Supporting Information

Withanolide A: Synthesis and Structural Requirements for Neurite Outgrowth

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I. General Methods and Materials

Unless otherwise stated, chemicals were purchased from Sigma-Aldrich or Acros and used without further purification. Solvents for work-up and chromatography were distilled from technical quality. Solvents used for chemical transformations were either puriss quality or dried by filtration through activated aluminium oxide under argon or nitrogen (H_2O content < 10 ppm, *Karl-Fischer* titration). Reactions involving air or moisture sensitive reagents or intermediates were performed under argon or nitrogen in glassware which had been oven dried or dried by a heat gun under high vacuum. Concentration under reduced pressure was performed by rotary evaporation at 40 °C (unless otherwise specified). Yields refer to purified, dried and spectroscopically pure compounds.

Analytical thin layer chromatography (TLC) was performed on Merck silica gel 60 F254 plates (0.25 mm thickness) precoated with fluorescent indicator. The developed plates were examined under UV light and stained with ceric ammonium molybdate followed by heating.

Flash chromatography was performed using silica gel 60 (230-240 mesh) from Fluka using a forced flow eluant at 0.3-0.5 bar pressure.

All ^{1}H and ^{13}C NMR spectra were recorded either using Bruker Avance 400 MHz (^{1}H) & 101 MHz (^{13}C) or Bruker Avance DRX 500 MHz (^{1}H) & 126 MHz (^{13}C) spectrometers at room temperature. Chemical shifts (δ-values) are reported in ppm, spectra were calibrated related to solvent's residual proton chemical shift ($CHCl_3$, δ = 7.26) and solvent's residual carbon chemical shift ($CDCl_3$, δ = 77.16), multiplicity is reported as follows: s = singlet, br. s = broad singlet, d = doublet, t = triplet, q = quartet, quint. = quintet, sext. = sextet, hept. = heptet, m = multiplet or unresolved and coupling constant *J* in Hz.

IR spectra were recorded using a *Varian 800 FT-IR ATR Spectrometer*. The absorptions are reported in cm^{-1}.

Optical rotations $[\alpha]_D^T$ were measured at the sodium D line using a 1 mL cell with a 1 dm path length on a Jasco P-2000 digital polarimeter and the concentration *c* is given in g/100mL and the used solvent is $CHCl_3$.

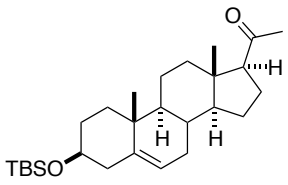
All masses spectra (HRMS-ESI) were recorded by the Mass spectrometric Service of University of Bern on Sciex QSTAR Pulsar mass spectrometer using electrospray ionization.

X-ray analyses:[1] Data collections for both crystal structures were performed at low temperature (123 K) using Mo K_a radiation on an Bruker KappaAPEX diffractometer. Integration of the frames and data reduction was carried out using APEX2. The structures were solved by direct methods using SIR92. All non hydrogen atoms were refined using anisotropically by full-matrix least-squares on *F* using CRYSTALS. Hydrogen atoms were placed in calculated positions by means of the "riding" model. Melting points (M.p.) were determined using a Büchi B-545 apparatus in open capillaries and are uncorrected.

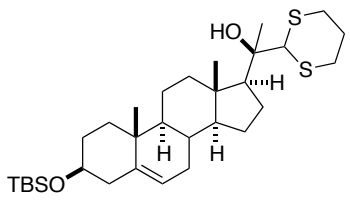
[1] i) Bruker Analytical X-ray Systems, Inc., **2006**. *Apex2*, Version 2 User Manual, M86-E01078, Madison, WI; ii) A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori, M. Camalli, *J. Appl. Cryst.* **1994**, *27*, 435; iii) P. W. Betteridge, J. R. Carruthers, R. I. Cooper, K. Prout, D. J. Watkin, *J. Appl. Cryst.* **2003**, *36*, 1487.

II. Experimental procedures

Towards the Total Synthesis of Withanolide A



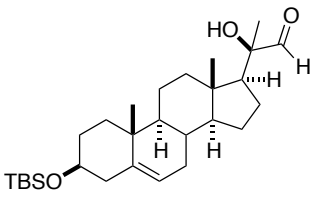
TBS protected pregnenolone (2a):[2] To a cold (0 °C) suspension of pregnenolone **2** (20.100 g, 63.513 mmol, 1 eq.) in dry THF (200 mL) was added imidazole (8.650 g, 127.075 mmol, 2 eq.) followed by TBDMSCl (14.360 g, 95.276 mmol, 1.5 eq.). Reaction mixture became a thick slurry. The reaction mixture was allowed to warm to RT and stirred for 18 h before being quenched with saturated aqueous NH_4Cl. The mixture was extracted with Et_2O and the combined organics were washed successively with H_2O, NH_4Cl and H_2O, then dried over $MgSO_4$ and concentrated to a white solid. Purification by recrystallisation from refluxing EtOAc (155 mL) afforded the TBS protected pregnenolone **2a** as clear cuboid crystals (26.867 g, 62.374 mmol, 98%). TLC (7:3 hexane/EtOAc) R_f = 0.85. $[\alpha]_D$ = +22.7° (c = 0.25, $CHCl_3$). M.p. 164-165 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.06 (6H, s), 0.63 (3H, s), 0.89 (9H, s), 0.98 (5H, m), 1.05 (1H, m), 1.18 (3H, m), 1.57 (12H, m), 1.82 (1H, dt, J = 13.2 Hz, J = 3.3 Hz), 2.01 (2H, m), 2.12 (3H, s), 2.20 (3H, m), 2.53 (1H, t, J = 9.0 Hz), 3.48 (1H, m), 5.31 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: -4.4, 13.4, 18.4, 19.6, 21.2, 23.0, 24.7, 26.1, 31.7, 32.0, 32.0, 32.2, 36.8, 37.6, 39.0, 42.9, 44.2, 50.2, 57.1, 63.9, 72.7, 121.0, 141.7, 209.7.



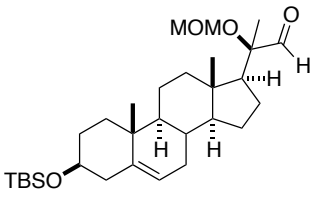
Dithian (3):[2] To a cold (-10 °C) solution of 1,3-dithiane (8.900 g, 0.074 mol, 2.0 eq.) in dry THF (65 mL) was added *n*-BuLi (1.6 M, 47.0 mL, 2.05 eq.) slowly and the reaction was stirred at -10 °C for 2 h. The mixture was then cooled to -78 °C and a cold (0 °C) solution of **2a** (15.943 g, 0.037 mol, 1.0 eq.) in dry THF (100 mL) was added slowly *via* syringe and the resulting mixture stirred at -78 °C for 5 h then allowed to warm slowly to RT and stirred for a further 18 h. The reaction was quenched with aqueous NH_4Cl (50 mL), then extracted with Et_2O, the combined organics were washed with H_2O, dried over $MgSO_4$ and concentrated to afford an off-white solid (ca. 25 g, *d.r.* [^{1}H NMR] = 15:1 [22*R*:22*S*]). The crude material was recrystallised from hot EtOAc/hexane (approx 1:1) affording the dithian **3** as a white solid (16.986 g, 0.031 mol, 84%). TLC (9:1 hexane/EtOAc) R_f = 0.36.

[2] B. B. Shingate, B. G. Hazra, V. S. Pore, R. G. Gonnade, M. Bhadbhade, *Tetrahedron* **2007**, *63*, 5622.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.05 (6H, s), 0.87 (3H, s), 0.89 (9H, s), 1.00 (3H, s), 1.44 (3H, s), 2.90 (4H, m), 3.48 (1H, m), 4.14 (1H, s), 5.31 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: -4.4, 13.5, 18.4, 19.6, 21.1, 21.8, 23.9, 24.3, 26.1, 26.2, 31.0, 31.5, 31.7, 31.9, 32.2, 36.7, 37.5, 40.3, 42.9, 43.1, 50.2, 55.3, 57.0, 61.4, 72.7, 76.9, 121.2, 141.7.

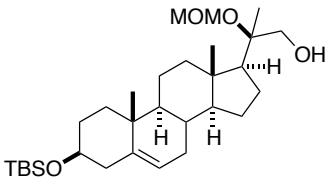


Aldehyde (3a): To a solution of dithian **3** (10.794 g, 19.591 mmol, 1.0 eq.) in CH_2Cl_2/H_2O (10:1, 150 mL) was added N-chlorosuccinimide (5.363 g, 40.161 mmol, 2.05 eq.) in portions under vigorous stirring. The reaction mixture was stirred at RT for 90 minutes then quenched with $Na_2S_2O_3/NaHCO_3$ (1:1, 100 mL) and the aqueous phase extracted into Et_2O (3 x 100 mL). The combined organics were washed with H_2O (3 x 100 mL), dried over $MgSO_4$ and concentrated to a white solid (10.550 g). Purification by filtration through a short pad of silica afforded aldehyde **3a** as a white solid (6.624 g, 14.375 mmol, 73%). TLC (4:1 hexane/EtOAc) R_f = 0.57. $[\alpha]_D$ = -56.8° (c = 0.45, $CHCl_3$). M.p. 199-201 °C. FTIR (neat) $\tilde{\nu}$ = 772, 837, 868, 887, 1080, 1254, 1358, 1385, 1470, 1728, 2858, 2858, 2936, 3375-3595 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.05 (6H, s), 0.79 (3H, s), 0.88 (9H, s), 0.96 (1H, m), 1.00 (3H, s), 1.07 (2H, m), 1.19 (1H, m), 1.32 (1H, m), 1.37 (3H, s), 1.44-1.64 (6H, m), 1.68 (1H, m), 1.70 (1H, m), 1.73 (1H, m,), 1.79 (1H, m), 1.83 (1H, m), 1.98 (1H, m), 2.15 (1H, m), 2.21 (2H, m), 2.28 (1H, m), 3.14 (1H, s, OH), 3.50 (1H, m), 5.26 (1H, d, J = 5.0 Hz), 9.56 (1H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ: -4.2, 14.0, 18.4, 19.6, 21.1, 22.3, 23.1, 24.3, 26.1, 31.6, 31.9, 32.2, 36.7, 37.5, 40.2, 42.9, 43.4, 50.3, 55.6, 56.7, 72.7, 79.7, 121.0, 141.8, 203.7. HRMS (ES$^-$) found M-H$^-$ 459.3303, $C_{28}H_{47}O_3Si$ calculated 459.3294.

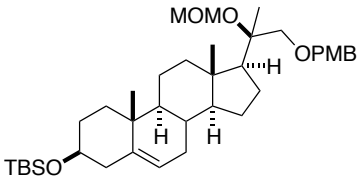


MOM protected aldehyde (4): To a cold (0 °C) solution of NaI (0.671 g, 4.479 mmol, 4 eq.) [that had been dried under high vacuum at 100 °C for 6 h] in dry dimethoxyethane (5 mL) was added freshly distilled MOMCl (0.451 mg, 5.599 mmol, 5 eq.) with vigourous stirring upon which a yellow suspension formed. The mixture was allowed to warm to RT and stirred for 10 minutes. This mixture was then added slowly *via* syringe to a cold (0 °C) solution

of aldehyde **3a** (0.516 g, 1.120 mmol, 1 eq.) and DIPEA (0.956 g, 6.159 mmol, 5.5 eq.) in dry DME (10 mL) and the reaction mixture heated at reflux for 18 h. The reaction mixture was allowed to cool to RT and quenched with 1 M aqueous Na_2CO_3 (10 mL) and then extracted with Et_2O. The combined organics were washed with H_2O, dried over $MgSO_4$, filtered and concentrated affording the crude material as an orange solid. The crude material was filtered through a short pad of silica (9:1 Hexane/EtOAc) and concentrated to afford MOM protected aldehyde **4** as an off-white solid (0.530 g). TLC (4:1 hexane/EtOAc) R_f = 0.70. The material was used crude in the next step.

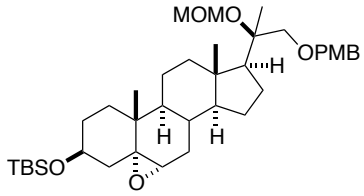


Alcohol (4a): To a suspension of aldehyde **4** (crude) in MeOH (20 mL) was added $NaBH_4$ (42 mg, 1.120 mmol) in four portions and the reaction mixture followed by TLC. After 1 h a further portion of $NaBH_4$ (10 mg) was added and the reaction mixture allowed to stir for another 1 h at RT until all the starting material has reacted. The mixture was quenched with H_2O (10 mL) and extracted into Et_2O (3 x 10 mL), the combined organics were washed with H_2O, dried over $MgSO_4$, filtered and concentrated affording the alcohol **4a** as a white solid (0.530 g) which displayed a single spot by TLC analysis. TLC (4:1 hexane/EtOAc) R_f = 0.40. The material was used crude in the next step.

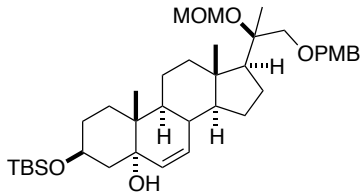


PMB protected alcohol (4b): To a cold (0 °C) solution of alcohol **4a** (crude) in a mixture of dry THF-DMF (4:1, 5 mL) was added NaH (38 mg, 1.569 mmol, 1.5 eq.) in 5 portions and the reaction mixture was allowed to warm to RT and stirred for 30 min during which time the solution turned cloudy. The reaction mixture was cooled to 0 °C and TBAI (77 mg, 0.209 mmol, 0.2 eq.) was added followed by the slow addition of PMBCl (328 mg, 2.092 mmol, 2 eq.). The reaction mixture was then allowed to warm to RT and followed by TLC. The reaction mixture was quenched with aqueous NH_4Cl and extracted with Et_2O, the combined organics were washed with H_2O, dried over $MgSO_4$, filtered and concentrated affording the crude material as an orange solid. Purification by silica gel chromatography (hexane/EtOAc, 98:2 to 95:5) furnished the PMB protected alcohol **4b** as a clear colourless oil (0.502 g, 0.801 mmol, 71% from **17**). TLC (95:5

hexane/EtOAc) R_f = 0.16. $[\alpha]_D$ = -36.4° (c = 0.34, $CHCl_3$). FTIR (neat) $\tilde{\nu}$ = 775, 833, 1034, 1088, 1246, 1369, 1462, 1512, 1612, 2855, 2932 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.06 (6H, s), 0.81 (3H, s), 0.89 (9H, s), 0.82-0.94 (1H, m), 0.95-1.16 (6H, m), 1.18-1.30 (2H, m), 1.38 (3H, s), 1.41-1.65 (8H, m), 1.67-1.76 (2H, m), 1.80 (1H, dt, J = 13.2 Hz, J = 3.3 Hz), 1.84-2.05 (3H, m), 2.16 (1H, m), 2.27 (1H, m), 3.33 (3H, s), 3.35 (2H, s), 3.48 (1H, m), 3.81 (1H, s), 4.42 (2H, q, J = 11.7 Hz), 4.69 (1H, d, J = 7.1 Hz), 4.77 (1H, d, J = 7.1 Hz), 5.31 (1H, m), 6.87 (2H, d, J = 8.7 Hz), 7.24 (2H, d, J = 8.7 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: -4.4, 13.9, 19.6, 20.8, 21.1, 22.2, 24.0, 26.1, 31.5, 32.0, 32.2, 36.7, 37.5, 40.3, 42.6, 43.0, 50.3, 55.4, 55.6, 56.0, 57.0, 72.8, 73.1, 76.7, 79.7, 91.4, 113.8, 121.3, 129.2, 130.9, 141.8, 159.1. HRMS (ES^+) found MNa^+ 649.4294, $C_{38}H_{62}NaO_5Si$ calculated 649.4265.

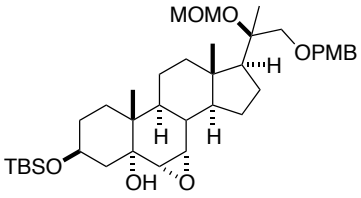


Epoxide (5): To a cold (0 °C) solution of PMB protected alcohol **4b** (4.445 g, 7.089 mmol, 1 eq.) in DCM (20 mL) was slowly added *m*CPBA (1.835 g, 10.634 mmol, 1.5 eq.) in 15 portions upon which a white precipitate formed. The reaction mixture was stirred at 0 °C for 10 min then allowed to warm to RT and followed by TLC. After 1 h the reaction was quenched by addition of saturated aqueous Na_2SO_3 (30 mL) and extracted with Et_2O, the combined organics were washed with Na_2SO_3 (3 x 20 mL) then H_2O, dried over $MgSO_4$, filtered and concentrated to afford epoxide **5** as a white solid (4.453 g, *d.r.* α:β 4.1:1) which displayed a single spot by TLC analysis. TLC (95:5 hexane/EtOAc) R_f = 0.24. The material was used crude in the next step.



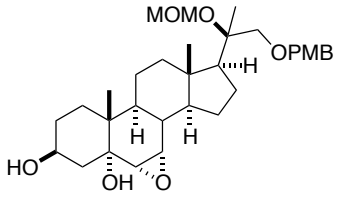
Allylic alcohol (6): To a solution of $(PhSe)_2$ (1.176 g, 3.767 mmol, 0.65 eq) in EtOH (70 mL) was added $NaBH_4$ (0.329 g, 8.692 mmol, 1.5 eq) in small portions and the reaction mixture stirred for 10 min. Three further portions of $NaBH_4$ (3 x 0.15 eq) were added upon which the solution turned from yellow to clear. To this mixture was slowly added a solution of epoxid **5** (3.726 g, 5.795 mmol, 1 eq) in dry THF (40 mL) *via* syringe and the reaction mixture brought to reflux and stirred for 3.5 h. After this time the reaction mixture was cooled to 0 °C in an ice bath and H_2O_2 (6.0 mL, 0.579 mol, 10 eq) was slowly added with

vigourous stirring and then the mixture was brought back to reflux for a further 30 min. The reaction mixture was cooled to RT, quenched with H_2O and extracted with Et_2O. The combined organics were washed with H_2O, dried over $MgSO_4$, filtered and concentrated to an off-white solid. Purification by silica gel chromatography (hexane/EtOAc, 95:5, 93:7, 9:1) afforded allylic alcohol **6** as a white solid (1.423 g, 2.213 mmol, 48%, 72% *brsm*). TLC (9:1 hexane/EtOAc) R_f = 0.30. $[\alpha]_D$ = -31.8° (*c* = 0.42, $CHCl_3$). M.p. 127-128 °C. FTIR (neat) $\tilde{\nu}$ = 772, 837, 907, 1034, 1084, 1246, 1358, 1462, 1516, 1616, 2886, 2932, 3414-3611 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.06 (6H, s), 0.83 (3H, s), 0.87-0.92 (12H, m), 1.15-1.49 (m), 1.50-1.71 (m), 1.75 (2H, m), 1.92 (2H, m), 2.04 (1H, m), 3.33 (3H, s), 3.34 (2H, s), 3.80 (3H, s), 4.09 (1H, m), 4.37 (1H, d, *J* = 11.7 Hz), 4.44 (1H, d, *J* = 11.7 Hz), 4.69 (1H, d, *J* = 7.1 Hz), 4.77 (1H, d, *J* = 7.1 Hz), 5.55 (1H, m), 5.61 (m, 1 H), 6.87 (2H, d, *J* = 8.7 Hz), 7.23 (2H, d, *J* = 8.7 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: -4.4, 14.0, 14.8, 18.4, 20.8, 21.0, 22.2, 23.5, 26.1, 28.7, 31.1, 37.9, 38.1, 40.5, 41.5, 43.9, 45.1, 54.1, 55.4, 55.7, 55.8, 67.9, 73.1, 74.2, 76.6, 79.6, 91.4, 113.8, 129.2, 130.8, 133.0, 133.7, 159.2. HRMS (ES^+) found MNa^+ 665.4194, $C_{38}H_{62}O_6SiNa$ calculated 665.4213.

