ESI) calcd for $C_{21}H_{36}O_6SiNa$ $[M+MeOH+Na]^+$ 435.2173, found 435.2168.



X-ray structure of **19**
(CCDC: 1027185)

Ketone 19. Al/Hg was prepared from small pieces of aluminum foil (2.8 g) by treating with 2 wt% aqueous $HgCl_2$ (100 mL) for 20 seconds and washing with EtOH and Et_2O. The freshly prepared Al/Hg was added to a solution of a 1 : 1 diastereomeric mixture of ketone **14** (7.14 g, 18.6 mol) in a mixture of THF (214 mL), EtOH (71 mL), H_2O (71 mL) and saturated aqueous $NaHCO_3$ (14 mL) at 0 ºC. The reaction mixture was stirred at 0 ºC

for 3 h. After Et_2O (1 L) cooled to -40 ºC was added, the resultant solution was filtered through a pad of Celite with Et_2O. The filtrate was washed with brine (400 mL), dried over Na_2SO_4, filtrated, and directly subjected to flash column chromatography on silica gel (50 g, Et_2O) to afford the impure diol **15**, which was used in the next reaction without further purification.

DIBAL-H (1.0 M in hexane, 93 mL, 93 mmol) was added to a solution of the above crude diol **15** in CH_2Cl_2 (370 mL) at -40 ºC over 20 min. The reaction mixture was stirred at -40 ºC for 10 min, and then saturated aqueous Rochelle's salt (100 mL) was added. The resultant solution was stirred at room temperature for 20 h. The mixture was extracted with EtOAc (350 mL x3), and the combined organic layers were washed with brine (400 mL), dried over Na_2SO_4, filtrated, and concentrated to afford the impure tetraol **16**, which was used in the next reaction without further purification.

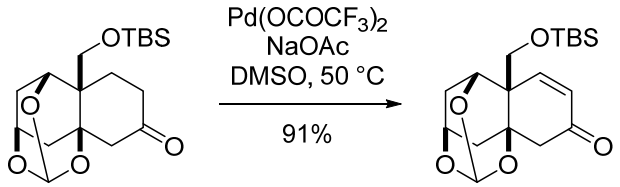
p-tolSO_3H·pyridine (466 mg, 1.85 mmol) was added to a solution of the above crude tetraol **16** and $HC(OMe)_3$ (100 mL, 920 mmol) in DMF (370 mL) at 0 ºC. The reaction mixture was stirred at 0 ºC for 2 h, and then saturated aqueous $NaHCO_3$ (100 mL) was added. The resultant solution was extracted with Et_2O (400 mL x3), and the combined organic layers were washed with H_2O (400 mL x2), brine (400 mL), dried over Na_2SO_4, filtrated, and concentrated. The residue was purified by flash column chromatography on silica gel (200g, hexane/Et_3N 100/1 to hexane/Et_2O/Et_3N 100/100/1) to afford the impure orthoester **17**, which was used in the next reaction without further purification.

$POCl_3$ (2.1 mL, 23 mmol) was added to a solution of the above crude orthoester **17** in pyridine (74 mL) at 0 ºC. The reaction mixture was stirred at 0 ºC for 16 h, and then saturated aqueous $NaHCO_3$ (50 mL) was added. After H_2O (20 mL) was added, the resultant solution was extracted with EtOAc (100 mL x3). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtrated, and concentrated. The residue was purified by flash column chromatography on silica gel (75 g, hexane to EtOAc) to afford the impure **18**, which was used in the next reaction without further purification:

For characterization of **18**, a small amount of the mixture was purified by flash column chromatography on silica gel (75 g, hexane to EtOAc). **18**: colorless oil; $[\alpha]_D^{26}$ +1.4 (*c* 1.8, $CHCl_3$); IR (neat) ν 2953, 2929, 2856, 1463, 1377, 1250, 1174, 1132, 1100, 1088, 991 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.066 (3H, s, C*H*$_3$ of TBS), 0.069 (3H, s, C*H*$_3$ of TBS), 0.90 (9H, s, *t*-Bu of TBS), 1.20 (1H, ddd, *J* = 13.2, 13.2, 5.2 Hz, H9$_a$), 1.66 (3H, s, C*H*$_3$), 1.69 (3H, s, C*H*$_3$), 1.76 (1H, dd, *J* = 13.8, 1.7 Hz, H2$_a$), 1.81 (1H, ddd, *J* = 13.2, 5.7, 2.3 Hz, H9$_b$), 1.94 (1H, ddd, *J* = 13.8, 3.5, 2.3 Hz, H4$_a$), 2.01-2.08 (1H, m, H4$_b$), 2.01-2.08 (1H, m, H8$_a$), 2.11 (1H, d, *J* = 13.7 Hz, H6$_a$), 2.35 (1H, d, *J* = 13.7 Hz, H6$_b$), 2.54-2.62 (2H, m, H2$_b$

and 8_b), 4.02 (1H, d, J = 9.8 Hz, $H19_a$), 4.15-4.17 (1H, m, H1), 4.21-4.23 (1H, m, H3), 4.42 (1H, d, J = 9.8 Hz, $H19_b$), 5.68 (1H, s, C*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ -5.54, -5.46, 18.3, 20.3, 20.4, 24.3, 25.0, 25.9, 28.8, 34.9, 36.9, 43.0, 59.0, 67.3, 69.8, 74.8, 106.3, 125.6, 126.1; HRMS (ESI) calcd for $C_{21}H_{36}O_4SiNa$ $[M+Na]^+$ 403.2275, found 403.2268.

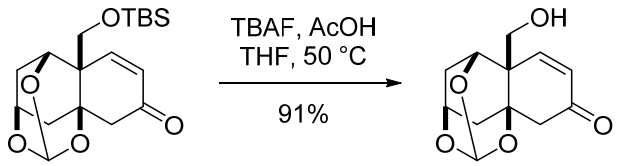
Ozone was bubbled into a stirred solution of the above crude **18** in CH_2Cl_2 (57 mL) at -78 ºC for 1 h. After oxygen was bubbled into the reaction mixture for 30 min, Me_2S (3.0 mL, 41 mmol) was added at -78 ºC. The resultant solution was warmed to room temperature, stirred for 12 h, and then concentrated. The residue was purified by flash column chromatography on silica gel (75 g, hexane to hexane/EtOAc 2/1) to afford ketone **19** (1.42 g, 4.01 mmol) in 22% yield over 5 steps: crystal; m.p. 118-119 ºC; $[\alpha]_D^{26}$ -11 (*c* 1.2, $CHCl_3$); IR (neat) ν 2954, 2931, 2897, 2856, 1716, 1470, 1284, 1249, 1146, 1091, 995, 974 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.09 (3H, s, CH_3 of TBS), 0.10 (3H, s, CH_3 of TBS), 0.90 (9H, s, *t*-Bu of TBS), 1.51 (1H, ddd, J = 13.7, 12.6, 6.3 Hz, $H9_a$), 1.82 (1H, dd, J = 13.8, 1.7, 1.7 Hz, $H2_a$), 1.86 (1H, d, J = 13.8 Hz, $H4_a$), 2.11 (1H, ddd, J = 13.7, 8.1, 1.8 Hz, $H9_b$), 2.13-2.19 (1H, m, $H4_b$), 2.27 (1H, dd, J = 14.9, 1.8 Hz, $H6_a$), 2.42 (1H, ddd, J = 16.6, 6.3, 1.8 Hz, $H8_a$), 2.55 (1H, ddd, J = 16.6, 12.6, 8.1 Hz, $H8_b$), 2.64 (1H, ddd, J = 13.8, 2.9, 2.9 Hz, $H2_b$), 2.68 (1H, d, J = 14.9 Hz, $H6_b$), 4.00 (1H, d, J = 10.3 Hz, $H19_a$), 4.23-4.27 (2H, m, H1 and 3), 4.48 (1H, d, J = 10.3 Hz, $H19_b$), 5.66 (1H, s, C*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ -5.6, 18.2, 23.4, 25.9, 28.5, 35.9, 37.5, 42.5, 50.2, 59.6, 66.4, 69.5, 73.9, 105.8, 207.0; HRMS (ESI) calcd for $C_{18}H_{30}O_5SiNa$ $[M+Na]^+$ 377.1755, found 377.1758.



19 **20**

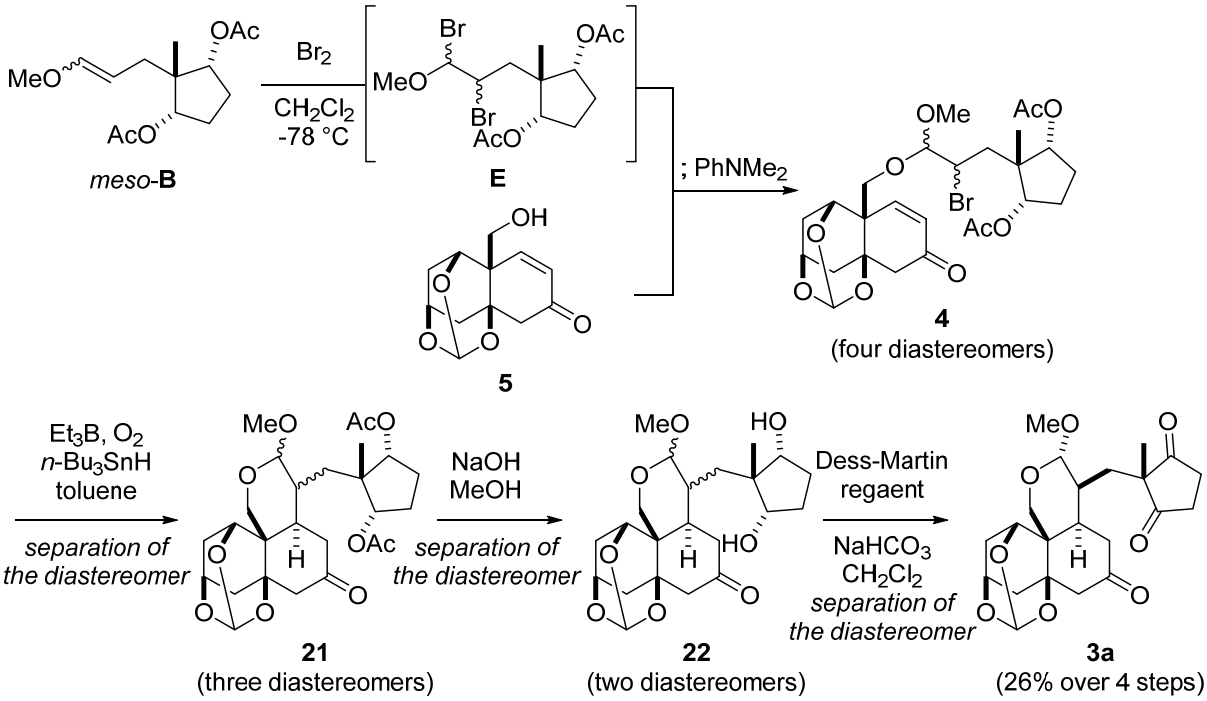
Enone 20. $Pd(OCOCF_3)_2$ (550 mg, 1.65 mmol) was added to a solution of ketone **19** (492 mg, 1.39 mmol) and NaOAc (342 mg, 4.17 mmol) in DMSO (28 mL) at room temperature. The reaction mixture was heated to 50 ºC, and stirred for 21 h. After $Pd(OCOCF_3)_2$ (208 mg, 0.636 mmol) and NaOAc (110 mg, 1.34 mmol) were added, the reaction mixture was further stirred at 50 ºC for 21 h. The mixture was cooled to room temperature, and then saturated aqueous $NaHCO_3$ (30 mL) was added. The resultant solution was extracted with EtOAc (50 mL x3), and the combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtrated, and concentrated. The residue was purified by flash column chromatography on silica gel (50 g, hexane to hexane/EtOAc 4/1) to afford enone **20** (445 mg, 1.26 mmol) in 91% yield: crystal; m.p. 118 ºC; $[\alpha]_D^{24}$ +110 (*c* 0.83, $CHCl_3$); IR (neat)

ν 2952, 2929, 2885, 2855, 1679, 1470, 1385, 1283, 1251, 1173, 1132, 1098, 995, 972 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.03 (6H, s, CH_3 of TBS x2), 0.85 (9H, s, *t*-Bu of TBS), 1.60 (1H, ddd, *J* = 13.8, 1.7, 1.7 Hz, H2$_a$), 2.12-2.20 (2H, m, H4), 2.34 (1H, d, *J* = 17.2 Hz, H6$_a$), 2.73 (1H, dddd, *J* = 13.8, 4.0, 4.0, 2.3 Hz, H2$_b$), 2.96 (1H, d, *J* = 17.2 Hz, H6$_b$), 4.22 (1H, d, *J* = 9.7 Hz, H19$_a$), 4.24 (1H, d, *J* = 9.7 Hz, H19$_b$), 4.26-4.27 (1H, m, H3), 4.40 (1H, d, *J* = 4.0 Hz, H1), 5.70 (1H, s, C*H*), 6.11 (1H, d, *J* = 9.7 Hz, H8), 6.69 (1H, d, *J* = 9.7 Hz, H9); ^{13}C NMR (125 MHz, $CDCl_3$) δ -5.7, -5.6, 18.2, 25.8, 30.2, 36.4, 46.4, 47.2, 66.3, 66.6, 69.7, 73.6, 105.8, 130.8, 150.4, 196.4; HRMS (ESI) calcd for $C_{18}H_{28}O_5SiNa$ $[M+Na]^+$ 375.1598, found 375.1599.



20 **5**

AB-Ring 5. TBAF (1.0 M in THF, 3.8 mL, 3.8 mmol) was added to a solution of enone **20** (445 mg, 1.26 mmol) and AcOH (290 μL, 5.0 mmol) in THF (13 mL) at room temperature. The reaction mixture was warmed to 50 ºC, and stirred for 17 h. After the reaction mixture was cooled to room temperature, pH 7 phosphate buffer solution (13 mL) was added. The resultant solution was extracted with CH_2Cl_2 (13 mL x5), and the combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 filtrated, and concentrated. The residue was purified by flash column chromatography on silica gel (50 g, hexane to EtOAc) to afford AB-ring **5** (273 mg, 1.15 mmol) in 91% yield: crystal; m.p. 187 ºC; $[\alpha]_D^{27}$ +100 (*c* 0.49, $CHCl_3$); IR (neat) ν 3468, 2996, 2957, 2919, 1673, 1427, 1384, 1286, 1224, 1146, 1125, 1070, 1039, 995, 963 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.62 (1H, ddd, *J* = 13.8, 1.7, 1.7 Hz, H2$_a$), 1.91 (1H, br s, O*H*), 2.14 (1H, br d, *J* = 13.2 Hz, H4$_a$), 2.19 (1H, ddd, *J* = 13.2, 3.4, 2.3 Hz, H4$_b$), 2.37 (1H, d, *J* = 17.2 Hz, H6$_a$), 2.75 (1H, dddd, *J* = 13.8, 4.0, 4.0, 2.3 Hz, H2$_b$), 2.96 (1H, d, *J* = 17.2 Hz, H6$_b$), 4.25 (1H, d, *J* = 10.3 Hz, H19$_a$), 4.28-4.31 (1H, m, H3), 4.37 (1H, d, *J* = 10.3 Hz, H19$_b$), 4.45-4.47 (1H, m, H1), 5.71 (1H, s, C*H*), 6.16 (1H, d, *J* = 9.8 Hz, H8), 6.77 (1H, d, *J* = 9.8 Hz, H9); ^{13}C NMR (125 MHz, $CDCl_3$) δ 30.1, 36.2, 46.3, 47.0, 66.22, 66.25, 69.5, 73.6, 105.8, 131.3, 149.7, 196.2; HRMS (ESI) calcd for $C_{12}H_{14}O_5Na$ $[M+Na]^+$ 261.0733, found 261.0731.



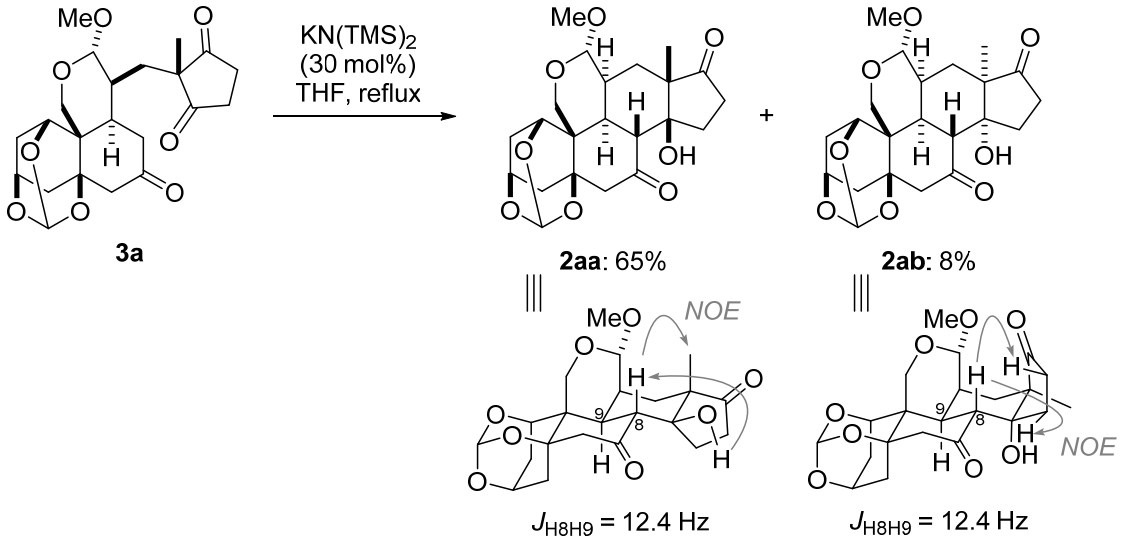
Triketone 3a. A solution of *meso*-**B** (577 mg, 2.13 mmol) in CH_2Cl_2 (2 mL) was added to a solution of Br_2 (88 μL, 1.7 mmol) in CH_2Cl_2 (2 mL) at -78 ºC over 20 min. After the color of the solution became clear, a solution of AB-ring **5** (204 mg, 0.856 mmol) and $PhNMe_2$ (430 μL, 3.4 mmol) in CH_2Cl_2 (24 mL) was added to the mixture at -78 ºC over 30 min. The reaction mixture was warmed to room temperature and stirred for 18 h, and then saturated aqueous $NaHCO_3$ (30 mL) was added. The resultant mixture was extracted with CH_2Cl_2 (30 mL x3), and the combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtrated, and concentrated. The residue was purified by flash column chromatography on silica gel (70 g, hexane to hexane/EtOAc 10/1 to 4/1 to 2/1 to 1/1 to 1/2) to afford a mixture of four diastereomers of bromoacetal **4**, which was used in the next reaction without further purification.

A solution of the above crude **4** and *n*-Bu_3SnH (67 μL, 0.25 mmol) in toluene (90 mL) was degassed by freeze-thaw cycles (x3), and then argon gas was charged into the flask. A solution of Et_3B (1.0 M in hexane, 2.5 mL, 2.5 mmol) was added to the mixture. Then a solution of *n*-Bu_3SnH (225 μL, 0.836 mmol) in toluene (saturated with oxygen, 5 mL) was added over 30 min. After the reaction mixture was stirred at room temperature for 30 min, toluene (saturated with oxygen, 5 mL) was added over 30 min. After further 30 min, 2,6-di-*tert*-butyl-4-methylphenol (448 mg, 2.03 mmol) was added as the radical scavenger. The resultant mixture was directly subjected to flash chromatography [a column consecutively packed with silica gel 15 g and 10% (w/w) KF contained silica gel 15 g, hexane to hexane/EtOAc 10/1 to EtOAc] to afford the impure **21**. The material was further purified by flash column chromatography on silica gel (50 g, hexane to

hexane/EtOAc 10/1 to 4/1 to 2/1 to 1/1 to 1/2) to afford a mixture of three diastereomers of **21**, which was used in the next reaction without further purification.

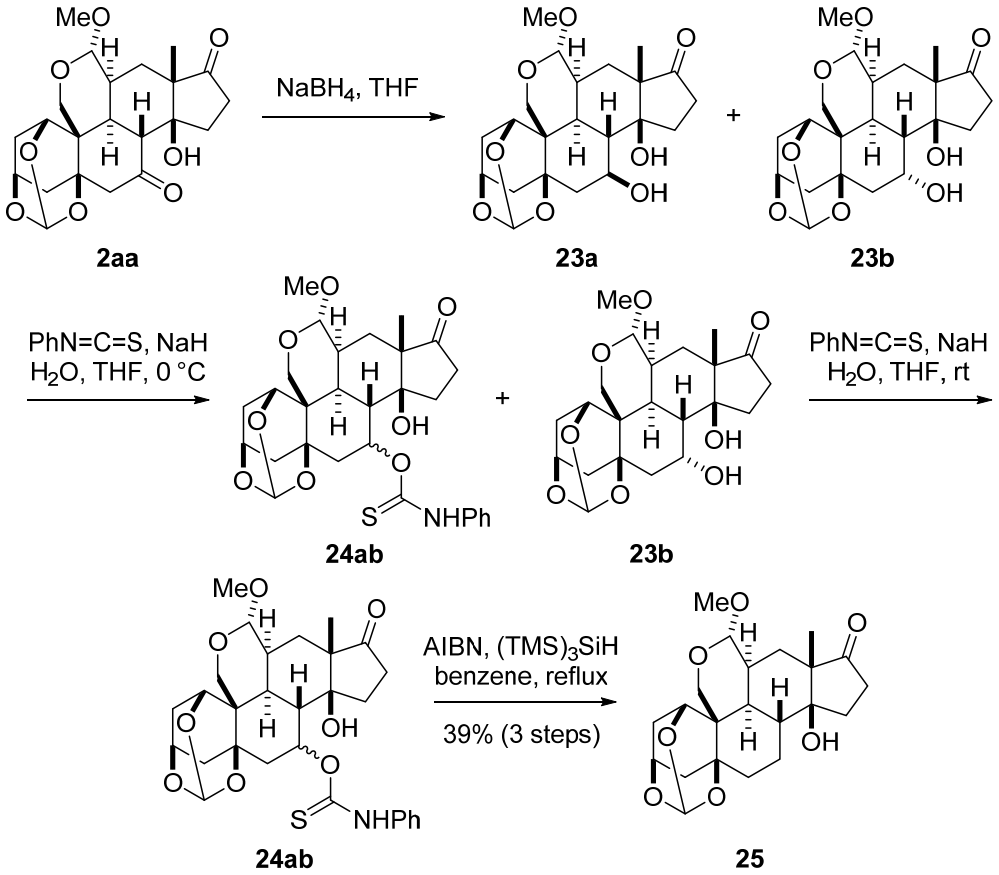
A 0.5 M NaOH aqueous solution (4 mL, 2.0 mmol) was added to a solution of the above crude **21** in MeOH (13 mL) at room temperature. The reaction mixture was stirred at room temperature for 2 h, and then AcOH (6 mL) was added. The pH value of the resultant solution was adjusted to 8-9 by addition of saturated aqueous $NaHCO_3$. After being diluted with EtOH, the mixture was concentrated. The residue was purified by flash column chromatography on silica gel (15 g, EtOAc) to afford the impure **22**. The material was further purified by flash column chromatography on silica gel (50 g, hexane to hexane/acetone 10/1 to 5/1 to 4/1 to 3/1 to 1/1) to afford a mixture of two diastereomers of **22**, which was used in the next reaction without further purification.

Dess-Martin periodinane (752 mg, 1.77 mmol) was added to a solution of the above crude **22** and $NaHCO_3$ (297 mg, 3.54 mmol) in CH_2Cl_2 (30 mL) at room temperature. The reaction mixture was stirred at room temperature for 2 h, and then a 1 : 1 mixture of saturated aqueous $Na_2S_2O_3$ and $NaHCO_3$ (30 mL) was added. The resultant mixture was extracted with CH_2Cl_2 (30 mL x3), and the combined organic layers were washed with brine (30 mL) and concentrated. The residue was purified by flash column chromatography on silica gel (15 g, hexane to hexane/EtOAc 10/1 to 4/1 to 3/1 to 2/1) to afford triketone **3a** (93 mg, 0.22 mmol) in 26% yield over 4 steps: white crystal: m.p. 196-200 ºC; $[\alpha]_D^{24}$ -26 (*c* 1.4, $CHCl_3$); IR (neat) ν 2966, 2933, 1762, 1721, 1449, 1293, 1253, 1147, 1078, 993, 916 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 1.09 (3H, s, H18), 1.36 (1H, dd, *J* = 14.6, 2.8 Hz, $H12_a$), 1.64-1.76 (2H, m, $H4_a$ and 11), 1.85 (1H, dd, *J* = 14.2, 1.8 Hz, $H2_a$), 1.97 (1H, ddd, *J* = 8.7, 8.7, 3.7 Hz, H9), 2.03 (1H, dd, *J* = 14.2, 11.9 Hz, $H12_b$), 2.18 (1H, ddd, *J* = 13.7, 3.6, 2.3 Hz, $H4_b$), 2.26 (1H, d, *J* = 15.1 Hz, $H6_a$), 2.50-2.82 (7H, m, $H2_b$, 8, 15 and 16), 2.71 (1H, d, *J* = 15.1 Hz, $H6_b$), 3.15 (3H, s, OCH_3), 4.10 (1H, d, *J* = 12.8 Hz, $H19_a$), 4.177 (1H, d, *J* = 12.8 Hz, $H19_b$), 4.181 (1H, d, *J* = 8.7 Hz, $CHOCH_3$), 4.24-4.29 (1H, m, H3), 4.40-4.45 (1H, m, H1), 5.61 (1H, s, C*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.1, 28.4, 33.0, 33.6, 34.3, 34.7, 35.4, 37.0, 39.0, 41.5, 49.1, 53.5, 55.6, 62.4, 65.9, 70.1, 73.3, 101.5, 105.6, 205.2, 213.7, 216.2: HRMS (ESI) calcd for $C_{22}H_{28}O_8Na$ $[M+Na]^+$ 443.1676, found 443.1683.



Steroids 2aa and 2ab. A solution of $KN(TMS)_2$ (0.67 M, 89 μL, 0.059 mmol) freshly prepared from KH and $HN(TMS)_2$ in THF[S5] was added to a solution of triketone **3a** (83 mg, 0.20 mmol) in refluxing THF (4 mL), and the reaction mixture was stirred for 1 h. After the mixture was cooled to room temperature, saturated aqueous NH_4Cl (4 mL) was added. The resultant mixture was extracted with a 2 : 1 mixture of $CHCl_3$ and EtOH (4 mL x5), and the combined organic layers were washed with brine (2 mL), dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel (15 g, hexane to hexane/THF 1/1) to afford **2aa** (54 mg, 0.13 mmol) and **2ab** (7.0 mg, 0.017 mmol) in 65% and 8% yields, respectively. **2aa**: crystal; m.p. 268-270 ºC (dec.); $[\alpha]_D^{25}$ -0.48 (*c* 1.1, $CHCl_3$); IR (neat) ν 3525, 2949, 1736, 1704, 1446, 1379, 1194, 1152, 1067, 993, 976 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.14 (3H, s, H18), 1.16 (1H, dd, *J* = 15.6, 5.9 Hz, $H12_a$), 1.66 (1H, d, *J* = 12.8 Hz, $H4_a$), 1.76 (1H, d, *J* = 14.2 Hz, $H2_a$), 1.79 (1H, d, *J* = 15.6 Hz, $H12_b$), 1.81-1.87 (1H, m, H11), 2.05-2.16 (2H, m, H9 and 15_a), 2.20 (1H, ddd, *J* = 12.8, 3.7, 2.7 Hz, $H4_b$), 2.28 (1H, ddd, *J* = 14.2, 9.6, 1.4 Hz, $H15_b$), 2.34 (1H, d, *J* = 13.7 Hz, $H6_a$), 2.42 (1H, ddd, *J* = 19.2, 9.6, 1.4 Hz, $H16_a$), 2.55 (1H, ddd, *J* = 19.2, 10.1, 9.6 Hz, $H16_b$), 2.70 (1H, dddd, *J* = 14.2, 3.6, 2.8, 2.7 Hz, $H2_b$), 2.80 (1H, d, *J* = 13.7 Hz, $H6_b$), 3.19 (1H, d, *J* = 12.4 Hz, H8), 3.52 (3H, s, OC*H*$_3$), 3.54 (1H, s, O*H*), 4.13 (1H, d, *J* = 12.4 Hz, $H19_a$), 4.29 (1H, m, H3), 4.75 (1H, m, H1), 4.81 (1H, dd, *J* = 12.4, 1.8 Hz, H19), 4.83 (1H, d, *J* = 9.1 Hz, C*H*OMe), 5.69 (1H, s, C*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.7, 27.56, 27.61, 31.1, 32.8, 35.2, 35.3, 39.7, 40.7, 50.8, 51.0, 51.9, 56.8, 63.2, 65.8, 68.7, 73.5, 79.7, 101.9, 105.8, 207.8, 218.4: HRMS (ESI) calcd for $C_{22}H_{28}O_8Na$ $[M+Na]^+$ 443.1676, found 443.1681. **2ab**: crystal; m.p. 261-264 ºC; $[\alpha]_D^{25}$ -24 (*c* 0.83, $CHCl_3$); IR (neat) ν 3511, 2965, 2932, 1737, 1702, 1446, 1194, 1149, 1074, 1056, 994, 971 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.00 (3H, s, H18), 1.31 (1H, dd, *J* = 15.1, 6.4 Hz, $H12_a$), 1.62-1.79 (3H, m, $H2_a$, 4_a and 11), 2.13 (1H, ddd, J = 13.7, 3.6, 2.8 Hz, $H4_b$), 2.17-2.23 (1H, m, $H15_a$), 2.20 (1H,

dd, J = 15.2, 10.5 Hz, H16$_a$), 2.28-2.37 (3H, m, 6$_a$, 9 and 15$_b$), 2.34 (1H, dd, J = 15.1, 1.8 Hz, H12$_b$), 2.54-2.68 (1H, m, H2$_b$), 2.59 (1H, ddd, J = 15.6, 8.2, 8.2 Hz, H16$_b$), 2.79 (1H, d, J = 12.4 Hz, H8), 2.86 (1H, d, J = 12.4 Hz, H6$_b$), 3.51 (3H, s, OCH_3), 3.73 (1H, s, OH), 4.02 (1H, d, J = 12.8 Hz, H19$_a$), 4.18 (1H, d, J = 8.7 Hz, CHCOCH$_3$), 4.24-4.28 (1H, m, H3), 4.69 (1H, dd, J = 12.8, 1.4 Hz, H19$_b$), 4.69-4.73 (1H, m, H1), 5.66 (1H, s, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.3, 27.6, 28.2, 30.9, 34.4, 34.5, 34.7, 36.7, 41.1, 51.3, 51.5, 52.7, 56.8, 62.8, 66.1, 69.1, 74.3, 77.1, 101.0, 105.9, 208.6, 218.2; HRMS (ESI) calcd for $C_{22}H_{28}O_8Na$ [M+Na] 443.1676, found 443.1679.

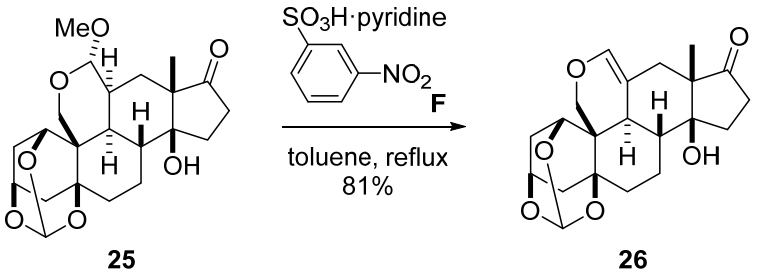


Compound 25. $NaBH_4$ (12 mg, 0.32 mmol) was added to a solution of **2aa** (88 mg, 0.21 mmol) in THF (20 mL) at room temperature. The reaction mixture was stirred at room temperature for 1 h, and then a 1 : 1 mixture of 1M HCl and CH_2Cl_2 (30 mL) was added. The resultant mixture was extracted with CH_2Cl_2 (15 mL x4), 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 (25 g, hexane to hexane/acetone 1/2) to afford a 2.5 : 1 diastereomeric mixture of **23ab**, which was used in the next reaction without further purification.

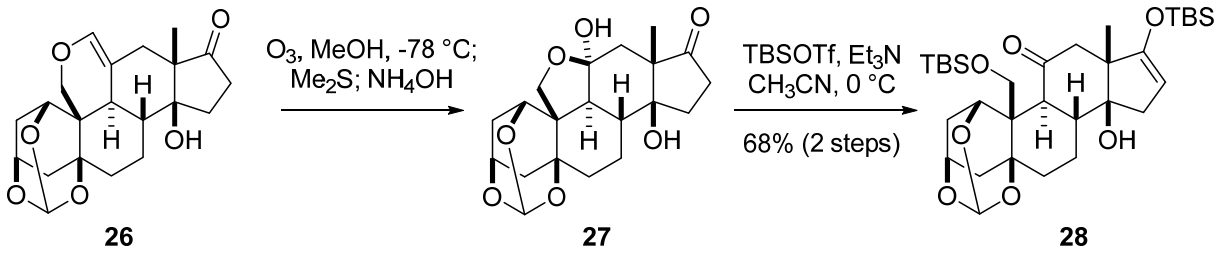
NaH (60% dispersion in mineral oil) was washed with hexane and dried in vacuo. The purified NaH (63 mg, 2.6 mmol) and PhNCS (630 μL, 5.3 mmol) were successively added

to the above crude **23ab** in THF (13 mL) at 0 ºC. The reaction mixture was stirred at 0 ºC for 2 h, and then H_2O (1 μL, 0.056 mmol) was added. The mixture was stirred at 0 ºC for further 2 h, and then saturated aqueous NH_4Cl (10 mL) was added. The resultant mixture was extracted with CH_2Cl_2 (15 mL x4), 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 (25 g, hexane to hexane/EtOAc 1/2 to hexane/acetone 1/1) to afford a mixture of thiocarbamate **24ab** and alcohol **23b**, which was again subjected to the thiocarbamate formation. NaH (26 mg, 1.1 mmol) and PhNCS (260 μL, 2.2 mmol) were successively added to a solution of the mixture and H_2O (1 μL, 0.06 mmol) in THF (5 mL) at room temperature. The reaction mixture was stirred at room temperature for 1 h, and then saturated aqueous NH_4Cl (6 mL) was added. The resultant mixture was extracted with CH_2Cl_2 (5 mL x4), and the combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (25 g, hexane to hexane/EtOAc 1/1) to afford the impure **24ab**, which were used in the next reaction.

A solution of the above crude **24ab**, AIBN (11 mg, 0.067 mmol) and $(TMS)_3SiH$ (410 μL, 1.3 mmol) in benzene (13 mL) was degassed by freeze-thaw procedure (x3). The reaction mixture was heated to reflux, and stirred for 1 h. After being cooled to room temperature, the mixture was directly subjected to flash column chromatography on silica gel (20 g, hexane to hexane/EtOAc 1/2) to afford **25** (33 mg, 0.081 mmol) in 39% over 3 steps: white solid: m.p. 260-266 ºC; $[\alpha]_D^{22}$ +14 (*c* 0.60, $CHCl_3$); IR (neat) ν 3487, 2948, 1731, 1451, 1149, 1069, 1053 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.15 (3H, s, H18), 1.14-1.20 (1H, m, $H12_a$), 1.38-1.54 (2H, m), 1.67-1.90 (5H, m), 1.80 (1H, dd, *J* = 15.5, 1.7 Hz, $H12_b$), 2.02-2.08 (2H, m, $H4_a$ and 7_a), 2.14 (1H, ddd, *J* = 13.7, 10.3, 10.3 Hz), 2.26 (1H, d, *J* = 13.8 Hz, $H4_b$), 2.35 (1H, ddd, *J* = 12.6, 12.6, 4.6 Hz, H8), 2.42-2.48 (2H, m), 2.61-2.68 (1H, m, $H2_a$), 3.49 (3H, s, OC*H*$_3$), 4.04 (1H, d, *J* = 12.0 Hz, $H19_a$), 4.29-4.33 (1H, m, H3), 4.64 (1H, dd, *J* = 12.0, 1.8 Hz, $H19_b$), 4.67-4.69 (1H, m, H1), 4.76 (1H, d, *J* = 9.8 Hz, OC*H*OCH_3), 5.67 (1H, s, C*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.9, 19.3, 26.4, 28.0, 31.8, 32.0, 33.0, 34.4, 35.3, 37.4, 39.0, 40.9, 52.4, 56.6, 63.4, 66.4, 68.8, 73.6, 82.1, 102.0, 105.8, 219.7; HRMS (ESI) calcd for $C_{22}H_{30}O_7Na$ $[M+Na]^+$ 429.1884, found 429.1892.



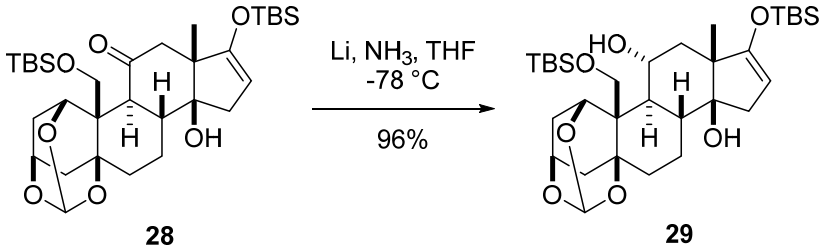
Enol ether 26. Reagent **F** (46 mg, 0.16 mmol) was added to a solution of **25** (33 mg, 0.081 mmol) in toluene (8 mL) at room temperature. The reaction mixture was heated to reflux, and stirred for 30 min. After the mixture was cooled to room temperature, saturated aqueous $NaHCO_3$ (8 mL) was added. The resultant mixture was extracted by CH_2Cl_2 (8 mL x4), and the combined organic layers were washed with brine (4 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (10 g, hexane to hexane/EtOAc 1/2) to afford enol ether **26** (25 mg, 0.067 mmol) in 81% yield: white crystal: m.p. >300 ºC; $[\alpha]_D^{23}$ -79 (*c* 1.00, $CHCl_3$); IR (neat) ν 3486, 3058, 2950, 1731, 1670, 1448, 1374, 1308, 1269, 1222, 1149 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.02 (3H, s, H18), 1.40-1.56 (2H, m), 1.64-1.76 (3H, m), 1.69 (1H, d, *J* = 13.8 Hz, $H12_a$), 1.88 (1H, d, *J* = 13.8 Hz, $H12_b$), 1.88-2.02 (3H, m), 2.13 (1H, ddd, *J* = 13.7, 3.6, 2.7 Hz, $H4_a$), 2.15-2.26 (1H, m), 2.25 (1H, d, *J* = 13.7 Hz, $H4_b$), 2.47-2.52 (2H, m), 2.66 (1H, dddd, *J* = 14.2, 3.2, 3.2, 3.2 Hz, $H2_a$), 4.14 (1H, d, *J* = 10.5 Hz, $H19_a$), 4.21 (1H, m, H1), 4.33 (1H, m, H3), 4.75 (1H, dd, *J* = 10.5, 1.8 Hz, $H19_b$), 5.70 (1H, s, C*H*), 6.16 (1H, s, C=C*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.5, 19.0, 26.8, 28.4, 32.1, 33.6, 35.0, 36.4, 37.2, 39.0, 47.5, 55.3, 63.9, 66.4, 68.5, 73.2, 81.8, 106.0, 109.5, 138.1, 219.9; HRMS (ESI) calcd for $C_{21}H_{26}O_6Na$ $[M+Na]^+$ 397.1622, found 397.1624.



TBS-enol ether 28. Ozone was bubbled into a solution of enol ether **26** (25 mg, 0.067 mmol) in MeOH (30 mL) at -78 ºC for 10 sec. The reaction mixture was stirred at -78 ºC for 5 min, and then oxygen was bubbled into the reaction mixture for 10 min. After Me_2S (3 mL) was added, the resultant solution was warmed to room temperature, and stirred for 30 min. Then, 28% aqueous NH_3 (3 mL) was added. The mixture was stirred at room temperature for 1 h, and then concentrated. The residue was purified by flash column

chromatography on silica gel (10 g, hexane to hexane/EtOAc 1/2) to afford the impure **27**, which was used in the next reaction without further purification.

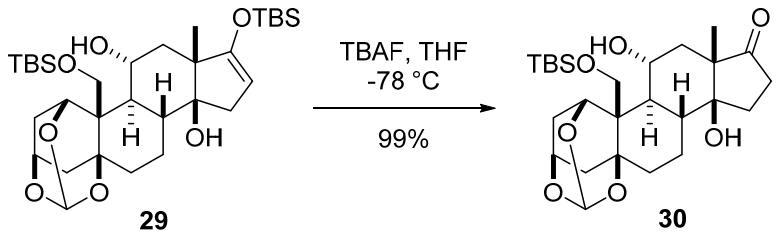
TBSOTf (75 μL, 0.33 mmol) was added to a solution of the above crude **27** and Et_3N (91 μL, 0.65 mmol) in CH_3CN (6.5 mL) at -35 ºC. The reaction mixture was stirred at -35 ºC for 10 min and at 0 ºC for 20 min, and then saturated aqueous $NaHCO_3$ (6 mL) was added. The resultant solution was extracted with EtOAc (6 mL x3), and the combined organic layers were washed with brine (6 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (10 g, hexane to hexane/EtOAc 3/1) to afford TBS-enol ether **28** (27 mg, 0.044 mmol) in 68% yield over 2 steps: white solid; m.p. 175-180 ºC; $[\alpha]_D^{25}$ -53 (*c* 0.63, $CHCl_3$); IR (neat) ν 3491, 2954, 2933, 2890, 2858, 1712, 1658, 1467, 1324, 1254, 1165, 1137, 1087, 997, 841 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 0.12 (3H, s, C*H*$_3$ of TBS), 0.135 (3H, s, C*H*$_3$ of TBS), 0.139 (3H, s, C*H*$_3$ of TBS), 0.20 (3H, s, C*H*$_3$ of TBS), 0.95 (9H, s, *t*-Bu of TBS), 0.99 (9H, s, *t*-Bu of TBS), 1.12-1.22 (1H, m), 1.16 (3H, s, H18), 1.25-1.31 (1H, m), 1.68-1.92 (6H, m), 2.03 (1H, dd, *J* = 17.2, 2.9 Hz, H15$_a$), 2.44 (1H, ddd, *J* = 13.2, 13.2, 4.6 Hz), 2.50 (1H, dd, *J* = 17.2, 2.3 Hz, H15$_b$), 2.57 (1H, d, *J* = 13.2 Hz, H12$_a$), 2.59-2.65 (1H, m, H2$_a$), 2.91 (1H, d, *J* = 13.2 Hz, H12$_b$), 3.91 (1H, m, H3), 4.22 (1H, d, *J* = 10.3 Hz, H19$_a$), 4.38 (1H, dd, *J* = 2.3, 2.3 Hz, H16), 4.78 (1H, d, *J* = 10.3 Hz, H19$_b$), 4.82-4.86 (1H, m, H1), 5.87 (1H, s, C*H*); ^{13}C NMR (125 MHz, C_6D_6) δ -5.5, -5.4, -5.0, -4.5, 18.3, 18.7, 19.9, 20.8, 25.8, 26.1, 28.9, 32.2, 35.3, 38.7, 41.3, 47.8, 48.0, 48.5, 53.0, 61.5, 67.1, 69.0, 74.4, 79.7, 96.0, 106.4, 156.0, 208.1; HRMS (ESI) calcd for $C_{32}H_{54}O_7Si_2Na$ $[M+Na]^+$ 629.3300, found 629.3298.



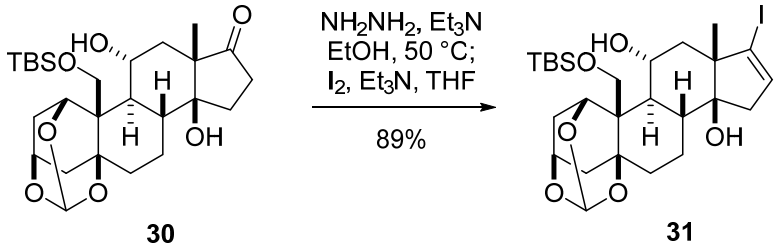
28 **29**

Diol 29. A Schlenk tube equipped with a dry-ice condenser was charged with liquid NH_3 (ca. 10 mL), and then Li metal (51 mg, 7.3 mmol) was added. The resultant blue solution was stirred -78 ºC for 1 h, and a solution of TBS-enol ether **28** (27 mg, 0.044 mmol) in THF (3 mL) was added. The reaction mixture was stirred at -78 ºC for 30 min, and then saturated aqueous NH_4Cl (7 mL) was added. The resultant mixture was extracted with EtOAc (10 mL x3), and the combined layers were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (5 g, hexane to hexane/EtOAc 3/1) to afford diol **29** (26 mg, 0.043 mmol) in 96% yield: amorphous; $[\alpha]_D^{27}$ -26 (*c* 0.87, $CHCl_3$); IR (neat) ν 3495, 2951,

2933, 2890, 2857, 1637, 1467, 1358, 1303, 1255, 1157, 1004, 839 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 0.128 (3H, s, C*H*$_3$ of TBS), 0.133 (6H, s, C*H*$_3$ of TBS x2), 0.16 (3H, s, C*H*$_3$ of TBS), 0.951 (9H, s, *t*-Bu of TBS), 0.955 (9H, s, *t*-Bu of TBS), 1.14 (1H, dddd, *J* = 13.2, 13.2, 13.2, 4.6 Hz, H7$_a$), 1.22 (3H, s, H18), 1.25-1.30 (1H, m), 1.38-1.55 (4H, m), 1.77 (1H, dd, *J* = 13.7, 1.2 Hz, H2$_a$), 1.82-1.99 (4H, m), 1.95 (1H, dd, *J* = 15.5, 2.9 Hz, H15$_a$), 2.23 (1H, dd, *J* = 13.2, 3.4 Hz, H12$_a$), 2.54-2.62 (1H, m, H2$_b$), 2.82 (1H, d, *J* = 4.6 Hz, O*H*), 4.02-4.10 (2H, m, H3 and 11), 4.16 (1H, d, *J* = 9.7 Hz, H19$_a$), 4.37 (1H, dd, *J* = 2.9, 1.8 Hz, H16), 4.73 (1H, d, *J* = 9.7 Hz, H19$_b$), 5.15 (1H, d, *J* = 4.6 Hz, H1), 5.90 (1H, s, C*H*); ^{13}C NMR (125 MHz, C_6D_6) δ -5.7, -5.4, -5.0, -4.5, 15.8, 18.3, 18.5, 20.1, 25.8, 26.1, 28.9, 32.2, 35.1, 36.8, 39.8, 45.6, 47.0, 47.1, 51.1, 61.4, 67.0, 69.4, 70.7, 74.3, 82.0, 93.6, 106.1, 161.6; HRMS (ESI) calcd for $C_{32}H_{56}O_7Si_2Na$ $[M+Na]^+$ 631.3457, found 631.3457.



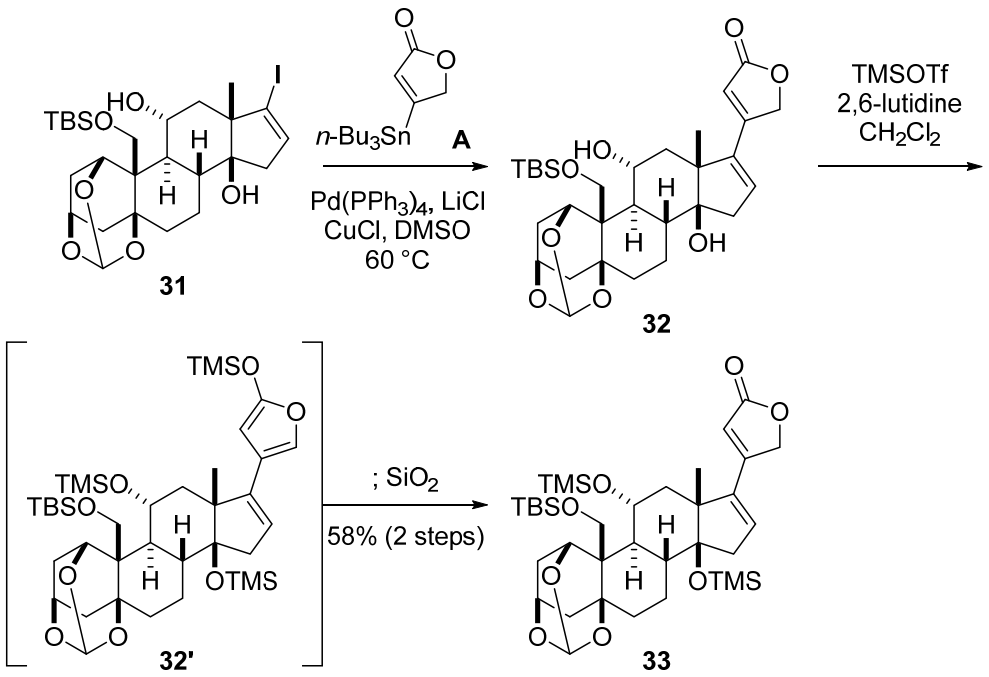
Ketone 30. TBAF (1.0 M in THF, 84 μL, 0.084 mmol) was added to a solution of diol **29** (34 mg, 0.056 mmol) in THF (6 mL) at -78 ºC. The reaction mixture was stirred at -78 ºC for 10 min, and then saturated aqueous NH_4Cl (5 mL) was added. The resultant solution was extracted with CH_2Cl_2 (5 mL x3), and the combined organic layers were washed with brine (4 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (5 g, hexane to hexane/EtOAc 1/2) to afford ketone **30** (27 mg, 0.055 mmol) in 99% yield: crystal: m.p. 184-188 ºC; $[\alpha]_D^{24}$ -3.9 (*c* 1.4, $CHCl_3$); IR (neat) ν 3482, 2951, 2932, 2883, 2856, 1732, 1469, 1379, 1256, 1154, 1076, 1005, 976, 836 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.13 (3H, s, C*H*$_3$ of TBS), 0.15 (3H, s, C*H*$_3$ of TBS), 0.92 (9H, s, *t*-Bu of TBS), 1.12 (3H, s, H18), 1.34 (1H, dd, *J* = 13.2, 12.6 Hz, H12$_a$), 1.35-1.52 (3H, m), 1.54 (1H, dd, *J* = 13.2, 3.5 Hz, H12$_b$), 1.72 (1H, dd, *J* = 11.5, 10.9 Hz, H9), 1.87-1.97 (3H, m), 2.00-2.06 (2H, m, H2$_a$ and 4$_a$), 2.19 (1H, ddd, *J* = 13.8, 10.3, 9.8 Hz), 2.26 (1H, d, *J* = 13.7 Hz, H4$_b$), 2.37-2.46 (1H, m), 2.48 (1H, ddd, *J* = 19.5, 10.3, 2.3 Hz), 2.58-2.65 (1H, m, H2$_b$), 2.69 (1H, brs, O*H*), 4.04-4.12 (1H, m, H11), 4.10 (1H, d, *J* = 10.3 Hz, H19$_a$), 4.30-4.34 (1H, m, H3), 4.53 (1H, d, *J* = 10.3 Hz, H19$_b$), 4.83 (1H, d, *J* = 4.0 Hz, H1), 5.64 (1H, s, C*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ -5.9, -5.5, 14.1, 18.3, 19.0, 25.9, 27.3, 28.5, 31.6, 32.8, 34.8, 40.3, 40.5, 45.1, 46.3, 53.9, 60.7, 66.6, 69.1, 70.1, 73.9, 81.7, 105.4, 218.9; HRMS (ESI) calcd for $C_{26}H_{42}O_7SiNa$ $[M+Na]^+$ 517.2592, found 517.2593.



30 **31**

Vinyl iodide 31. $NH_2NH_2 \cdot H_2O$ (52 μL, 1.1 mmol) and Et_3N (150 μL, 1.1 mmol) were added to a solution of ketone **30** (27 mg, 0.054 mmol) in EtOH (5 mL) at room temperature. The reaction mixture was heated to 50 ºC, and stirred for 7 h. After being cooled to room temperature, the mixture was concentrated.

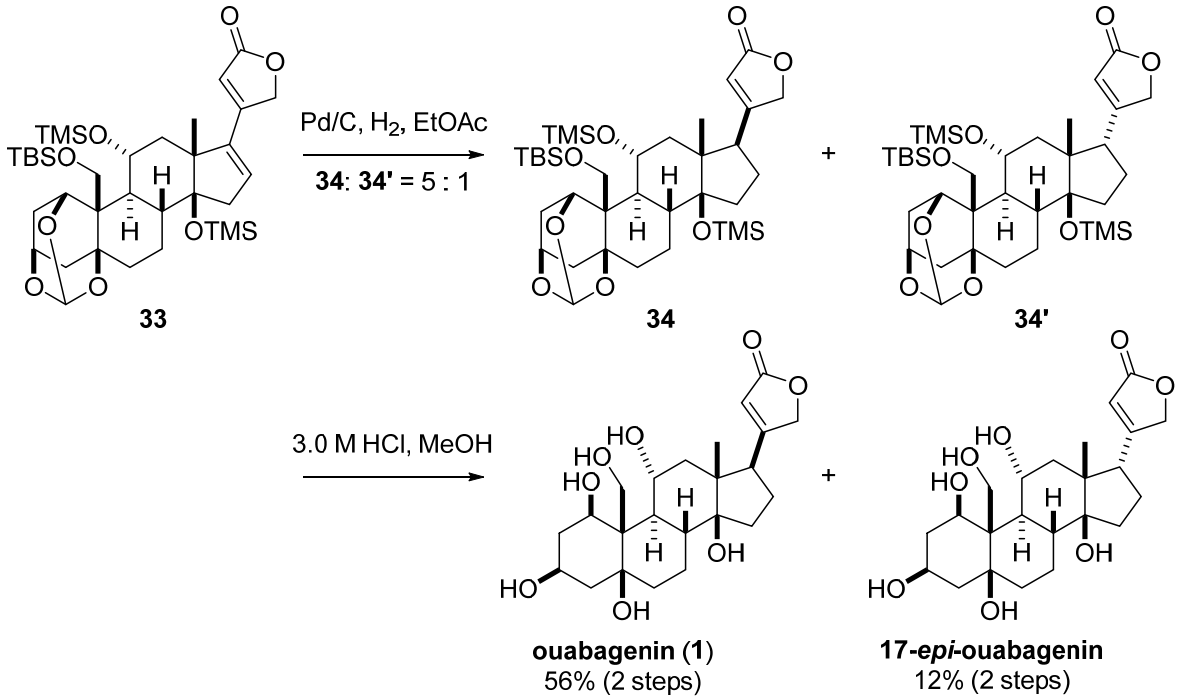
A solution of I_2 (41 mg, 0.16 mmol) in THF (1 mL) was added to a solution of the residue and Et_3N (150 μL, 1.1 mmol) in THF (5 mL). The mixture was stirred at room temperature for 30 min, and then a 1 : 1 mixture of saturated aqueous $Na_2S_2O_3$ and $NaHCO_3$ (4 mL) was added. The resultant mixture was extracted with CH_2Cl_2 (5 mL x4), and the combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (5 g, hexane to hexane/EtOAc 2/1) to afford vinyl iodine **31** (29 mg, 0.048 mmol) in 89% yield: white solid: m.p. 233-237 ºC; $[\alpha]_D^{23}$ -13 (*c* 1.5, $CHCl_3$); IR (neat) ν 3467, 2953, 2930, 2885, 2856, 1461, 1365, 1254, 1146, 1126, 1014, 978 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.14 (3H, s, C*H*$_3$ of TBS), 0.16 (3H, s, C*H*$_3$ of TBS), 0.93 (9H, s, *t*-Bu of TBS), 1.09 (1H, dd, *J* = 13.2, 12.6 Hz, H12$_a$), 1.13 (3H, s, H18), 1.25-1.37 (2H, m), 1.47-1.61 (2H, m), 1.73 (1H, br s, O*H*), 1.90-2.07 (5H, m), 2.24 (1H, d, *J* = 13.8 Hz), 2.31 (1H, dd, *J* = 16.6, 2.9 Hz, H15$_a$), 2.58 (1H, dd, *J* = 16.6, 1.7 Hz, H15$_b$), 2.59-2.65 (1H, m, H2), 3.04 (1H, d, *J* = 4.0 Hz, O*H*), 3.86-3.94 (1H, m, H11), 4.11 (1H, d, *J* = 10.3 Hz, H19$_a$), 4.29-4.33 (1H, m, H3), 4.53 (1H, d, *J* = 10.3 Hz, H19$_b$), 4.83-4.87 (1H, d, *J* = 4.0 Hz, H1), 5.64 (1H, s, C*H*), 6.14 (1H, dd, *J* = 2.9, 1.7 Hz, H16); ^{13}C NMR (125 MHz, $CDCl_3$) δ -5.9, -5.5, 18.3, 19.3, 20.4, 25.9, 28.5, 31.6, 34.8, 39.8, 42.9, 45.0, 46.1, 46.6, 55.4, 60.7, 66.6, 68.7, 70.1, 74.0, 81.7, 105.4, 109.9, 133.4; HRMS (ESI) calcd for $C_{26}H_{41}IO_6SiNa$ $[M+Na]^+$ 627.1609, found 627.1613.



Butenolide 33. A Schlenk tube was charged with $Pd(PPh_3)_4$ (28 mg, 0.024 mmol), LiCl (18 mg, 0.42 mmol) and CuCl (35 mg, 0.35 mmol) in a glove box filled with Ar. A solution of vinyl iodide **31** (29 mg, 0.048 mmol) in DMSO (3 mL) and a solution of butenolide **A** (54 mg, 0.14 mmol) in DMSO (1.8 mL) were successively added, and then the mixture was degassed by the freeze-thaw procedure (x3). The reaction mixture was heated to 60 ºC, and stirred for 1 h. After the mixture was cooled to room temperature, pH 7 phosphate buffer (5 mL) was added. The resultant mixture was extracted with CH_2Cl_2 (5 mL x5), and the combined organic layers were washed with brine (5 mL), and dried over Na_2SO_4. The solution was filtered through a pad of 10% (w/w) KF contained silica gel (5 g), and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (5 g, hexane to EtOAc) to afford the impure butenolide **32** (23 mg). A part of the crude material (21 mg) was used in the next reaction without further purification.

TMSOTf (36 μL, 0.20 mmol) was added to a solution of the above crude butenolide **32** and 2,6-lutidine (47 μL, 0.40 mmol) in CH_2Cl_2 at -78 ºC. The reaction mixture was warmed to room temperature, stirred for 20 min, and then saturated aqueous $NaHCO_3$ (3 mL) was added. The resultant solution was extracted with CH_2Cl_2 (3 mL x3), and the combined organic layers were washed with brine (3 mL), dried over Na_2SO_4, filtered, and concentrated to give siloxyfuran **32'**. Silica gel (10 g, Merck 40-63 μm Silica-gel 60) was added to a solution of the **32'** in CH_2Cl_2 (20 mL). After CH_2Cl_2 was removed in vacuo, the resultant solid was stood at room temperature for 10 h. Then, Et_2O was added. The suspension was passed through a pad of cotton, and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (3 g, hexane to

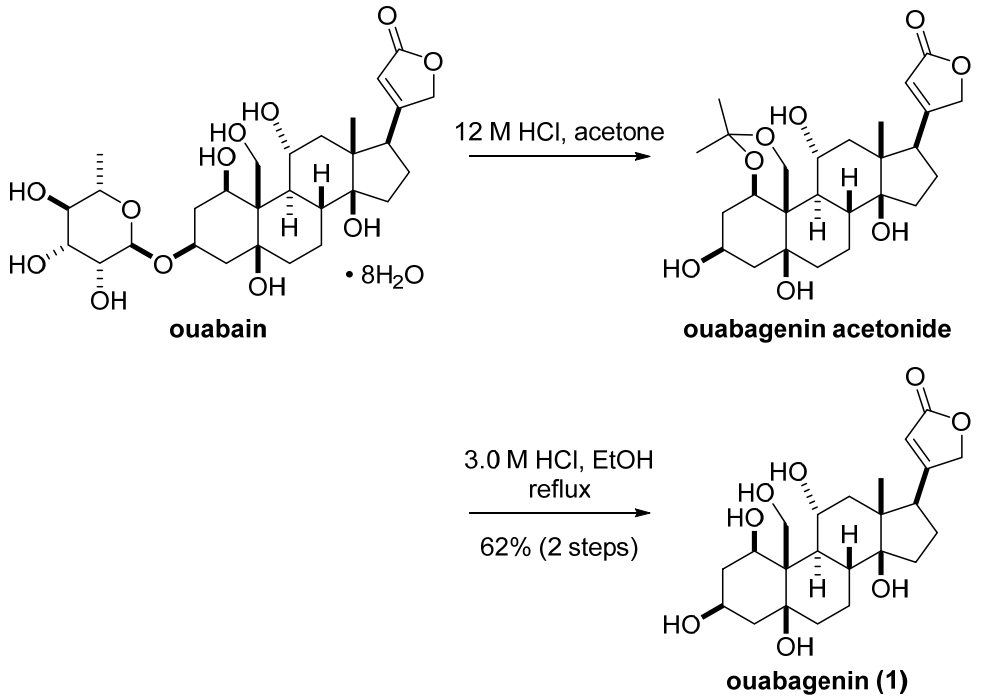
hexane/Et_2O 1/1) to afford the impure **33**. The material was further purified by flash column chromatography on silica gel (1.5g, CH_2Cl_2 to CH_2Cl_2/EtO_2 4/1) to afford **33** (18 mg, 0.026 mmol). The yield of **33** was calculated to be 58% over 2 steps: white solid: m.p. 186-189 ºC; $[\alpha]_D^{26}$ +23 (*c* 0.90, $CHCl_3$); IR (neat) ν 2953, 2930, 2856, 1784, 1752, 1623, 1252, 1156, 1081, 985, 839 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ -0.06 (9H, s, C*H*$_3$ of TMS), 0.08 (9H, s, C*H*$_3$ of TMS), 0.18 (3H, s, C*H*$_3$ of TBS), 0.21 (3H, s, C*H*$_3$ of TBS), 0.95-1.09 (2H, m, H7$_a$ and 12$_a$), 1.02 (9H, s, *t*-Bu of TBS), 1.10 (3H, s, H18), 1.37-1.42 (1H, m), 1.48 (1H, dd, *J* = 10.0, 9.5 Hz, H9), 1.85 (1H, d, *J* = 14.0 Hz, H2$_a$), 1.86-1.92 (1H, m), 1.98-2.10 (5H, m), 2.15 (1H, d, *J* = 18.0 Hz, H15$_a$), 2.51-2.59 (2H, m, H2$_b$ and 8), 4.13 (1H, m, H3), 4.27 (1H, ddd, *J* = 11.0, 10.0, 4.0 Hz, H11), 4.33 (2H, s, H21), 4.45 (1H, d, *J* = 11.5 Hz, H19$_a$), 4.80 (1H, d, *J* = 11.5 Hz, H19$_b$), 4.89 (1H, d, *J* = 4.5 Hz, H1), 5.23 (1H, s, H16), 5.91 (1H, s, H22), 5.92 (1H, s, C*H*); ^{13}C NMR (125 MHz, C_6D_6) δ -5.5, -4.9, 1.1, 2.7, 18.2, 18.7, 21.9, 26.4, 29.4, 33.0, 35.4, 38.7, 39.7, 45.1, 47.4, 48.6, 53.5, 63.9, 67.1, 68.6, 70.9, 72.0, 74.8, 89.0, 106.1, 113.0, 131.4, 144.4, 157.4, 173.1; HRMS (ESI) calcd for $C_{36}H_{60}O_8Si_3Na$ $[M+Na]^+$ 727.3488, found 727.3482.



Ouabagenin (1).[S6] A mixture of **33** (18 mg, 0.026 mmol) and Pd/C (5 wt%, 18 mg, 8.5 μmol) in EtOAc (3 mL) was stirred under H_2 atmosphere at room temperature for 1 h, and then was filtered through a pad of Celite with Et_2O. The filtrate was concentrated, and the residue was purified by flash column chromatography on silica gel (8 g, hexane to hexane/EtO_2 2/1 to EtOAc) to afford a 5:1 diastereomeric mixture of **34** and **34'**. The

mixture was dissolved in MeOH (1.00 mL), and 9/10 volume of the solution (0.90 mL) was used in the next reaction.

3.0 M HCl (1.0 mL) and MeOH (3.0 mL) were added to the above solution of the mixture of **34** and **34'** in MeOH (0.9 mL). The reaction mixture was stirred at room temperature for 15 h, and then saturated aqueous $NaHCO_3$ (2 mL) was added. The pH value of the resultant solution was adjusted to 6 by addition of 1.0 M HCl. The solution was extracted with a 2 : 1 mixture of $CHCl_3$ and EtOH (4 mL x6), and the combined organic layers were dried over Na_2SO_4, and filtered through a pad of silica gel (0.5 g) with MeOH. The filtrate was concentrated, and the residue was purified by flash column chromatography on silica gel (1 g, CH_2Cl_2/MeOH 3/1) to afford a mixture of ouabagenin (**1**) and 17-*epi*-ouabagenin. The mixture was further purified by HPLC (Inertsil ODS-3, 20 mm x 250 mm, MeOH/H_2O 20/80 to 25/75, 15 mL/min) to afford 17-*epi*-ouabagenin (t_R = 24 min, 1.2 mg, 2.8 μmol) and ouabagenin (**1**, t_R = 34 min, 5.5 mg, 0.013 mmol). The yields of ouabagenin (**1**) and 17-*epi*-ouabagenin were calculated to be 56% and 12% yields, respectively, over 2 steps. **Ouabagenin** (**1**): $[\alpha]_D^{26}$ -11 (*c* 0.28 DMSO/$CHCl_3$ 2/1); IR (neat) ν 3390, 2944, 1732, 1623, 1437, 1122, 1079, 1026 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 0.95 (3H, s, H18), 1.24-1.39 (1H, m), 1.43-1.64 (4H, m), 1.66-1.81 (3H, m), 1.82-2.24 (8H, m), 2.92 (1H, dd, *J* = 8.7, 5.5 Hz, H17), 3.99-4.11 (1H, br s), 4.18 (1H, d, *J* = 11.9 Hz, $H19_a$), 4.22-4.32 (1H, br s), 4.37 (1H, d, *J* = 11.9 Hz, $H19_b$), 4.91 (1H, dd, *J* = 18.8, 1.4 Hz, $H21_a$), 5.02 (1H, dd, *J* = 18.8, 1.4 Hz, $H21_b$), 5.91 (1H, dd, *J* = 1.4, 1.4 Hz, H22), one proton peak was not observed due to overlap with HDO peak or broadening of the peak; ^{13}C NMR (125 MHz, $(CD_3)_2SO$/$CDCl_3$ 2/1) δ 16.9, 22.6, 26.0, 32.3, 47.1, 48.3, 49.0, 49.7, 60.5, 65.3, 66.1, 70.7, 72.9, 74.9, 83.4, 116.3, 173.6, 175.0, five ^{13}C peaks were not observed due to overlap with the solvent peak and broadening of the peaks; HRMS (ESI) calcd for $C_{23}H_{34}O_8Na$ $[M+Na]^+$ 461.2146, found 461.2140. **17-*epi*-Ouabagenin**: ^1H NMR (400 MHz, CD_3OD) δ 1.10 (3H, s, H18), 1.24-1.38 (3H, m), 1.45-1.80 (5H, m), 1.81-2.21 (8H, m), 3.14 (1H, dd, *J* = 10.1, 9.2 Hz, H17), 3.95-4.27 (2H, m), 4.19 (1H, d, *J* = 11.9 Hz, $H19_a$), 4.37 (1H, d, *J* = 11.9 Hz, $H19_b$), 4.83 (1H, dd, *J* = 18.3, 1.0 Hz, $H21_a$), 4.97 (1H, dd, *J* = 18.3, 1.8 Hz, $H21_b$), 5.95-5.98 (1H, m, H22), one proton peak was not observed due to overlap with HDO peak or broadening of the peak; HRMS (ESI) calcd for $C_{23}H_{34}O_8Na$ $[M+Na]^+$ 461.2146, found 461.2147.