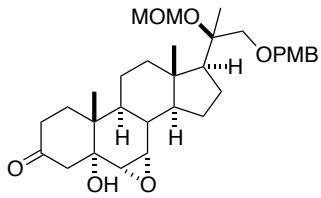


Epoxy alcohol (6a): To a cold (0°C) solution of allylic alcohol **6** (1.423 g, 2.213 mmol, 1 eq) in CH_2Cl_2 (10 mL) was added *m*CPBA (0.497 g, 2.877 mmol, 1.3 eq). The reaction mixture was allowed to warm to RT and stirred for 2 h and then quenched with saturated aqueous Na_2SO_3 (10 mL). The mixture was extracted with Et_2O, the combined organics were washed with saturated aqueous Na_2SO_3 then H_2O, dried over $MgSO_4$, filtered and concentrated affording epoxy alcohol **6a** as a white foam (1.398 g, 2.121 mmol, 96%). TLC (4:1 hexane/EtOAc) R_f = 0.50. $[\alpha]_D$ = -30.3° (*c* = 0.24, $CHCl_3$). M.p. 112.5-113.5 °C. FTIR (neat) $\tilde{\nu}$ = 772, 837, 910, 1038, 1080, 1246, 1358, 1385, 1462, 1516, 2882, 2936, 3360-3595 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.07 (6H, s), 0.82 (3H, s), 0.83 (3H, s), 0.89 (9H, s), 1.06 (1H, m), 1.12-1.88 (23H, m), 1.90-2.05 (2H, m), 2.89 (1H, d, *J* = 0.8 Hz, OH), 2.94 (1H, d, *J* = 3.8 Hz), 3.25 (1H, m), 3.30-3.37 (5H, m), 3.81 (3H, s), 4.13 (1H, m), 4.37 (1H, d, *J* = 11.7 Hz), 4.44 (1H, d, *J* = 11.7 Hz), 4.69 (1H, d, *J* = 7.1 Hz), 4.77 (1H, d, *J* = 7.1 Hz), 6.88 (2H, d, *J* = 8.7 Hz), 7.23 (2H, d, *J* = 8.6 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: -4.5, -4.4, 14.0, 15.1, 18.4, 20.6, 20.9, 22.3,

23.1, 26.1, 28.0, 30.9, 35.3, 37.8, 38.4, 40.2, 42.3, 43.8, 51.7, 55.4, 55.6, 55.7, 58.1, 58.5, 67.7, 71.0, 73.1, 76.7, 79.9, 91.4, 113.8, 129.2, 130.8, 159.2. HRMS (ES^+) found MNa^+ 681.4156, $C_{38}H_{62}O_7SiNa$ calculated 681.4163.

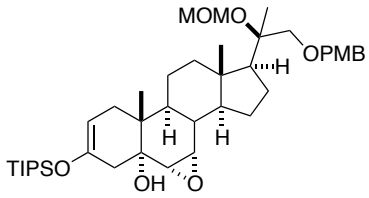


Diol (7): To a solution of epoxy alcohol **6a** (1.191 g, 1.807 mmol, 1 eq) in dry THF (7 mL) was added TBAF (1 M in THF, 7.2 mL, 7.229 mmol, 4 eq) at RT and the reaction mixture followed by TLC. After 20 h the reaction mixture was concentrated directly onto silica gel and purified by silica gel chromatography (1:1, 1:0 EtOAc/hexane) affording diol **7** as a white solid (0.841 g, 1.543 mmol, 85%). TLC (EtOAc) R_f = 0.52. $[\alpha]_D$ = -38.3° (c = 0.20, $CHCl_3$). M.p. 155.5-156.5 °C. FTIR (neat) $\tilde{\nu}$ = 903, 1038, 1088, 1254, 1381, 1470, 1512, 1612, 2940, 3348-3603 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.83 (3H, s), 0.84 (3H, s), 1.02-1.34 (8H, m), 1.34-1.42 (2H, m), 1.47-1.55 (3H, m), 1.58-1.83 (7H, m), 1.83-2.06 (5H, m), 2.94 (1H, m), 2.96 (1H, d, J = 3.9 Hz), 3.26 (1H, m), 3.33 (5H, m), 3.81 (3H, s), 4.17 (1H, m), 4.37 (1H, d, J = 11.7 Hz), 4.44 (1H, d, J = 11.7 Hz), 4.69 (1H, d, J = 7.1 Hz), 4.77 (1H, d, J = 7.1 Hz), 6.88 (2H, d, J = 8.6 Hz), 7.23 (2H, d, J = 8.7 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.0, 15.0, 20.5, 20.9, 22.2, 23.1, 27.9, 30.3, 35.3, 37.8, 38.3, 40.2, 41.6, 43.9, 51.7, 55.4, 55.6, 55.7, 58.0, 58.4, 67.1, 70.9, 73.1, 76.6, 79.5, 91.4, 113.8, 129.2, 130.7, 159.2. HRMS (ES^+) found MNa^+ 567.3346, $C_{32}H_{48}O_7Na$ calculated 567.3292.

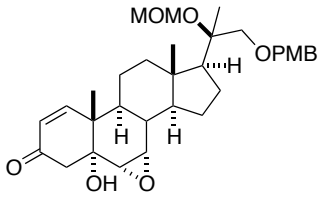


Ketone (7a): To a solution of diol **7** (1.485 g, 2.725 g, 1 eq) and NMO (0.479 g, 4.088 mmol, 1.5 eq) in dry DCM (15 mL) containing molecular sieves was added TPAP (48 mg, 0.136 mmol, 0.05 eq) in a single portion and the reaction followed by TLC. After 4 h the reaction was quenched with saturated aqueous Na_2SO_3 (20 mL) and extracted with Et_2O. The combined organics were washed with H_2O, dried over $MgSO_4$, filtered and concentrated to a white solid. The crude material was purified by recrystallisation from refluxing hexane/EtOAc (3:1) affording ketone **7a** as thin needle like crystals (1.050 g, 1.935 mmol, 71%). The filtrate was purified by silica gel chromatography (1:1 hexane/EtOAc) affording the title compound **7a** (0.205 g, 0.378 mmol, 14%; combined yield (1.255 g, 85%). TLC

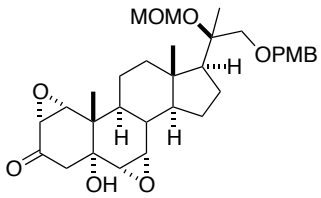
(1:1 hexane/EtOAc) R_f = 0.31. $[\alpha]_D$ = -18.9° (c = 0.33, $CHCl_3$). M.p. 135-136 °C. FTIR (neat) $\tilde{\nu}$ = 818, 891, 1034, 1092, 1250, 1385, 1450, 1512, 1612, 1720, 2330, 2361, 2928, 3333-3607 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.25 (2H, d), 6.88 (2H, d), 4.80 (1H, d), 4.69 (1H, d), 4.47 (1H, d), 4.38 (1H, d), 3.82 (3H, s), 3.35-3.39 (5H, m), 3.34 (1H, m), 2.94-3.00 (2H, m, OH), 2.64 (1H, dd), 2.33-2.50 (3H, m), 2.07 (1H, m), 2.02 (1H, m), 1.88 (1H, m), 1.76-1.86 (3H, m), 1.68 (1H, m), 1.50 (1H, m), 1.40 (4H, m), 1.38 (2H, m), 1.27-1.35 (2H, m), 1.16 (1H, m), 1.02 (3H, s), 0.87 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 13.5, 15.0, 19.8, 20.5, 21.8, 22.6, 28.6, 34.1, 36.2, 37.5, 37.6, 39.5, 43.5, 48.8, 51.3, 3 x 55, 56.8 (*C*-6), 57.8, 72.6, 73.1, 76.2, 79.4, 91.0, 113.0, 128.0, 130.7, 159.1, 210.0. HRMS (ES^+) found MH^+ 565.3157, $C_{32}H_{46}NaO_7$ calculated 565.3141.



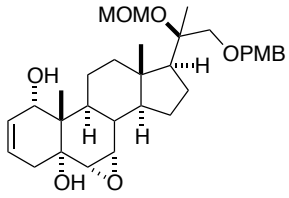
TIPS protected enol (7b): To a cold (0 °C) solution of ketone **7a** (50 mg, 9.2 x 10-5 mol, 1 eq) and Et_3N (17 mg, 23 µL, 1.66 x 10-4 mol, 1.8 eq) in dry DCM (1 mL) was added freshly distilled TIPSOTf (34 mg, 30 µL, 1.11 x 10-4 mol, 1.2 eq) dropwise. The reaction mixture stirred at 0 °C for 10 min then allowed to warm to RT and followed by TLC. Reaction complete after 2 h. The reaction was quenched with aqueous 1 M $NaHCO_3$ (1 mL) and extracted into Et_2O. The combined organics were washed with H_2O, dried over $MgSO_4$, filtered and concentrated to a yellow oil (67 mg). Purification by silica gel chromatography (95:5 to 9:1 hexane/EtOAc) afforded the TIPS protected enol **7b** as a clear colourless oil (61 mg, 8.7 x 10-5 mol, 94% ; 1.26 g Scale gave 69% yield). TLC (9:1 hexane/EtOAc) R_f = 0.23. $[\alpha]_D$ = +0.38 (c = 0.27, $CHCl_3$). FTIR (neat) $\tilde{\nu}$ = 802, 883, 1038, 1096, 1196, 1246, 1381, 1462, 1512, 1612, 1670, 2866, 2943, 3414-3645 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.78 (3H, s), 0.84 (3H, s), 1.04-1.44 (m), 1.52-1.84 (6H, m), 1.90-2.03 (3H, m), 2.15 (1H, dd, J = 16.8 Hz, J = 1.1 Hz), 2.34 (1H, dd, J = 16.9 Hz, J = 1.5 Hz), 2.83 (1H, d, J = 1.4 Hz), 2.96 (1H, d, J = 3.8 Hz), 3.26 (1H, dd, J = 3.7 Hz, J = 2.1 Hz), 3.34 (5H, m), 3.81 (3H, s), 4.37 (1H, d, J = 11.7 Hz), 4.44 (1H, d, J = 11.7 Hz), 4.70 (1H, d, J = 7.1 Hz), 4.78 (2H, m), 6.88 (2H, d, J = 8.7 Hz), 7.23 (2H, d, J = 8.7 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 12.8, 13.9, 15.7, 18.2, 20.4, 20.9, 22.2, 23.2, 31.4, 35.0, 37.1, 37.7, 40.0, 40.1, 43.6, 51.6, 55.4, 55.65, 55.67, 57.5, 57.9, 69.7, 73.1, 76.6, 79.6, 91.4, 101.6, 113.8, 129.2, 130.8, 147.2, 159.2. HRMS (ES^+) found MH^+ 699.4650, $C_{41}H_{67}O_7Si$ calculated 699.4651.



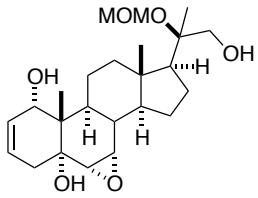
Enone (8): To a solution of TIPS protected enol **7b** (1.082 g, 1.548 mmol, 1 eq) in MeCN (15 mL) was added $Pd(OAc)_2$ (0.347 g, 1.548 mmol, 1 eq) in small portions and the reaction followed by TLC. Reaction complete after 8 h. Crude reaction mixtur filtered through a short pad of silica gel (1:1 hexane/EtOAc) affording the crude material as a red oil (0.925 g). Purification by silica gel chromatography (3:2 hexane/EtOAc) afforded enone **8** as a white solid (0.449 g, 0.831 mmol, 54%). TLC (1:1 hexane/EtOAc) R_f = 0.47. $[\alpha]_D$ = -3.6 (c = 0.30, $CHCl_3$). M.p. 117-118 °C. FTIR (neat) $\tilde{\nu}$ = 775, 818, 907, 1026, 1092, 1246, 1369, 1462, 1516, 1616, 1678, 2858, 2932, 2974, 3395-3591 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.88 (3H, s), 1.15 (3H, s), 1.23-1.35 (3H, m), 1.36-1.55 (7/8H, m), 1.60-1.72 (3H, m), 1.76-1.88 (3/4H, m), 2.00 (1H, m), 2.10 (1H, dt, J = 12.2 Hz, J = 2.4 Hz), 2.65 (1H, d, J = 17.1 Hz), 2.84 (1H, dd, J = 17.0 Hz, J = 2.0 Hz), 3.07 (1H, d, J = 3.8 Hz), 3.19 (1H, d, J = 2.0 Hz), 3.33-3.38 (7H, m), 3.81 (3H, s), 4.38 (1H, d, J = 11.7 Hz), 4.45 (1H, d, J = 11.7 Hz), 4.70 (1H, d, J = 7.1 Hz), 4.78 (1H, d, J = 7.1 Hz), 5.98 (1H, d, J = 10.1 Hz), 6.88 (2H, d, J = 8.6 Hz), 6.97 (1H, d, J = 10.3 Hz), 7.23 (2H, d, J = 8.7 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.0, 20.6, 20.7, 20.9, 22.2, 23.1, 30.5, 35.3, 35.6, 39.9, 42.8, 43.6, 46.6, 51.6, 55.4, 55.5, 55.7, 56.6, 57.7, 72.1, 73.1, 76.5, 79.4, 91.4, 113.8, 128.0, 129.2, 130.6, 153.3, 159.2, 196.8. HRMS (ES^+) found MNa^+ 563.2985, $C_{32}H_{44}O_7Na$ calculated 563.2986.



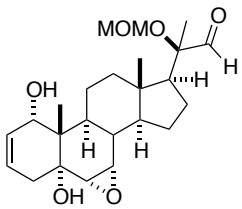
Epoxy ketone (8a): To a cold (0 °C) solution of enone **8** (24 mg, 4.4 x 10^{-5} mol, 1 eq) in THF (1 mL) was added H_2O_2 (45 μL, 4.44 x 10^{-4} mol, 10 eq) then K_2CO_3 (6.1 mg, 4.4 x 10^{-5} mol, 1 eq) as a solution in H_2O (0.1 mL). The reaction mixture was stirred at 0 °C for 10 min then allowed to warm to RT and followed by TLC. Reaction complete after 3 h. The reaction was quenched with saturated aqueous NH_4Cl and extracted with Et_2O, the combined organics were washed with H_2O, dried over $MgSO_4$, filtered and concentrated. Purification by silica gel chromatography (1:1 hexane/EtOAc) afforded the epoxy ketone **8a** as a white foam (13.3 mg, 2.4 x 10^{-5} mol, 54%). TLC (1:1 hexane/EtOAc) R_f = 0.25.



Allylic alcohol (8b): A mixture of N_2H_4 HCl (4.9 mg, 7.2 x 10^{-5} mol, 3 eq) and Et_3N (15 μL, 1.10 x 10^{-4} mol, 4.6 eq) in dry MeCN (0.3 mL) were sonicated for 2 h. The reaction mixture was then cooled in an ice bath and a solution of epoxy ketone **8a** (13.3 mg, 2.4 x 10^{-5} mol, 1 eq) in dry MeCN (0.3 mL) was added dropwise. The reaction mixture was allowed to warm to RT and stirred for 1.5 h or until no starting material remains. The reaction was quenched with H_2O and extracted with Et_2O, the combined organics were washed with H_2O, dried over $MgSO_4$, filtered and concentrated to afford the crude allylic alcohol **8b** as an off-white solid (9.5 mg), which displayed a single spot by TLC analysis. TLC (3:2 hexane/EtOAc) R_f = 0.41. The material was used without purification in the next step.

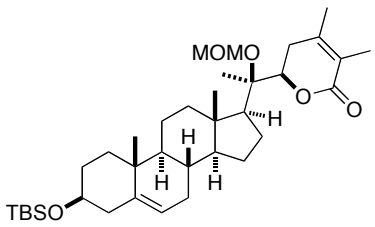


Triol (9): To a solution of allylic alcohol **8b** (9.5 mg, 1.8 x 10^{-5} mol, 1 eq) in CH_2Cl_2/H_2O mixture (10:1, 0.5 mL) was added DDQ (4.8 mg, 2.1 x 10-5 mol, 1.2 eq) in a single portion and the reaction mixture stirred at RT and followed by TLC. After 1 h the reaction mixture was quenched with H_2O and extracted with Et_2O, the combined organics were washed with H_2O, dried over $MgSO_4$, filtered and concentrated to afford triol **9** as a yellow solid. Purification by silica gel chromatography (2:3 hexane/EtOAc) afforded the title compound as a white solid (5.0 mg, 1.2 x 10^{-5} mol, 50% over two steps). TLC (2:3 hexane/EtOAc) R_f = 0.27.

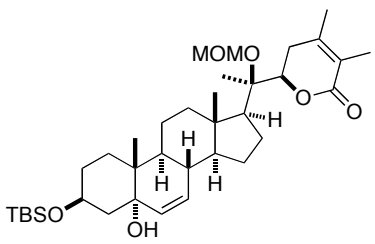


Aldehyde (10): To a solution of triol **9** (5.0 mg, 1.2 x 10^{-5} mol, 1 eq) and NMO (3.5 mg, 3.0 x 10-5 mol, 2.5 eq) in dry DCM (0.5 mL) containing molecular sieves was added TPAP (0.5 mg, 1.0 x 10-6 mol, 0.1 eq) in a single portion and the reaction followed by TLC. After 2.5 h the reaction was quenched with saturated aqueous Na_2SO_3 and extracted with Et_2O. The combined organics were washed with H_2O, dried over $MgSO_4$, filtered and concentrated to afford aldehyde **10** as an off-white solid (3.8 mg, 75%).