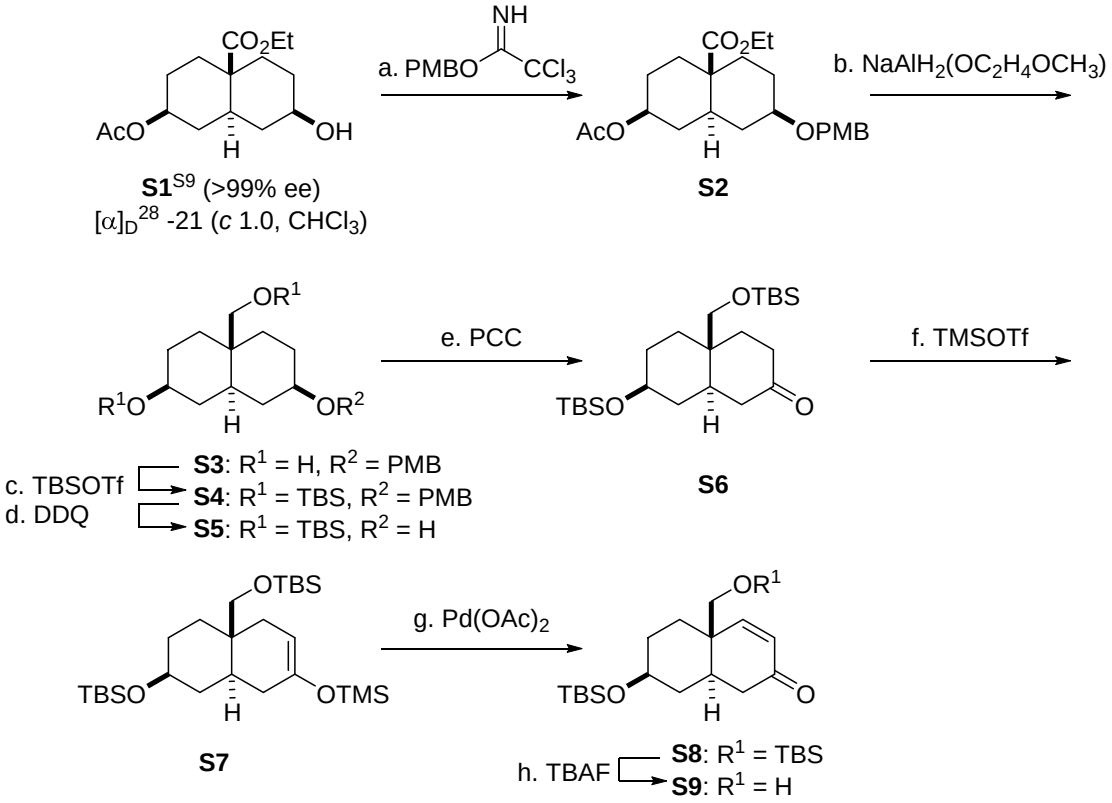


Synthesis of authentic ouabagenin (1).[S6,7] 12 M HCl (0.3 mL) was added to a solution of ouabain octahydrate (537 mg, 0.737 mmol) in acetone (25 mL) at room temperature. The reaction mixture was stirred for 9 days at room temperature, and then was cooled to 0 ºC for 1 h. After the solvent was removed by decantation, the resultant solid was washed with acetone (20 mL). The remaining acetone was azeotropically removed with EtOH (40 mL) to afford ouabagenin acetonide, which was used in the next reaction without further purification.

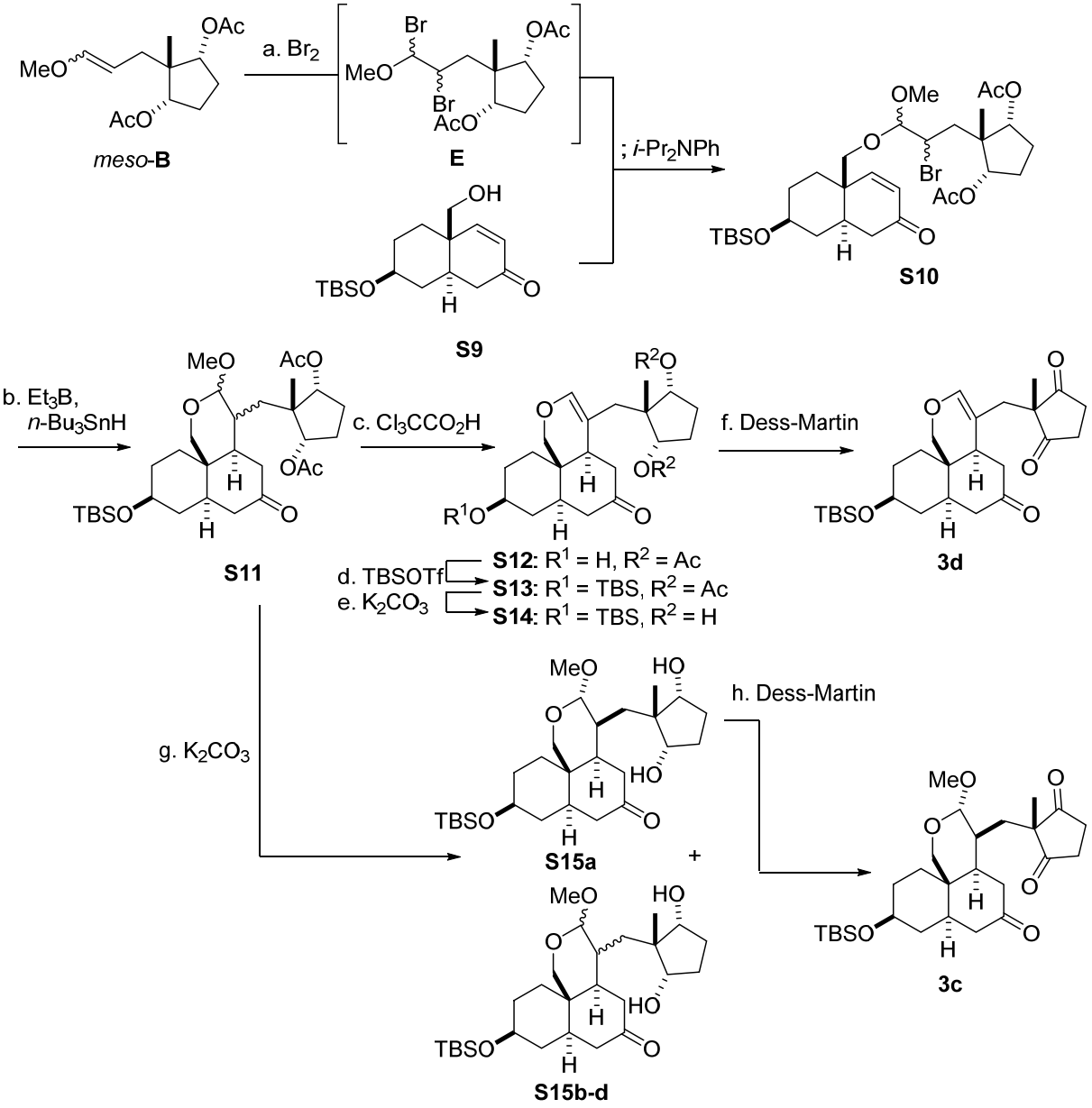
The solid of ouabagenin acetonide was dissolve in EtOH (40 mL). The mixture was heated to reflux, and stirred for 1 h. Then, 0.5 M HCl in MeOH (1 mL) was added. The reaction mixture was stirred at reflux temperature for 1 h, and then 3.0 M aqueous HCl (6 mL) was added. The mixture was stirred at reflux temperature for further 1 h. After the mixture was cooled to room temperature, solid $NaHCO_3$ was added. The pH value of the resultant solution was adjusted to 6 by addition of 1.0 M HCl and solid $NaHCO_3$. The solution was extracted with a 2 : 1 mixture of $CHCl_3$ and EtOH (25 mL x6), and the combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, and filtered through a pad of silica gel (0.5 g) with MeOH. The filtrate was concentrated, and the residue was purified by flash column chromatography on silica gel (15 g, CH_2Cl_2 to CH_2Cl_2/MeOH 10/1 to 3/1) to afford ouabagenin (**1**, 201 mg, 0.458 mmol) in 62% yield over 2 steps[S8]: $[\alpha]_D^{26}$ -6.3 (*c* 0.87 DMSO/$CHCl_3$ 2/1); IR (neat) ν 3398, 2946, 1734, 1625, 1440, 1122, 1025 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 0.95 (3H, s, H18), 1.23-1.40 (1H, m), 1.40-2.50 (15H, m), 2.92 (1H, dd, J = 8.7, 5.5 Hz, H17), 3.99-4.15 (1H, br s), 4.18 (1H, d, J = 11.9 Hz, $H19_a$), 4.25-4.40 (1H, br s), 4.37 (1H, d, J = 11.9 Hz, $H19_b$), 4.91 (1H, d, J

= 18.3 Hz, $H21_a$), 5.02 (1H, dd, J = 18.3 Hz, $H21_b$), 5.92 (1H, s, H22), one proton peak was not observed due to the overlap with HDO peak or broadening of the peak; ^{13}C NMR (125 MHz, $(CD_3)_2SO/CDCl_3$ 2/1) δ 16.9, 22.6, 26.1, 32.3, 34.5, 39.2 (deduced from the HMBC correlation), 47.1, 48.3, 49.0, 49.7, 60.5, 65.2, 66.1, 70.8, 73.0, 75.0, 83.4, 116.3, 173.6, 175.0, three ^{13}C peaks were not observed due to broadening of the peaks; HRMS (ESI) calcd for $C_{23}H_{34}O_8Na$ $[M+Na]^+$ 461.2146, found 461.2154.

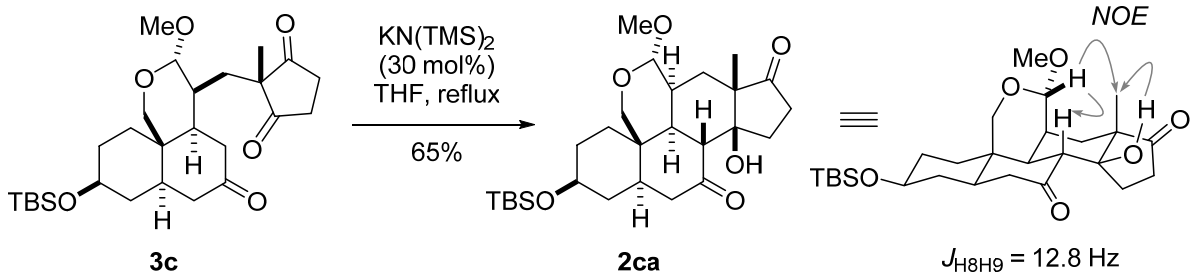
Model Study for the Stereoselective C-Ring Formation.



Scheme S1. Synthesis of the model AB-ring from **S1**.[S9] Reagents and conditions: (a) (4-methoxyphenyl)methyl 2,2,2-trichloroethanecarboximidate, CSA, CH_2Cl_2; (b) $NaAlH_2(OC_2H_4OCH_3)$, toluene, 100 ºC; (c) TBSOTf, 2,6-lutidine, CH_2Cl_2, 52% (3 steps); (d) DDQ; CH_2Cl_2, pH 7 phosphate buffer; (e) PCC, CH_2Cl_2, 71% (2 steps); (f) TMSOTf, Et_3N, CH_2Cl_2, 0 ºC; (g) $Pd(OAc)_2$, O_2, DMSO, 72% (2 steps); (h) TBAF, THF, 56%.

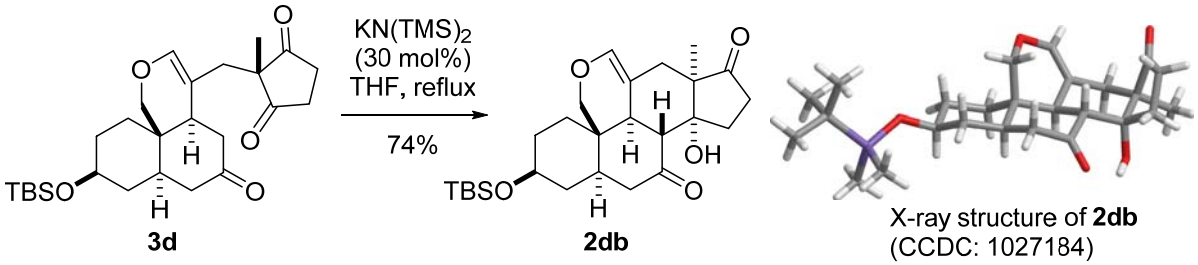


Scheme S2. Synthesis of the model compounds. Reagents and conditions: (a) *meso*-**B** (3-5 equiv), Br_2, CH_2Cl_2, -78 °C; **S9** (1.0 equiv), *i*-Pr_2NPh; (b) Et_3B, *n*-Bu_3SnH, O_2; (c) Cl_3CCO_2H, toluene, reflux; (d) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 ºC; (e) K_2CO_3, MeOH, 42% (5 steps from **S9**); (f) Dess-Martin reagent, $NaHCO_3$, CH_2Cl_2, 96%; (g) K_2CO_3, MeOH; (h) Dess-Martin reagent, $NaHCO_3$, CH_2Cl_2, 19% for **3c** (4 steps from **S9**);



3c **2ca**

Steroid 2ca. A solution of $KN(TMS)_2$ (0.99 M, 8 μL, 8 μmol) freshly prepared from KH and $HN(TMS)_2$ in THF was added to a solution of triketone **3c** (13 mg, 0.026 mmol) in refluxing THF (270 μL), and the reaction mixture was stirred for 2 h. After the mixture was cooled to room temperature, saturated aqueous NH_4Cl (0.3 mL) was added. The resultant mixture was extracted with EtOAc (10 mL x3), and the combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel (1 g, hexane/EtOAc 5/1) to afford **2ca** (8.2 mg, 0.017 mmol) in 65% yield: crystal; m.p. 209-210 ºC; $[\alpha]_D^{25}$ 15 (*c* 0.72, $CHCl_3$); IR (neat) ν 3525, 2931, 2857, 1739, 1699, 1467, 1381, 1254, 1197, 1102, 1056, 1002 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 0.09 (6H, s, CH_3 of TBS x2), 0.29 (1H, ddd, *J* = 13.7, 13.7, 2.8 Hz), 0.74 (1H, dd, *J* = 15.1, 6.0 Hz, CH_AH$_B$CCH$_3$), 0.84-0.94 (1H, m), 1.01 (9H, s, *t*-Bu of TBS), 1.02-1.09 (1H, m), 1.16-1.28 (2H, m, COCHC*H*), 1.37 (3H, s, CH_3), 1.50-1.79 (5H, m, COCH$_2$CH_AH$_B$), 1.84 (1H, d, *J* = 15.1 Hz, CH$_A$$H_BCCH_3$), 1.86-1.92 (1H, m, CH(OCH$_3$)C*H*), 2.09-2.20 (2H, m, COCH_AH$_B$CH$_A$$H_B$), 2.33 (1H, ddd, *J* = 13.3, 3.6, 3.6 Hz), 2.46 (1H, ddd, *J* = 19.2, 9.6, 9.6 Hz, COCH$_A$$H_BCH_2$), 2.57 (1H, *J* = 13.3 Hz, COC*H*CH), 3.07 (1H, d, *J* = 12.4 Hz, CH_AH$_B$OCH), 3.33 (3H, s, OCH_3), 3.38 (1H, dddd, *J* = 5.5, 5.5, 5.5, 5.5 Hz, C*H*OTBS), 3.70 (1H, dd, *J* = 12.4, 1.4 Hz, CH$_A$$H_B$OCH), 3.80 (1H, s, O*H*), 4.44 (1H, d, *J* = 9.6 Hz, C*H*OCH$_3$); ^{13}C NMR (125MHz, C_6D_6) δ -4.4, -4.3, 17.2, 18.3, 26.1, 27.9, 30.9, 31.4, 32.3, 33.0, 35.8, 36.4, 38.5, 41.6, 44.8, 48.6, 50.5, 52.0, 56.1, 61.2, 71.1, 80.2, 102.5, 211.4, 217.3; HRMS (ESI) calcd for $C_{27}H_{44}O_6SiNa$ $[M+Na]^+$ 515.2799, found 515.2799.



3d **2db**

Steroid 2db. A solution of $KN(TMS)_2$ (0.97 M, 16 μL, 0.016 mmol) freshly prepared from KH and $HN(TMS)_2$ in THF was added to a solution of triketone **3d** (24 mg, 0.053

mmol) in refluxing THF (0.53 mL), and the reaction mixture was stirred for 2 h. After the mixture was cooled to room temperature, saturated aqueous NH_4Cl (0.5 mL) was added. The resultant mixture was extracted with EtOAc (10 mL x3), and the combined organic layers were washed with brine (3 mL), dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel (2 g, hexane/EtOAc 5/1 to 3/1 to 1/1 to EtOAc) to afford **2db** (18 mg, 0.039 mmol) in 74% yield, respectively: white solid; m.p. 200-202 ºC; $[\alpha]_D^{25}$ -37 (*c* 0.36, $CHCl_3$) ; IR (neat) ν 3507, 2929, 2856, 1740, 1701, 1471, 1378, 1294, 1255, 1192, 1125, 1097, 1055 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 0.06 (3H, s, C*H*$_3$ of TBS), 0.07 (3H, s, C*H*$_3$ of TBS), 0.40 (1H, ddd, *J* = 13.8, 13.8, 3.4 Hz), 1.00 (9H, *t*-Bu of TBS), 1.03 (3H, s, C*H*$_3$), 1.11-1.32 (5H, m), 1.52-1.64 (3H, m), 1.78 (1H, ddd, *J* = 19.5, 10.3, 10.3 Hz), 1.88-1.94 (4H, m), 2.00 (1H, ddd, *J* = 13.8, 4.0, 3.6 Hz), 2.12 (1H, d, *J* = 11.4 Hz), 2.10-2.20 (1H, m), 2.59 (1H, d, *J* = 13.2 Hz), 3.34 (1H, m, C*H*OTBS), 3.40 (1H, d, *J* = 11.4 Hz, C*H*$_A$H$_B$OCH=C), 3.85 (1H, dd, *J* = 11.4, 1.8 Hz, CH$_A$*H*$_B$OCH=C), 4.29 (1H, s, O*H*), 6.21 (1H, s, CH$_2$OC*H*=C); ^{13}C NMR (125MHz, C_6D_6) δ -4.47, -4.37, 18.3, 19.3, 26.1, 30.8, 31.1, 31.5, 33.7, 34.1, 34.7, 38.2, 44.2, 45.5, 46.1, 56.1, 59.0, 61.8, 71.2, 78.5, 112.8, 136.1, 211.7, 215.0; HRMS (ESI) calcd for $C_{26}H_{40}O_5SiNa$ $[M+Na]^+$ 483.2537, found 483.2558.

Computer Simulation

Optimized geometries of the structures of **2aa-2ah** and **2ba-2bh**, and their stabilities were evaluated in silico. The initial structures of **2aa-2ah** and **2ba-2bh** were built by the molecular mechanics simulation using a 1000-steps of mixed torsional/low-mode sampling conformational search and PRCG energy minimization with Merck Molecular Force Field (MMFFs, MacroModel).[S10,11] The geometry optimizations and frequency calculations of the resulting conformations were performed at the PM6 semiempirical method[S12] using the Gaussian 09 program package.[S13] The difference in the Gibbs free energies (ΔG at 339.15 K, 1 atm), which are computed for the gas phase, are given in kcal mol^{-1}.

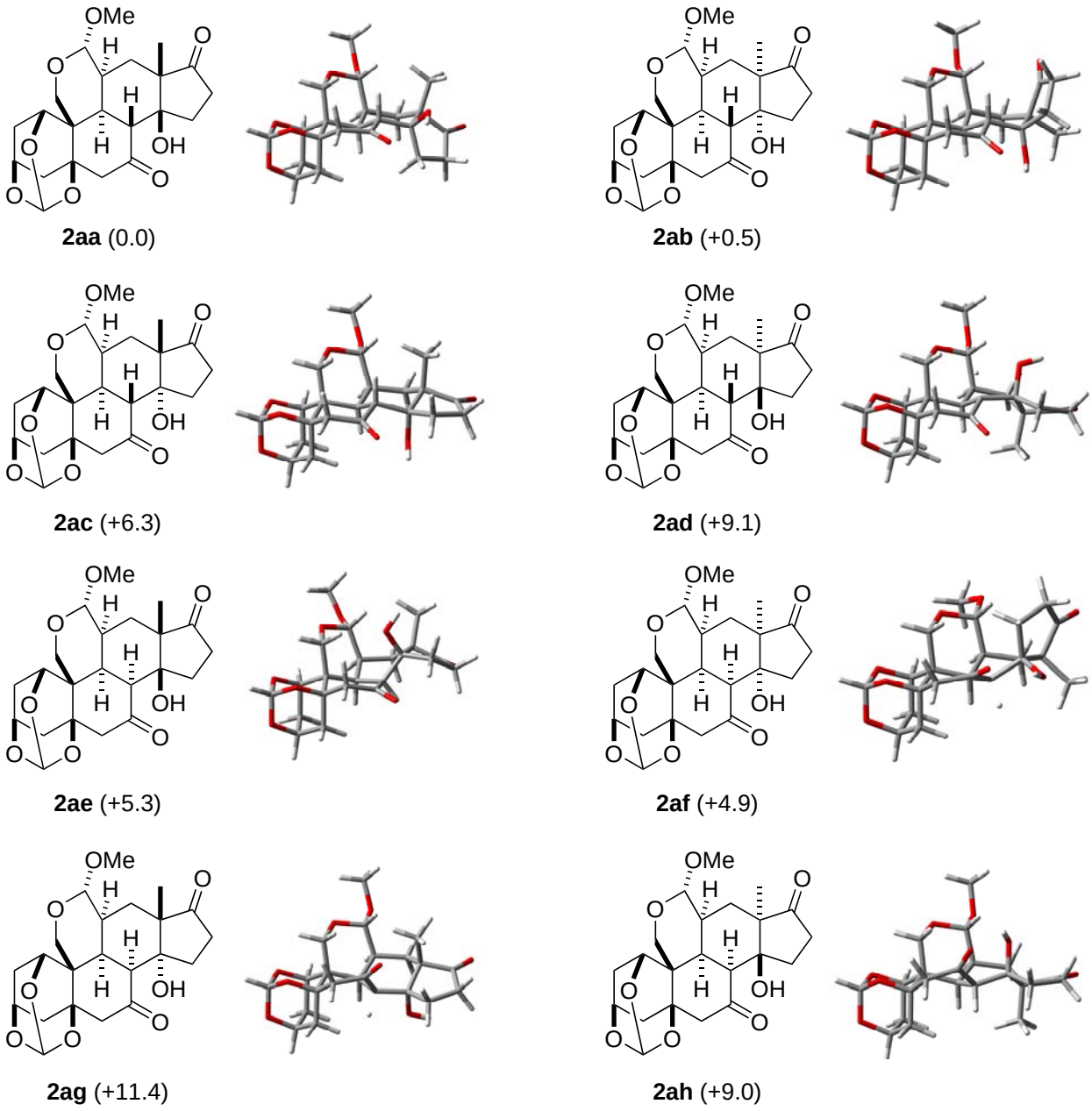


Figure S1. Optimized geometries of the structures of **2aa**-**2ah**.
Number in parenthesis shows the relative energy (kcal mol^{-1}).

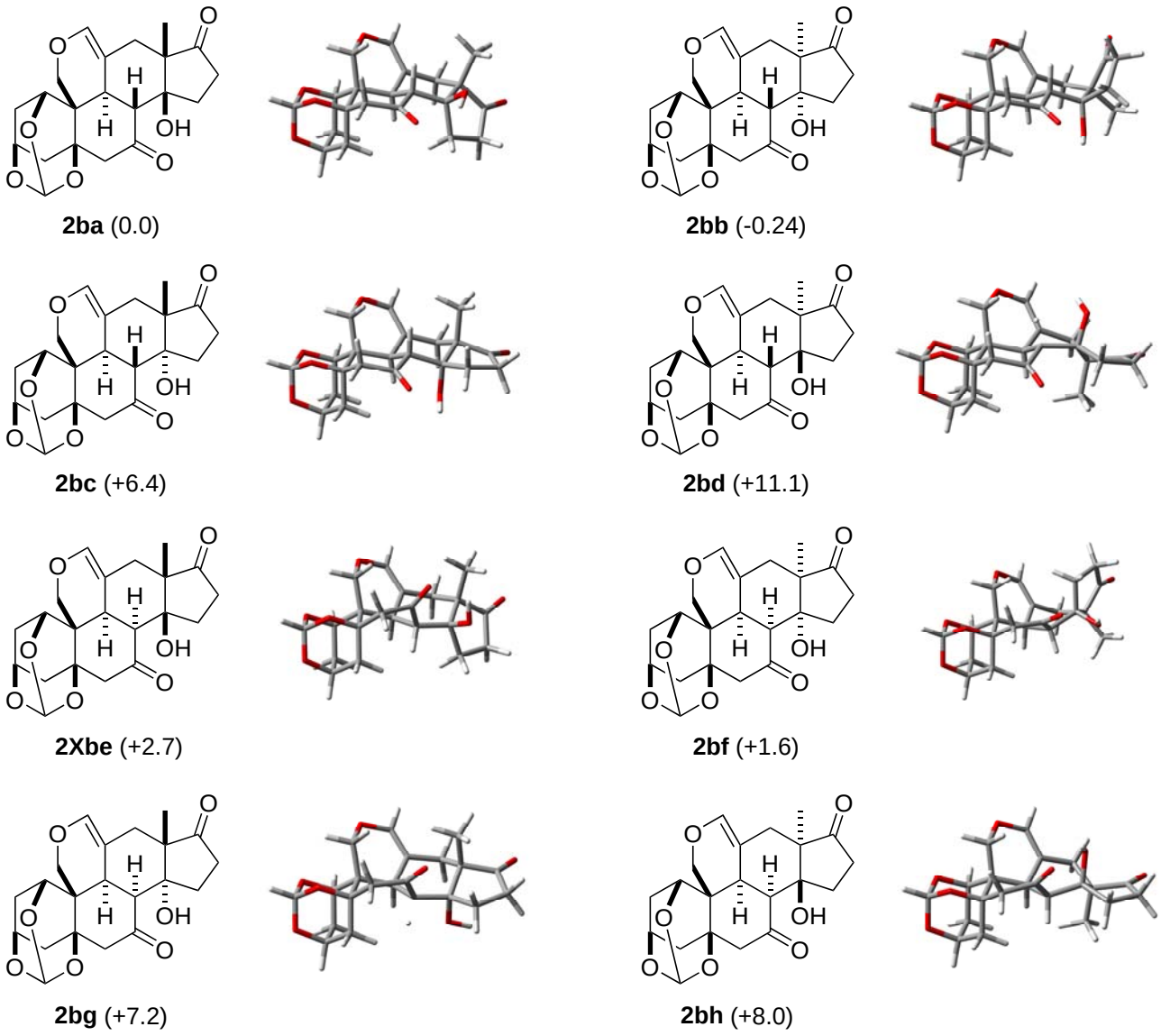


Figure S2. Optimized geometries of the structures of **2ba**-**2bh**.
Number in parenthess shows the relative energy (kcal mol^{-1}).

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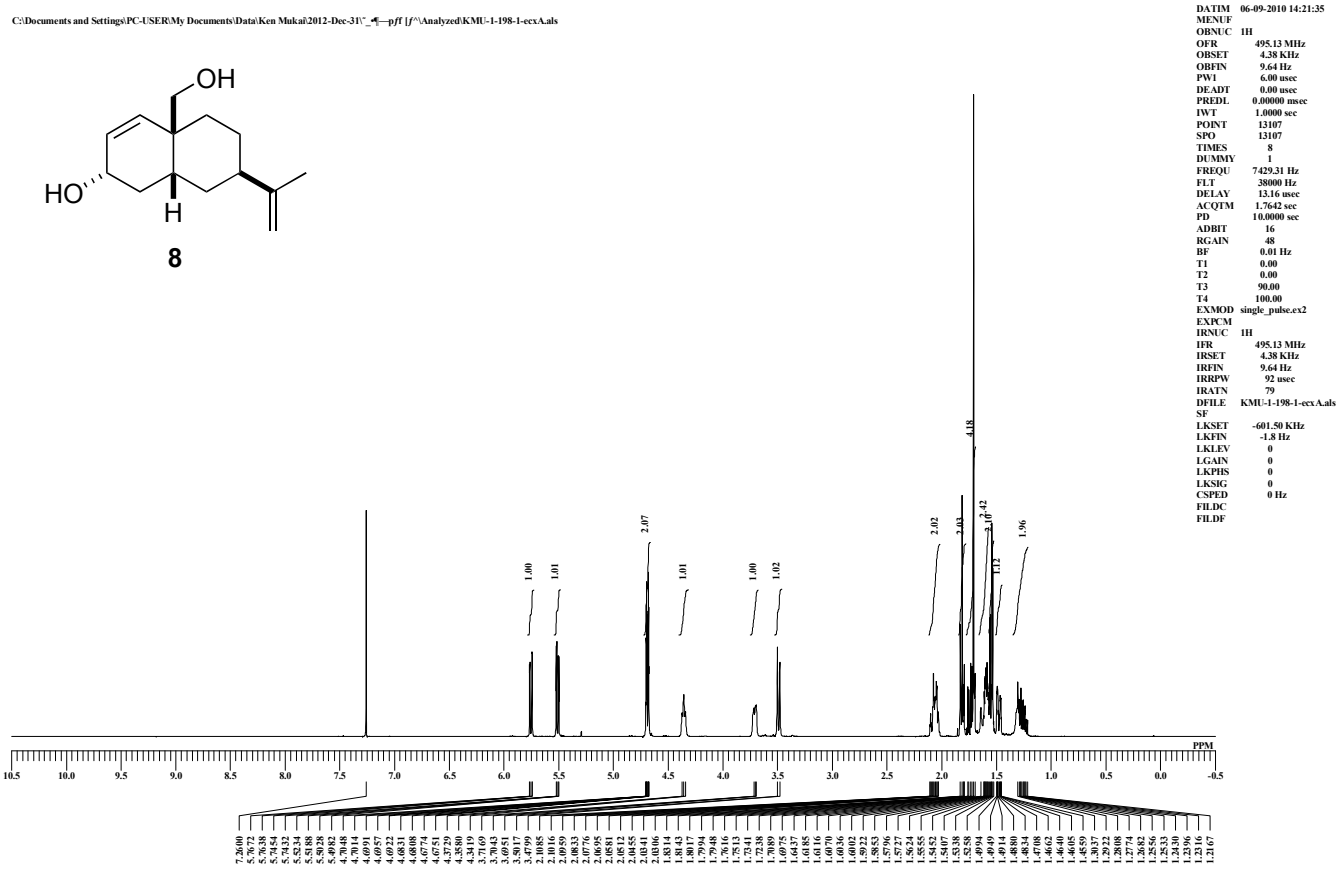

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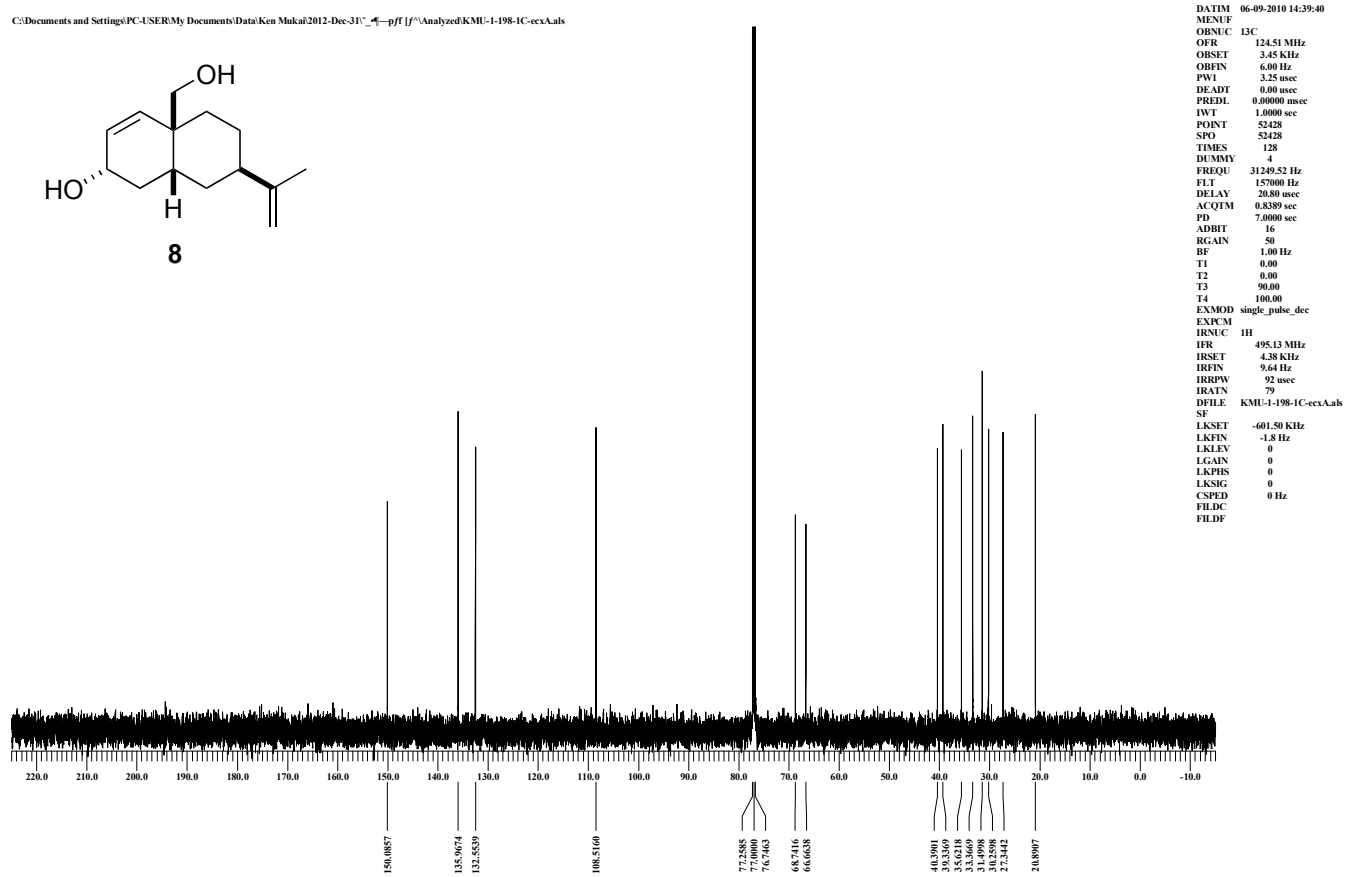

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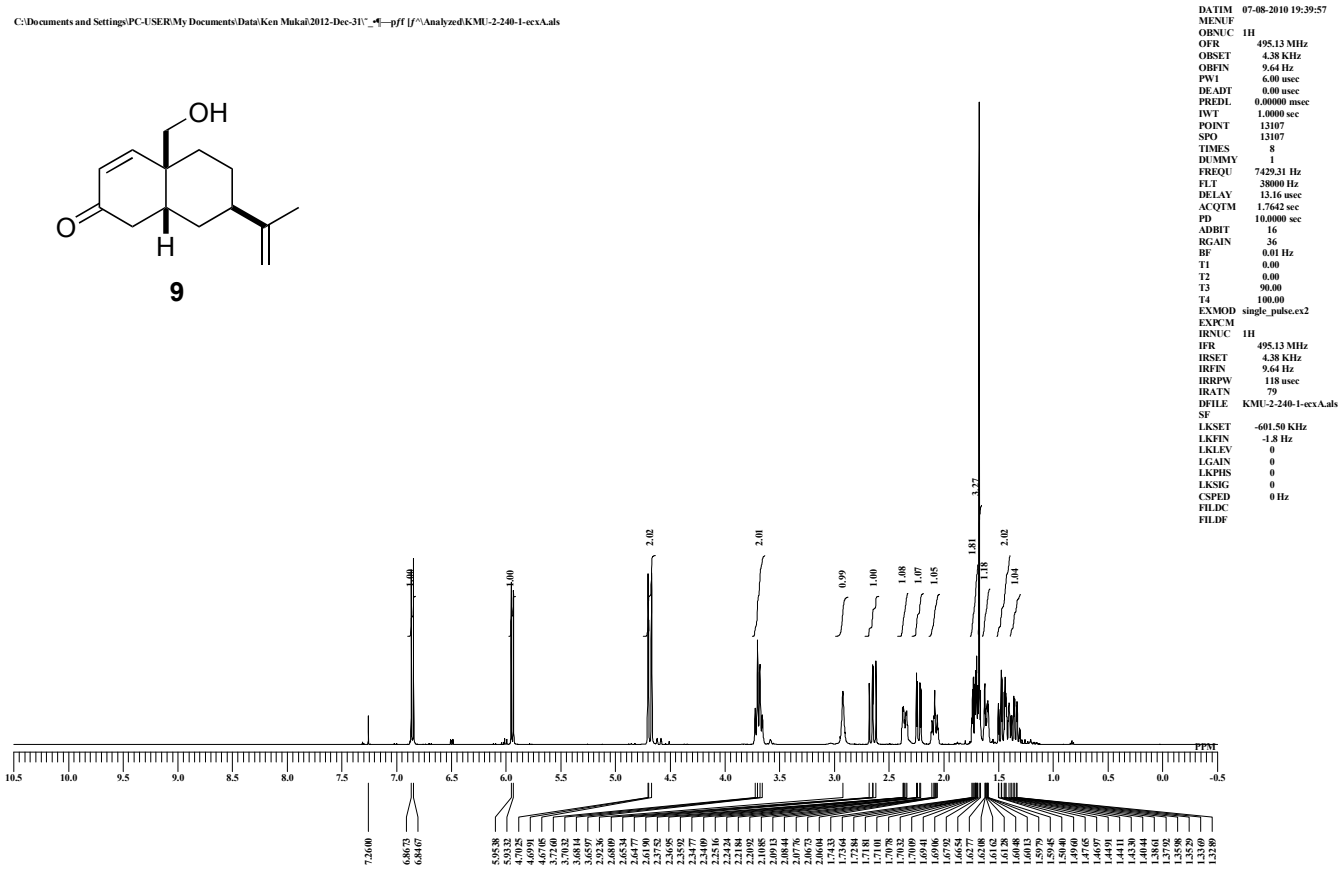

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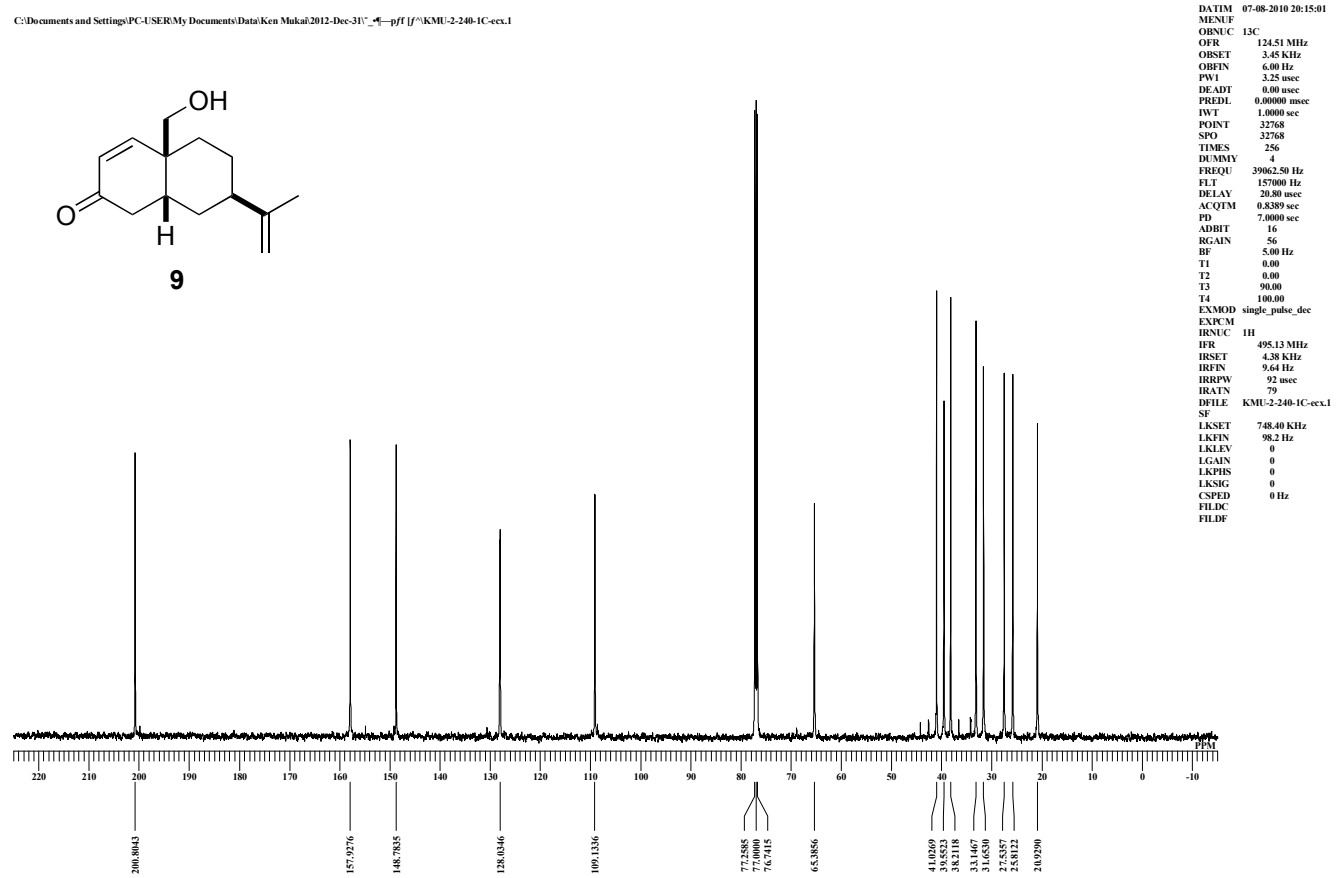

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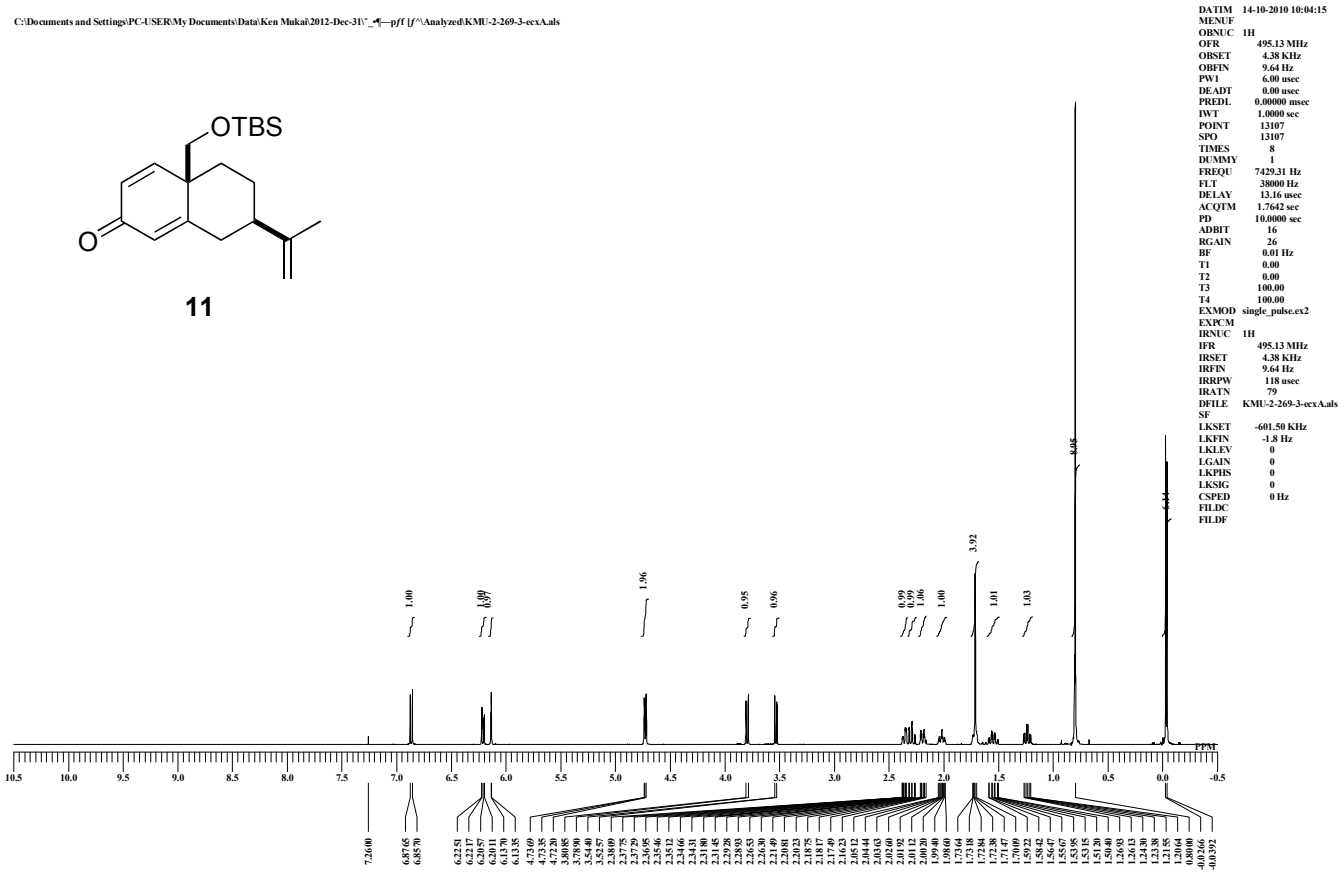

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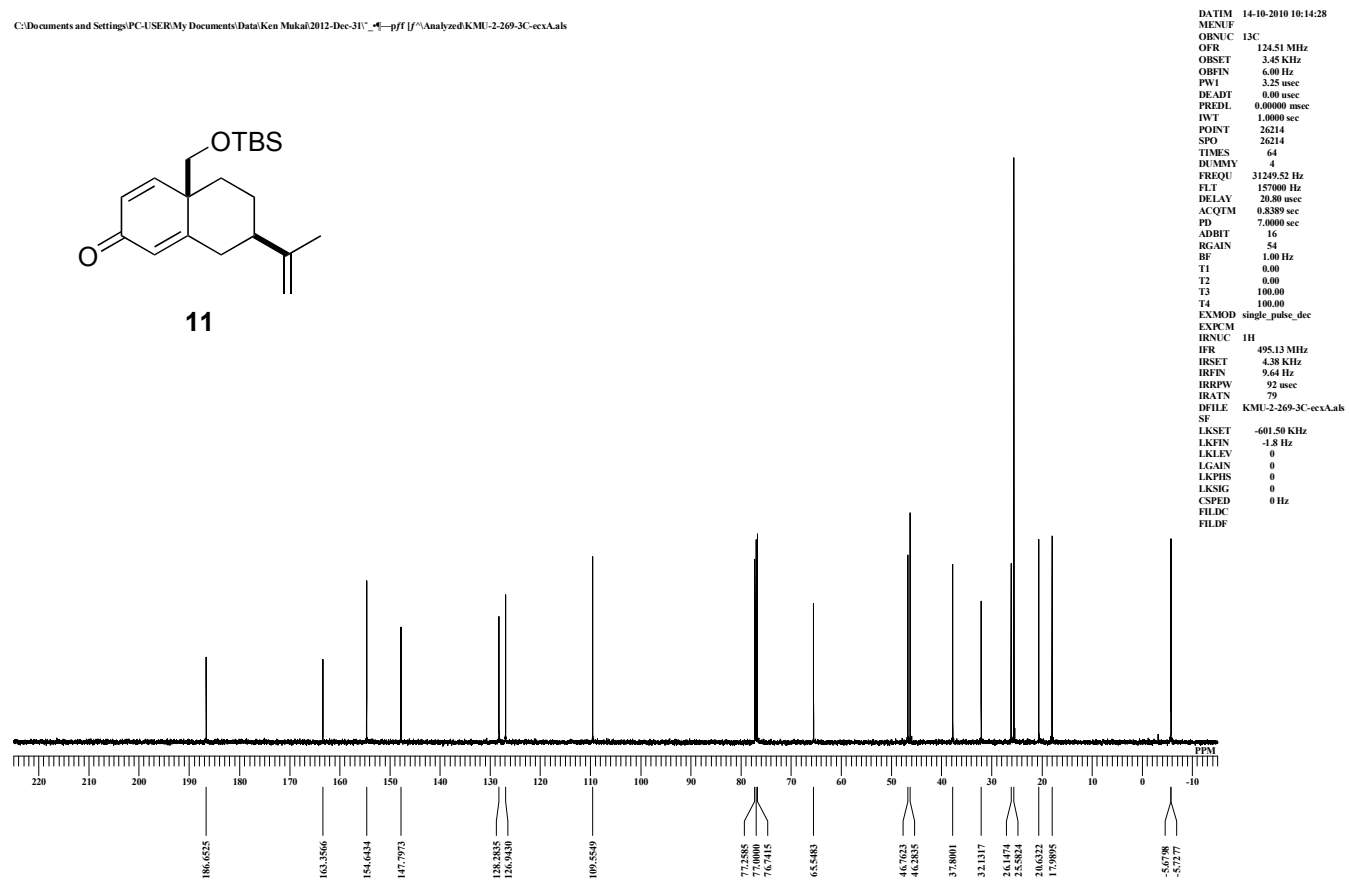

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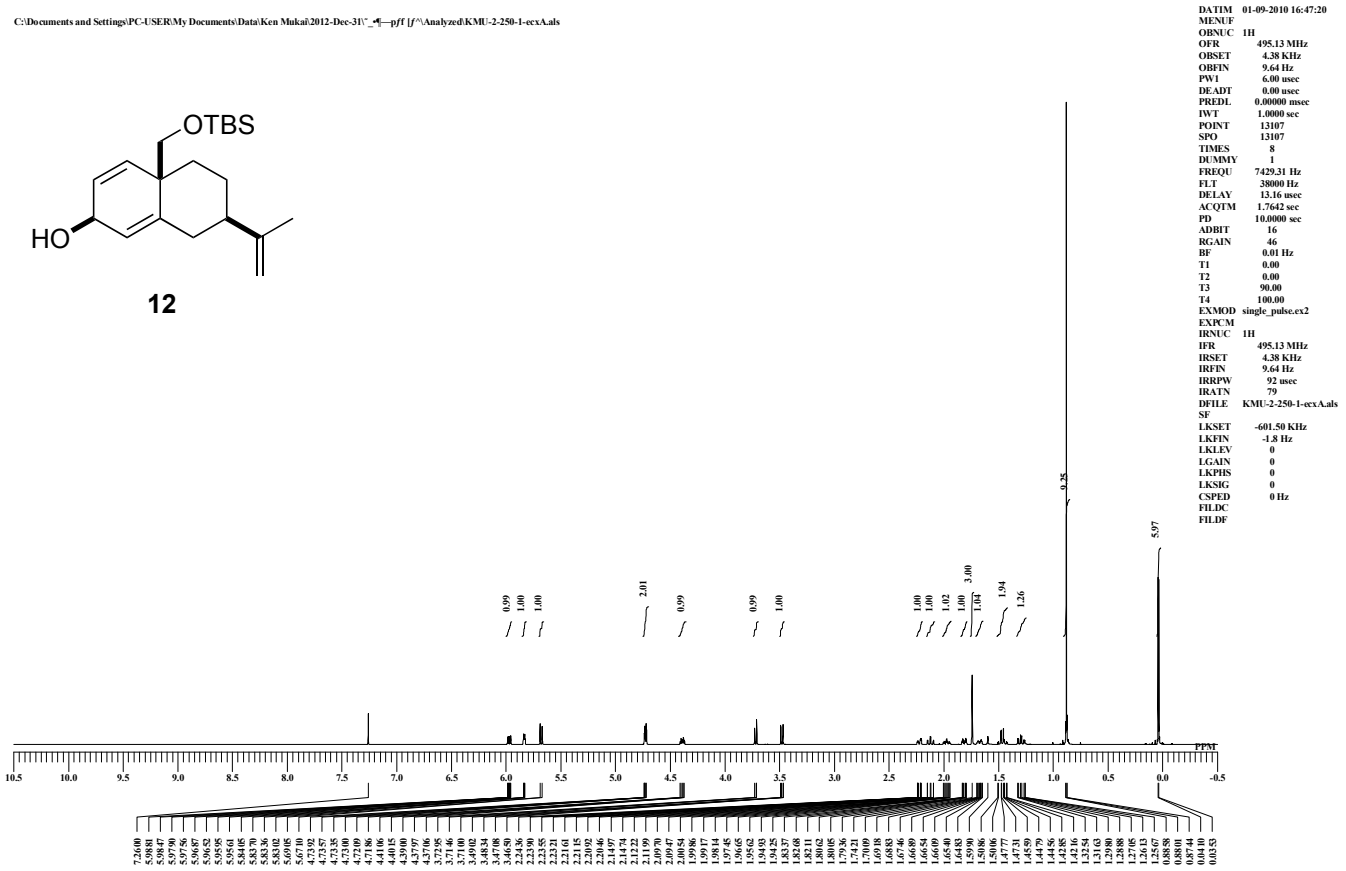

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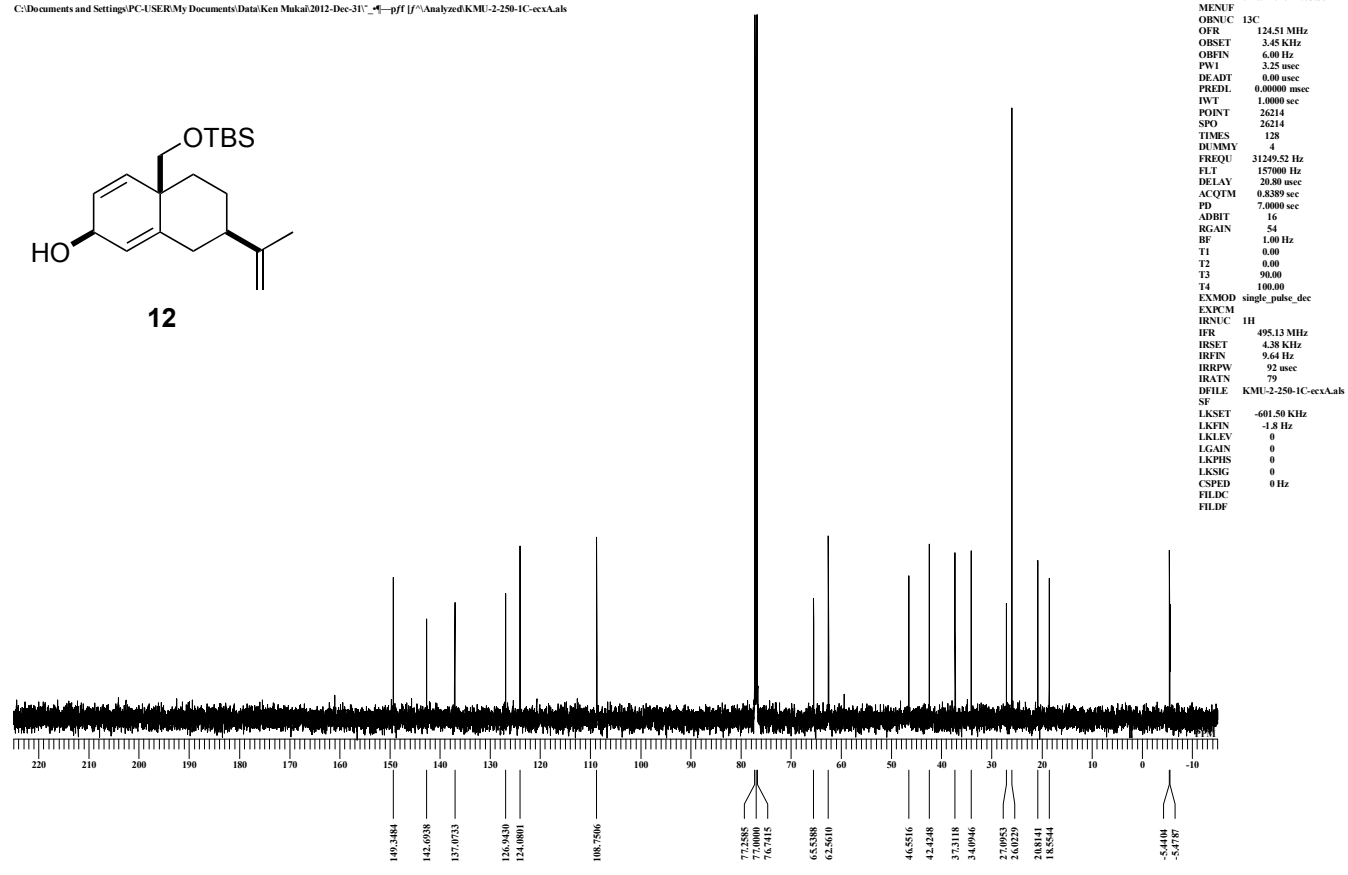

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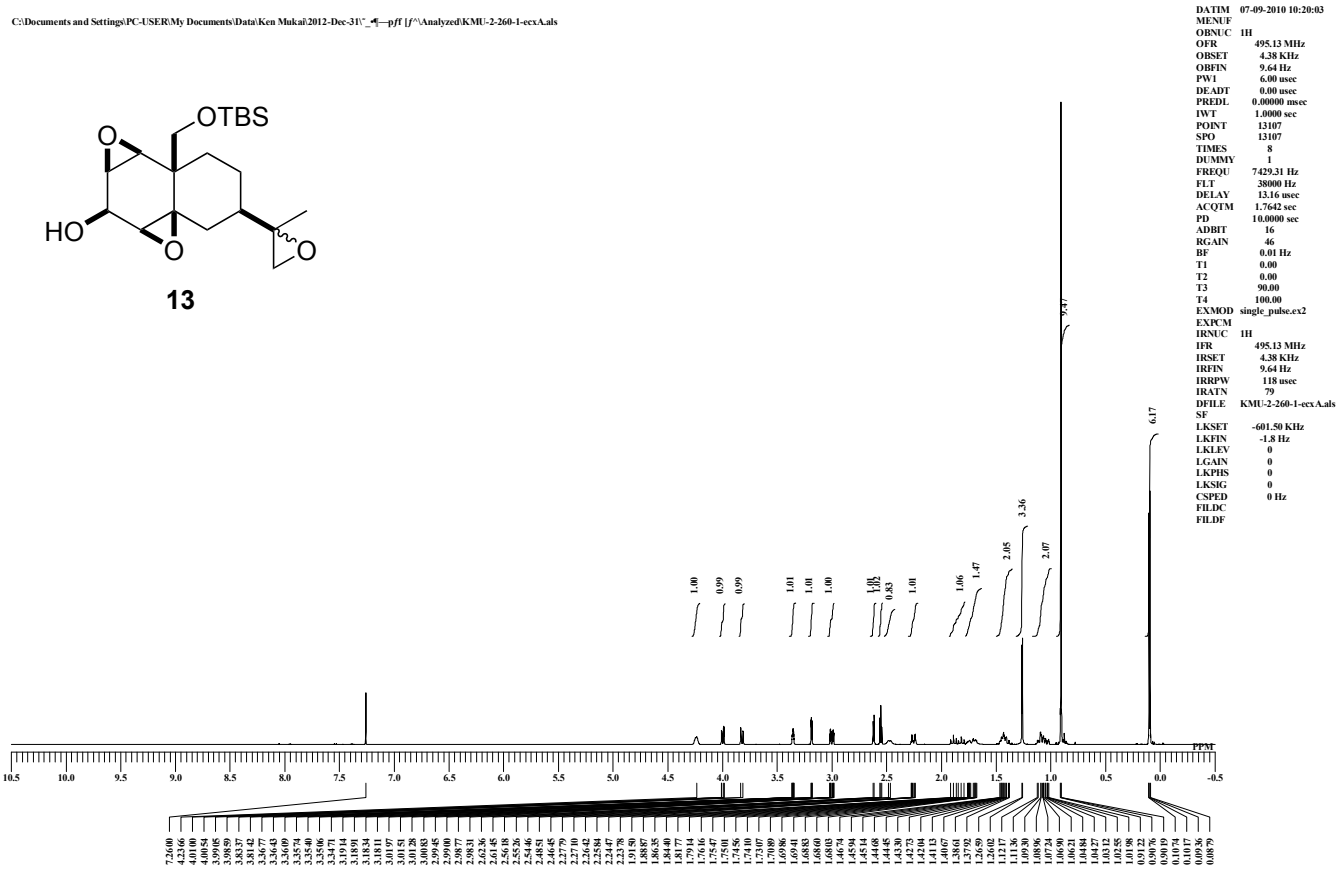

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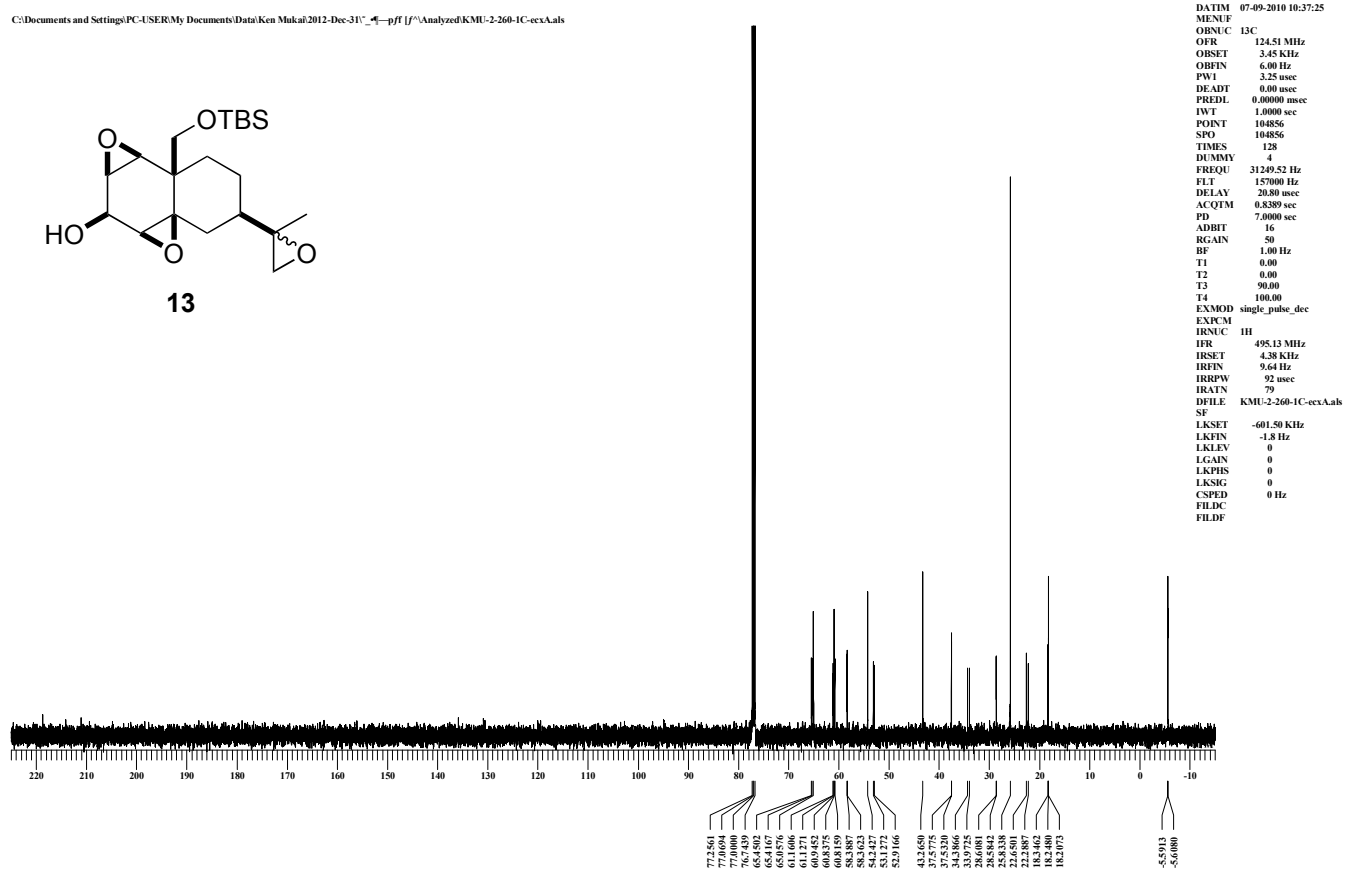

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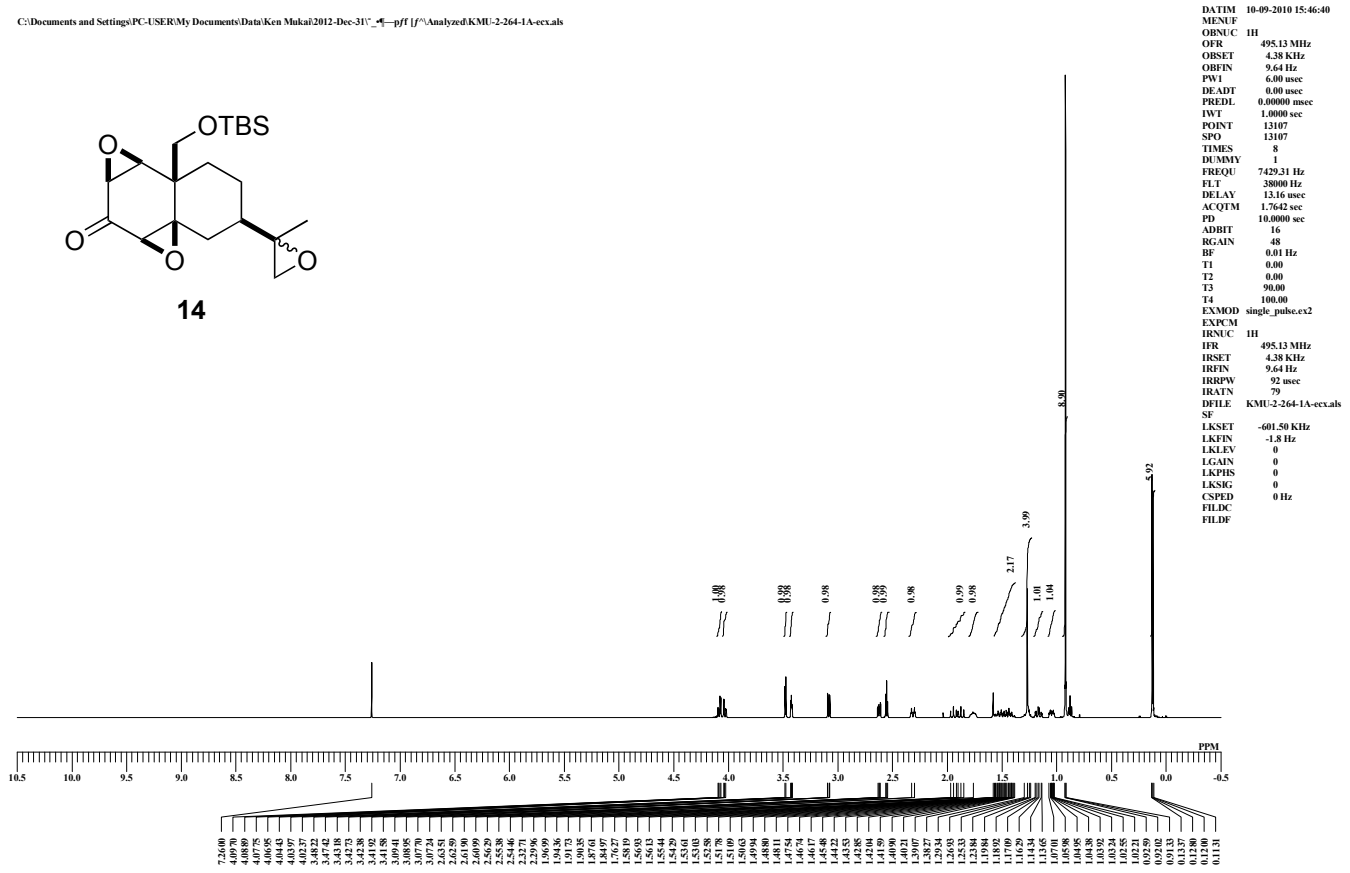