Total synthesis of withanolide A

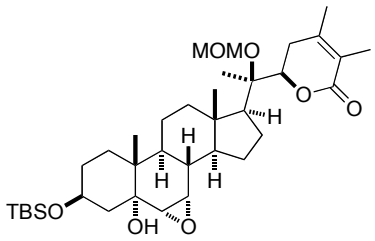


Lactone 12: A solution of ethyl 2,3-dimethylbut-2-enoate (384 mg, 2.70 mmol) and DMPU (2.5 mL, distilled freshly over CaH_2) in THF (2.5 mL) was added dropwise to a solution of LiHMDS (3.0 mL 1.0 M in THF, 3.0 mmol) in THF (2.5 mL) at -78 °C (dry ice-acetone bath) and the mixture was stirred for 1.5h at that temperature. A solution of protected aldehyde **4** (0.5 g, 1.0 mmol) in THF (3.0 mL) was then added dropwise and the resulting mixture was stirred at -78 °C for 6 h. The temperature of the reaction mixture was allowed to increase to RT during overnight. Then, the reaction was quenched by addition of saturated NH_4Cl solution. The mixture was extracted with Et_2O. The combined organic layers were washed brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (pentane:Et_2O 3:1) to afford lactone **12** as a 93:7 mixture of diasteroisomers (518 mg, 0.862 mmol, 87%) as white foam. TLC: R_f = 0.3 (pentane:EtOAc 7:1). $[\alpha]_D$ = +19.4° (c = 0.44, $CHCl_3$). FTIR (neat) $\tilde{\nu}$ = 2931, 1714, 1463, 1381, 1318, 1253, 1083, 1016, 889, 836, 775, 670 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 5.32-5.29 (m, 1H), 4.97 (d, J = 6.6 Hz, 1H), 4.82 (d, J = 6.6 Hz, 1H), 4.25 (dd, J = 13.3, 3.3 Hz, 1H), 3.51-3.44 (m, 1H), 3.37 (s, 3H), 2.53-2.44 (m, 1H), 2.29-2.22 (m, 1H), 2.18-2.10 (m, 2H), 2.02-1.96 (m, 3H), 1.93 (s, 3H), 1.86 (s, 3H), 1.84-1.67 (m, 4H), 1.65-1.45 (m, 7H), 1.39 (s, 3H), 1.35-1.27 (m, 2H), 1.07-1.00 (m, 2H), 0.99-0.96 (m, 3H), 0.88 (s, 9H), 0.86 (s, 3H), 0.05 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 166.3, 148.9, 141.8, 122.0, 121.1, 92.8, 82.3, 80.0, 72.7, 56.8, 56.4, 54.5, 50.2, 43.1, 42.9, 40.3, 37.5, 36.7, 32.2, 32.2, 31.9, 31.5, 26.1, 24.1, 22.0, 21.0, 20.6, 19.5, 18.4, 18.0, 13.9, 12.6, -4.5. Analyses calculated for $C_{36}H_{60}O_5Si$ requires: C = 71.95, H = 10.06, found: C = 72.04, H = 9.86.



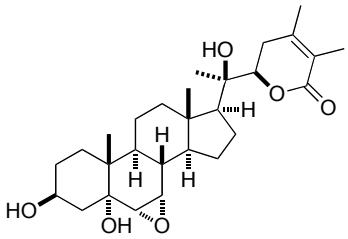
Allylic alcohol 13: *meso*-Tetraphenylporphyrin (30 mg, 49 µmol) was added to a solution of alkene **12** (0.42 g, 0.70 mmol) in pyridine (5 mL) and the mixture was stirred for 4 h at RT with continuous bubbling of O_2 under Na-light (150 W) irradiation. After the disappearance of the starting material, the oxygen flow was stopped, the Na-light was removed and the mixture was charged with triphenylphosphene (0.63 g,

2.4 mmol). The resulting mixture was stirred for 1 h at RT. The solvent was removed under vacuum and the residue was purified by flash column chromatography (pentane:Et_2O 1:1) to obtain allylic alcohol **13** (0.26 g, 0.42 mmol, 61%) as pale yellow foam. TLC: R_f = 0.2 (pentane:Et_2O 2:1). $[\alpha]_D$ = +32.5° (c = 0.6, $CHCl_3$). FTIR (neat) $\tilde{\nu}$ = 3467, 2932, 2890, 2857, 1709, 1469, 1382, 1253, 1130, 1094, 1065, 1012, 871, 836, 759 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 5.60 (d, *J* = 10.2 Hz, 1H), 5.56 (dd, *J* = 9.9, 2.1 Hz, 1H), 5.00 (d, *J* = 6.6 Hz, 1H), 4.83 (d, *J* = 6.6 Hz, 1H), 4.25 (dd, *J* = 13.3, 3.2 Hz, 1H), 4.11-4.05 (m, 1H), 3.37 (s, 3H), 2.48-2.42 (m, 1H), 2.13-2.09 (m, 1H), 2.07-2.00 (m, 2H), 1.97-1.95 (m, 1H), 1.92 (s, 3H), 1.87 (s, 3H), 1.75-1.65 (m, 5H), 1.59-1.43 (m, 5H), 1.41 (s, 3H), 1.38-1.19 (m, 6H), 0.91 (s, 3H), 0.90 (s, 3H), 0.88 (s, 9H), 0.06 (br. s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 166.2, 148.8, 133.9, 132.6, 122.1, 93.0, 82.3, 79.9, 74.1, 67.9, 56.4, 54.6, 54.0, 45.1, 44.5, 41.5, 40.7, 38.1, 37.8, 32.3, 31.1, 28.7, 26.1, 23.6, 22.0, 21.0, 20.6, 18.4, 17.8, 14.8, 14.0, 12.6, -4.4, -4.5. HRMS (ESI) Exact mass calculated for $C_{36}H_{60}O_6NaSi$ ($[M+Na]^+$): 639.4051, found: 639.4066.

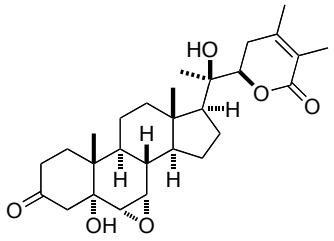


Epoxy alcohol 13a: *m*CPBA (100 mg, 579 μmol) was added to an ice cold solution of allylic alcohol **13** (200 mg, 324 μmol) in CH_2Cl_2 (2 mL), the ice bath was then removed and the mixture was stirred at RT for 4h. The mixture was diluted with Et_2O and the reaction was quenched with saturated aqueous Na_2SO_3 solution. The mixture was extracted with Et_2O and the combined organic layers were washed with saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by flash column chromatography (pentane:Et_2O 2:1) to give epoxy alcohol **13a** as 96:4 mixtures of diasteroisomers (197 mg, 311 mmol, 96%) as white foam. TLC: R_f = 0.2 (pentane:Et_2O 2:1). $[\alpha]_D$ = +33.3° (*c* = 0.55, $CHCl_3$). FTIR (neat) $\tilde{\nu}$ = 3541, 2934, 2899, 2858, 1713, 1469, 1384, 1254, 1131, 1096, 1015, 836, 776 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 5.00 (d, *J* = 6.6 Hz, 1H), 4.80 (d, *J* = 6.6 Hz, 1H), 4.22 (dd, *J* = 13.3, 3.3 Hz, 1H), 4.13-4.07 (m, 1H), 3.34 (s, 3H), 3.24-3.22 (m, 1H), 2.92 (d, *J* = 3.9 Hz, 1H), 2.83 (s, 1H), 2.41-2.35 (m, 1H), 2.04-1.99 (m, 3H), 1.90 (s, 3H), 1.83 (s, 3H), 1.81-0.97 (m, 16H), 1.39 (s, 3H), 0.88 (s, 3H), 0.86 (s, 9H), 0.81 (s, 3H), 0.04 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 166.1,

148.7, 122.0, 93.0, 82.3, 79.7, 70.8, 67.6, 58.4, 57.9, 56.4, 54.7, 51.6, 44.2, 42.1, 40.4, 38.3, 37.7, 35.1, 32.3, 30.7, 27.9, 26.0, 23.1, 21.9, 20.6, 20.5, 18.3, 17.5, 15.0, 13.8, 12.5, -4.5, -4.6. HRMS (ESI) Exact mass calculated for $C_{36}H_{60}O_7NaSi$ ($[M+Na]^+$): 655.4001, found: 655.4011.

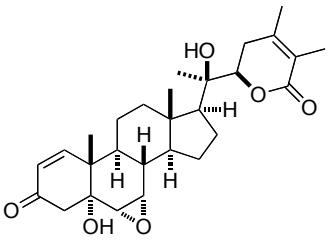


Triol 14: An aqueous solution of HCl (0.5 mL, 6 M) was added to a solution of epoxide **13a** (197 mg, 311 µmol) in THF (6 mL) at RT. The reaction mixture was stirred for 1 h at RT. The mixture was then diluted with CH_2Cl_2 (5 mL) and the reaction was quenched with saturated $NaHCO_3$ solution. The mixture was extracted with CH_2Cl_2 and the combined organic layers were washed brine, dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by flash column chromatography (CH_2Cl_2:MeOH 36:1) to give triol **14** (118 mg, 249 µmol, 80 %) as white solid. M.p.: 311- 312 °C. TLC: R_f = 0.3 (CH_2Cl_2:MeOH 20:1). $[\alpha]_D$ = +37.0° (c = 0.46, $CHCl_3$). FTIR (neat) $\tilde{\nu}$ = 3463, 2941, 2872, 1699, 1384, 1319, 1134, 1096, 1038, 755 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 4.20 (dd, J = 13.4, 3.4 Hz, 1H), 4.19-4.13 (m, 1H), 3.28-3.26 (m, 1H), 2.98 (d, J = 3.8 Hz, 1H), 2.42-2.36 (m, 1H), 1.95 (s, 3H), 1.89 (s, 3H), 2.12-1.07 (m, 19H), 1.30 (s, 3H), 0.92 (s, 3H), 0.85 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 166.2, 149.0, 122.2, 81.1, 75.2, 70.9, 67.1, 58.4, 58.0, 54.5, 51.8, 44.3, 41.6, 40.3, 38.4, 37.8, 35.2, 31.8, 30.3, 27.9, 23.1, 22.2, 21.2, 20.7, 20.6, 15.0, 13.9, 12.6. HRMS (ESI) Exact mass calculated for $C_{28}H_{42}O_6Na$ ($[M+Na]^+$): 497.2874, found: 497.2877.

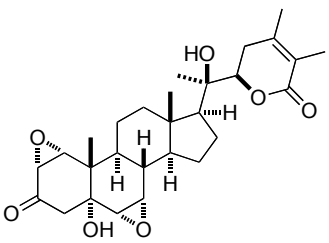


Ketone 14a: Powdered 4Å molecular sieves (200 mg) were added to a solution of alcohol **14** (51 mg, 0.11 mmol) in CH_2Cl_2 (7 mL) and the mixture was stirred for 5 min at RT. Then *N*-methyl morpholine *N*-oxide (21 mg, 0.18 mmol) and TPAP (2 mg, 6 µmol) were successively added to the solution and the mixture was stirred at RT for 3 h. The mixture was diluted with CH_2Cl_2 and the reaction was quenched with saturated aqueous $Na_2S_2O_3$ solution. The mixture was then extracted with CH_2Cl_2. The combined organic layers were washed brine, dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by flash column chromatography

(CH_2Cl_2:MeOH 100:1) to give ketone **14a** (48 mg, 0.1 mmol, 95%) as white solid. M.p.: 262.5 - 264 °C. TLC: R_f = 0.5 (CH_2Cl_2:MeOH 20:1). $[\alpha]_D$ = +56.5° (c = 0.31, $CHCl_3$). FTIR (neat) $\tilde{\nu}$ = 3504, 2944, 2874, 1708, 1385, 1318, 1134, 1098, 757 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 4.20 (dd, J = 13.3, 3.4 Hz, 1H), 3.31 (m, 1H), 2.95 (d, J = 3.7 Hz, 1H), 2.91 (d, J = 2.3 Hz, 1H), 2.66 (dd, J = 15.2, 2.1 Hz, 1H), 2.44-2.33 (m, 5H), 2.12-2.00 (m, 3H), 1.94 (s, 3H), 1.88 (s, 3H), 1.86-1.79 (m, 3H), 1.63-1.56 (m, 1H), 1.51-1.46 (m, 2H), 1.42-1.23 (m, 5H), 1.30 (s, 3H), 1.17-1.12 (m, 1H), 0.99 (s, 3H), 0.94 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 209.3, 166.1, 149.0, 122.1, 81.1, 75.2, 72.6, 58.0, 57.4, 54.4, 51.7, 49.1, 44.1, 40.1, 38.1, 37.9, 37.1, 34.8, 31.7, 29.1, 23.2, 22.2, 21.2, 20.7, 20.5, 15.3, 13.8, 12.6. HRMS (ESI) Exact mass calculated for $C_{28}H_{41}O_6$ ($[M+H]^+$): 473.2898, found: 473.2888.

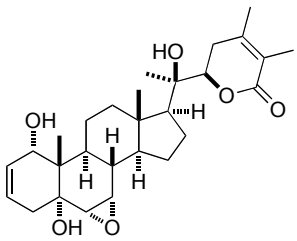


Enone 15: 2-Iodoxybenzoic acid (36 mg, 0.13 mmol) and 4-methoxypyridine-*N*-oxide hydrate (16 mg, 0.13 mmol) were dissolved in DMSO (0.5 mL) under stirring for 20 min at RT. The mixture was then charged with ketone **14a** (20 mg, 42 µmol) and the mixture was stirred for 5 d at 40 °C. The reaction was quenched with aqueous saturated $NaHCO_3$ solution and the mixture was extracted with CH_2Cl_2. The combined organic layers were washed brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash column chromatography (CH_2Cl_2:MeOH 100:1) to give enone **15** as a mixture with ca. 10% inseparable starting material (18 mg, 34 µmol of enone, 81%) as white solid which was directly used for the next step without further purification. TLC: R_f = 0.5 (CH_2Cl_2:MeOH 20:1).

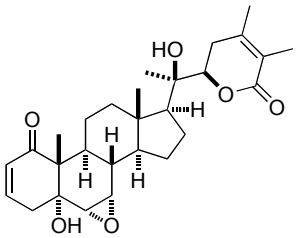


Epoxy ketone 15a: Benzyltrimethylammonium hydroxide (Trition B; 40 wt% solution in methanol, 10 µL) was added to an ice-cold solution of enone **15** (15 mg of 10:1 mixture, 29 µmol of enone) and H_2O_2 (30 wt% solution in H_2O, 0.25 mL) in THF (1 mL). The reaction mixture was stirred at 0 °C for 3 h. The reaction was then quenched with saturated aqueous NH_4Cl solution and the mixture was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash column chromatography

(EtOAc:hexane:$CHCl_3$, 8:7:1) to give epoxy ketone **15a** (8.5 mg, 17 µmol, 60%) as white foam. TLC: R_f = 0.2 (EtOAc:hexane:$CHCl_3$, 8:7:1). $[\alpha]_D$ = +65.7° (*c* = 0.25, $CHCl_3$). FTIR (neat) $\tilde{\nu}$ = 3480, 2926, 1707, 1463, 1385, 1261, 1134, 1098, 1033, 754 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 4.21 (dd, *J* = 13.4, 3.5 Hz, 1H), 4.18 (s, 1H), 3.56 (d, *J* = 4.0 Hz, 1H), 3.44 (d, *J* = 4.0 Hz, 1H), 3.20-3.18 (m, 1H), 2.86-2.81 (m, 2H), 2.61 (d, *J* =19.1 Hz, 1H), 2.41 (br. s, 1H), 2.38-2.34 (m, 1H), 2.20-2.17 (m, 1H), 2.13-2.01 (m, 3H), 1.97 (s, 3H), 1.89 (s, 3H), 1.85-1.79 (m, 1H), 1.75-1.71 (m, 1H), 1.62-1.35 (m, 7H), 1.33 (s, 3H), 1.02 (s, 3H), 0.98 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 203.1, 166.2, 149.0, 122.2, 81.1, 75.2, 69.5, 60.9, 56.3, 55.2, 54.8, 54.4, 51.4, 47.8, 44.2, 39.8, 39.1, 35.9, 34.5, 31.8, 23.1, 22.1, 21.4, 21.1, 20.8, 16.9, 13.8, 12.6. HRMS (ESI) Exact mass calculated for $C_{28}H_{39}O_7$ ($[M+H]^+$): 487.2690, found: 487.2680.

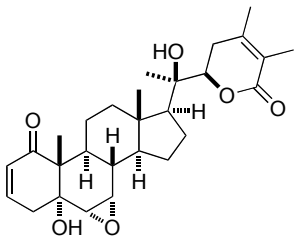


Allylic alcohol 16: Solid hydrazine monohydrochloride (10 mg, 0.15 mmol) was added to a solution of Et_3N (31µL, 0.22 mmol) in dry CH_3CN (0.7 mL) and the mixture was sonicated for 2 h at RT. Then the turbid reaction mixture was cooled to 0 °C and charged with a suspension of epoxy ketone **15a** (10 mg, 21 µmol) in CH_3CN (1.0 mL). The resulting mixture was allowed to warm to RT and stirred for 3 h at that temperature. The solvent was removed under reduced pressure and the residue was dissolved in CH_2Cl_2 and water. The mixture was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash column chromatography (EtOAc:hexane:$CHCl_3$, 8:7:1) to give allylic alcohol **16** (6.0 mg, 13 µmol, 62 %) as white solid. TLC: R_f = 0.6 (EtOAc:hexane:$CHCl_3$, 8:1:1). $[\alpha]_D$ = +98.4° (*c* = 0.25, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ = 5.96-5.93 (m, 1H), 5.75-5.72 (m, 1H), 4.22 (dd, *J* = 13.3, 3.4 Hz, 1H), 3.56 (dd, *J* = 11.3, 4.7 Hz, 1H), 3.50 (d, *J* = 11.4 Hz, 1H), 3.33 (m, 1H), 3.15 (s, 1H), 2.96 (d, *J* = 3.8 Hz, 1H), 2.41-2.33 (m, 2H), 2.30-2.22 (m, 2H), 2.14-2.01 (m, 4H), 1.95 (s, 3H), 1.89 (s, 3H), 1.87-1.79 (m, 3H), 1.64-1.23 (m, 6H), 1.32 (s, 3H), 0.96 (s, 3H), 0.78 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 166.9, 148.9, 129.8, 124.1, 122.2, 81.1, 75.3, 71.4, 70.8, 58.0, 57.5, 54.5, 52.0, 44.3, 40.4, 40.1, 35.7, 34.9, 34.7, 31.8, 23.2, 22.1, 21.3, 20.7, 20.3, 15.3, 13.8, 12.6.



Withanolide A (1): Powdered 4 Å molecular sieves (50 mg) were added to the solution of allylic alcohol **16** (6.5 mg, 14 µmol) in CH_2Cl_2 (1.0 mL) and the mixture was stirred for 5 min at RT. Pyridinium dichromate (10 mg, 26 µmol) was added and the mixture was stirred for 5 h at RT. The mixture was filtered through a pad of celite and the celite pad was washed with CH_2Cl_2 (10 mL). The combined organic layer was successively washed with 1N HCl and brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash column chromatography (EtOAc:hexane:$CHCl_3$, 8:7:1) to afford withanolide A **1** (5.2 mg, 11 µmol, 80%) as white solid. M.p.: 284.2-285 °C [lit: 282-284 °C]. TLC: R_f = 0.5 (EtOAc:hexane:$CHCl_3$, 8:1:1). $[\alpha]_D$ = +86.6° (c = 0.18, $CHCl_3$) [lit: $[\alpha]_D$ = +88° (c = 0.02, $CHCl_3$)]. FTIR (neat) $\tilde{\nu}$ = 3507, 2922, 1720, 1690, 1384, 1291, 1132, 907, 756 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 6.59 (ddd, J = 10.0, 5.0, 2.0 Hz, 1H), 5.85 (dd, J = 10.1, 2.5 Hz, 1H), 4.21 (dd, J = 13.3, 3.4 Hz, 1H), 3.32 (m, 1H), 3.12 (s, 1H, OH), 3.04 (d, J = 3.8 Hz, 1H), 2.75-2.67 (m, 2H), 2.53 (dd, J = 18.7, 5.1 Hz, 1H), 2.42-2.36 (m, 2H), 2.14-2.00 (m, 3H), 1.96 (s, 3H), 1.89 (s, 3H), 1.87-1.81 (m, 1H), 1.80-1.75 (m, 1H), 1.61-1.34 (m, 8H), 1.32 (s, 3H), 1.18 (s, 3H), 0.96 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 203.3, 166.2, 148.9, 139.8, 129.2, 122.2, 81.2, 75.2, 73.4, 57.5, 56.5, 54.6, 52.1, 51.1, 44.0, 40.5, 36.9, 35.7, 35.2, 31.8, 23.3, 21.9, 21.9, 21.2, 20.7, 14.9, 13.9, 12.6. HRMS (ESI) Exact mass calculated for $C_{28}H_{39}O_6$ ($[M+H]^+$): 471.2741, found: 471.2729.