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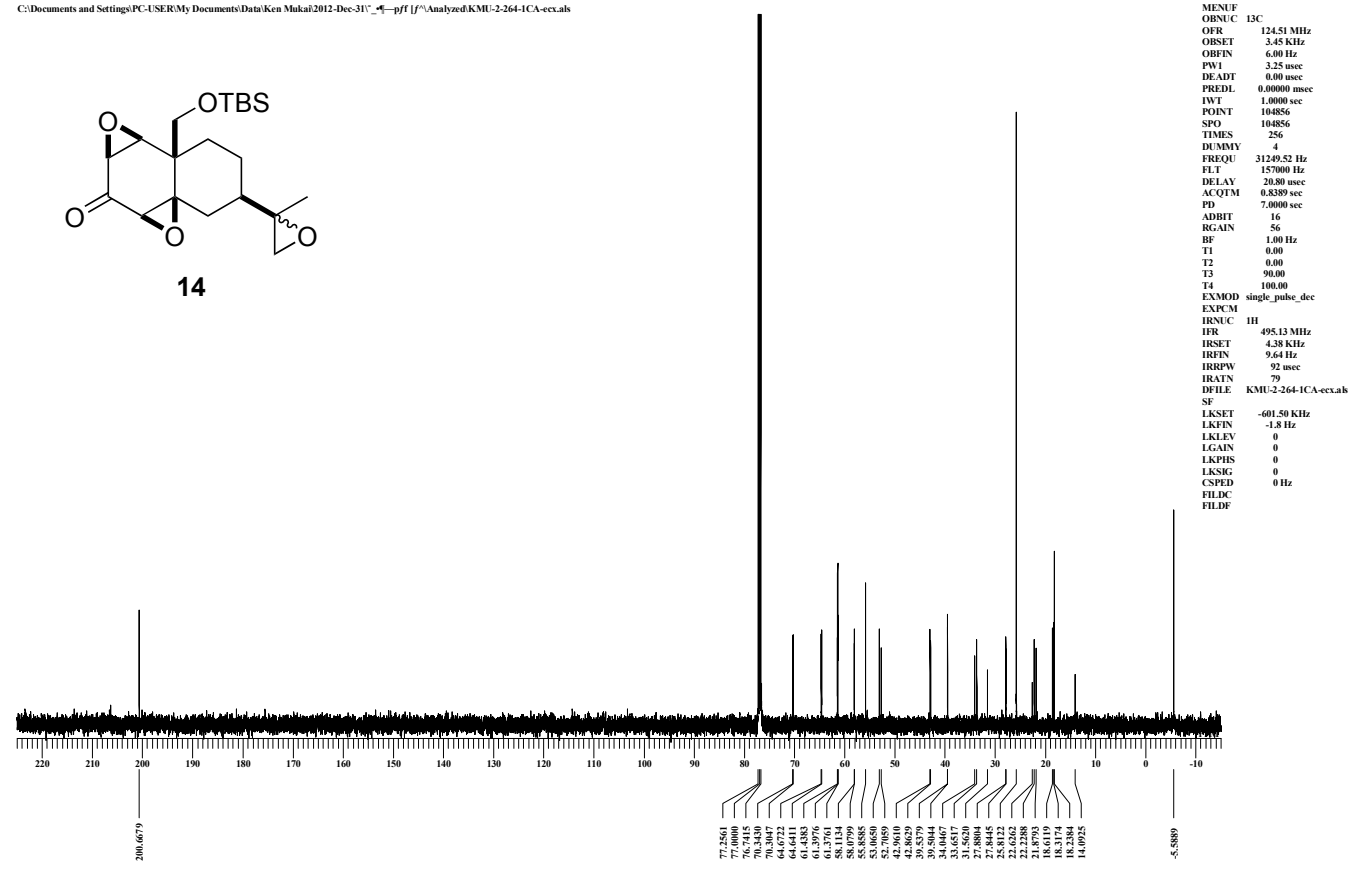
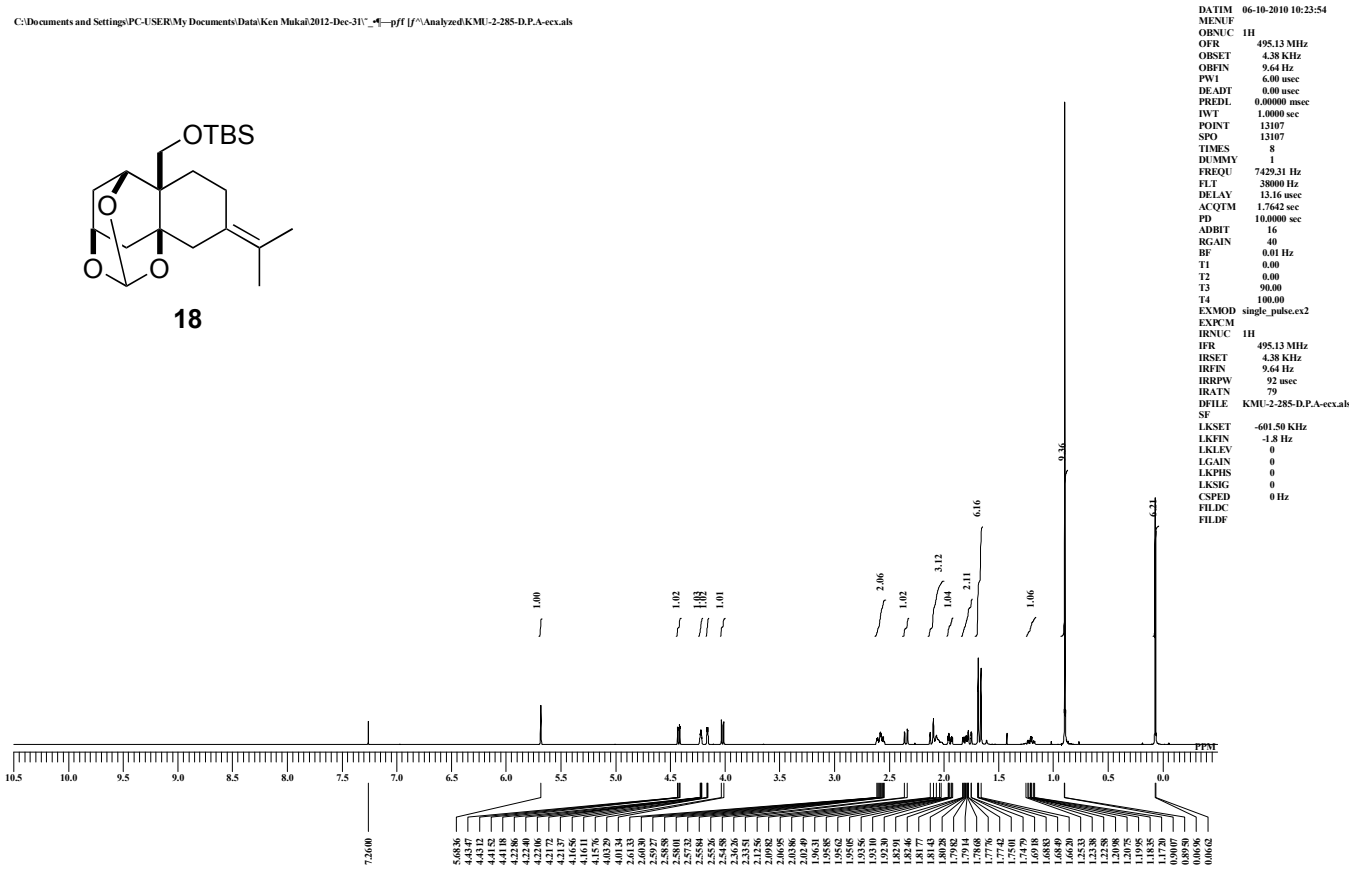


KMU-2-285-D.P.-ecx



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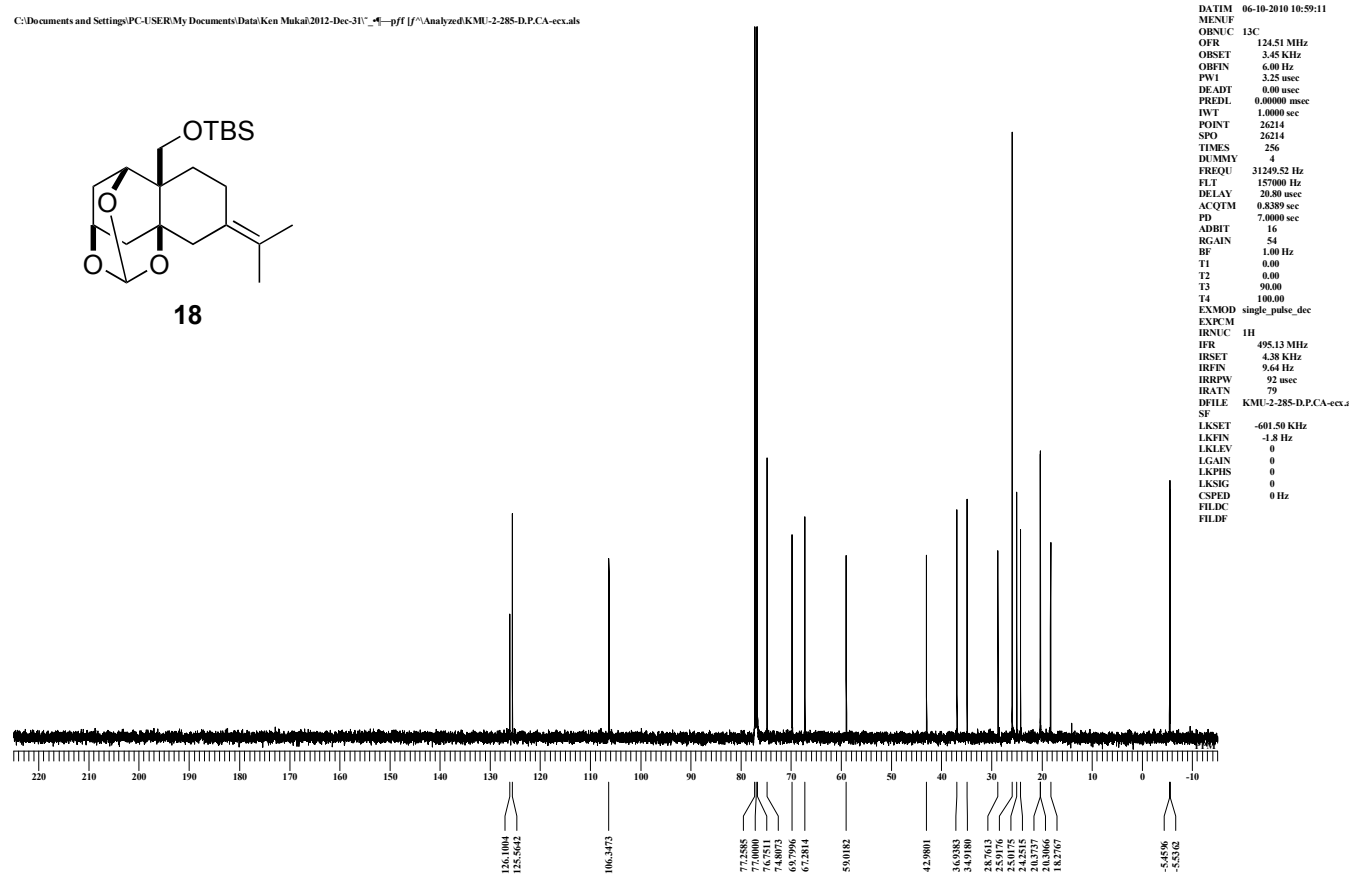

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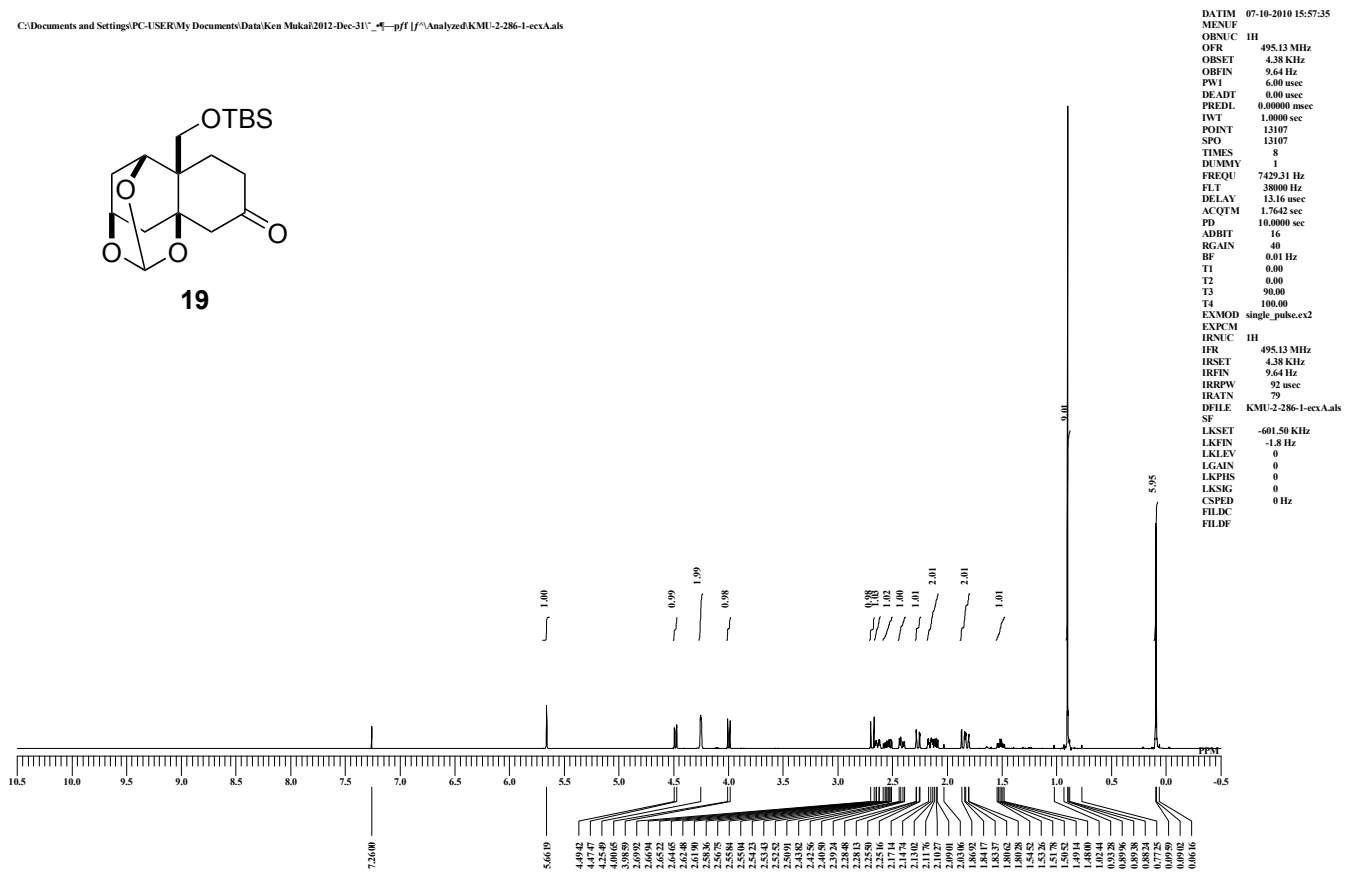

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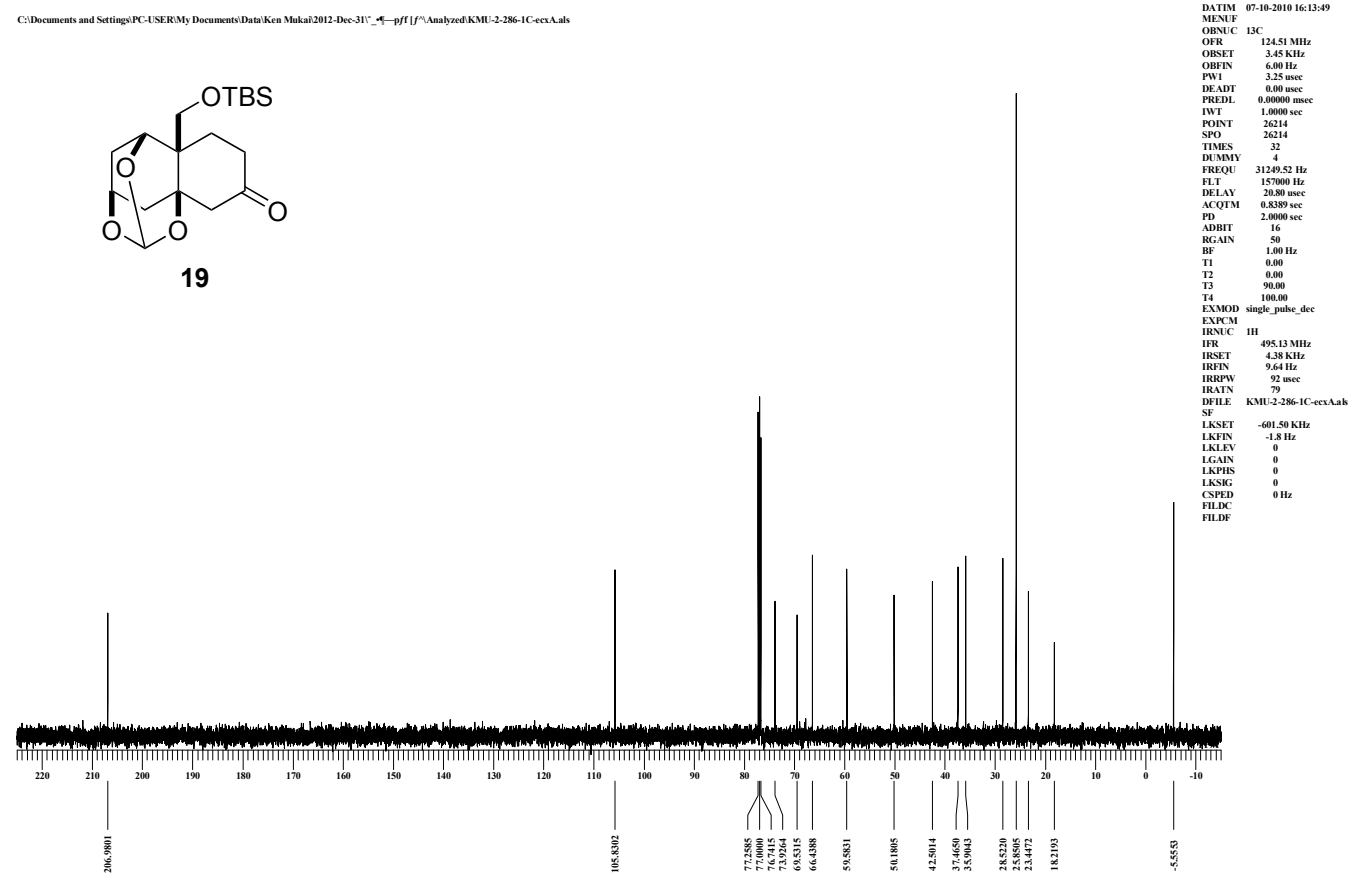

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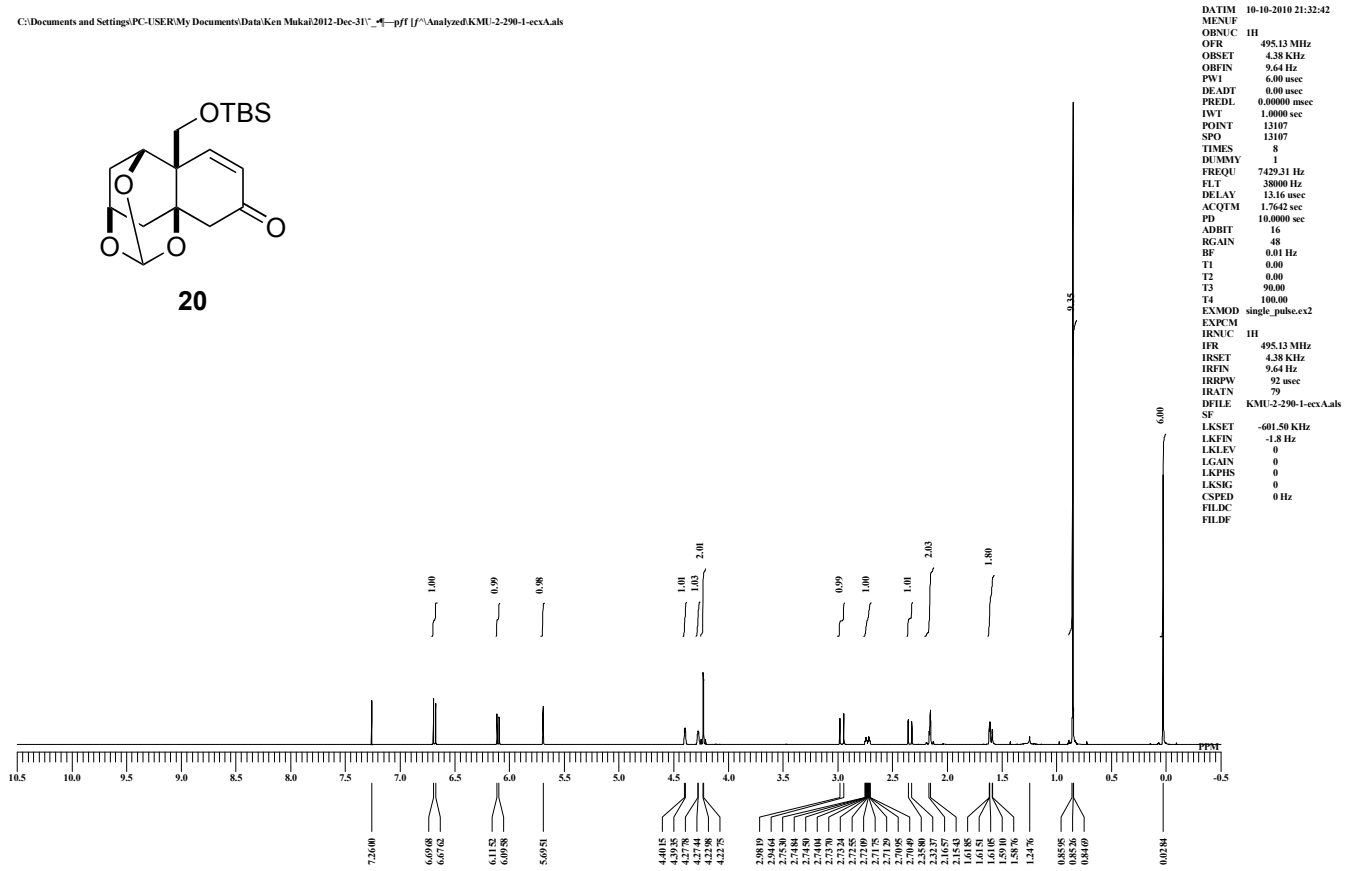

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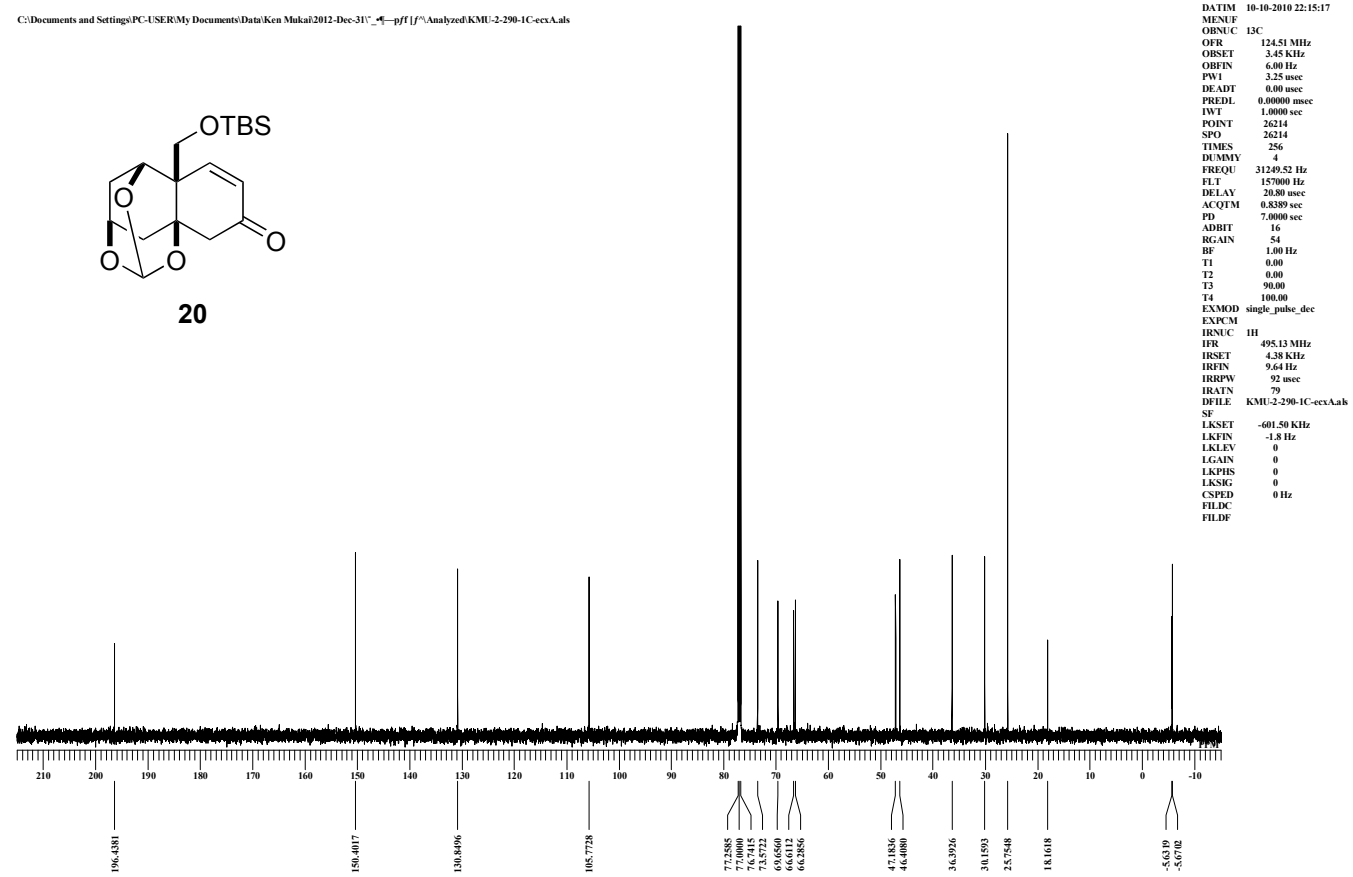

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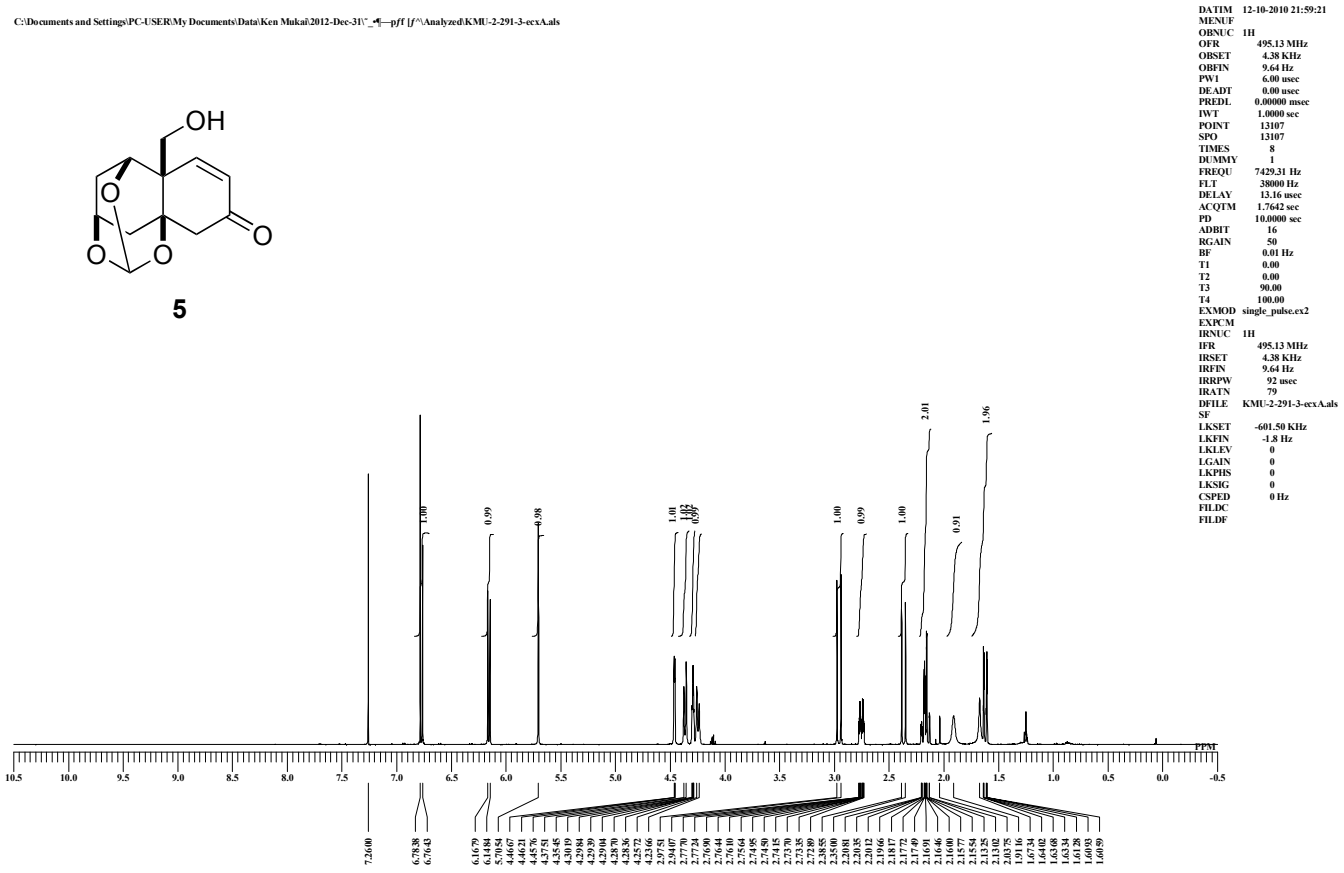

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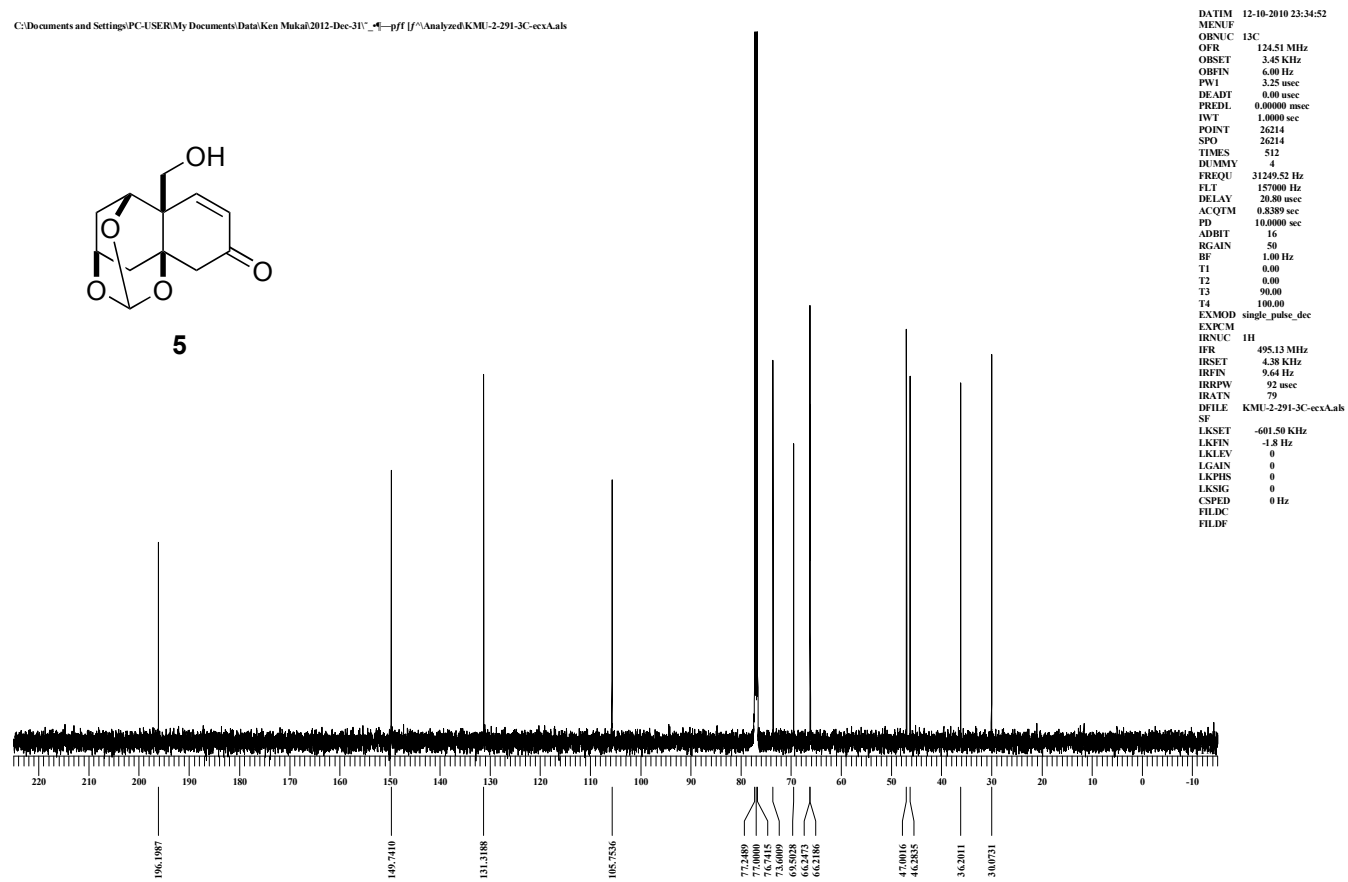
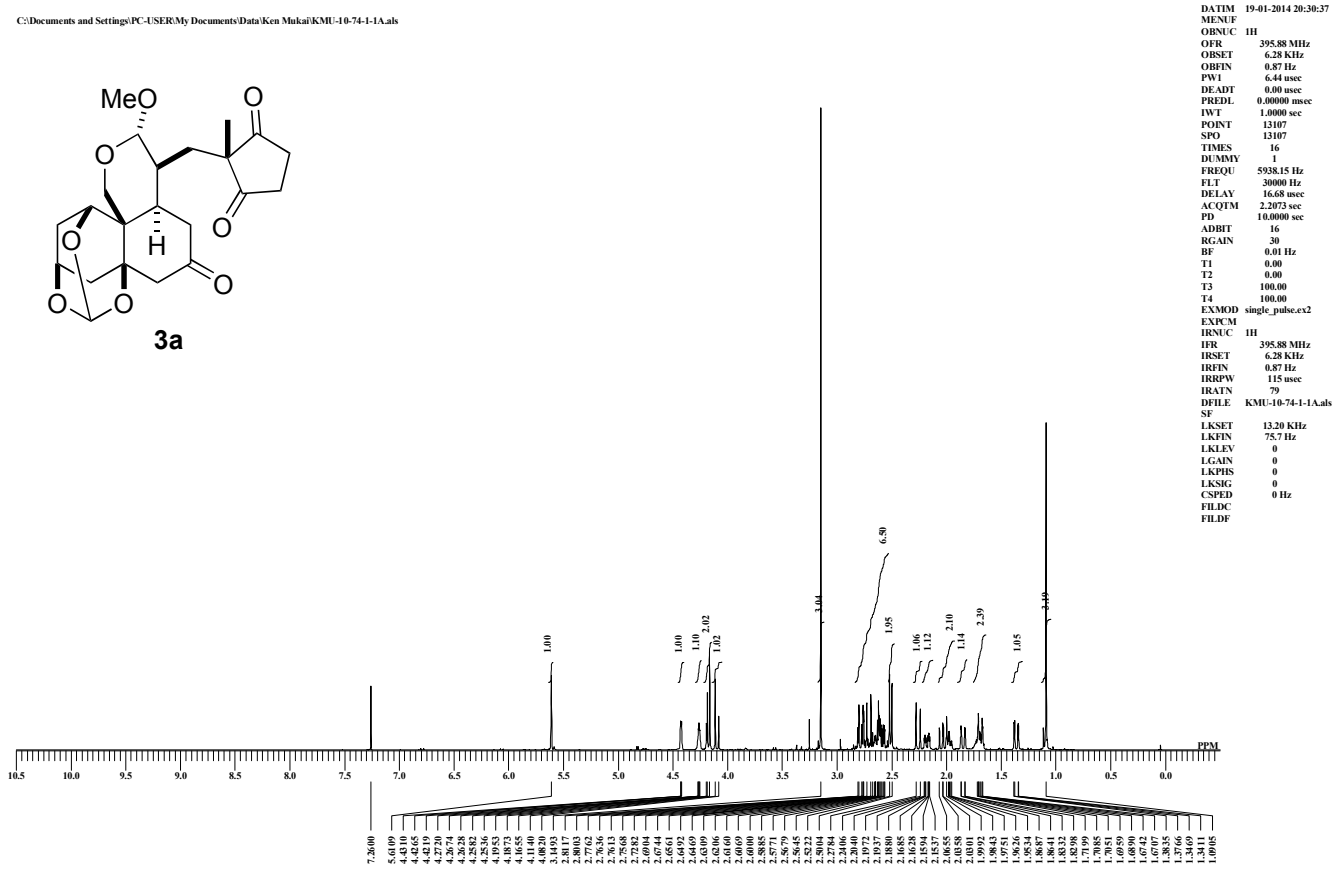
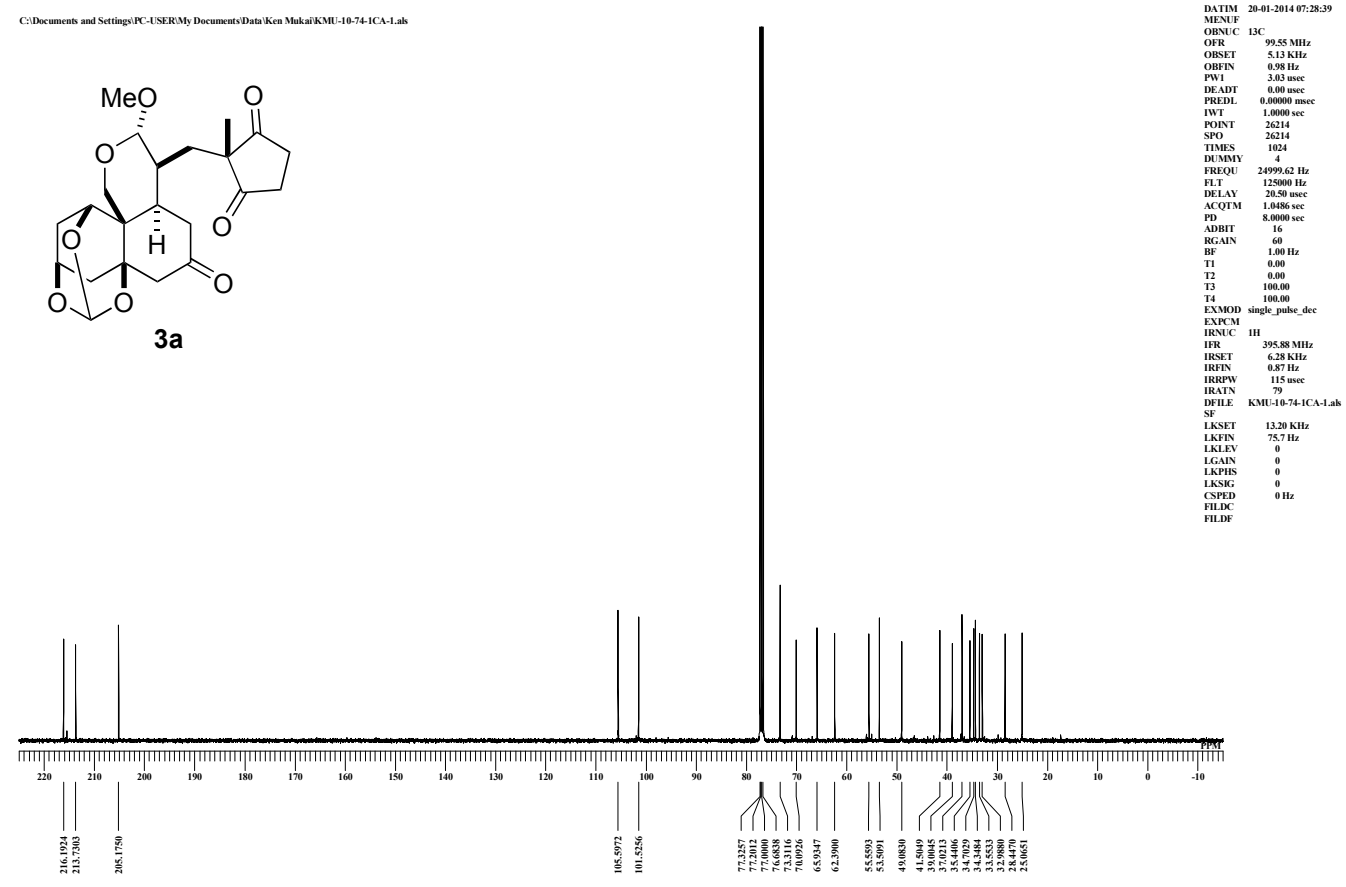