Semisynthetic studies:



Isolation Procedure for Withanolide A (1): The dried Ashwagandha roots (1.5 kg) were placed in a large column and percolated with MeOH (3 L) several times. The MeOH extracts were concentrated from 3 L to 1 L under reduced pressure and then washed with *n*-pentane (3 x 250 mL). The MeOH extracts were then carefully concentrated under reduced pressure affording a thick brown oil, which was suspended in EtOAc (300 mL), washed with H_2O (3 x 200 mL), dried over $MgSO_4$ and concentrated to a brown oil (4.39 g). The crude material was purified by silica gel chromatography using a graduated eluent system (40% to 100% EtOAc/pentane at intervals of 10%, 1.5 column lengths of eluent/fraction) and each fraction was collected in an Erlenmeyer and concentrated separately and analyzed by HPLC and TLC. Withanolide A was found to be present in the 70% and 80% fractions. These two fractions were combined and purified by column chromatography [CH_2Cl_2:MeOH 30:1 (25 g SiO_2) and 40:1 (50 g SiO_2)] affording withanolide A (340 mg, 0.722 mmol, 0.025% from mass of dried roots) as an off-white solid. M.p.: 287.2-289 °C [lit: 282-284 °C] TLC: R_f = 0.5 (EtOAc:hexane:$CHCl_3$, 8:1:1). $[\alpha]_D$ = + 86.8 (c = 1.15, $CHCl_3$). HPLC/MS: R_t = 48.9 min, *m/z* (ES^+) 493.2 (MNa^+). UV vis: 228.5 nm. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.58 (ddd, J = 10.1, 5.0, 2.1 Hz, 1H), 5.83 (dd, J = 10.2, 2.2 Hz, 1H), 4.20 (dd, J = 13.3, 3.4 Hz, 1H), 3.31 (s, 1H), 3.16 (s, 1H, OH), 3.04 (d, J = 3.9 Hz, 1H), 2.76-2.62 (m, 2H), 2.51 (dd, J = 18.8, 5.1 Hz, 1H), 2.44-2.33 (m, 2H), 2.20-1.99 (m, 3H), 1.95 (s, 3H), 1.88 (s, 3H), 1.85-1.72 (m, 2H), 1.61-1.33 (m, 7H), 1.31 (s, 3H), 1.17 (s, 3H), 0.95 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 203.3, 166.2, 149.0, 139.8, 129.1, 122.1, 81.1, 75.2, 73.4, 57.4, 56.5, 54.5, 52.0, 51.1, 44.0, 40.5, 36.9, 35.7, 35.2, 31.8, 23.3, 21.9, 21.9, 21.2, 20.7, 14.9, 13.9, 12.6.

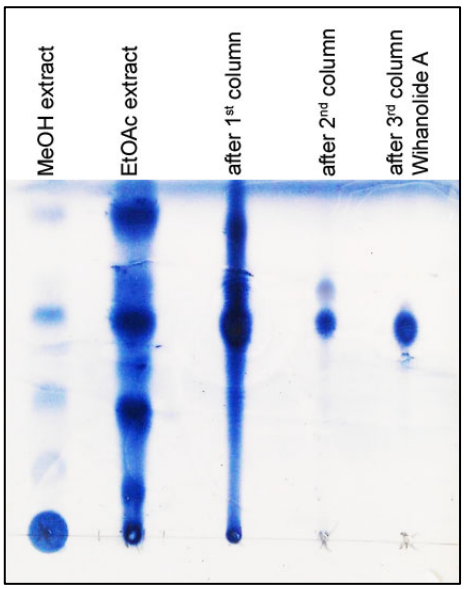
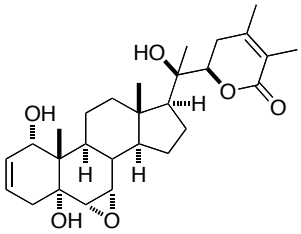
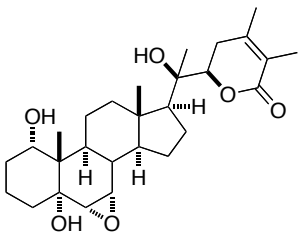


Figure 1: TLC of the MeOH extract, EtOAc extract and after 1st, 2nd and 3rd column; eluent: pure EtOAc; Cerium-ammonium-molybdate (CAM) stain.

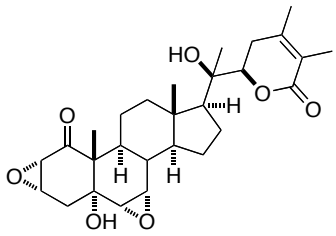


Allylic alcohol (16):[3] To a cold solution (0 °C) of withanolide A **1** (50.0 mg, 0.106 mmol, 1 eq) in $CHCl_3$/MeOH (3.0 mL, 1:1) was added $CeCl_3$ x 7 H_2O (79.2 mg, 0.212 mmol, 2 eq). After 5 min $NaBH_4$ (40.2 mg, 1.060 mmol, 10 eq) was added over a period of 3 h in 4 portions until TLC indicated full conversion. The reaction was quenched by addition of saturated NH_4Cl solution, extracted with CH_2Cl_2, dried over Na_2SO_4 and evaporated. The crude product was subjected to flash chromatography (EtOAc/pentane, 3:2) to yield allylic alcohol **16** (29.0 mg, 0.062 mmol, 58%) as a colorless solid. M.p. : 255-257 °C. TLC : R_f = 0.6 (EtOAc:hexane:$CHCl_3$, 8:1:1). $[\alpha]_D$ = +112.2° (c = 0.40, $CHCl_3$). FTIR (neat): $\tilde{\nu}$ = 3480, 2944, 1703, 1384, 1290, 1217, 1132, 1028, 910, 784 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 5.89 (d, J = 9.9 Hz, 1H), 5.72-5.66 (m, 1H), 4.18 (dd, J = 13.0, 3.7 Hz, 1H), 3.52 (s, 1H), 3.51 (s, 1H), 3.43 (s, 1H), 3.31-3.27 (m, 1H), 2.95 (d, J = 3.8 Hz, 1H), 2.40 (s, 1H), 2.35-1.95 (m, 6H), 1.92 (s, 3H), 1.85 (s, 3H), 1.84-1.72 (m, 3H), 1.63 – 1.31 (m, 7H), 1.28 (s, 3H), 0.93 (s, 3H), 0.75 (s, 3H).

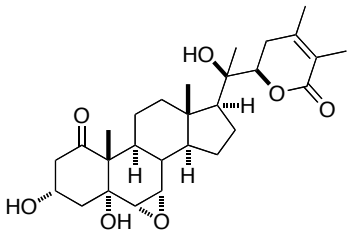


Alcohol 17: Allylic alcohol **16** (10.0 mg, 0.021 mmol, 1.0 eq) and Crabtree's catalyst (0.34 mg, 2 mol%) were dissolved in CH_2Cl_2 (0.2 mL) in a small vial. The vial was placed in an autoclave and the mixture was stirred at RT for 2 h under a H_2 atmosphere (10 bar). The solvent was removed, the residue filtered through a short pad of silica (EtOAc) and evaporated to yield alcohol **17** (10.0 mg, 0.021 mmol, quant.) as a colorless solid. M.p. = 251 °C (decomposed). TLC: R_f = 0.74 (EtOAc). $[\alpha]_D$ = +46.4° (c = 0.5, $CHCl_3$). FTIR (neat): $\tilde{\nu}$ = 3578, 3464, 3362, 2938, 1717, 1445, 1381, 1316, 1103, 1021, 949, 913, 854, 757, 687 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 4.49 (d, J = 10.7 Hz, 1H), 4.21 (dd, J = 13.3, 3.5 Hz, 1H), 3.58-3.51 (m, 1H), 3.50 (d, J = 1.2 Hz, 1H), 3.28 (dd, J = 3.9, 2.4 Hz, 1H), 2.90 (d, J = 3.9 Hz, 1H), 2.43-2.31 (m, 2H), 2.18-2.00 (m, 4H), 1.95 (s, 3H), 1.89 (s, 3H), 1.86-1.33 (m, 15H), 1.31 (s, 3H), 0.94 (s, 3H), 0.80 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 166.14, 148.89, 122.19, 81.15, 75.24, 72.37, 72.07, 58.52, 57.80, 54.48, 52.00, 44.50, 40.25, 40.22, 35.39, 35.24, 32.53, 31.79, 28.81, 23.13,

22.17, 21.25, 20.69, 19.89, 16.06, 15.86, 13.88, 12.62. UPLC/MS: R_t = 2.015 min, *m/z* (ES^+) 971.5 ($2M + Na^+$).

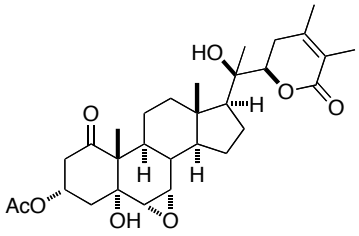


Epoxy ketone 18: To a solution of withanolide A **1** (100 mg, 0.21 mmol, 1.0 eq) and TBHP (5.5 M in decane, 100 µL, 0.55 mmol, 2.6 eq) in CH_2Cl_2 (1.3 mL) was added dropwise TBAF (1 M in THF, 425 µL, 0.43 mmol, 2 eq) and the mixture was stirred at RT for 15 h. The reaction was then diluted with water and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (EtOAc/pentane, 2:1 to pure EtOAc) to give epoxy ketone **18** (78.4 mg, 0.16 mmol, 76%) as a colorless solid. M.p. = 285 °C (decomposed). TLC: R_f = 0.37 (EtOAc). $[\alpha]_D$ = +107.1° (*c* = 0.5, $CHCl_3$). FTIR (neat): $\tilde{\nu}$ = 3476, 2967, 2924, 1981, 1706, 1517, 1468, 1382, 1318, 1221, 1187, 1141, 1107, 1069, 1009, 952, 897, 852, 815, 757. 648 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 4.17 (dd, *J* = 13.3, 3.5 Hz, 1H), 3.61-3.54 (m, 1H), 3.29 (d, *J* = 3.4 Hz, 1H), 3.26-3.18 (m, 2H), 2.94 (d, *J* = 3.8 Hz, 1H), 2.54-2.41 (m, 2H), 2.42-2.29 (m, 2H), 2.23 (dd, *J* = 15.9, 2.4 Hz, 1H), 2.14-1.97 (m, 3H), 1.94 (s, 3H), 1.87 (s, 3H), 1.84-1.21 (m, 12H), 1.10 (s, 3H), 0.92 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 203.68, 166.10, 148.97, 122.06, 81.09, 75.15, 70.75, 56.36, 54.43, 53.44, 52.77, 52.09, 51.67, 43.86, 40.23, 35.17, 34.84, 33.32, 31.77, 23.26, 21.87, 21.50, 21.21, 20.66, 13.76, 13.50, 12.56. HRMS (ESI) Exact mass calculated for $C_{28}H_{39}O_7^+$ $[M+H]^+$: 487.2690, found: 487.2689.

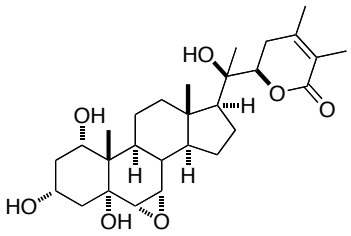


β-Hydroxy ketone 19: To a solution of $(PhSe)_2$ (96.2 mg) in EtOH (1.0 mL) was added $NaBH_4$ (23.3 mg) and acetic acid (10 µL). The stock solution was stirred for 10 min at RT and then added (0.2 mL, 0.123 mmol, 3 eq) to a solution of epoxy ketone **18** (20 mg, 0.041 mmol, 1.0 eq) in CH_2Cl_2 (0.2 mL). The resulting yellow mixture was stirred at RT for 1 h, then diluted with CH_2Cl_2 and washed with saturated brine. The organic phase was dried over $NaSO_4$, concentrated and subjected to flash column chromatography (EtOAc) to yield β-hydroxy ketone **19** (16 mg, 0.033 mmol, 80%) as

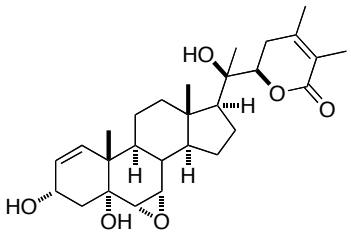
a colorless solid. M.p. = 275-276 °C. TLC: R_f = 0.37 (EtOAc). $[\alpha]_D$ = +148.2° (*c* = 0.36, $CHCl_3$). FTIR (neat): $\tilde{\nu}$ = 3478, 2924, 1707, 1388, 1142, 1008, 897, 814, 759, 649 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 4.40-4.33 (m, 1H), 4.20 (dd, *J* = 13.3, 3.5 Hz, 1H), 4.16-4.07 (m, 1H), 3.46 (d, *J* = 2.0 Hz, 1H), 3.30 (dd, *J* = 3.9, 2.2 Hz, 1H), 3.14 (dd, *J* = 8.1, 6.1 Hz, 1H), 3.10 (d, *J* = 3.9 Hz, 1H), 2.56-2.26 (m, 4H), 2.19-1.99 (m, 4H), 1.96 (s, 3H), 1.89 (s, 3H), 1.86-1.78 (m, 1H), 1.77-1.67 (m, 1H), 1.66-1.34 (m, 7H), 1.31 (s, 3H), 1.27-1.20 (m, 1H), 1.19 (s, 3H), 0.94 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 210.33, 166.13, 148.91, 122.21, 81.14, 75.21, 68.92, 57.57, 56.40, 54.53, 53.73, 51.95, 47.20, 44.32, 40.42, 38.49, 35.53, 34.83, 31.83, 23.23, 22.02, 21.65, 21.26, 20.72, 16.02, 13.98, 12.63. HRMS (ESI) Exact mass calculated for $C_{28}H_{41}O_7^+$ $[M+H]^+$: 489.2847, found: 489.2837.



Acetate 20: To a solution of β-hydroxy ketone **19** (10 mg, 0.021 mmol, 1.0 eq) in CH_2Cl_2 (0.3 mL) was added acetic anhydride (9.6 µL, 0.102 mmol, 5 eq), DMAP (2.5 mg, 0.021 mmol, 1.0 eq), and Et_3N (29 µL, 0.210 mmol, 10 eq). The colorless solution was stirred at RT for 45 min, then quenched with 0.1 M HCl and extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography (pentane/EtOAc 1:2) affording acetate **20** (8.4 mg, 0.016 mmol, 78%) as a colorless solid. M.p. = 237-238 °C. TLC: R_f = 0.51 (EtOAc). $[\alpha]_D$ = +69.5° (*c* = 0.42, $CHCl_3$). FTIR (neat): $\tilde{\nu}$ = 3518, 3470, 2956, 2932, 1703, 1380, 1282, 1144, 1026, 900, 813, 758, 651 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 5.49-5.41 (m, 1H), 4.20 (dd, *J* = 13.3, 3.5 Hz, 1H), 3.29 (dd, *J* = 4.0, 2.0 Hz, 1H), 3.16 (d, *J* = 2.0 Hz, 1H), 3.01 (d, *J* = 3.9 Hz, 1H), 2.98 (dd, *J* = 9.6, 7.3 Hz, 1H), 2.59 (dd, *J* = 16.9, 4.9 Hz, 1H), 2.51 (ddd, *J* = 15.6, 7.3, 2.1 Hz, 1H), 2.45-2.36 (m, 2H), 2.15-1.98 (m, 4H), 2.07 (s, 3H), 1.95 (s, 3H), 1.89 (s, 3H), 1.86-1.79 (m, 1H), 1.77-1.70 (m, 1H), 1.58-1.21 (m, 8H), 1.31 (s, 3H), 1.08 (s, 3H), 0.94 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 208.89, 170.79, 166.12, 148.90, 122.19, 81.13, 75.20, 73.17, 67.58, 57.50, 56.59, 54.54, 52.54, 51.94, 44.11, 43.06, 40.43, 37.93, 35.72, 34.90, 31.83, 23.31, 21.99, 21.82, 21.48, 21.23, 20.71, 15.00, 13.90, 12.62. UPLC/MS: R_t = 1.785 min, *m/z* (ES^+) 1061.5 ($2M + Na^+$).

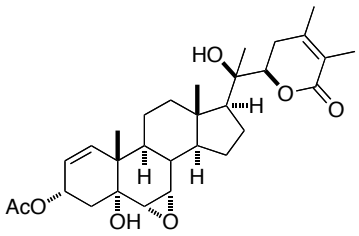


Tetraol 21: To a solution of β-hydroxy ketone **20** (30 mg, 0.061 mmol, 1.0 eq) in $CHCl_3$/MeOH (1.0 mL, 1:1) was added $NaBH_4$ (9.5 mg, 0.246 mmol, 4 eq). After stirring for 1 h at RT the reaction mixture was quenched with 0.1 M HCl solution. Saturated aqueous Rochelle's solution (40 mL) and EtOAc (40 mL) were added to the mixture and stirred for 1 h. Then the layers were separated and the aqueous was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography (CH_2Cl_2/MeOH, 25:1) to yield tetraol **21** (19.5 mg, 0.040 mmol, 65%) as a colorless solid. M.p. = 234-235 °C. TLC: R_f = 0.22 (CH_2Cl_2/MeOH, 25:1). $[\alpha]_D$ = +38.0° (c = 0.27, $CHCl_3$). FTIR (neat): $\tilde{\nu}$ = 3551, 2943, 1705, 1440, 1382, 1305, 1106, 1093, 910, 843, 746 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 4.21 (dd, J = 13.3, 3.5 Hz, 1H), 4.18-4.12 (m, 1H), 3.85 (s, 1H), 3.78 (d, J = 10.7 Hz, 1H), 3.67 (d, J = 9.0 Hz, 1H), 3.62 (ddd, J = 10.7, 4.4, 2.0 Hz, 1H), 3.33 (dd, J = 3.9, 2.3 Hz, 1H), 2.98 (d, J = 3.8 Hz, 1H), 2.44-2.33 (m, 2H), 2.31-2.23 (m, 1H), 2.18-1.99 (m, 6H), 1.95 (s, 3H), 1.89 (s, 3H), 1.87-1.74 (m, 3H), 1.66-1.28 (m, 10H), 0.95 (s, 3H), 0.77 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 166.11, 148.88, 122.20, 81.11, 75.21, 73.98, 71.90, 66.82, 58.23, 57.93, 54.46, 51.93, 44.46, 40.69, 40.10, 38.44, 36.89, 35.15, 31.77, 23.13, 22.16, 21.22, 20.70, 19.91, 16.40, 13.88, 12.62. UPLC/MS: R_t = 1.612 min, m/z (ES^+) 981.6 ($2M + H^+$).

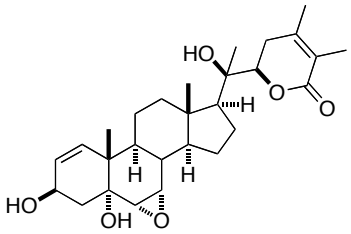


Allylic alcohol 22: A solution of epoxy ketone **18** (100 mg, 0.21 mmol, 1.0 eq) in MeOH/CH_2Cl_2 (4.0 mL, 1:1) was cooled to 0 °C, and hydrazine hydrate (100 µl, 2.1 mmol, 10.0 eq) was added dropwise. After stirring for 15 min, AcOH (50 µL) was added dropwise and the reaction mixture was stirred for additional 15 min at 0 °C. Then the reaction mixture was allowed to come to RT and stirred for 3 h. The slightly yellow solution was diluted with CH_2Cl_2 and quenched with saturated aqueous $NaHCO_3$. The mixture was extracted with CH_2Cl_2, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to flash column chromatography (EtOAc/pentane, 1:1 to 2:1) to give allylic alcohol **22** (59 mg, 0.13 mmol, 61%) as a colorless solid. M.p. =

248-249 °C. TLC: R_f = 0.51 (EtOAc). $[\alpha]_D$ = -7.0° (c = 0.5, $CHCl_3$). FTIR (neat): $\tilde{\nu}$ = 3495, 2939, 1700, 1384, 1318, 1092, 1029, 895, 748, 644 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 5.87-5.80 (m, 2H), 4.20 (dd, J = 13.3, 3.5 Hz, 1H), 4.16-4.09 (m, 1H), 3.35 (d, J = 11.2 Hz, 1H), 3.33-3.28 (m, 1H), 3.22 (d, J = 1.6 Hz, 1H), 3.09 (d, J = 3.8 Hz, 1H), 2.45-2.25 (m, 3H), 2.21-2.00 (m, 4H), 1.95 (s, 3H), 1.89 (s, 3H), 1.87-1.74 (m, 2H), 1.68-1.54 (m, 2H), 1.52-1.34 (m, 5H), 1.31 (s, 3H), 1.29-1.20 (m, 1H), 0.95 (s, 3H), 0.92 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 166.13, 148.91, 132.74, 128.48, 122.21, 81.13, 75.21, 70.14, 64.81, 57.93, 57.57, 54.45, 51.80, 44.35, 40.85, 40.23, 38.61, 36.35, 35.50, 31.85, 23.16, 22.21, 21.27, 21.16, 20.72, 13.87, 12.62. HRMS (ESI) Exact mass calculated for $C_{28}H_{41}O_6^+$ $[M+H]^+$: 473.2898, found: 473.2890. For X-ray analysis see section **IV**.

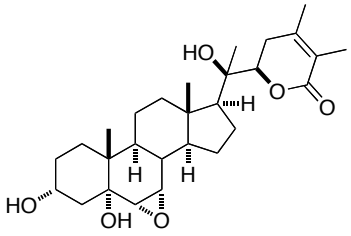


Acetate 23: To a solution of allylic alcohol **22** (6 mg, 0.013 mmol, 1.0 eq) in CH_2Cl_2 (0.1 mL) was added acetic anhydride (4.8 µL, 0.052 mmol, 4 eq), DMAP (0.16 mg, 0.001 mmol, 0.1 eq), and Et_3N (5.4 µL, 0.039 mmol, 3 eq). The colorless solution was stirred at RT for 45 min, then quenched with 0.1 M HCl and extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography (pentane/EtOAc, 1:1) affording acetate **23** (5.7 mg, 0.011 mmol, 87%) as a colorless solid. M.p. = 245-246 °C. TLC: R_f = 0.60 (EtOAc). $[\alpha]_D$ = -4.3° (c = 0.29, $CHCl_3$). FTIR (neat): $\tilde{\nu}$ = 3502, 2922, 2324, 1718, 1462, 1374, 1310, 1248, 1139, 1100, 1015, 970, 891, 813, 754 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 6.07 (dd, J = 10.2, 1.7 Hz, 1H), 5.75-5.69 (m, 1H), 5.45-5.39 (m, 1H), 4.20 (dd, J = 13.4, 3.5 Hz, 1H), 3.31 (dd, J = 3.8, 2.4 Hz, 1H), 3.08 (d, J = 1.6 Hz, 1H), 3.05 (d, J = 3.8 Hz, 1H), 2.47-2.30 (m, 3H), 2.10 (s, 3H), 2.19-2.00 (m, 4H), 1.95 (s, 3H), 1.89 (s, 3H), 1.87-1.75 (m, 2H), 1.68-1.51 (m, 2H), 1.42 (m, 5H), 1.32 (s, 3H), 1.26-1.19 (m, 1H), 0.96 (s, 3H), 0.92 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 170.99, 166.13, 148.87, 136.29, 124.39, 122.22, 81.14, 75.22, 67.89, 65.88, 57.68, 57.26, 54.38, 51.81, 44.37, 40.77, 40.32, 37.15, 36.15, 35.40, 31.91, 23.16, 22.19, 21.67, 21.33, 21.13, 20.71, 20.61, 13.83, 12.62. HRMS (ESI) Exact mass calculated for $C_{30}H_{43}O_7^+$ $[M+H]^+$: 515.3003, found: 515.2987.



Allylic alcohol 24: A stirred mixture of allylic alcohol **22** (10.0 mg, 0.021 mmol, 1.0 eq), 4-nitrobenzoic acid (14.4 mg, 0.085 mmol, 4.0 eq) and PPh_3 (21.1 mg, 0.080 mmol, 3.8 eq) in CH_2Cl_2 (0.2 mL) was cooled to 0 °C. To the cold solution was added DEAD (17.1 mg, 0.095 mmol, 4.5 eq), and the mixture was stirred at RT overnight. The solvent was removed under reduced pressure and the residue subjected to flash column chromatography (pentane/EtOAc, 1:1) to yield the 4-nitrobenzoate (8.7 mg, 0.014 mmol, 66%) as a yellowish solid. TLC: R_f = 0.79 (EtOAc, 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.33-8.17 (m, 5H), 6.03 (dd, *J* = 10.3, 1.8 Hz, 1H), 5.98-5.91 (m, 1H), 5.77 – 5.70 (m, 1H), 4.21 (dd, *J* = 13.3, 3.5 Hz, 1H), 3.33 (dd, *J* = 3.8, 2.5 Hz, 1H), 3.17 (d, *J* = 1.5 Hz, 1H), 3.08 (d, *J* = 3.8 Hz, 1H), 2.57-2.46 (m, 1H), 2.46-2.31 (m, 2H), 2.28-1.98 (m, 5H), 1.96 (s, 3H), 1.89 (s, 3H), 1.87-1.77 (m, 2H), 1.52-1.34 (m, 6H), 1.32 (s, 3H), 1.12 (s, 3H), 0.97 (s, 3H).

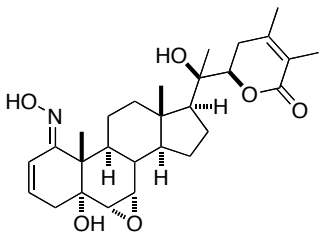
To a solution of 4-nitrobenzoate (8.7 mg, 0.014 mmol, 1 eq) in THF/CH_2Cl_2 (0.4 mL, 1:1) was added 5% aqueous NaOH solution (0.2 mL) and tetrabutyl-ammonium hydroxide solution (7 µL, 1 M in methanol) and the mixture was stirred at RT for 2 h. The mixture was then diluted with CH_2Cl_2 and washed with 1 M HCl and water. The organic phase was dried over Na_2SO_4, evaporated and the residue subjected to flash column chromatography (EtOAc) to yield allylic alcohol **24** (5.0 mg, 0.011 mmol, 76%) as a colorless solid. M.p. = 240 °C (decomposed). TLC: R_f = 0.27 (pentane/EtOAc, 1:1). $[\alpha]_D$ = +39.1° (*c* = 0.25, $CHCl_3$). FTIR (neat): $\tilde{\nu}$ = 3475, 2925, 1696, 1453, 1384, 1139, 1098, 1061, 1022, 923, 817, 763, 610 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.85 (dd, *J* = 10.3, 1.8 Hz, 1H), 5.67 (ddd, *J* = 10.1, 2.8, 1.1 Hz, 1H), 4.75-4.63 (m, 1H), 4.20 (dd, *J* = 13.4, 3.5 Hz, 1H), 3.30 (dd, *J* = 3.8, 2.5 Hz, 1H), 3.10 (d, *J* = 1.6 Hz, 1H), 3.06 (d, *J* = 3.9 Hz, 1H), 2.46-2.24 (m, 3H), 2.19-1.98 (m, 4H), 1.95 (s, 3H), 1.89 (s, 3H), 1.86-1.72 (m, 3H), 1.68-1.52 (m, 3H), 1.50-1.33 (m, 5H), 1.31 (s, 3H), 1.05 (s, 3H), 0.95 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 166.15, 148.91, 133.69, 128.84, 122.21, 81.15, 75.22, 71.52, 66.75, 57.92, 57.73, 54.43, 51.79, 44.42, 41.01, 40.28, 39.87, 36.02, 35.34, 31.88, 23.13, 22.71, 22.19, 21.29, 20.75, 20.71, 13.87, 12.62. HRMS (ESI) Exact mass calculated for $C_{28}H_{41}O_6^+$ $[M+H]^+$: 473.2898, found: 473.2885.



Alcohol 25: Allylic alcohol **22** (5.0 mg, 0.011 mmol, 1.0 eq) and Crabtree's catalyst (0.17 mg, 2 mol%) were dissolved in CH_2Cl_2 (0.1 mL) in a small vial. The vial was placed in an autoclave and the mixture was stirred at RT for 2.5 h under a H_2 atmosphere (10 bar). The solvent was removed, the residue filtered through a short pad of silica (EtOAc) and evaporated to yield alcohol **25** (5.0 mg, 0.011 mmol, quant.) as a colorless solid. M.p. = 205-206°C. TLC: R_f = 0.52 (EtOAc). $[\alpha]_D$ = +19.1° (c = 0.36, $CHCl_3$). FTIR (neat): $\tilde{\nu}$ = 3475, 2922, 1705, 1382, 1142, 1102, 1024, 895, 855, 811, 759, 652 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 4.53 (d, J = 9.7 Hz, 1H), 4.21 (d, J = 9.8 Hz, 1H), 4.04-3.93 (m, 1H), 3.35 (s, 1H), 3.31-3.24 (m, 1H), 2.95 (d, J = 3.8 Hz, 1H), 2.46-2.31 (m, 2H), 2.17 (s, 1H), 2.14-1.97 (m, 3H), 1.95 (s, 3H), 1.92-1.90 (m, 1H), 1.89 (s, 3H), 1.85-1.65 (m, 5H), 1.50 (t, J = 9.5 Hz, 1H), 1.44-1.33 (m, 3H), 1.30 (s, 3H), 1.28-1.04 (m, 5H), 0.92 (s, 3H), 0.81 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 166.15, 148.94, 122.19, 81.10, 75.23, 71.60, 67.11, 58.07, 57.92, 54.48, 51.83, 44.31, 40.25, 38.44, 38.23, 37.94, 35.15, 31.78, 29.25, 24.29, 23.08, 22.22, 21.16, 20.72, 20.18, 14.56, 13.87, 12.62. HRMS (ESI) Exact mass calculated for $C_{28}H_{43}O_6^+$ $[M+H]^+$: 475.3054, found: 475.3042.

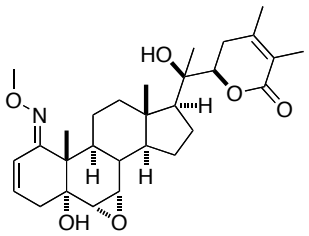
General Procedure A for oxime ethers 26-30

To a solution of withanolide A (1.0 eq) in pyridine was added the hydroxylamine hydrochloride (2.0 eq) and the mixture was heated at 70 °C for the indicated time. The solvent was removed under high vacuum, and the residue dissolved in CH_2Cl_2. Saturated aqueous NH_4Cl solution was added and the aqueous phase was extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4, evaporated, and the residue subjected to flash column chromatography to yield oxime ethers **26-30** as colorless solids.

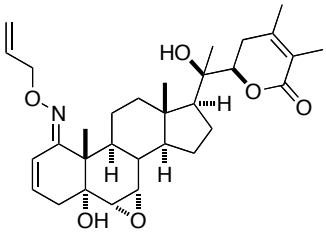


Hydroxylamine 26: Following General Procedure A: Withanolide A **1** (20 mg, 0.04 mmol, 1.0 eq) in pyridine (0.50 mL), hydroxylamine hydrochloride (5.9 mg, 0.08 mmol, 2.0 eq), 70 °C for 20 h. Additional hydroxylamine hydrochloride (3.0 mg, 0.04 mmol, 1.0 eq), 70 °C

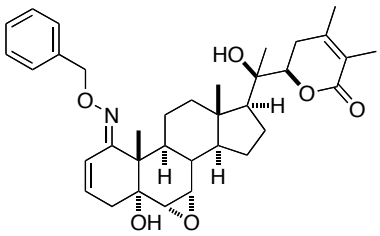
for 5 h, flash column chromatography (pentane/EtOAc, 1:1), 58% yield. M.p. = 180-181 °C. TLC: R_f = 0.55 (EtOAc). $[\alpha]_D$ = +175.0° (c = 0.69, $CHCl_3$). FTIR (neat): $\tilde{\nu}$ = 3417, 2922, 2360, 1691, 1382, 1290, 1023, 907, 815, 750, 645 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.19 (s, 1H), 6.75 (ddd, *J* = 10.3, 2.9, 1.2 Hz, 1H), 6.02 (ddd, *J* = 10.3, 4.7, 2.5 Hz, 1H), 4.21 (dd, *J* = 13.3, 3.5 Hz, 1H), 3.30 (dd, *J* = 4.0, 2.1 Hz, 1H), 3.01 (d, *J* = 3.9 Hz, 1H), 2.98 (d, *J* = 1.5 Hz, 1H), 2.73-2.66 (m, 1H), 2.53-2.33 (m, 4H), 2.17-2.08 (m, 1H), 2.03-1.97 (m, 1H), 1.95 (s, 3H), 1.88 (s, 3H), 1.87-1.77 (m, 2H), 1.64-1.32 (m, 8H), 1.30 (s, 3H), 1.08 (s, 3H), 0.96 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 166.21, 159.55, 149.01, 131.00, 122.12, 117.81, 81.14, 75.24, 71.42, 57.43, 56.82, 54.61, 52.39, 45.37, 44.02, 40.52, 37.42, 36.70, 35.43, 31.79, 23.33, 22.85, 22.07, 21.15, 20.72, 15.98, 14.07, 12.61. HRMS (ESI) Exact mass calculated for $C_{28}H_{40}NO_6^+$ $[M+H]^+$: 486.2850, found: 486.2839.



Methyloxime 27: Following General Procedure A: Withanolide A **1** (10 mg, 0.02 mmol, 1.0 eq) in pyridine (0.25 mL), methoxylamine hydrochloride (3.6 mg, 0.04 mmol, 2.0 eq), 70 °C for 3 h. Additional methoxylamine hydrochloride (1.8 mg, 0.02 mmol, 1.0 eq), 70 °C for 2 d, flash column chromatography (pentane/EtOAc, 1:1), 58% yield (as an inseparable diastereomeric mixture). M.p. = 157-158 °C. TLC: R_f = 0.81 (EtOAc). $[\alpha]_D$ = +217.1° (*c* = 0.18, $CHCl_3$). FTIR (neat): $\tilde{\nu}$ = 3500, 2937, 2325, 1702, 1463, 1381, 1289, 1187, 1130, 1046, 896, 829, 733, 683, 614 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 6.67-6.60 (m, 1H), 6.01-5.94 (m, 1H), 4.21 (dd, *J* = 13.3, 3.5 Hz, 1H), 3.87 and 3.84 (s, 3H), 3.30 (dd, *J* = 4.0, 2.1 Hz, 1H), 3.00 (d, *J* = 3.9 Hz, 1H), 2.95 (d, *J* = 1.5 Hz, 1H), 2.93-2.85 (m, 1H), 2.51-2.30 (m, 4H), 2.17-1.98 (m, 3H), 1.95 (s, 3H), 1.89 (s, 3H), 1.87-1.77 (m, 1H), 1.67-1.34 (m, 8H), 1.32 (s, 3H), 1.12 and 1.07 (s, 3H, diastereomers), 0.97 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 166.19, 157.97, 148.89, 130.78, 122.19, 118.30, 81.17, 75.25, 71.31, 61.81, 57.46, 56.86, 54.60, 52.36, 45.19, 44.02, 40.63, 37.41, 36.74, 35.41, 31.87, 23.38, 22.74, 22.02, 21.24, 20.71, 16.10, 14.00, 12.62. HRMS (ESI) Exact mass calculated for $C_{29}H_{42}NO_6^+$ $[M+H]^+$: 500.3007, found: 500.2996.

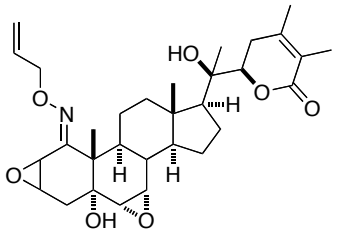


Allyloxime 28: Following General Procedure A: Withanolide A **1** (50 mg, 0.11 mmol, 1.0 eq) in pyridine (1.25 mL), *O*-allylhydroxylamine hydrochloride (23.3 mg, 0.21 mmol, 2.0 eq), 70 °C for 14 h. Additional *O*-allylhydroxylamine hydrochloride (11.7 mg, 0.11 mmol, 1.0 eq), 70 °C for 14 h, flash column chromatography (pentane/EtOAc, 1:1), 72% yield. M.p. = 117-118 °C. TLC: R_f = 0.75 (EtOAc). $[\alpha]_D$ = +218.3° (c = 0.24, $CHCl_3$). FTIR (neat): $\tilde{\nu}$ = 3506, 2925, 1702, 1382, 1289, 1131, 1097, 1025, 906, 826, 664 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 6.73-6.62 (m, 1H), 6.03-5.90 (m, 2H), 5.27-5.20 (m, 1H), 5.17-5.11 (m, 1H), 4.61-4.45 (m, 2H), 4.20 (dd, J = 13.3, 3.5 Hz, 1H), 3.29 (dd, J = 4.0, 2.1 Hz, 1H), 2.99 (d, J = 3.9 Hz, 1H), 2.94 (s, 1H), 2.89-2.79 (m, 1H), 2.51-2.28 (m, 4H), 2.18-1.97 (m, 4H), 1.94 (s, 3H), 1.88 (s, 3H), 1.88-1.74 (m, 2H), 1.60-1.38 (m, 5H), 1.31 (s, 3H), 1.29-1.23 (m, 1H), 1.06 (s, 3H), 0.96 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 166.16, 158.08, 148.88, 134.84, 130.73, 122.13, 118.43, 117.22, 81.15, 75.20, 74.86, 71.29, 57.43, 56.82, 54.55, 52.35, 45.27, 44.01, 40.57, 37.37, 36.74, 35.38, 31.83, 23.34, 22.74, 21.99, 21.21, 20.68, 16.07, 13.97, 12.59. HRMS (ESI) Exact mass calculated for $C_{31}H_{44}NO_6^+$ $[M+H]^+$: 526.3163, found: 526.3148.