KMU-10-74-1



KMU-10-74-1C



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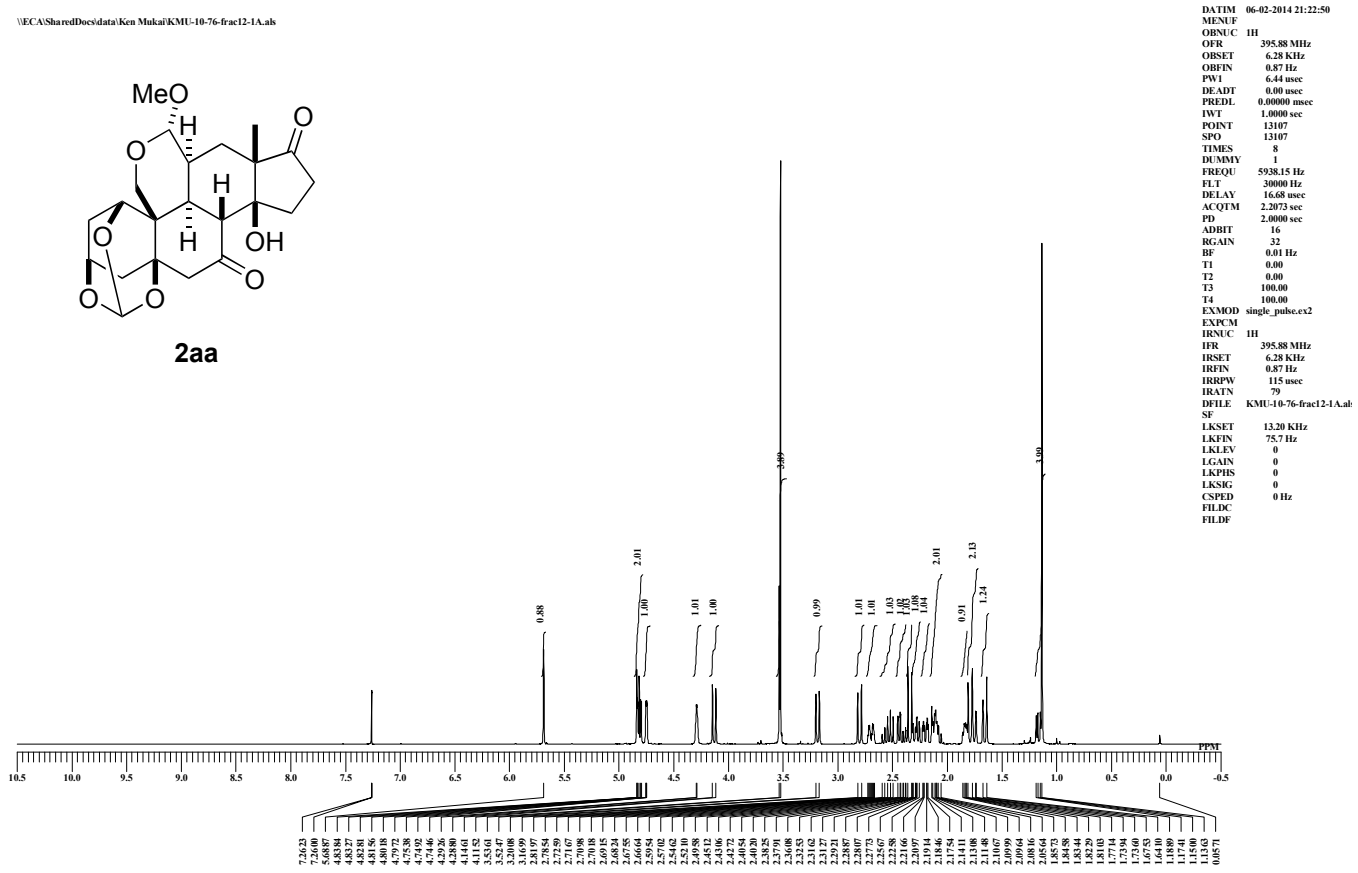
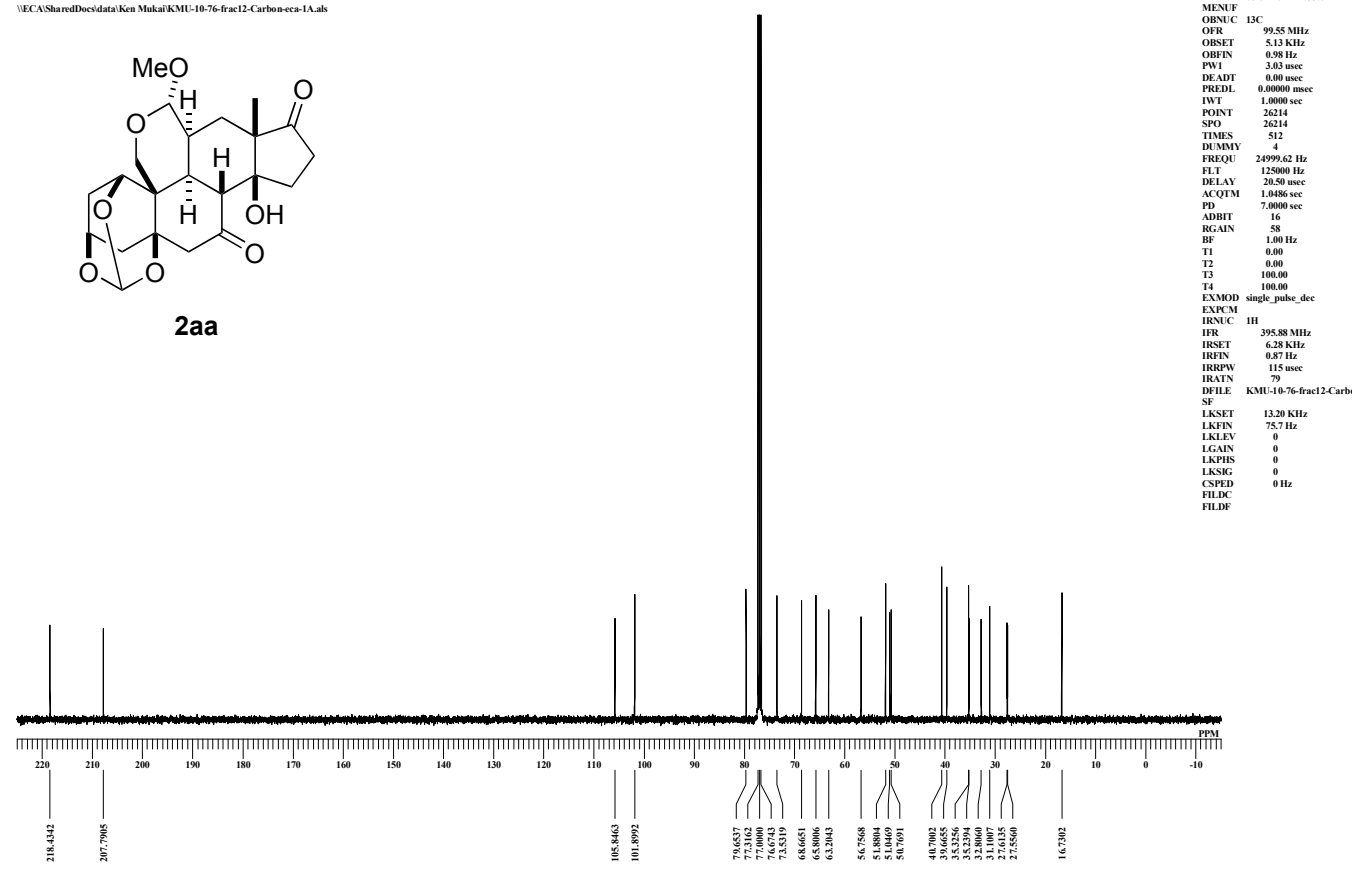


KMU-10-76-frac12-Carbon-eca



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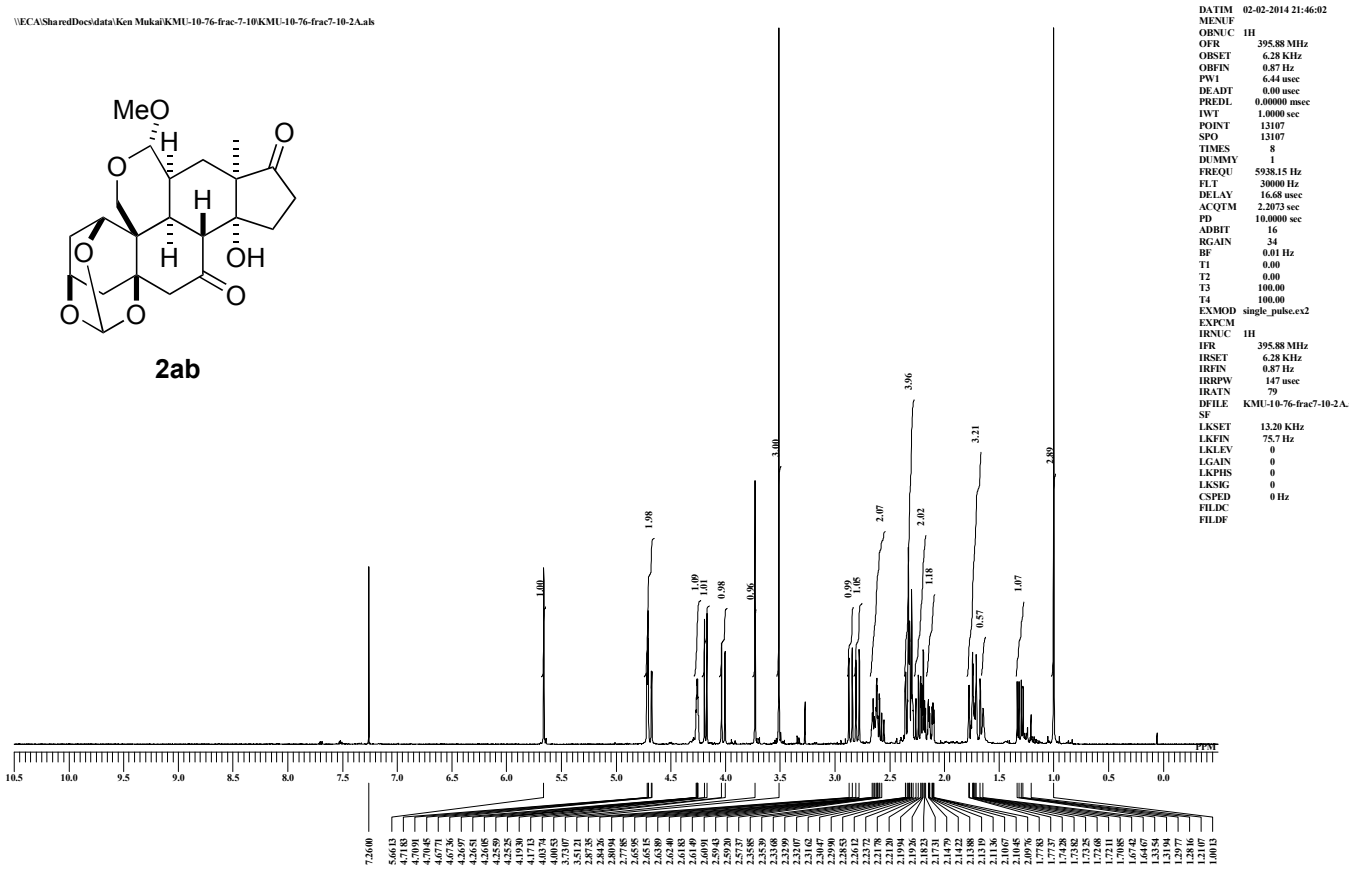

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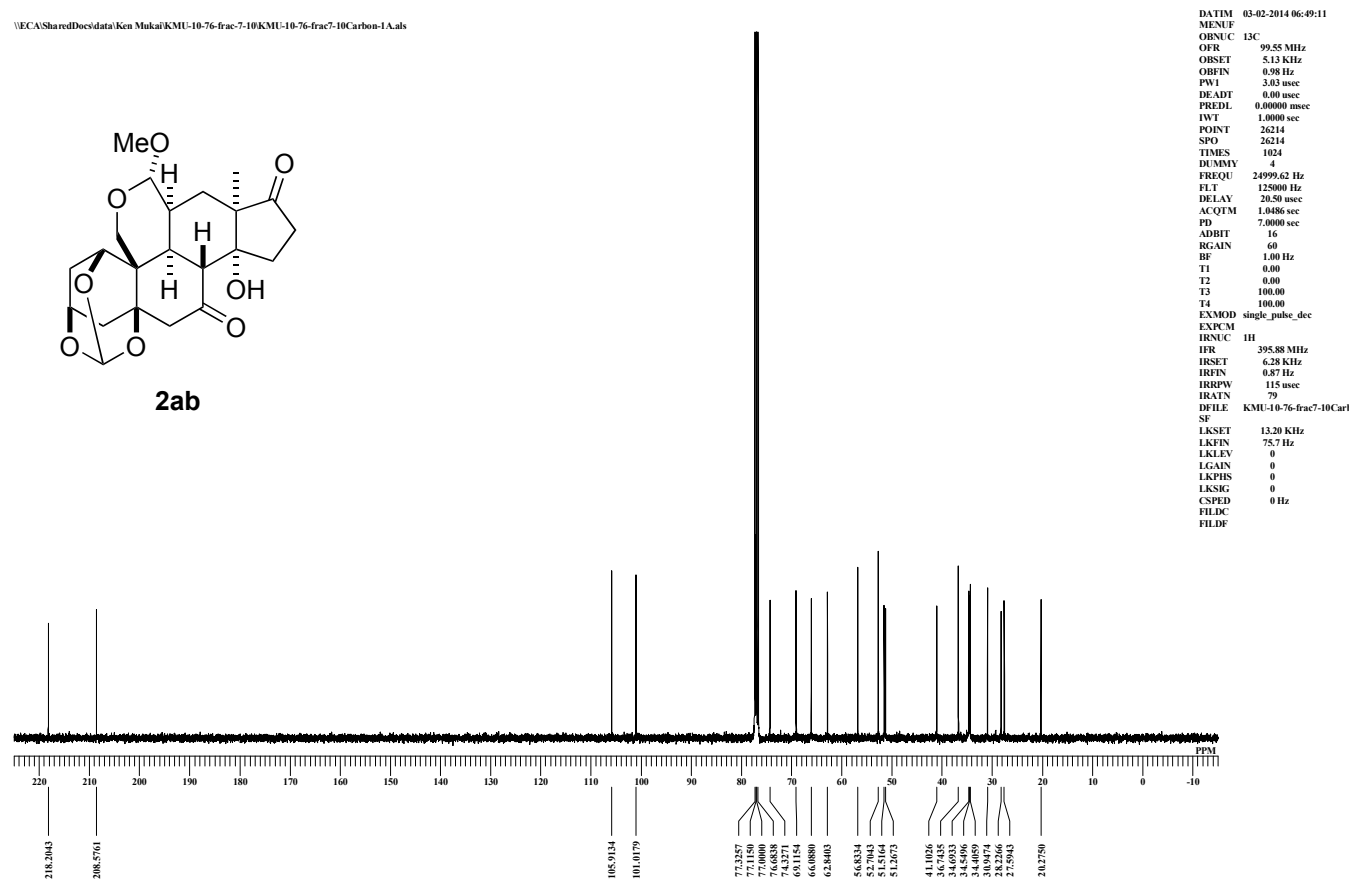

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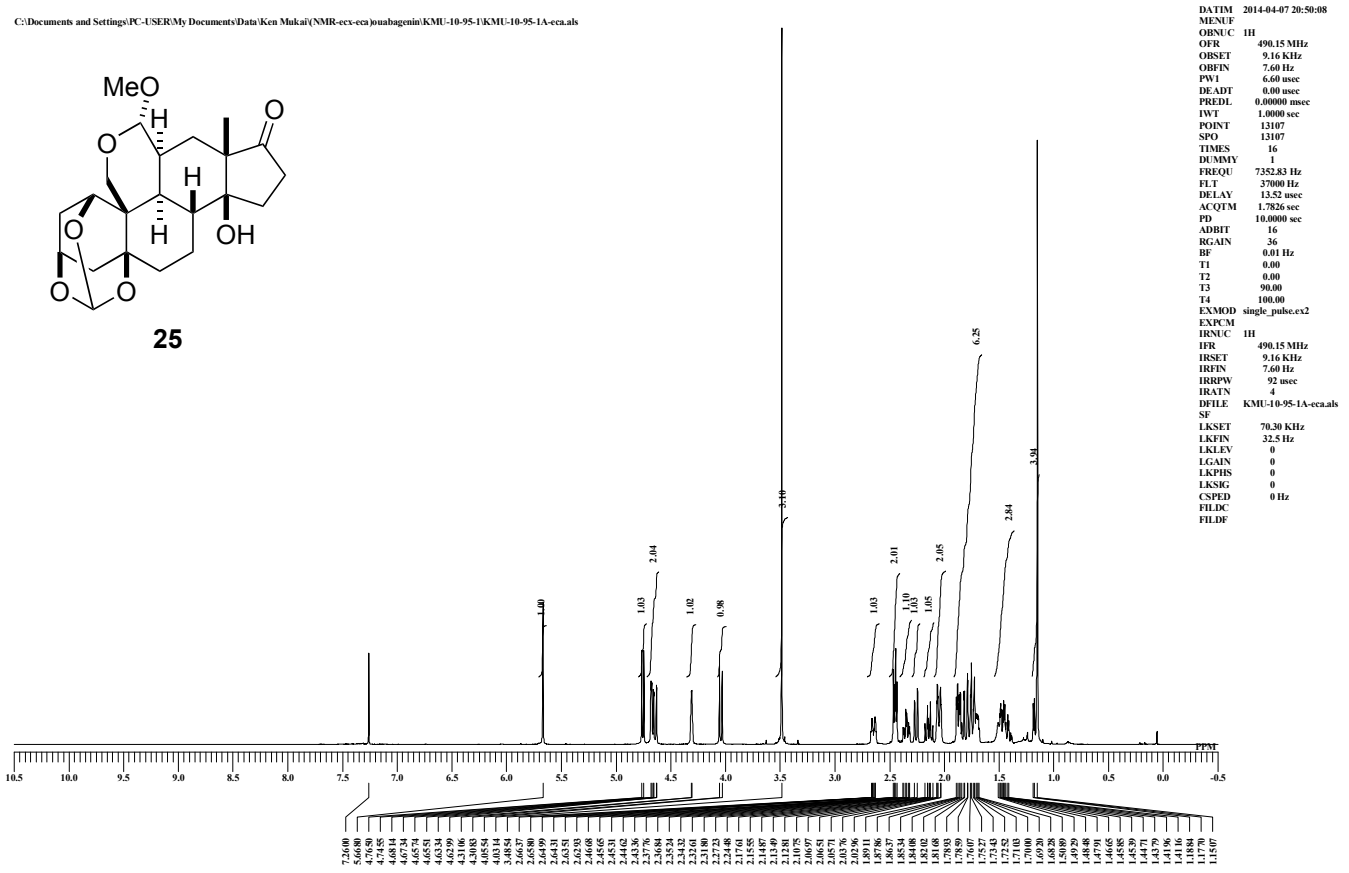

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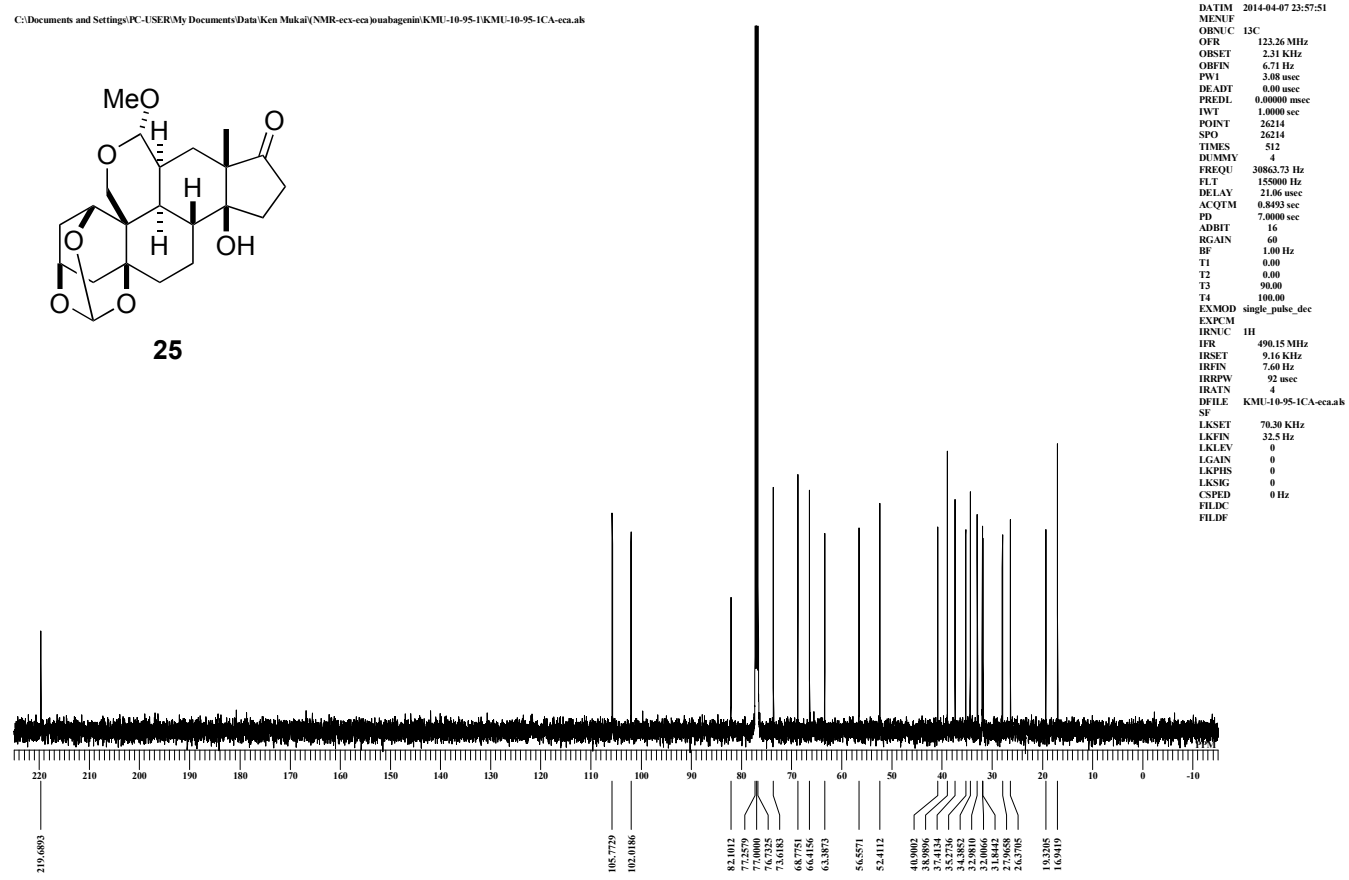

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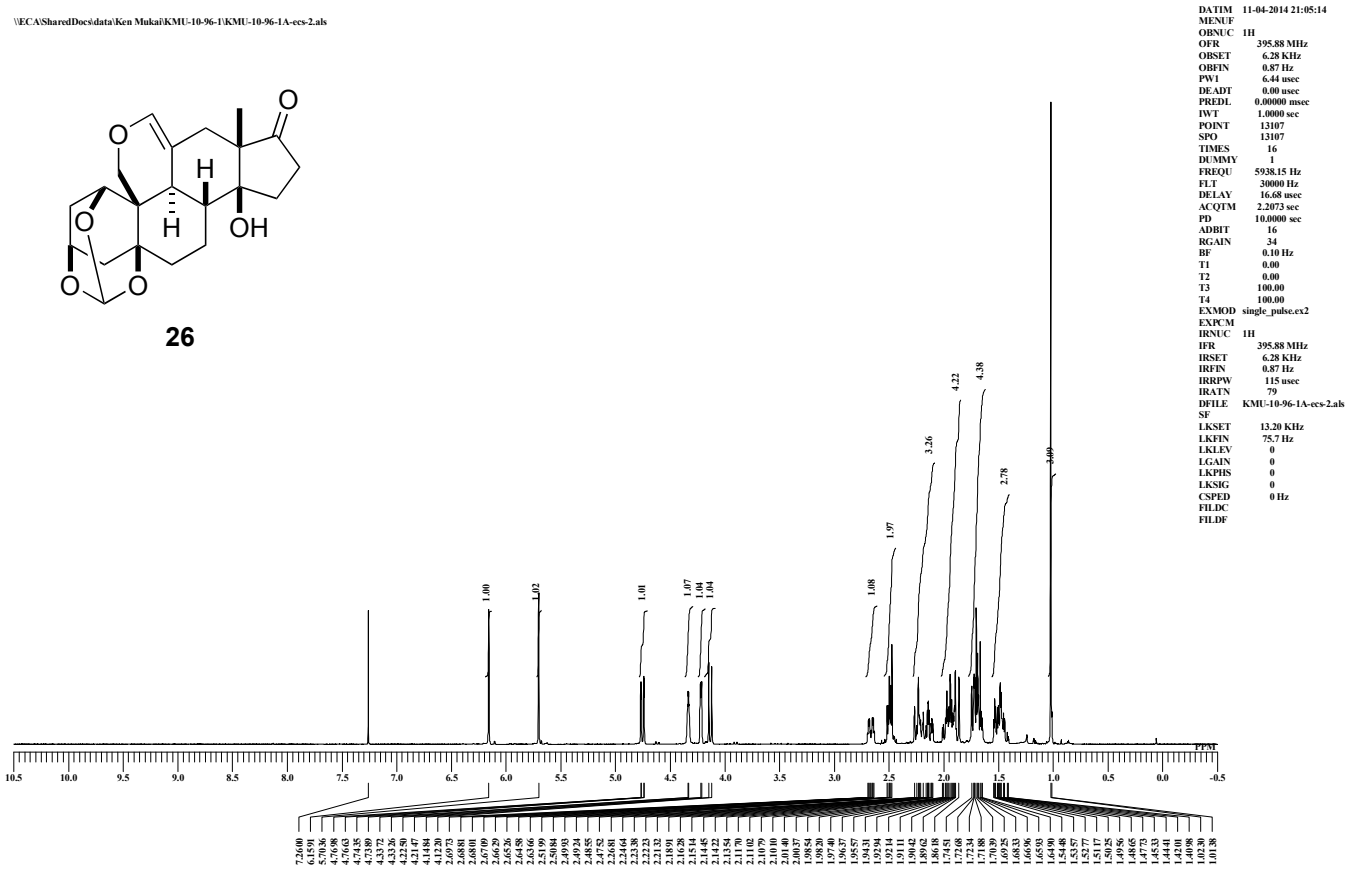

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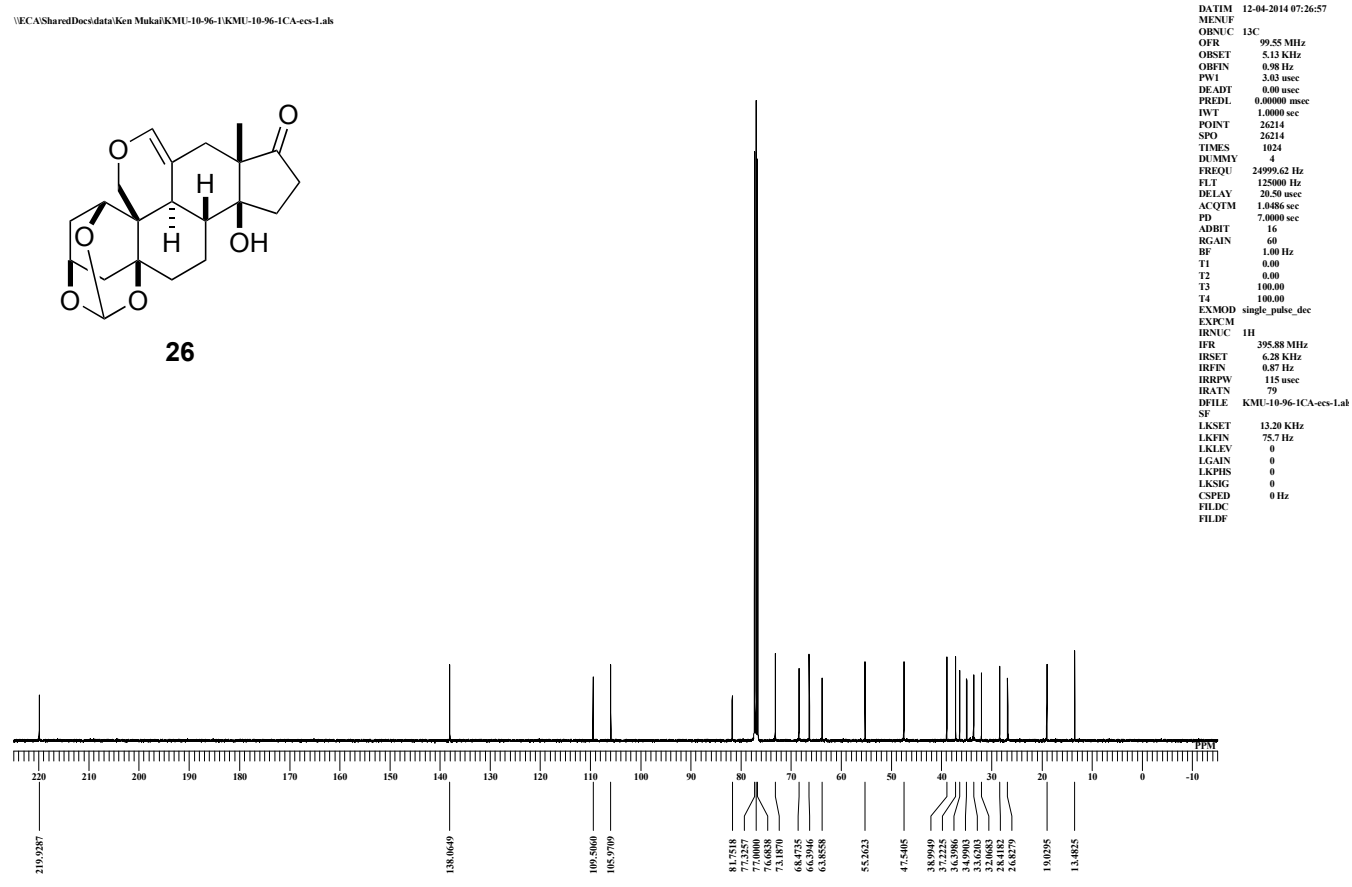