Benzyloxime 29: Following General Procedure A: Withanolide A **1** (10 mg, 0.02 mmol, 1.0 eq) in pyridine (0.25 mL), *O*-benzylhydroxylamine hydrochloride (6.8 mg, 0.04 mmol, 2.0 eq), 70 °C for 14 h. Additional *O*-benzylhydroxylamine hydrochloride (3.4 mg, 0.02 mmol, 1.0 eq), 70 °C for 14 h, flash column chromatography (pentane/EtOAc, 2:1)), 63% yield (as an inseparable diastereomeric mixture). M.p. = 106-107 °C. TLC: R_f = 0.79 (EtOAc). $[\alpha]_D$ = +174.0° (c = 0.37, $CHCl_3$). FTIR (neat): $\tilde{\nu}$ = 3485, 2922, 2361, 1703, 1455, 1381, 1289, 1212, 1131, 1095, 1019, 906, 815, 753, 698, 613 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.39-7.27 (m, 5H), 6.75-6.68 (m, 1H), 6.01-5.93 (m, 1H), 5.16-5.01 (m, 2H), 4.26-4.17 (m, 1H), 3.32-3.27 (m, 1H), 3.00 (d, J = 3.9 Hz, 1H), 2.95 (d, J = 1.4 Hz, 1H), 2.84-2.77 (m, 1H), 2.52-2.29 (m, 4H), 2.17-1.98 (m, 3H), 1.96 (s, 3H), 1.90 (s, 3H), 1.85-1.74 (m, 2H), 1.63-1.36 (m, 6H), 1.33 (s, 3H), 1.32-1.29 (m, 1H), 1.08 and 1.05 (s, 3H, diastereomers), 0.96 and

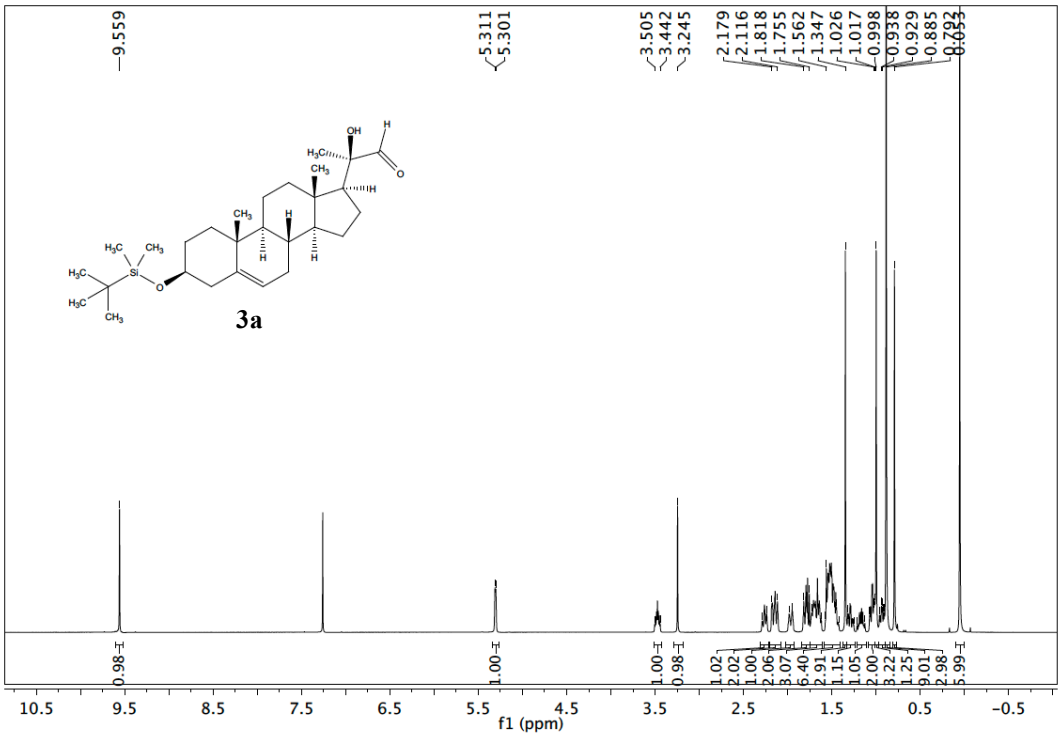
0.95 (s, 3H, diastereomers). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 166.18, 158.33, 148.90, 138.50, 130.76, 128.33, 128.30, 127.65, 122.20, 118.64, 81.18, 75.99, 75.26, 71.35, 57.46, 56.86, 54.60, 52.40, 45.33, 44.06, 40.63, 37.41, 36.77, 35.43, 31.88, 23.36, 22.77, 22.04, 21.25, 20.72, 16.10, 14.02, 12.64. HRMS (ESI) Exact mass calculated for $C_{35}H_{46}NO_6^+$ $[M+H]^+$: 576.3320, found: 576.3323.

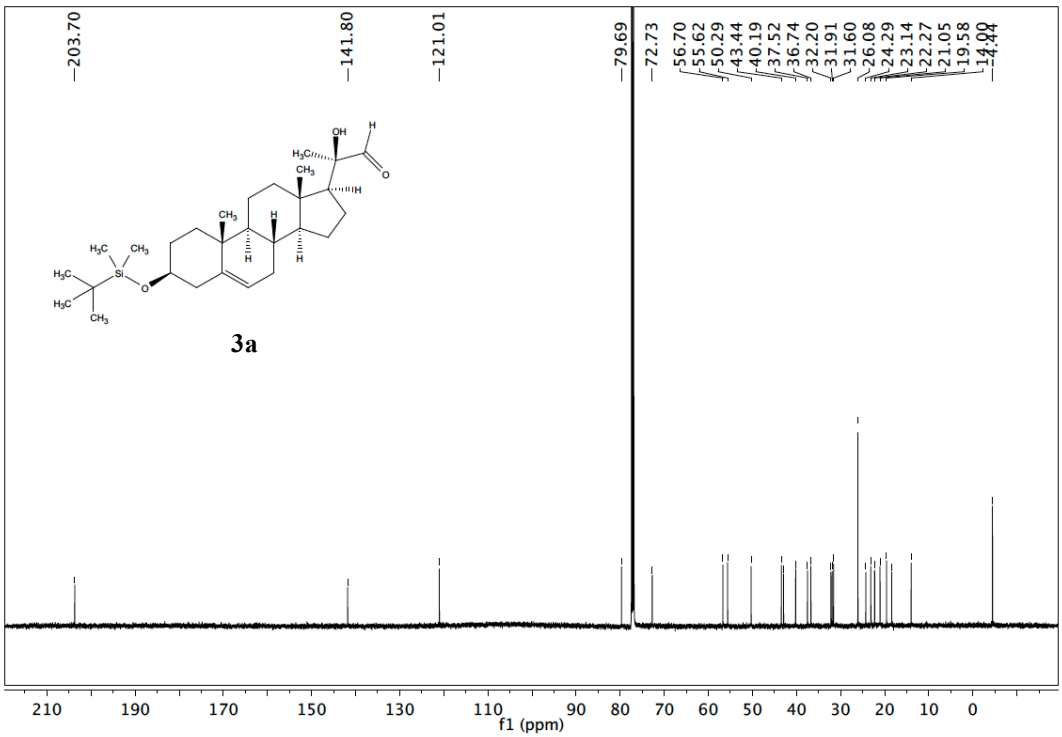


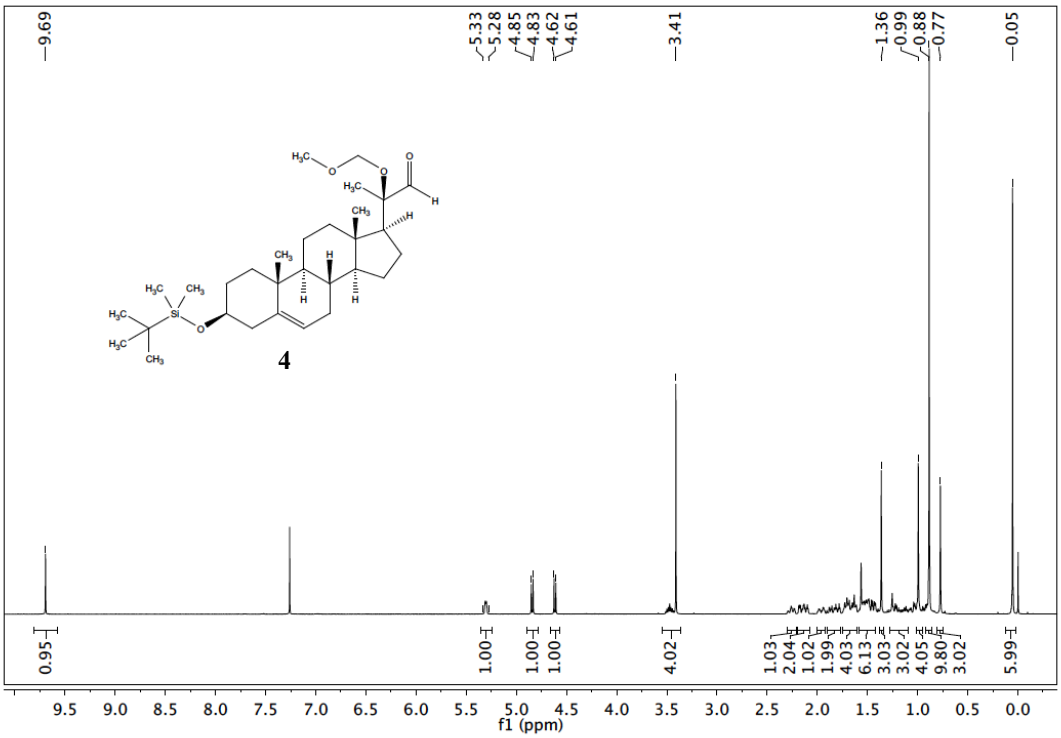
Epoxy allyloxime 30: To a solution of epoxy ketone **18** (5 mg, 0.01 mmol, 1.0 eq) in pyridine (0.15 mL) was added O-allylhydroxylamine hydrochloride (2.3 mg, 0.02 mmol, 2.0 eq) and the mixture was heated at 70 °C for 7 h. The solvent was removed under high vacuum, and the residue dissolved in CH_2Cl_2. Saturated NH_4Cl solution was added and the aqueous phase was extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4, evaporated, and the residue subjected to flash column chromatography (pentane:EtOAc, 4:6) to yield the allylhydroxylamie **30** (2.7 mg, 0.005 mmol, 49%) as a colorless solid. M.p. = 109-110°C. TLC: R_f = 0.54 (EtOAc). $[\alpha]_D$ = +126.7° (c = 0.16, $CHCl_3$). FTIR (neat): $\tilde{\nu}$ = 3495, 2922, 2362, 1704, 1462, 1383, 1315, 1261, 1096, 1006, 919, 805, 754, 665 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.08-5.89 (m, 1H), 5.33-5.23 (m, 1H), 5.22-5.14 (m, 1H), 4.67-4.56 (m, 2H), 4.20 (dd, J = 13.3, 3.7 Hz, 1H), 3.93 (d, J = 3.7 Hz, 1H), 3.51 (t, J = 3.2 Hz, 1H), 3.24-3.10 (m, 1H), 2.94 (s, 1H), 2.90 (d, J = 3.8 Hz, 1H), 2.63 (d, J = 11.6 Hz, 1H), 2.47-2.30 (m, 2H), 2.22-2.00 (m, 5H), 1.95 (s, 3H), 1.89 (s, 3H), 1.76-1.63 (m, 3H), 1.46 (d, J = 19.6 Hz, 6H), 1.32 (s, 3H), 1.04 (s, 3H), 0.96 and 0.92 (s, 3H, diastereomers). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 166.05, 155.33, 148.77, 134.37, 122.04, 117.63, 81.03, 75.29 and 75.11 (diastereomers), 70.35, 56.28, 55.69, 54.36, 52.17, 51.86, 46.97, 46.03, 43.87 and 43.79 (diastereomers), 40.22 and 40.07 (diastereomers), 35.74, 35.70, 35.30, 33.85, 31.74, 29.70, 23.21, 21.96 and 21.87 (diastereomers), 21.17, 20.58, 15.40, 13.75, 12.48. HRMS (ESI) Exact mass calculated for $C_{31}H_{44}NO_7^+$ $[M+H]^+$: 542.3112, found: 542.3099.

III. ^{1}H and ^{13}C NMR spectra

Towards the Total Synthesis (**Scheme 1**)



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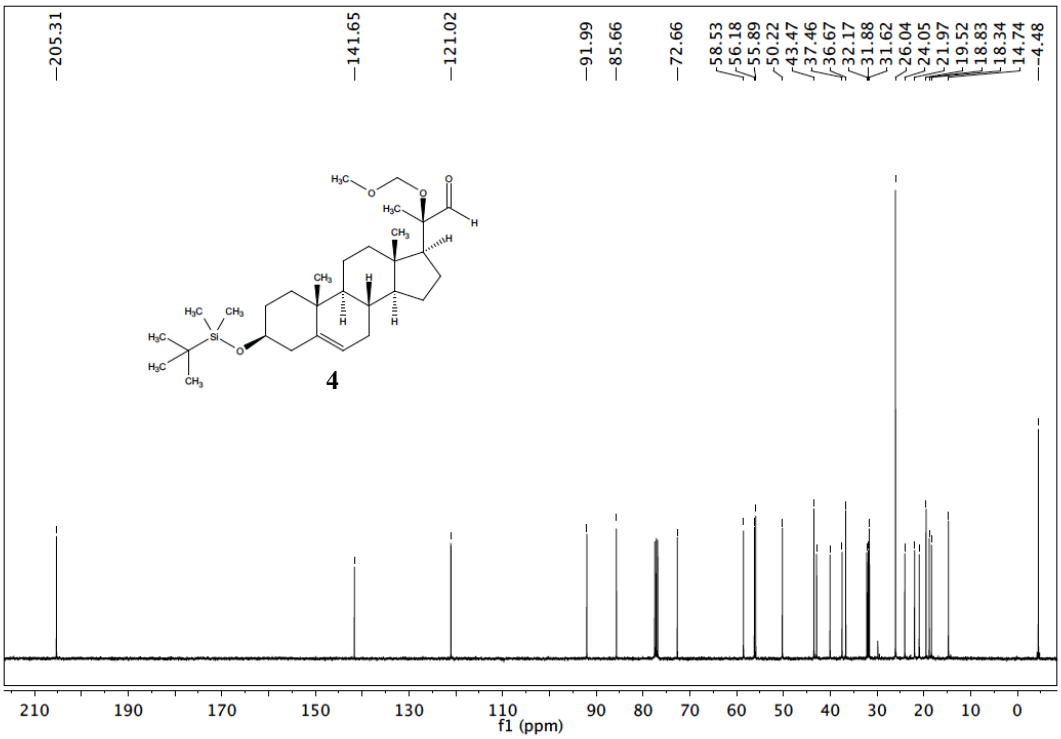
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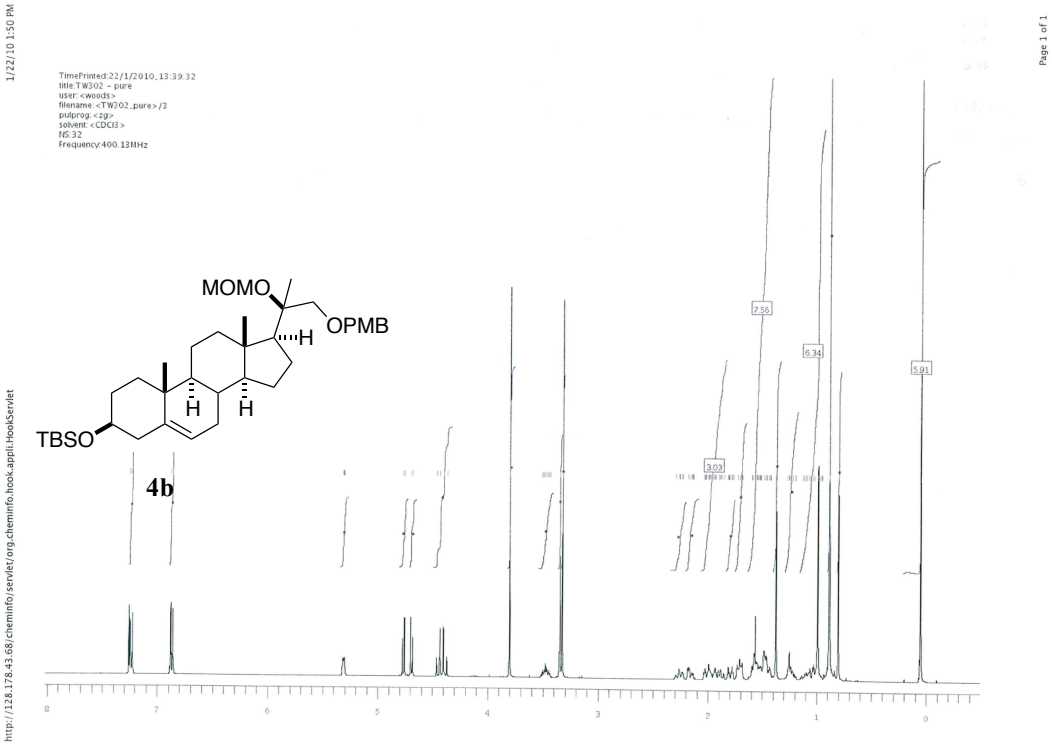
f1 (ppm)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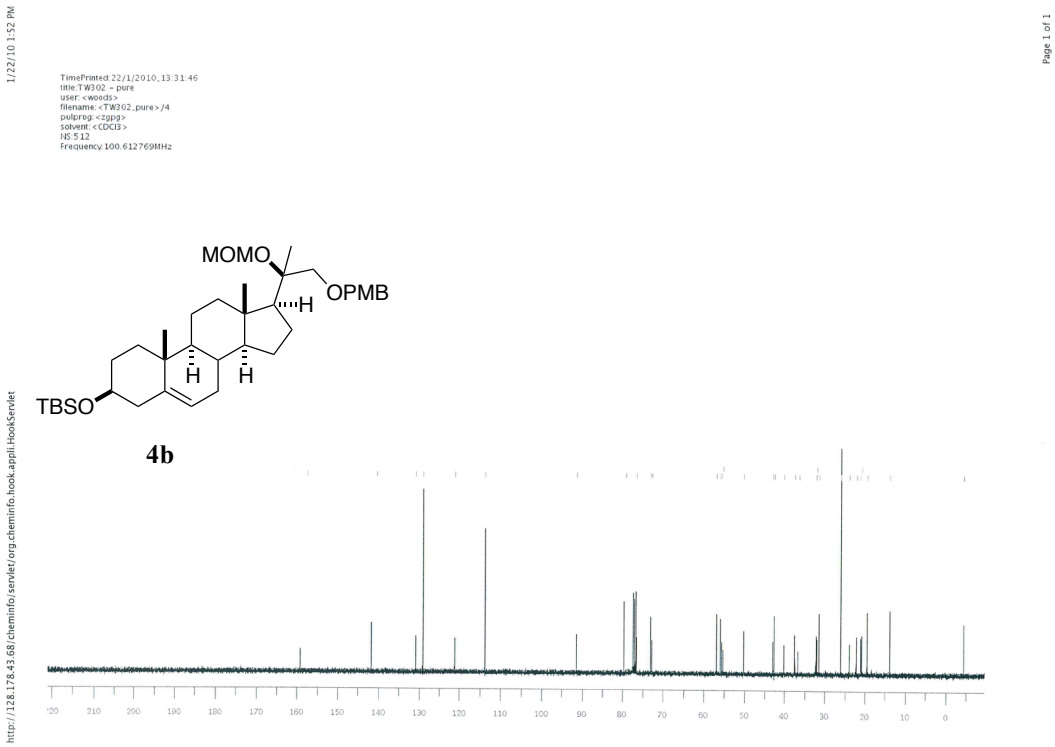
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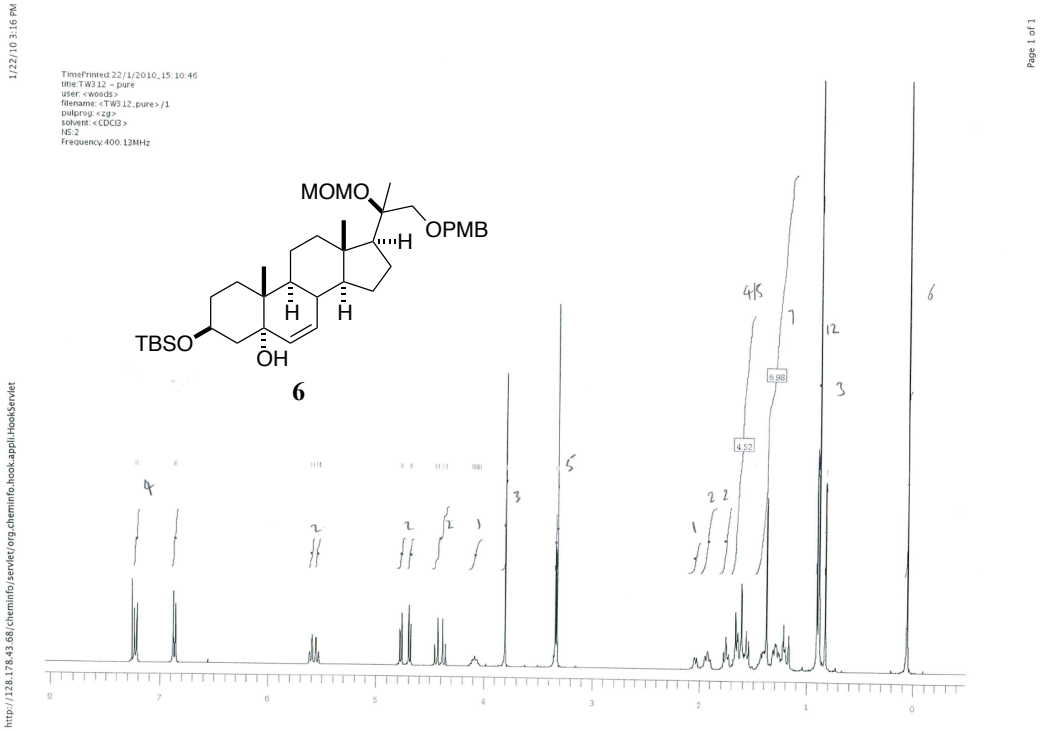
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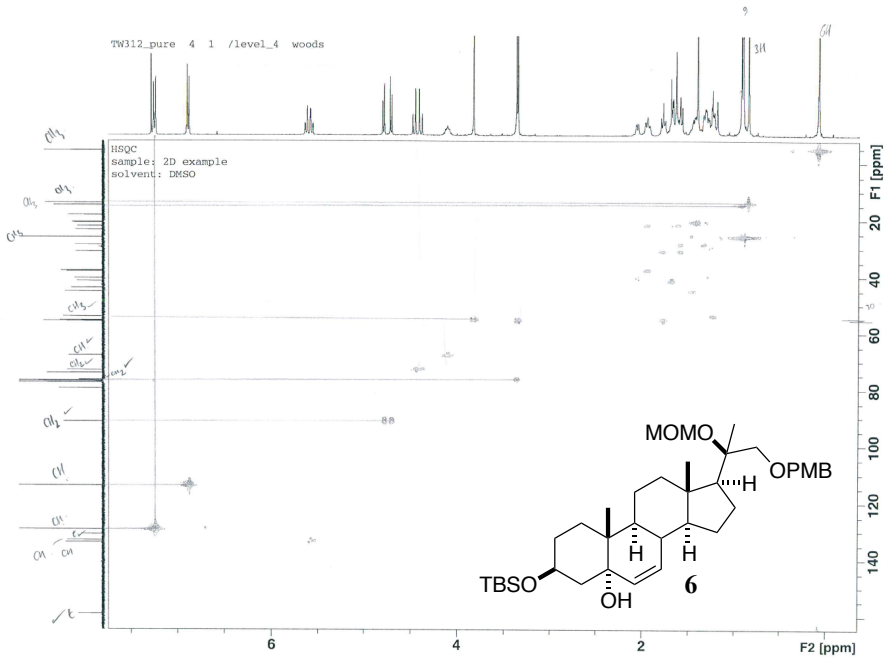
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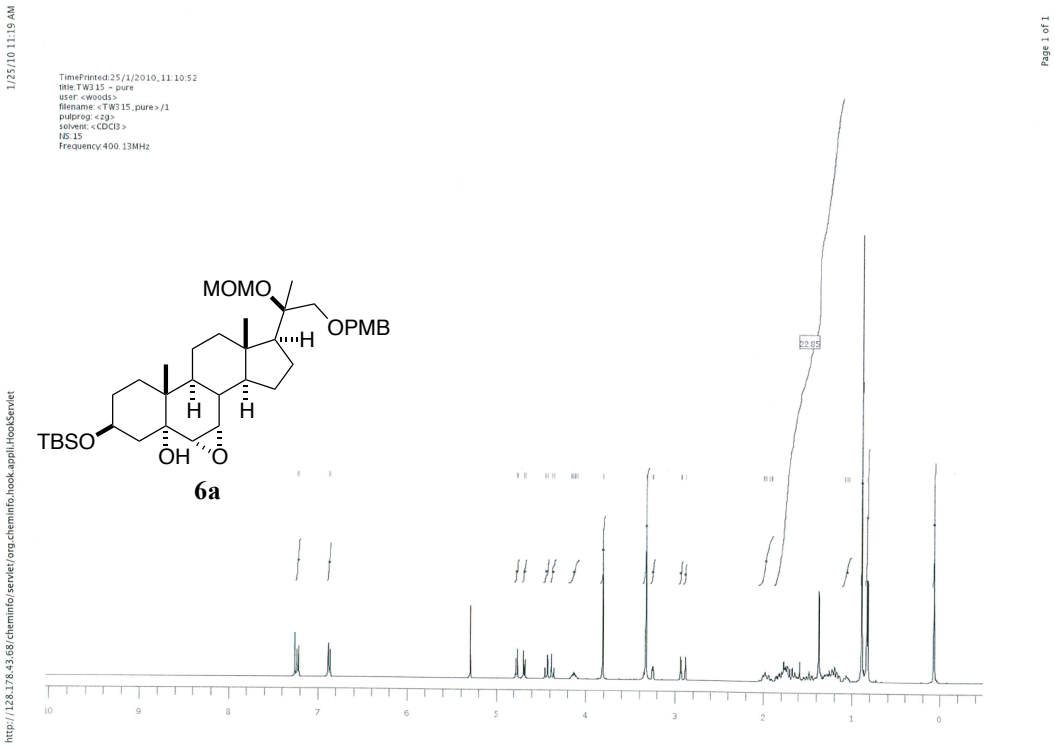
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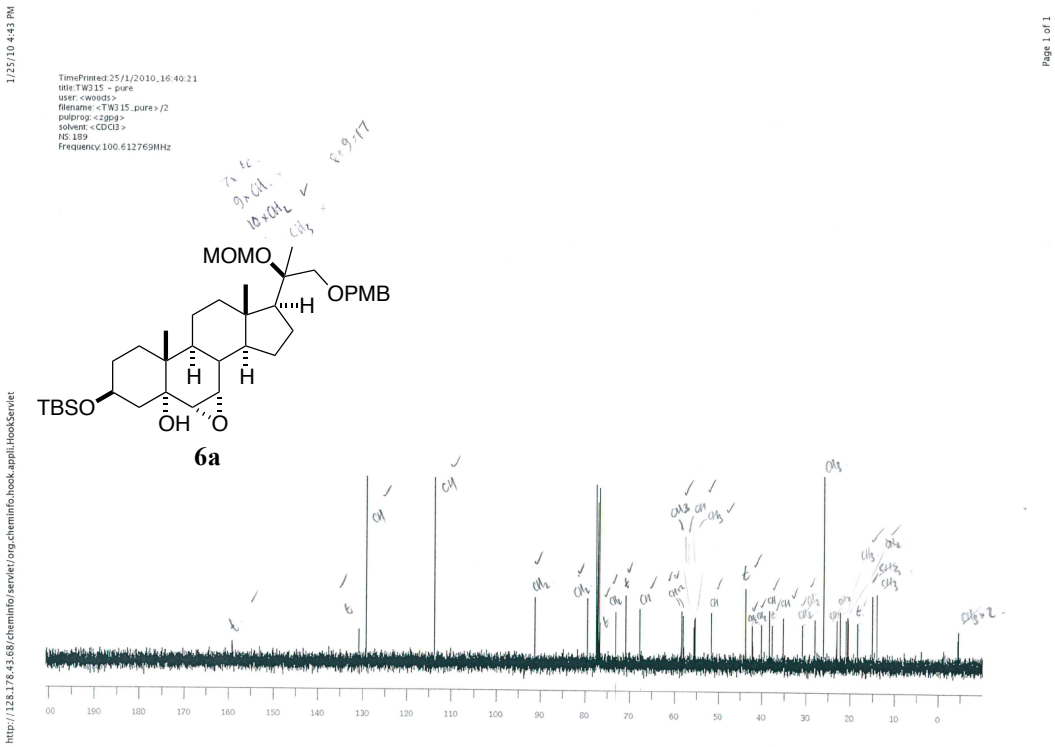
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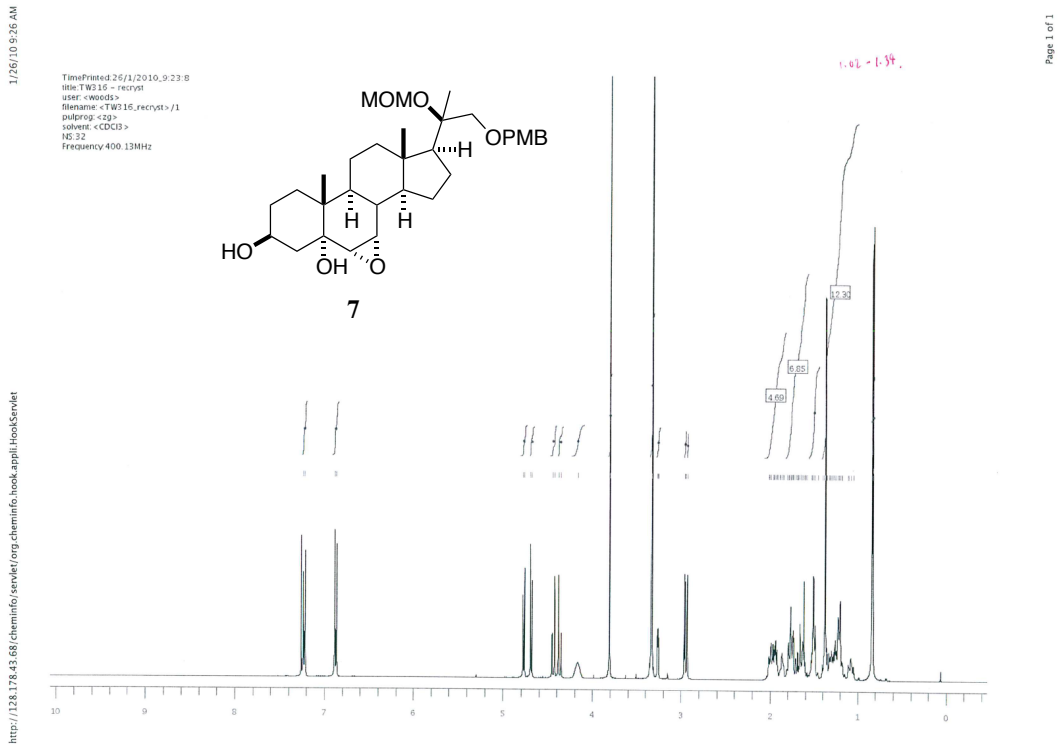