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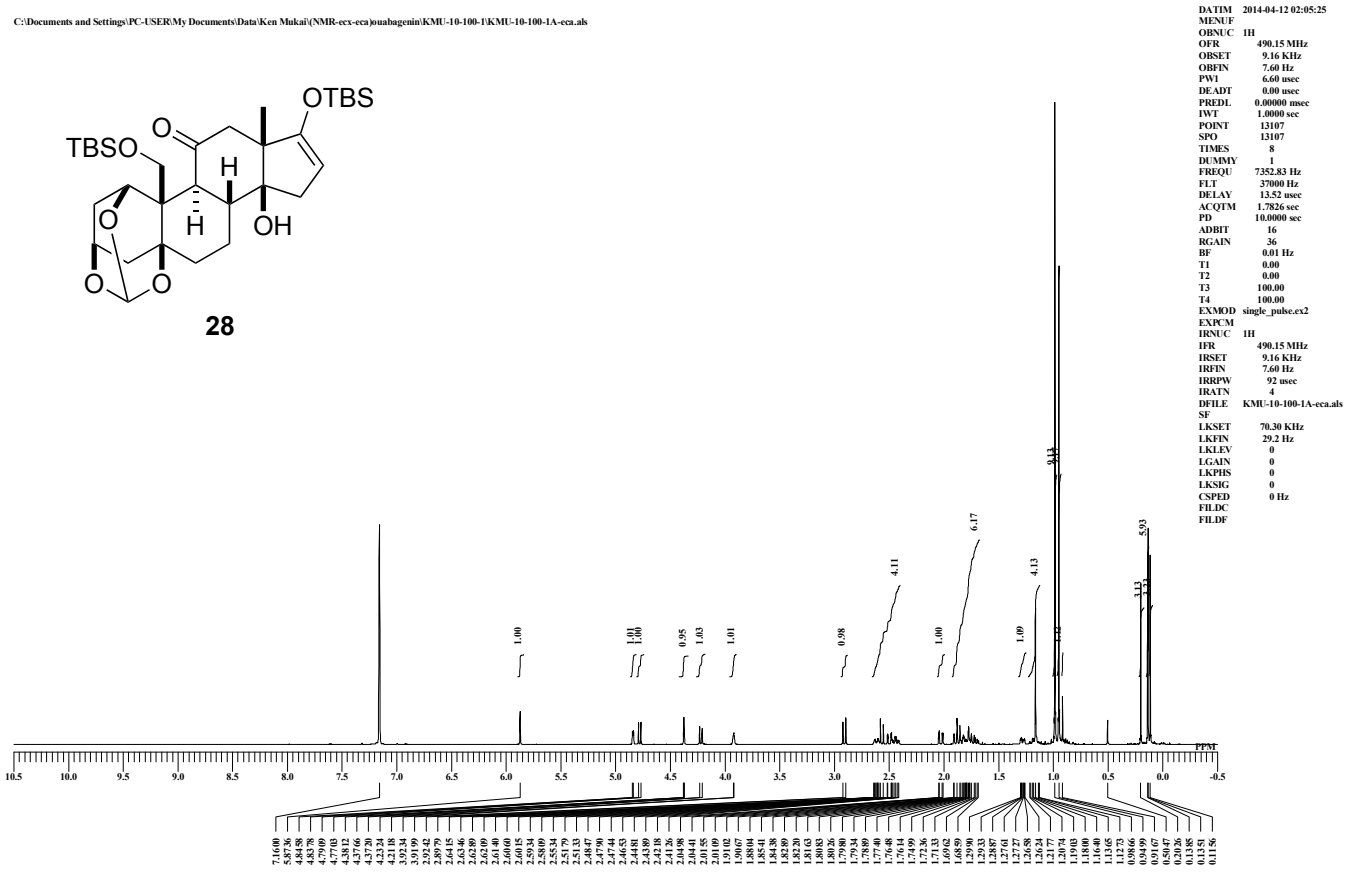

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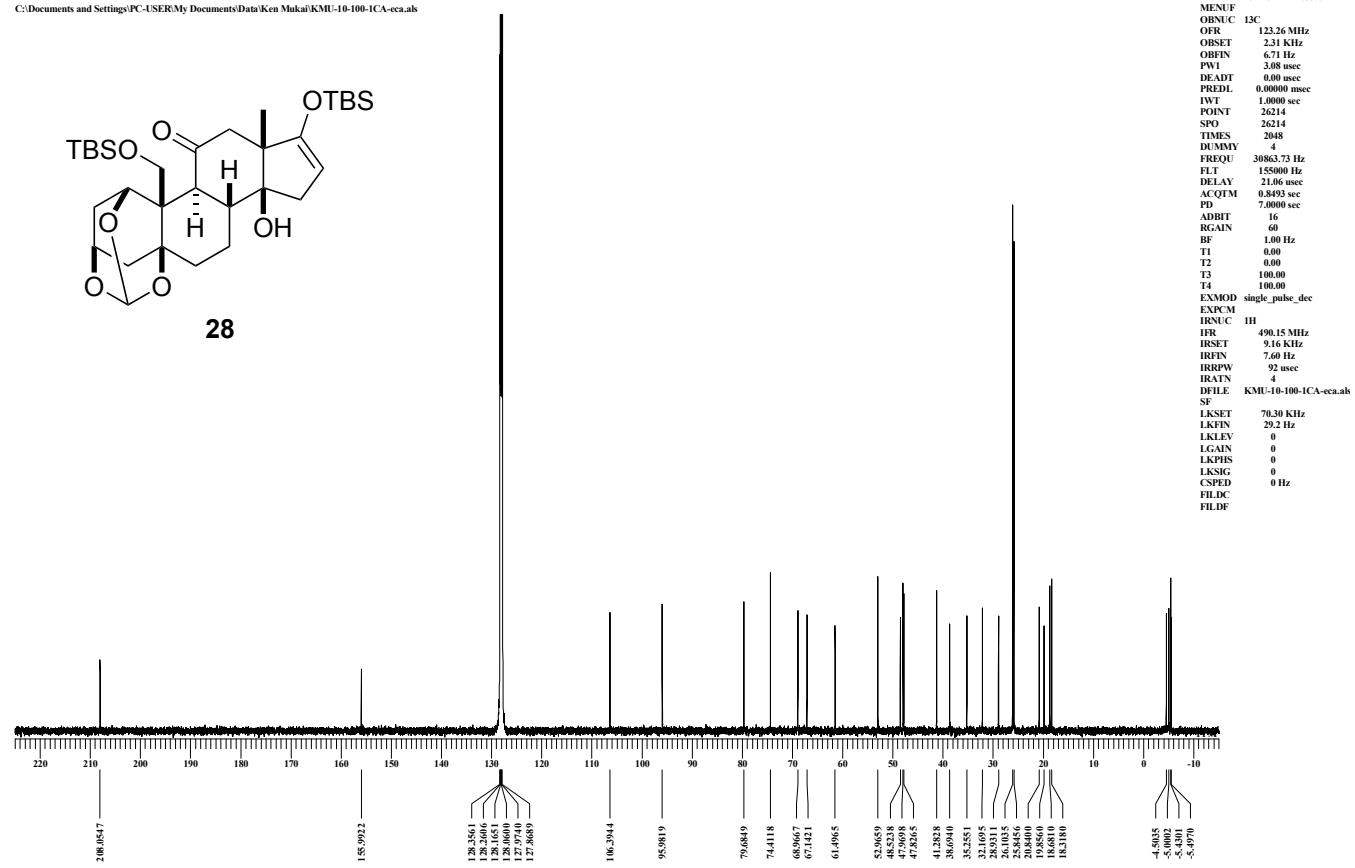

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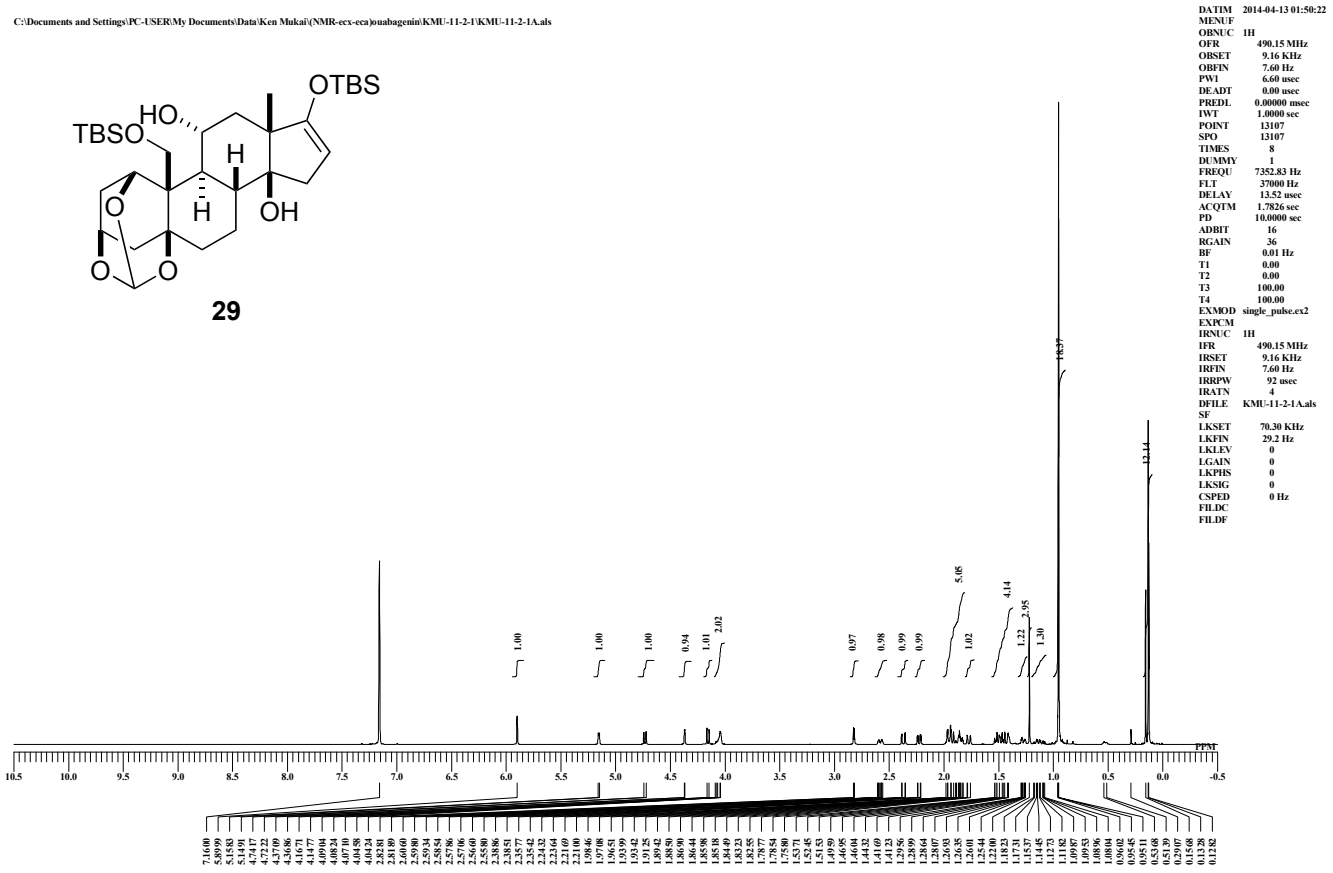

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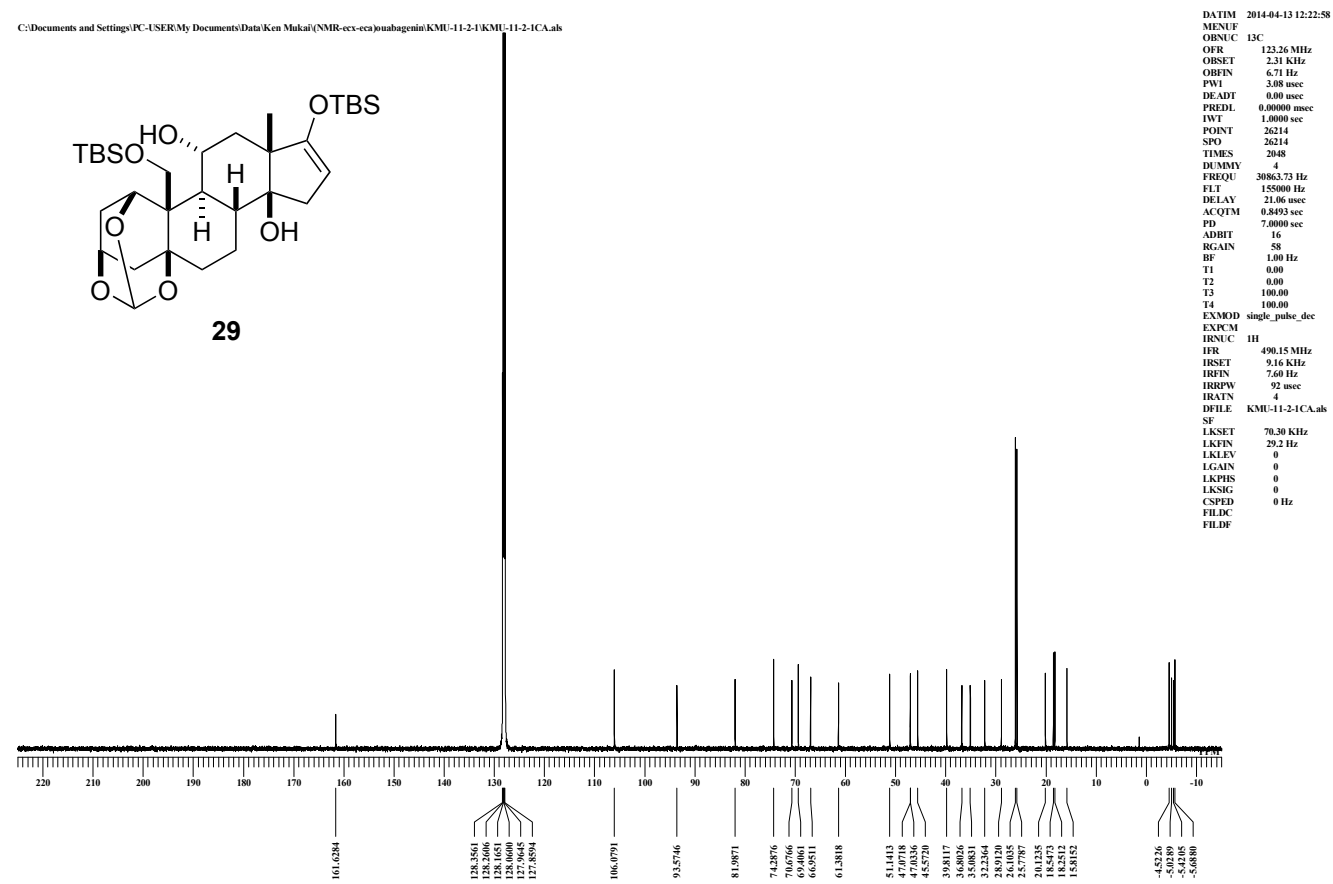

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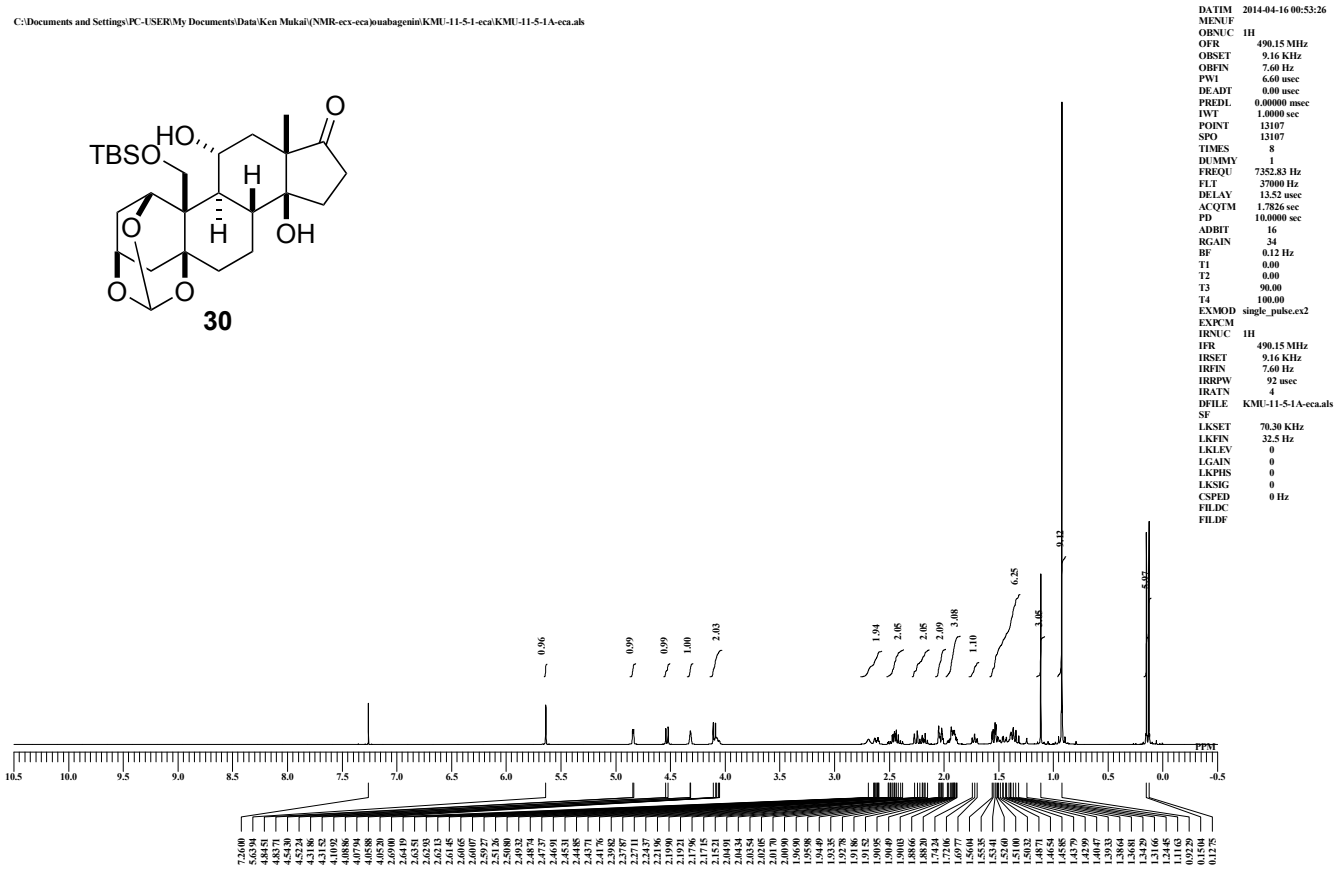

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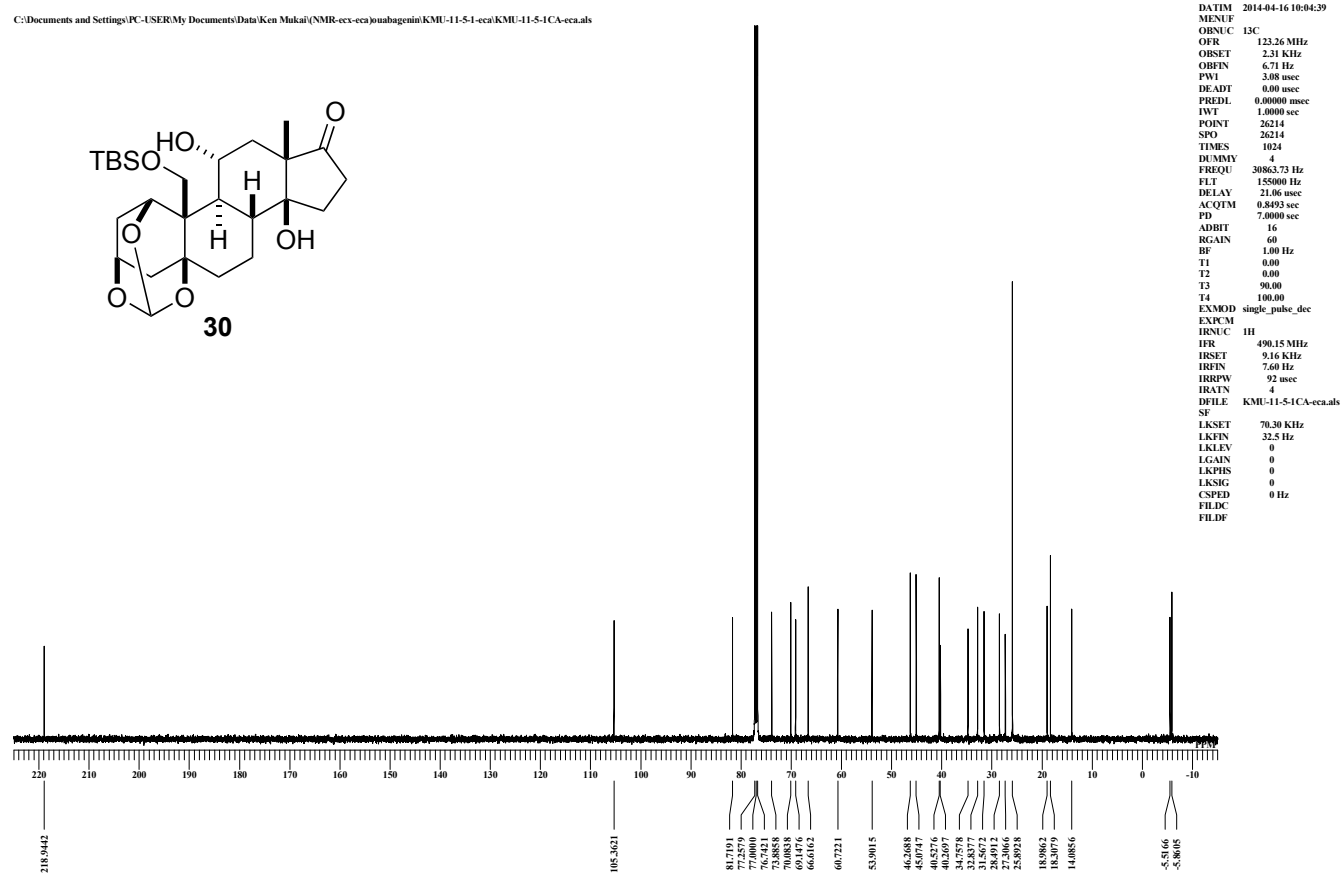

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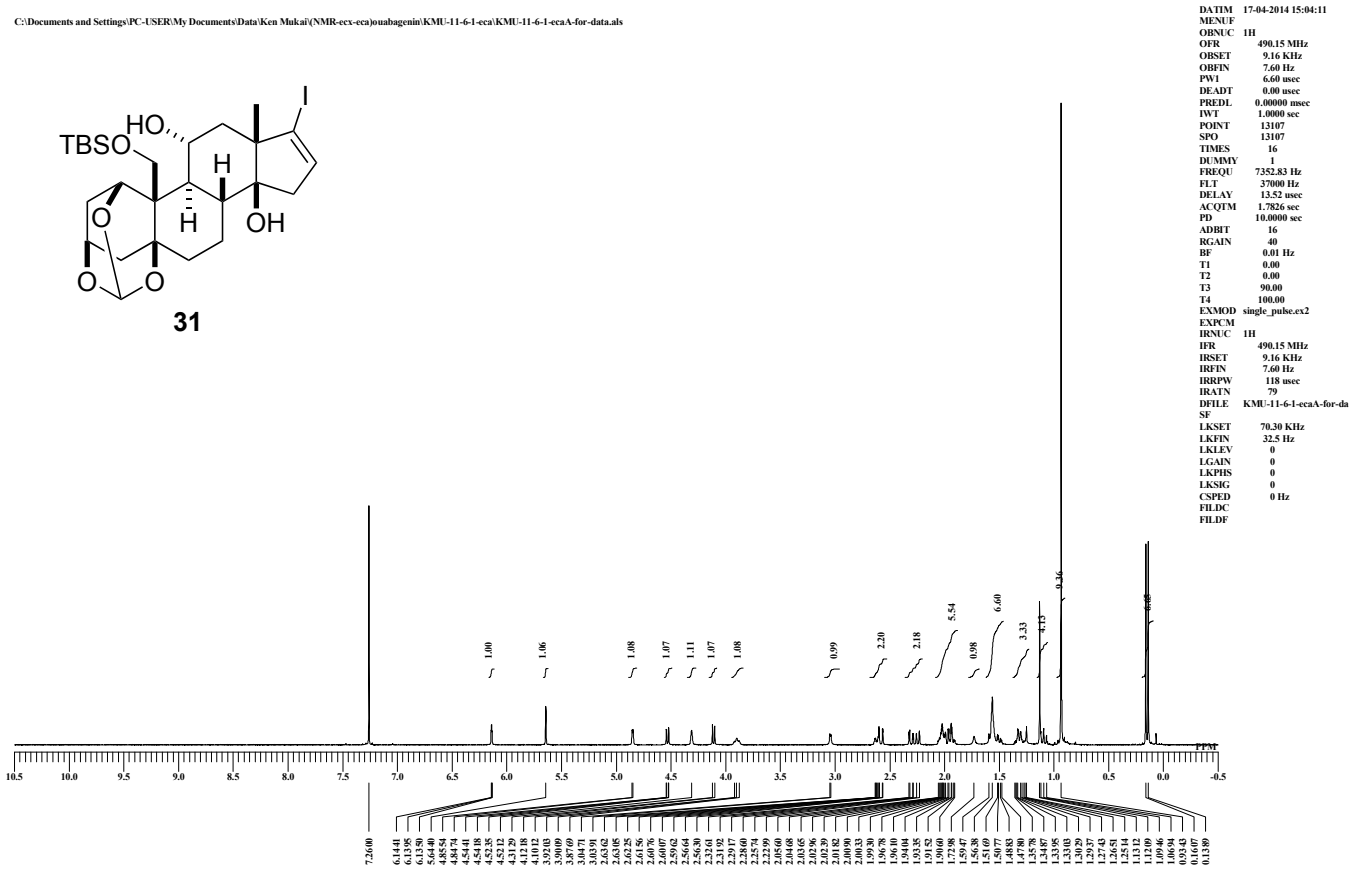

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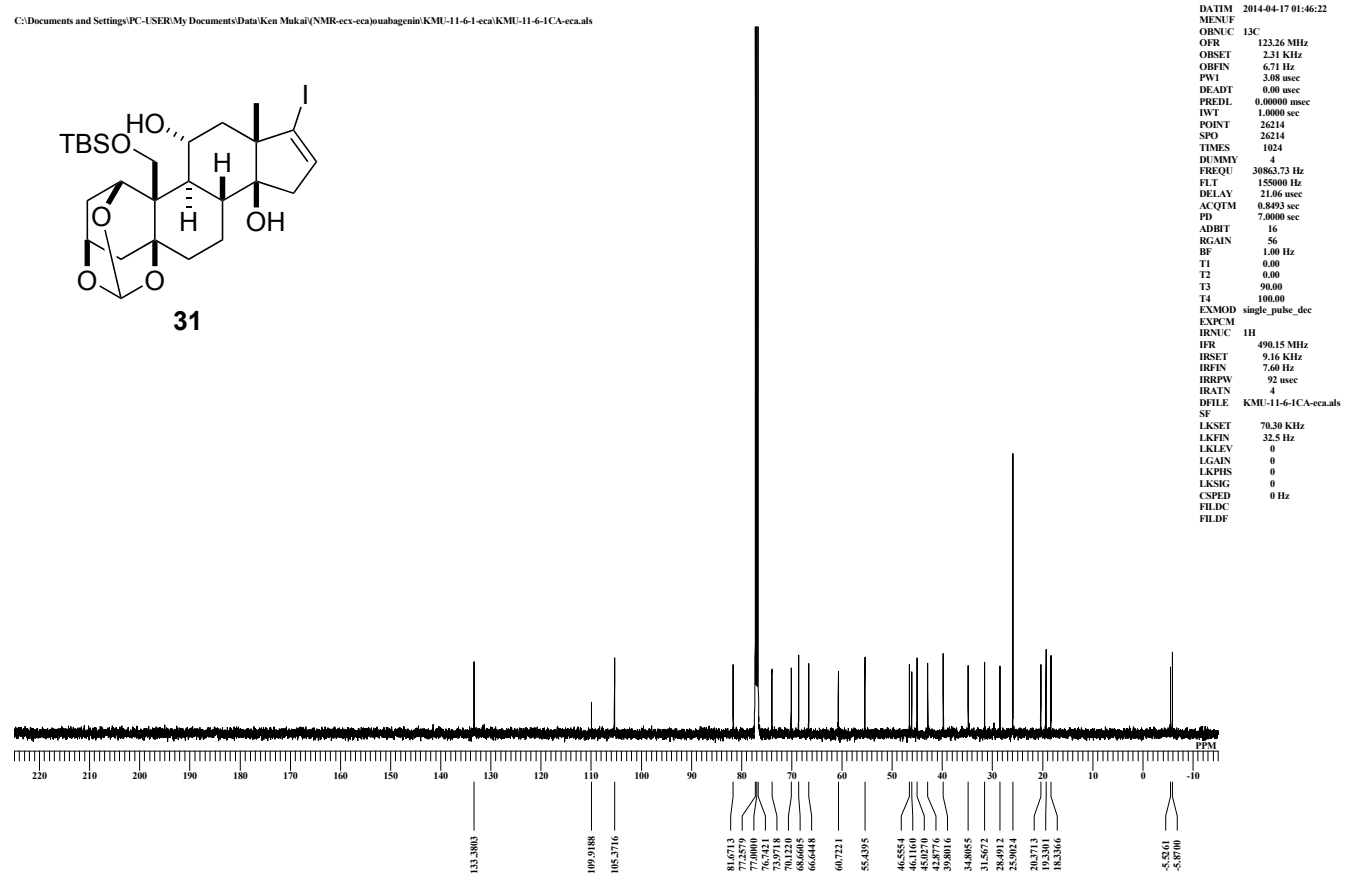
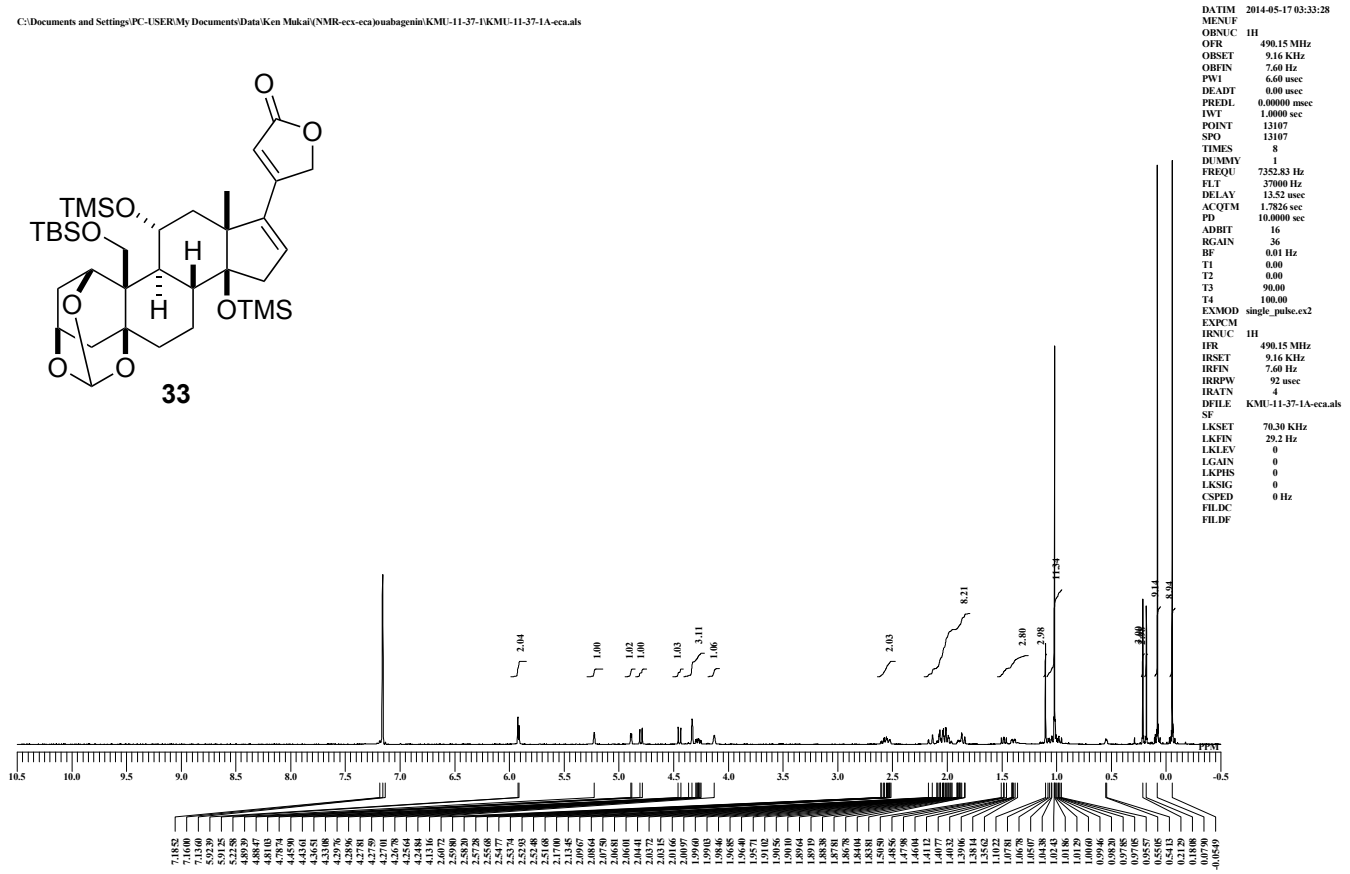


KMU-11-37-1-eca



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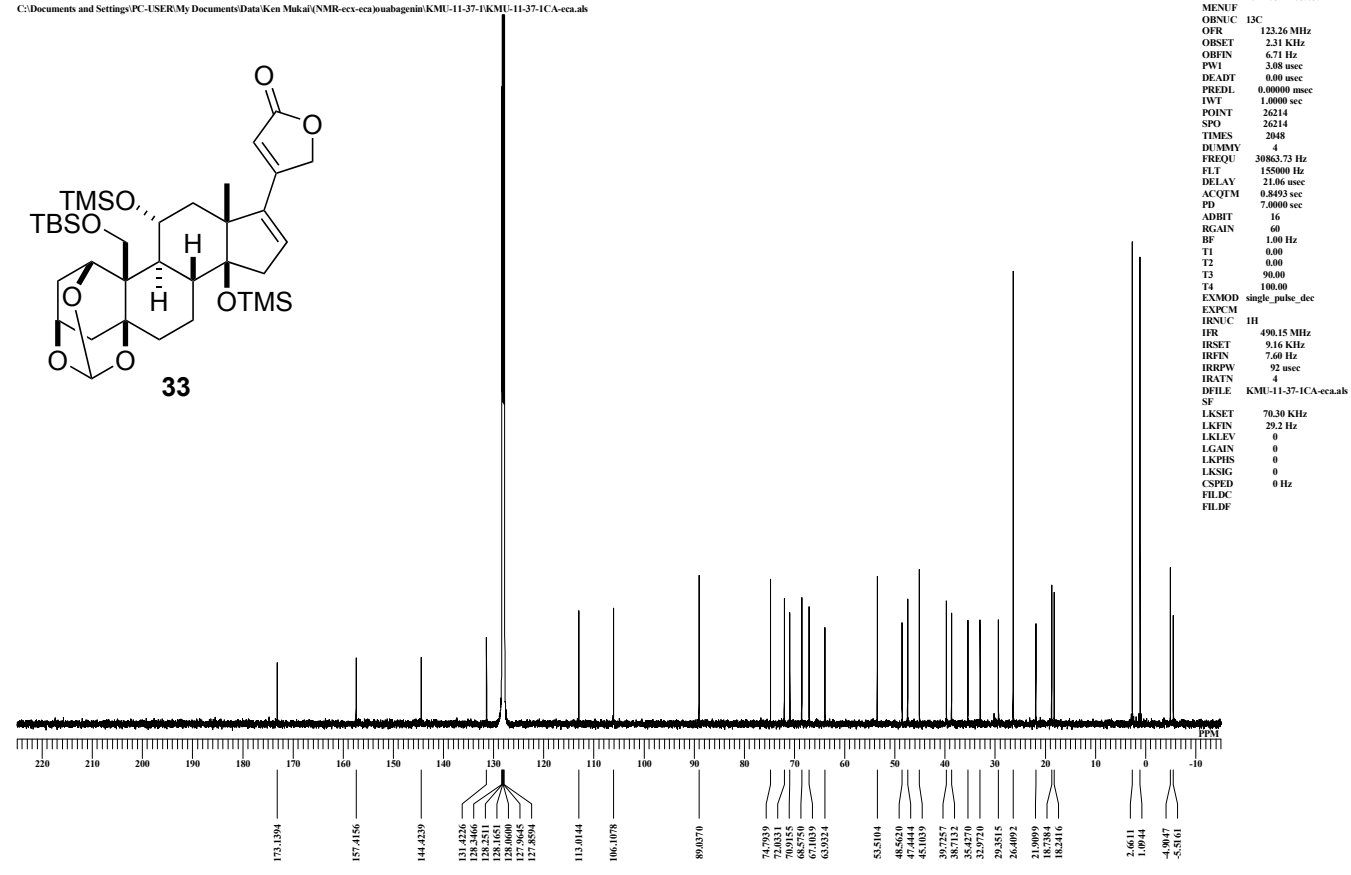
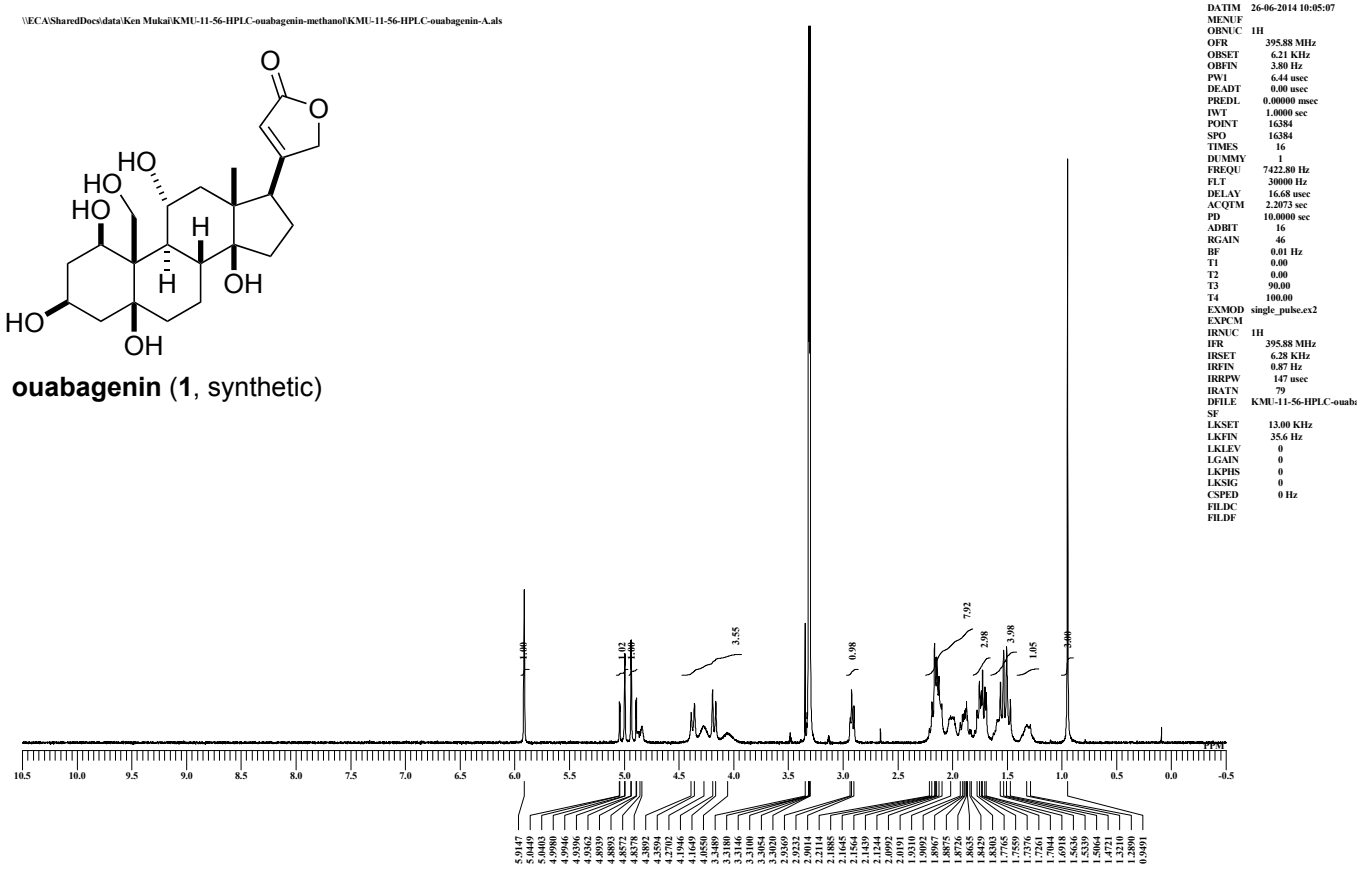
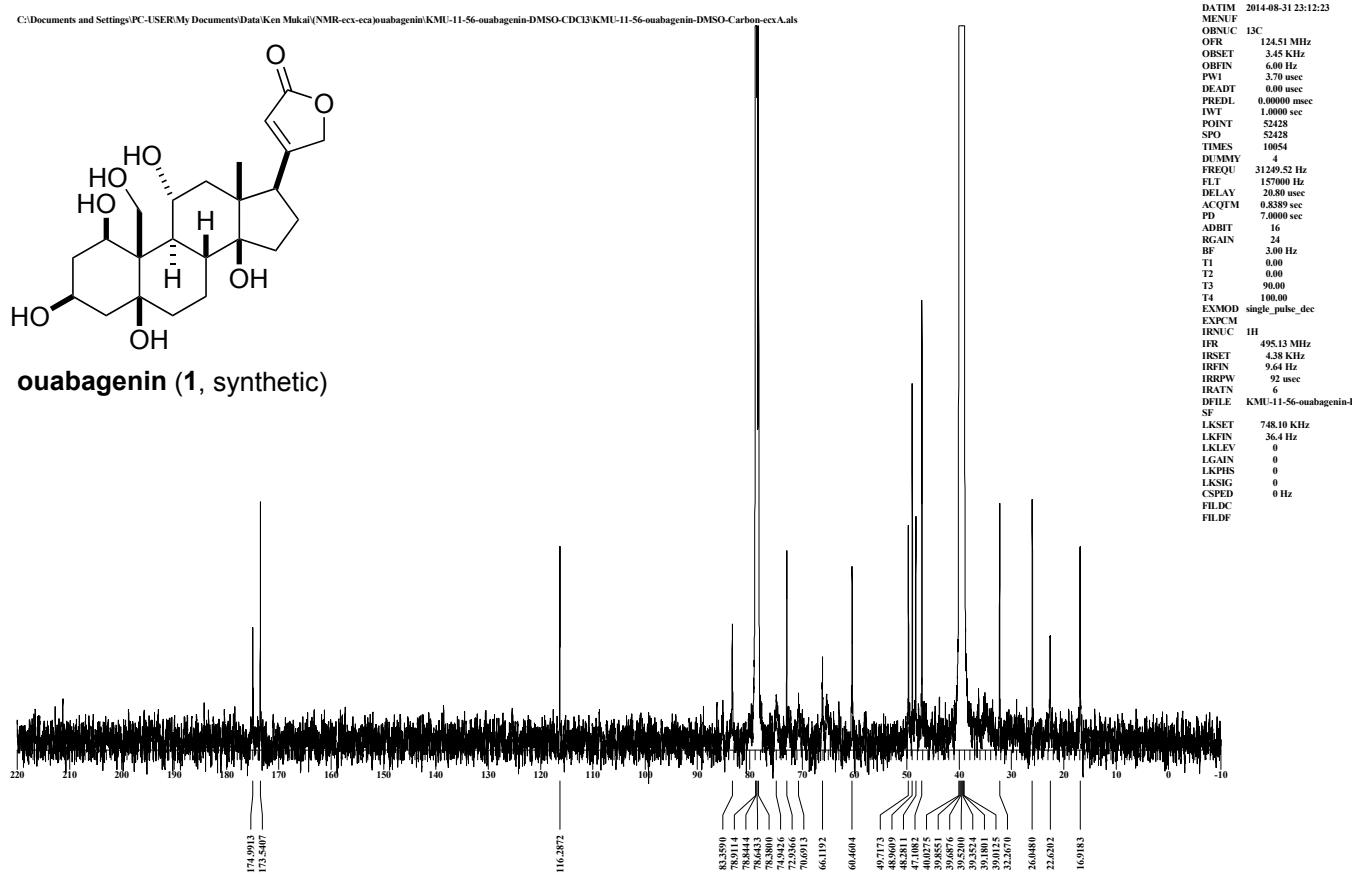


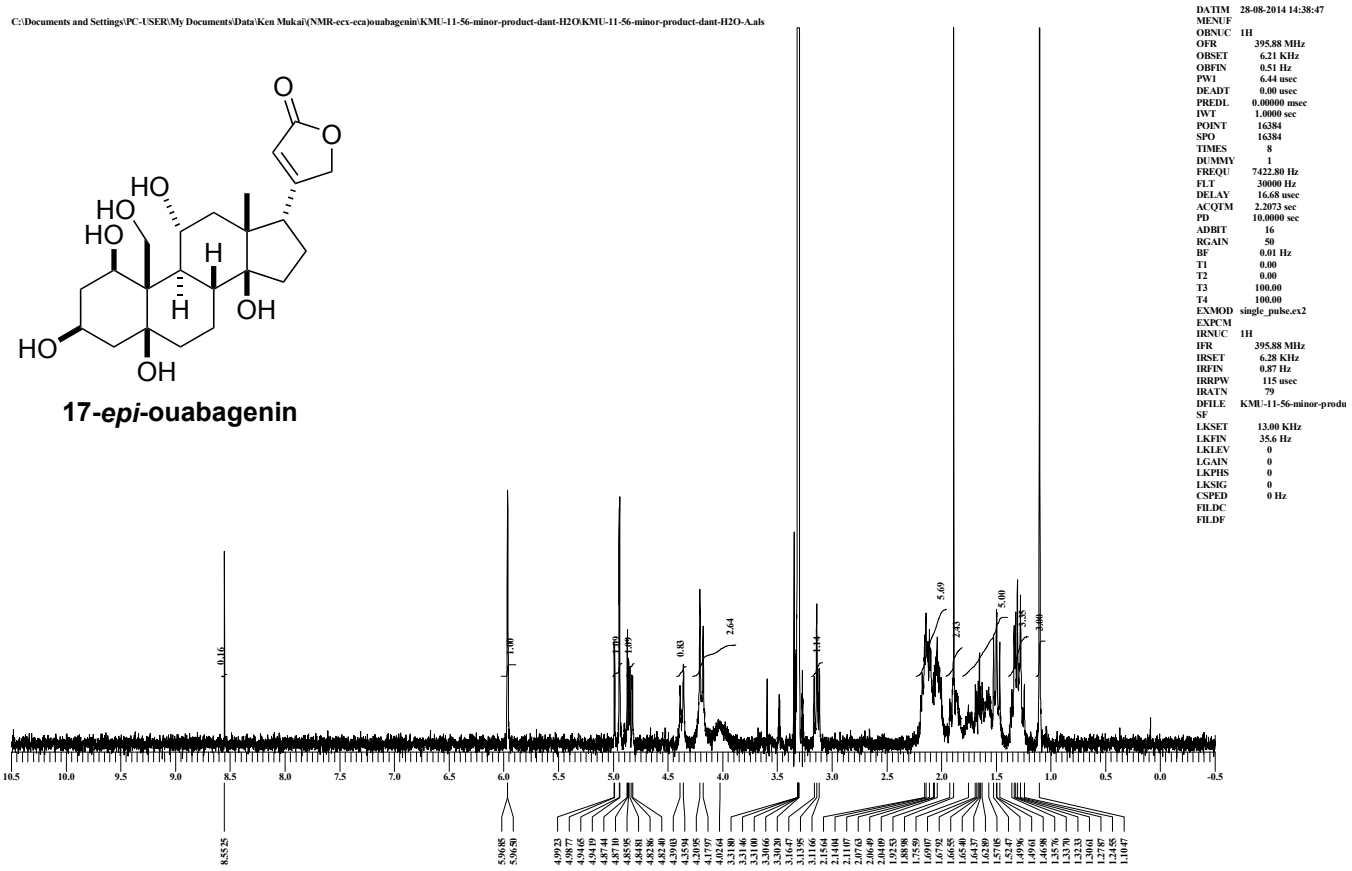
KMU-11-56-HPLC-ouabagenin

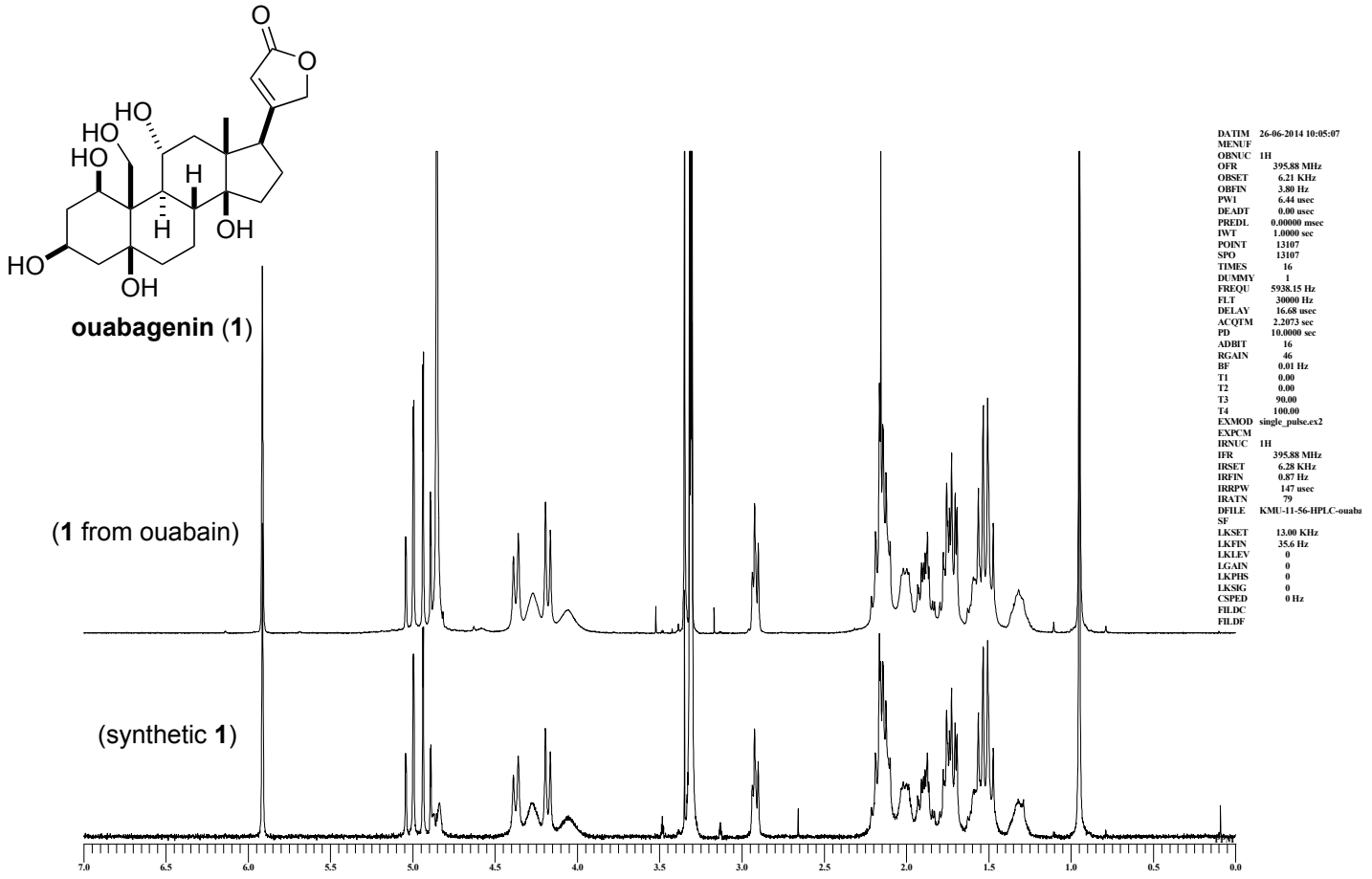


KMU-11-56-ouabagenin-DMSO-Carbon-ecx



KMU-11-56-minor-product-dant-H2O

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(1 from ouabain)
(synthetic 1)
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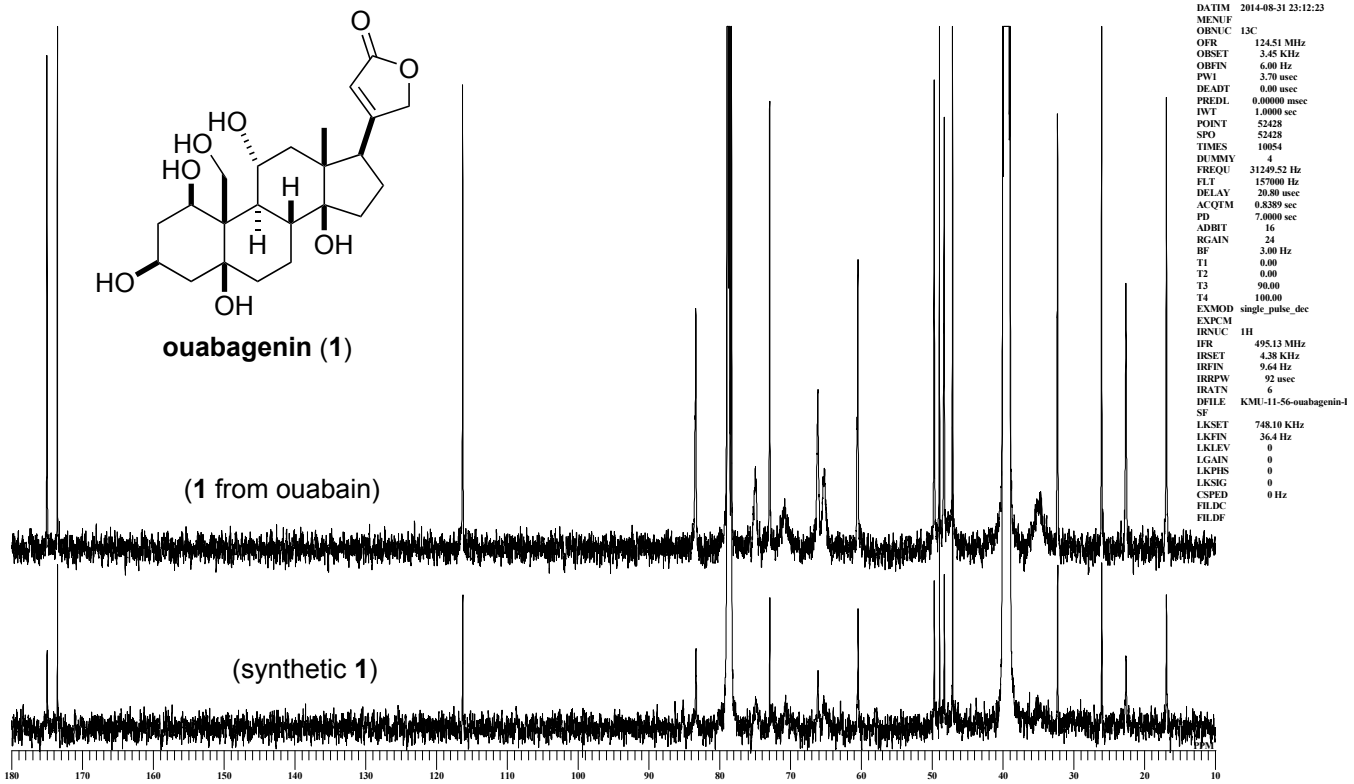
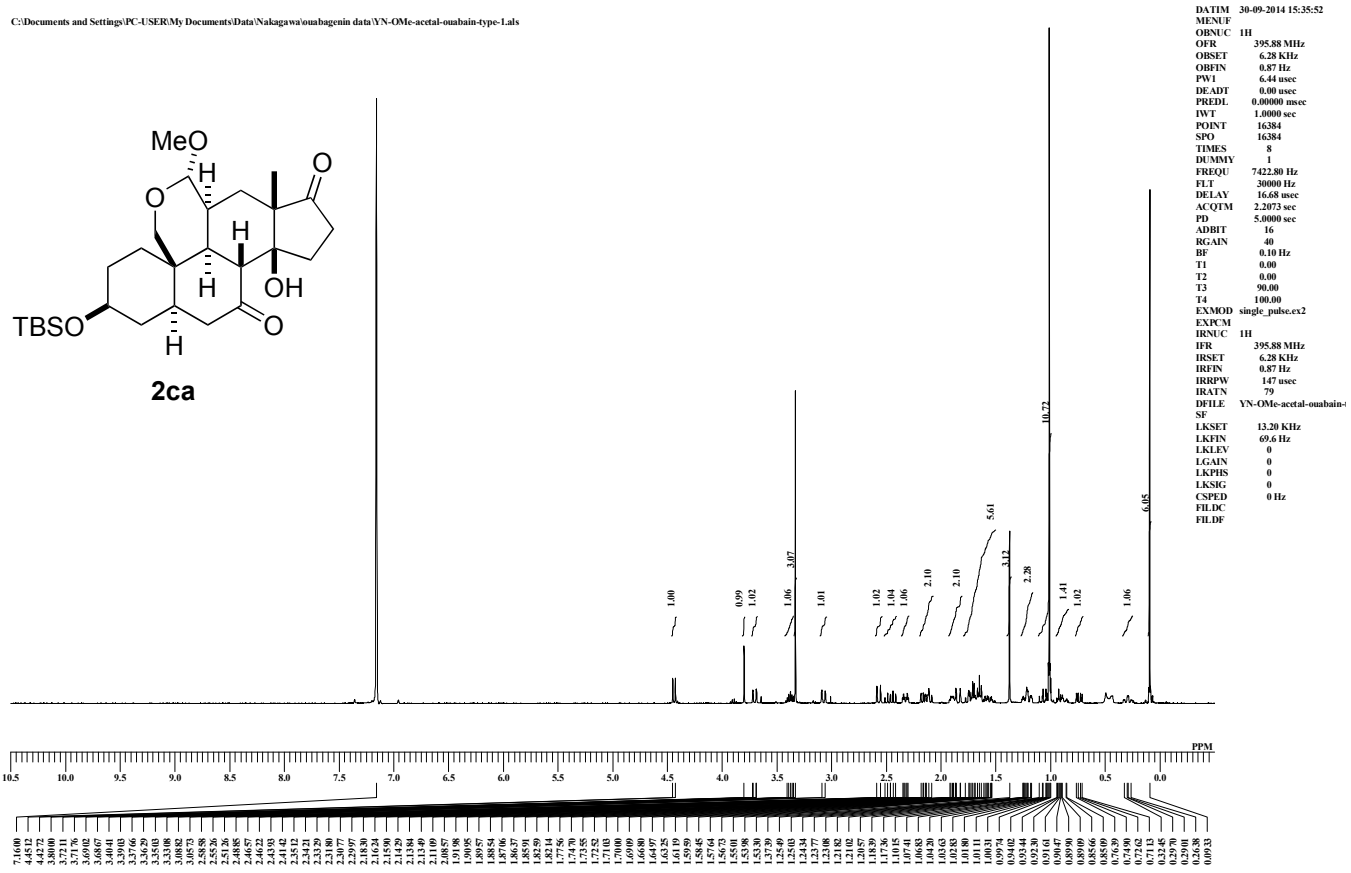
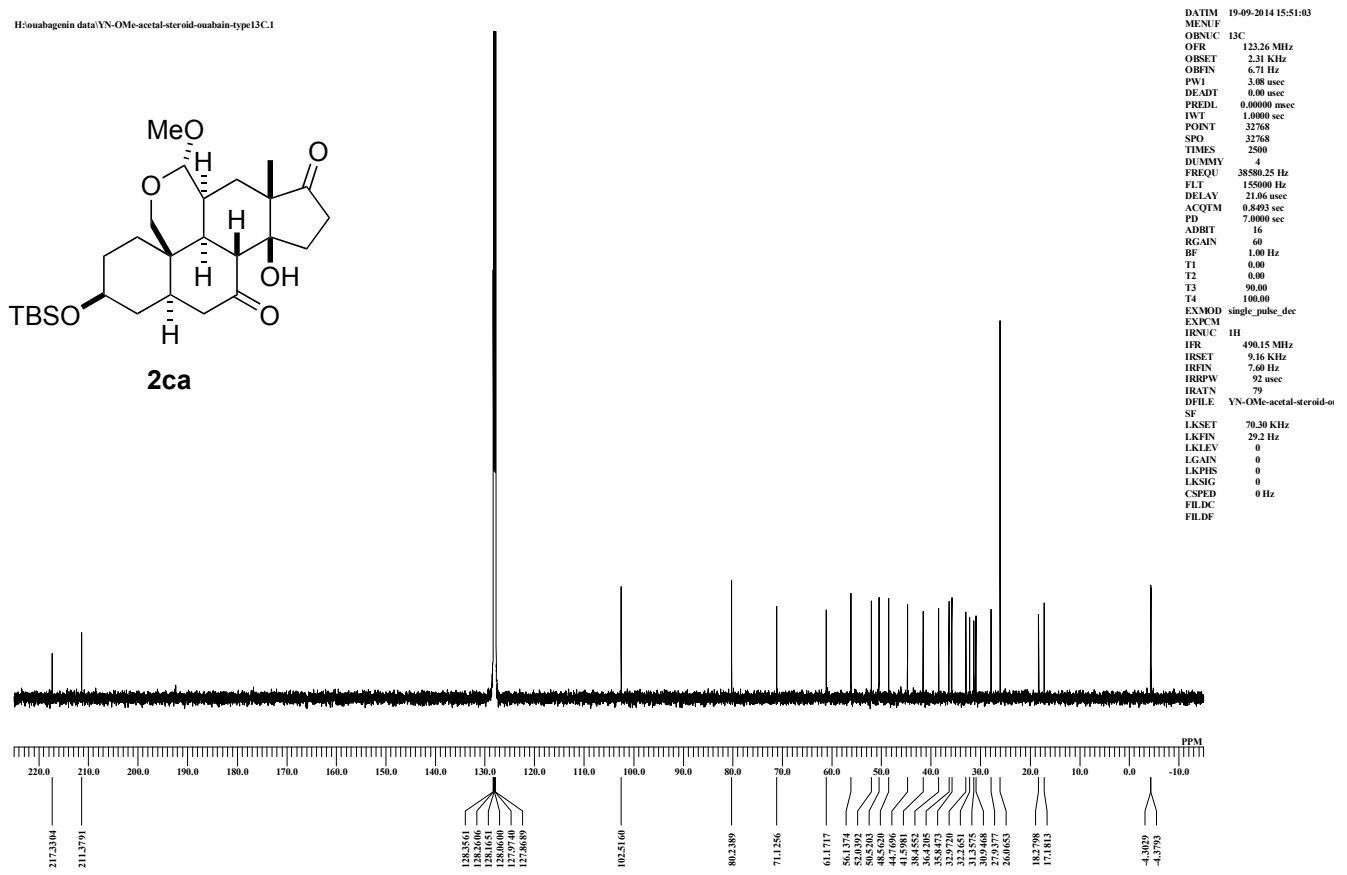
OBNUC 1H
OFR 395.88 MHz
OBSET 6.21 KHz
OBFIN 3.80 Hz
PW1 6.44 usec
DEADT 0.00 usec
PREDL 0.00000 msec
IWT 1.0000 sec
POINT 13107
SPO 13107
TIMES 16
DUMMY 1
FREQU 5938.15 Hz
FLT 30000 Hz
DELAY 16.68 usec
ACQTM 2.2073 sec
PD 10.0000 sec
ADBIT 16
RGAIN 46
BF 0.01 Hz
T1 0.00
T2 0.00
T3 90.00
T4 100.00
EXMOD single_pulse.ex2
IRNUC 1H
IFR 395.88 MHz
IRSET 6.28 KHz
IRFIN 0.87 Hz
IRRPW 147 usec
IRATN 79
LKSET 13.00 KHz
LKFIN 35.6 Hz
LKLEV 0
LGAIN 0
LKPHS 0
LKSIG 0
CSPED 0 Hz


ouabagenin (1)
(1 from ouabain)
(synthetic 1)
DATIM 2014-08-31 23:12:23
OBNUC 13C
OFR 124.51 MHz
OBSET 3.45 KHz
OBFIN 6.00 Hz
PW1 3.70 usec
DEADT 0.00 usec
PREDL 0.00000 msec
IWT 1.0000 sec
POINT 52428
SPO 52428
TIMES 10054
DUMMY 4
FREQU 31249.52 Hz
FLT 157000 Hz
DELAY 20.80 usec
ACQTM 0.8389 sec
PD 7.0000 sec
ADBIT 16
RGAIN 24
BF 3.00 Hz
T1 0.00
T2 0.00
T3 90.00
T4 100.00
EXMOD single_pulse_dec
IRNUC 1H
IFR 495.13 MHz
IRSET 4.38 KHz
IRFIN 9.64 Hz
IRRPW 92 usec
IRATN 6
LKSET 748.10 KHz
LKFIN 36.4 Hz
LKLEV 0
LGAIN 0
LKPHS 0
LKSIG 0
CSPED 0 Hz

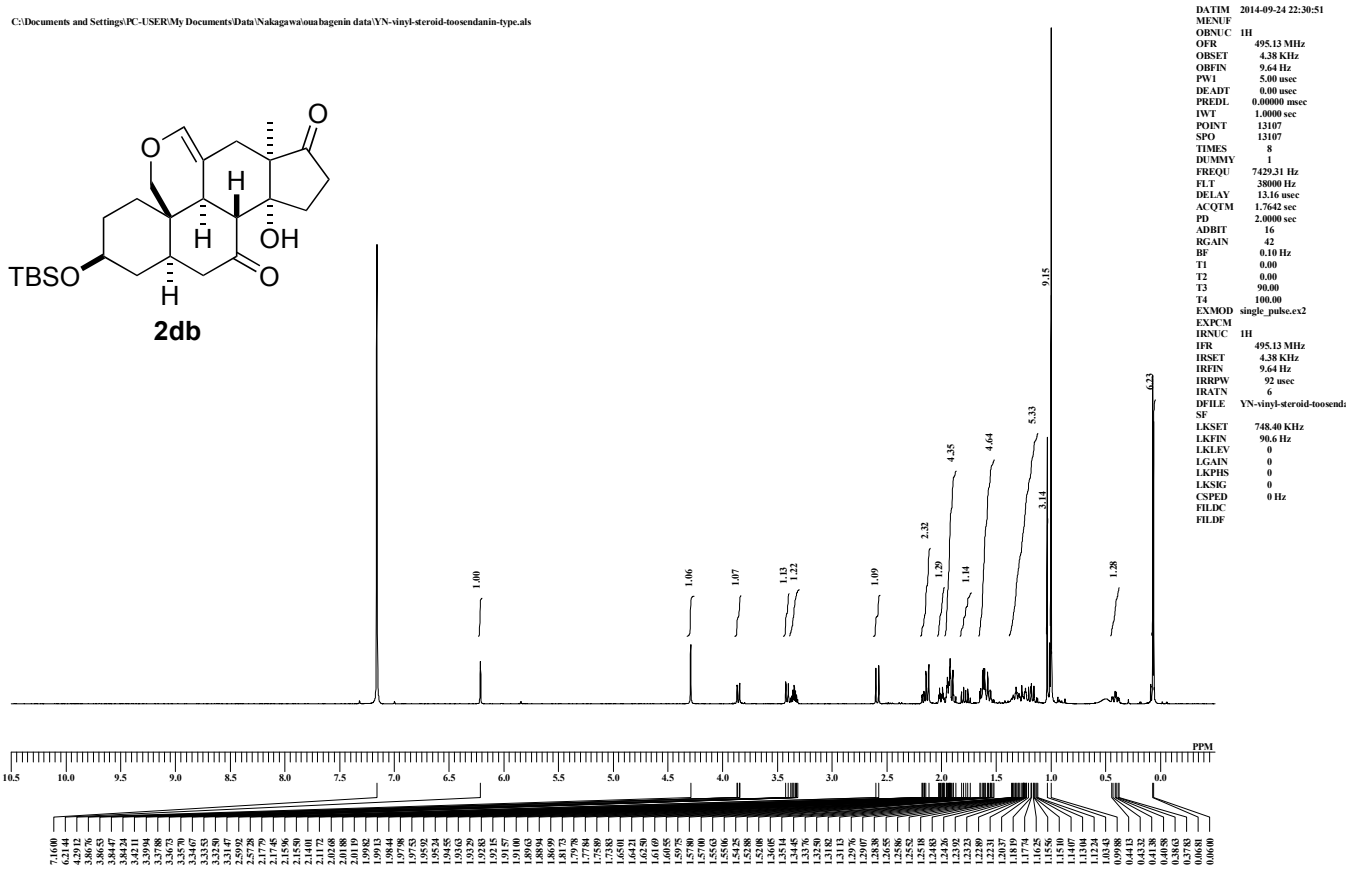
YN-OMe-acetal-ouabain-type



YN-OMe-acetal-steroid-ouabain-type13C



YN-vinyl-steroid-toosendanin-type



YN-vinyl-steroid-toosendanin-type-13C