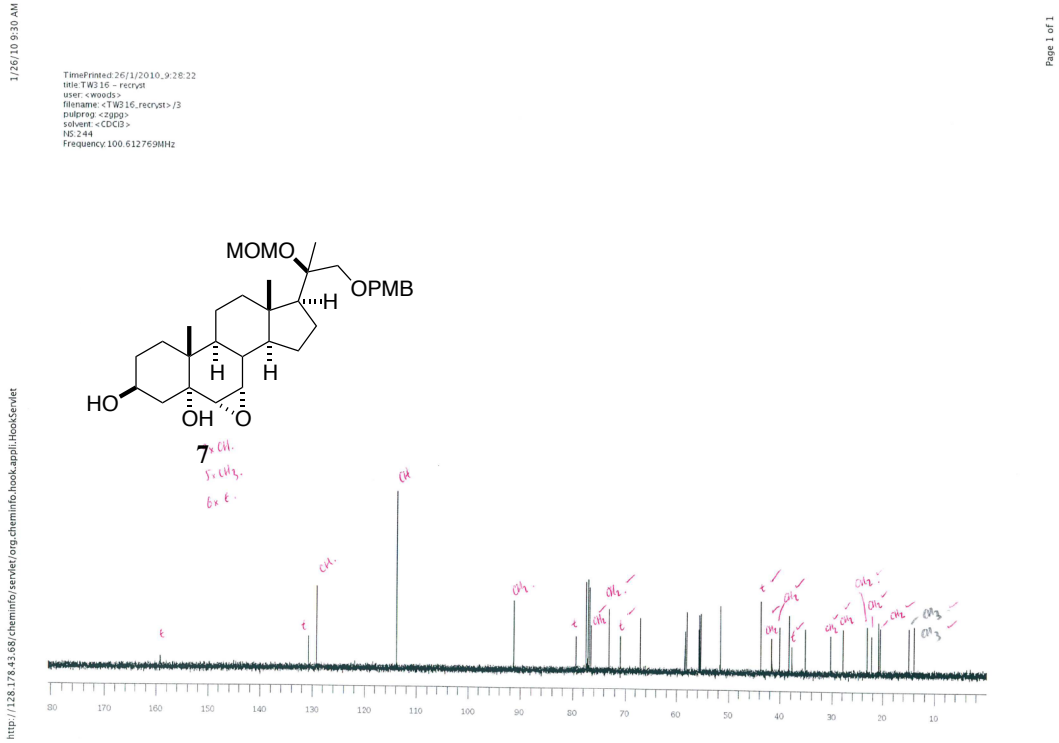

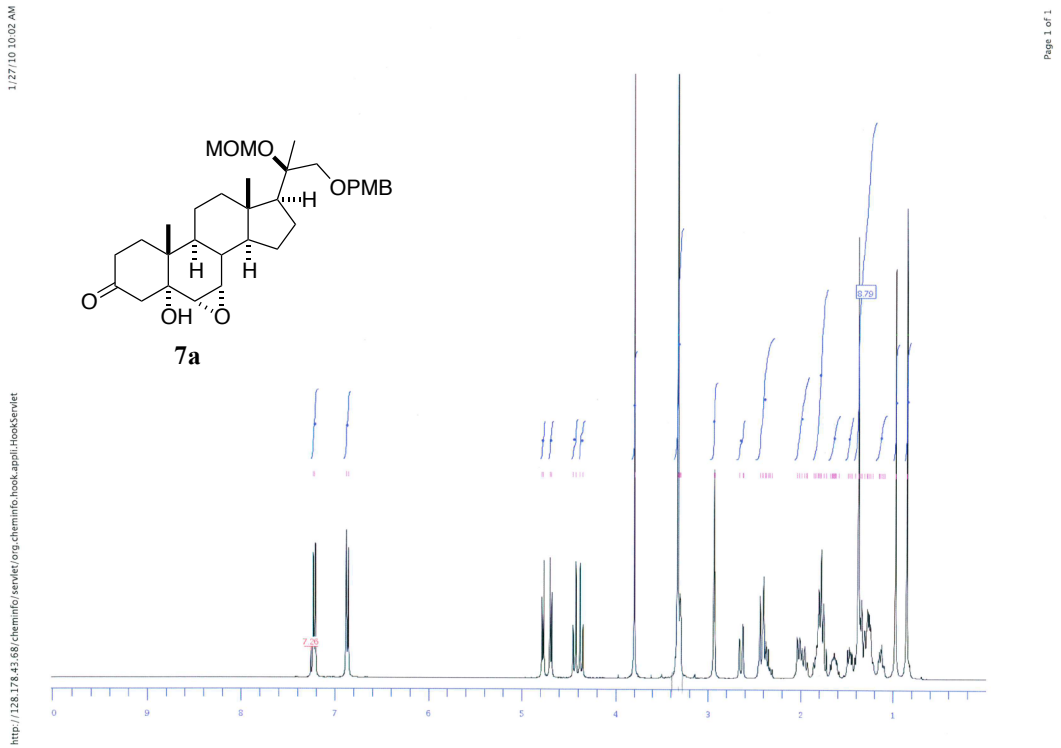
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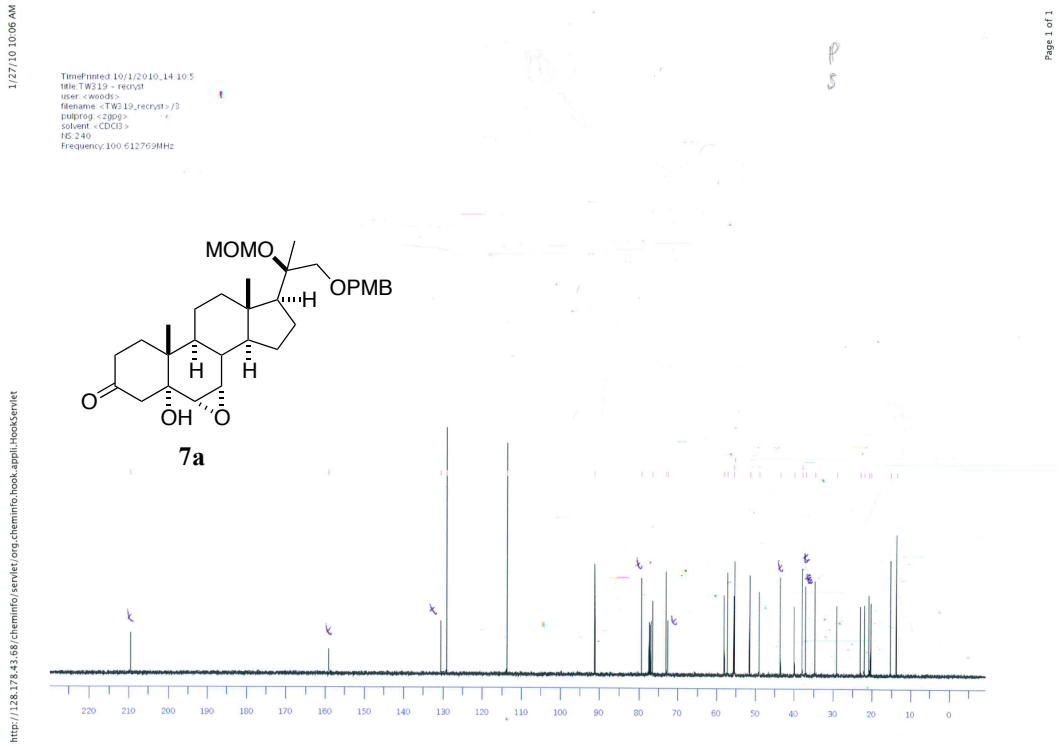
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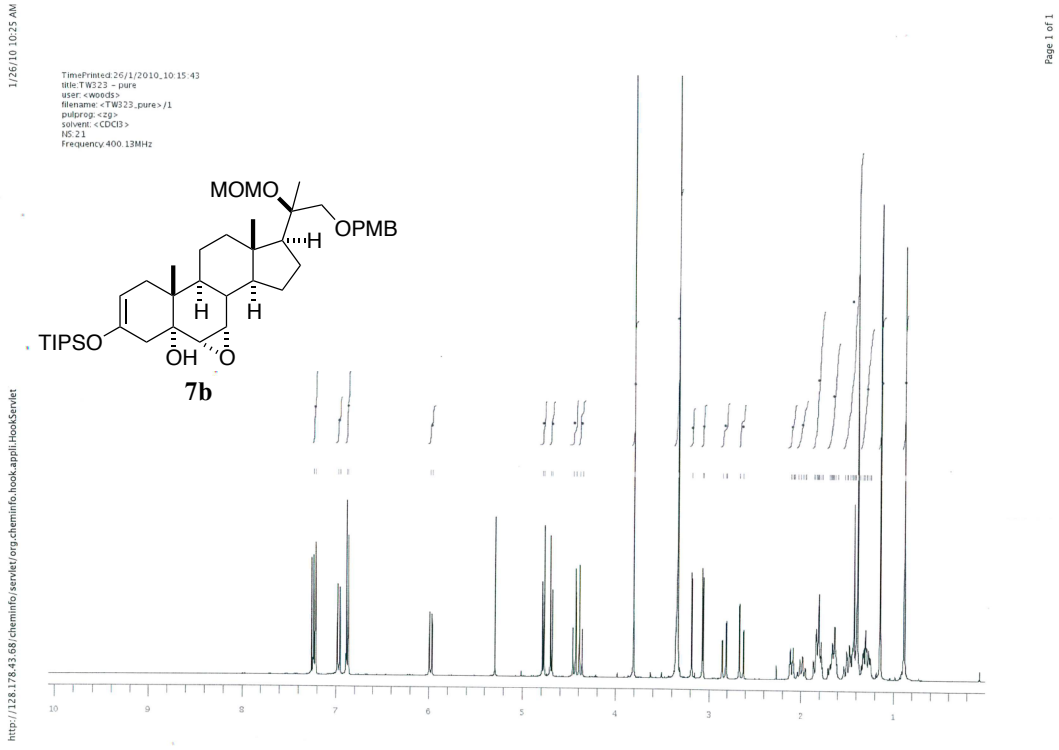
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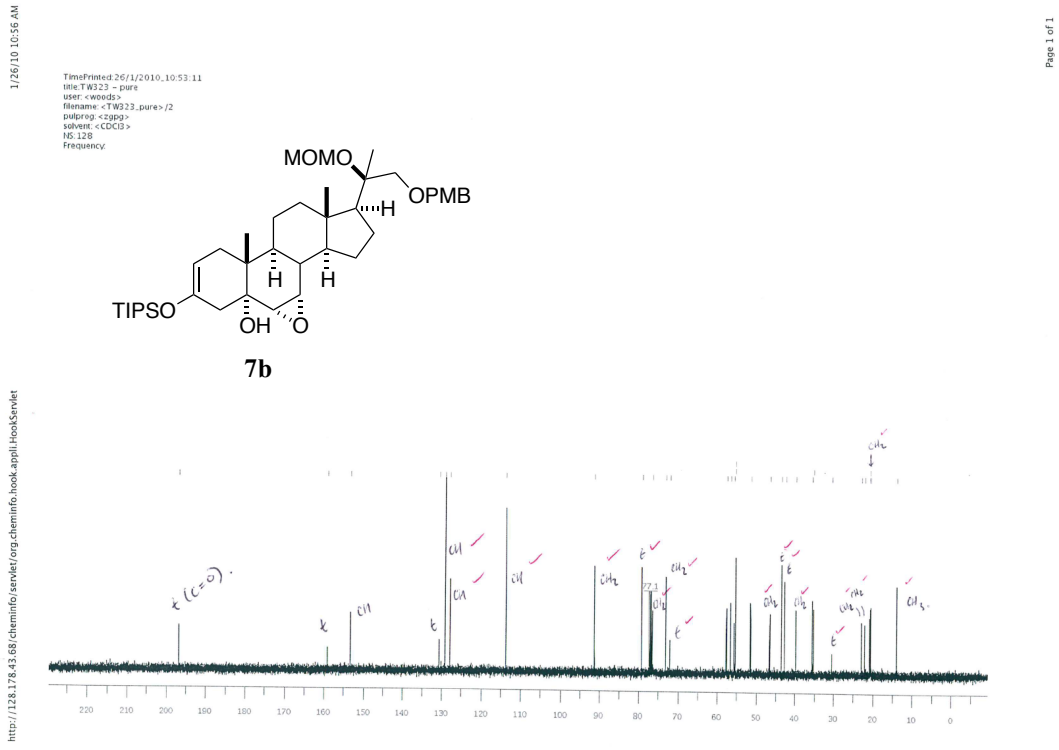
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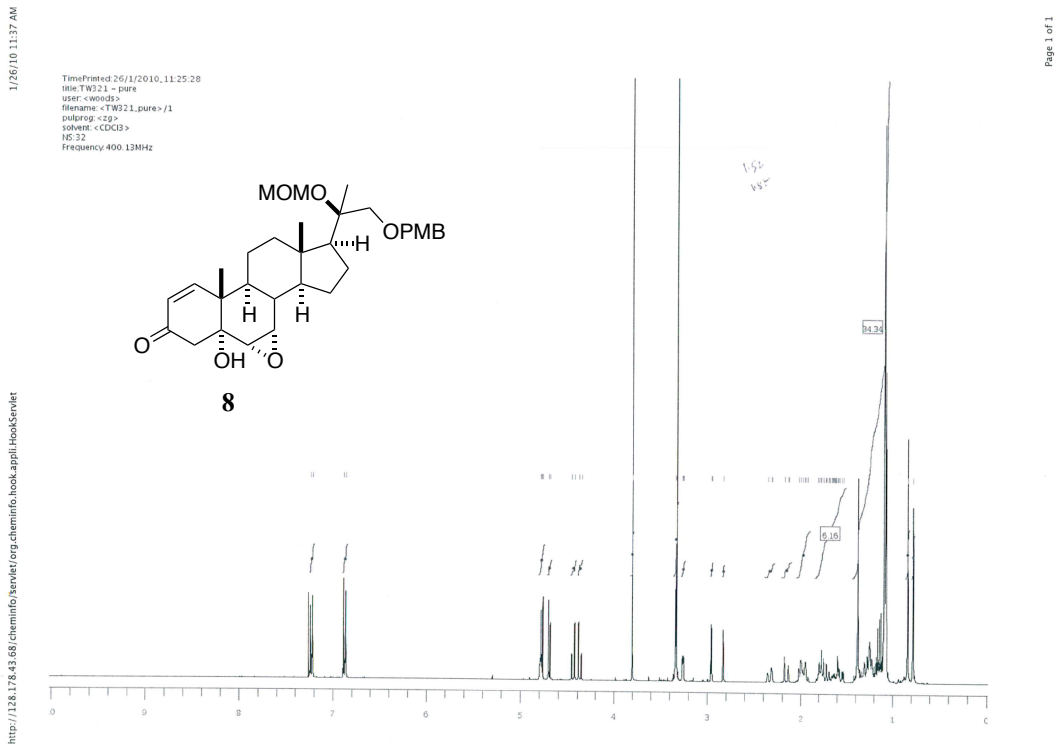
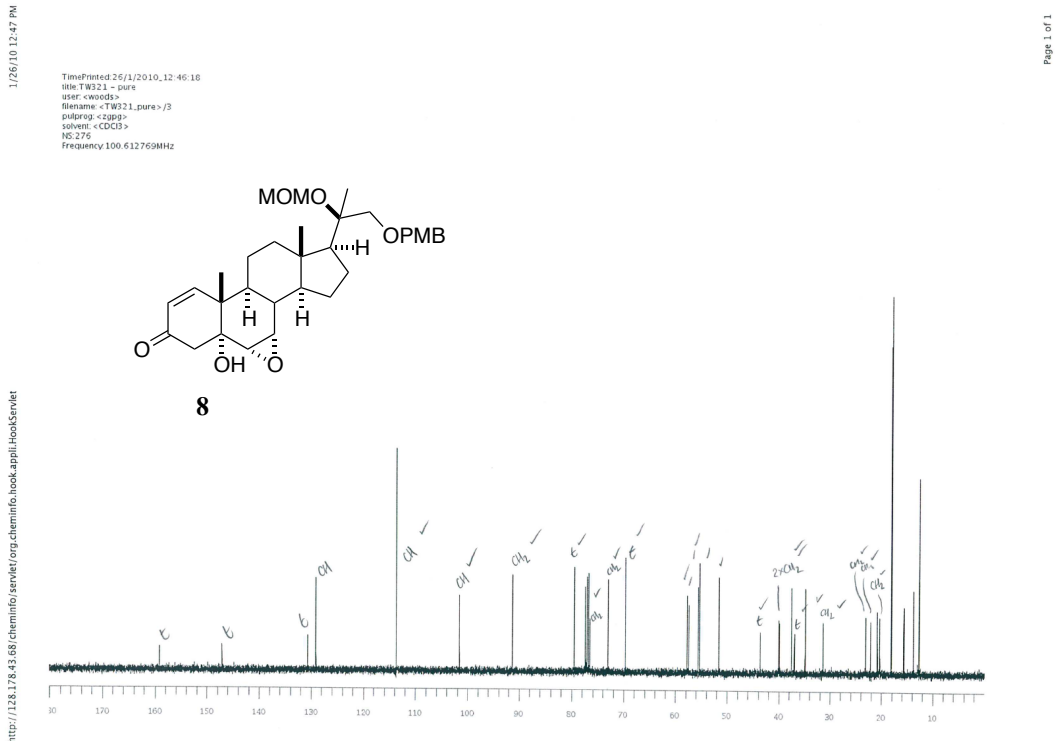
TIPSO
OH
O
http://128.178.43.68/cheminfo/servlet/org.cheminfo.hook.appli.HookServlet

7b


1/26/10 11:37 AM
TimePrinted:26/1/2010_11:25:28
title:TW321 – pure
user:<woods>
filename:<TW321_pure>/1
pulprog:<zg>
solvent:<CDCl3>
NS:32
Frequency:400.13MHz
MOMO
OPMB
H
H
H
O
OH
O
8
6.16
4.34
Page 1 of 1
http://128.178.43.68/cheminfo/servlet/org.cheminfo.hook.appli.HookServlet


1/26/10 12:47 PM
TimePrinted:26/1/2010_12:46:18
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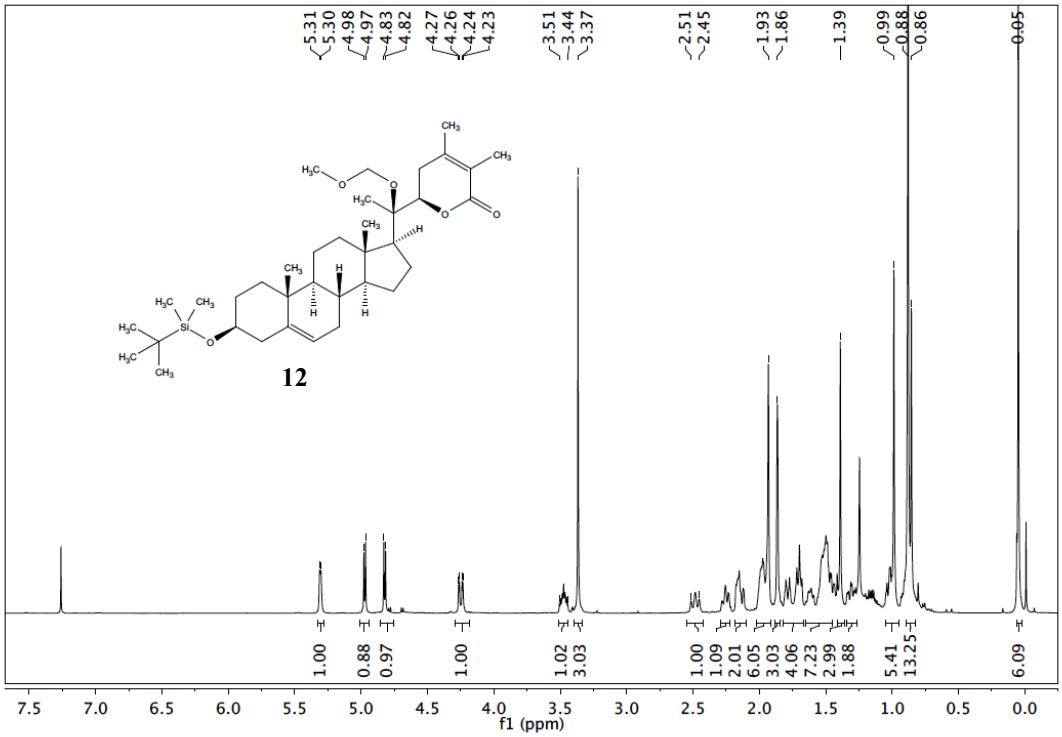
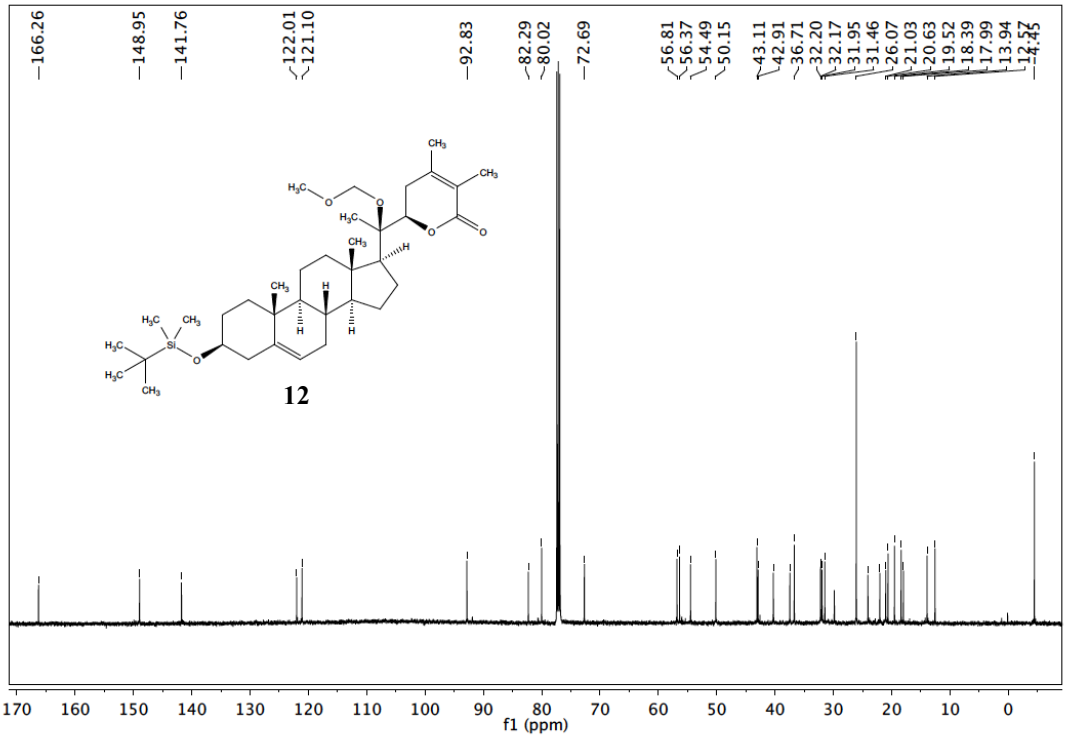
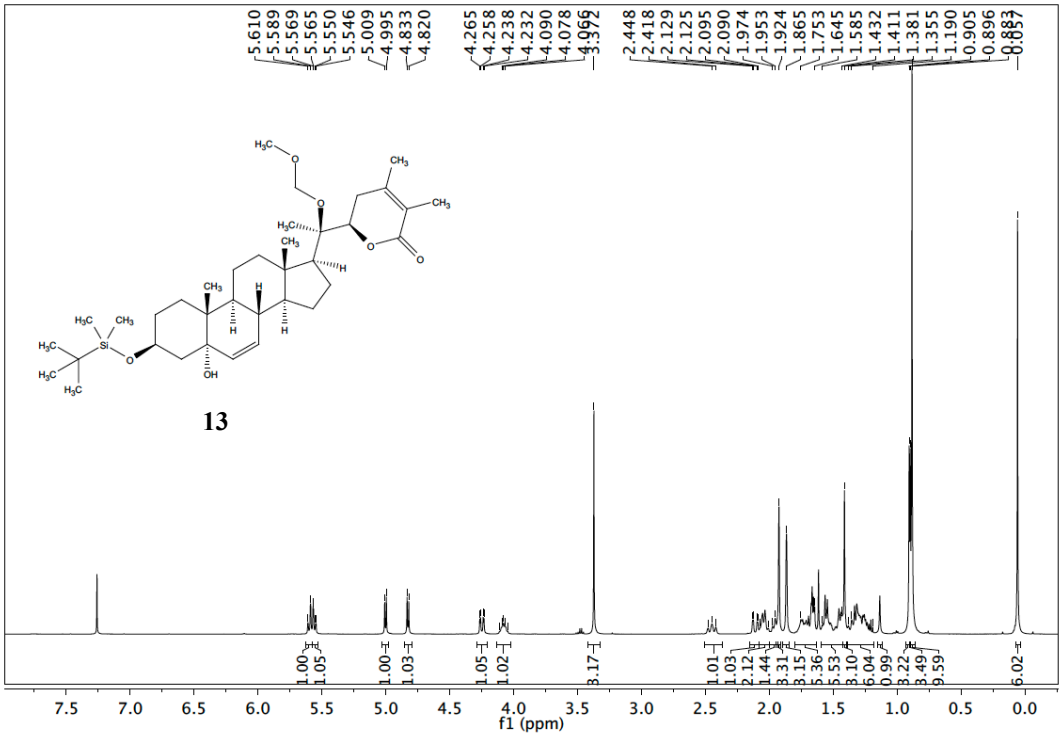
user:<woods>
filename:<TW321_pure>/3
pulprog:<zgpg>
solvent:<CDCl3>
NS:276
Frequency:100.612769MHz
MOMO
OPMB
H
H
H
O
OH
O
8
Page 1 of 1
http://128.178.43.68/cheminfo/servlet/org.cheminfo.hook.appli.HookServlet

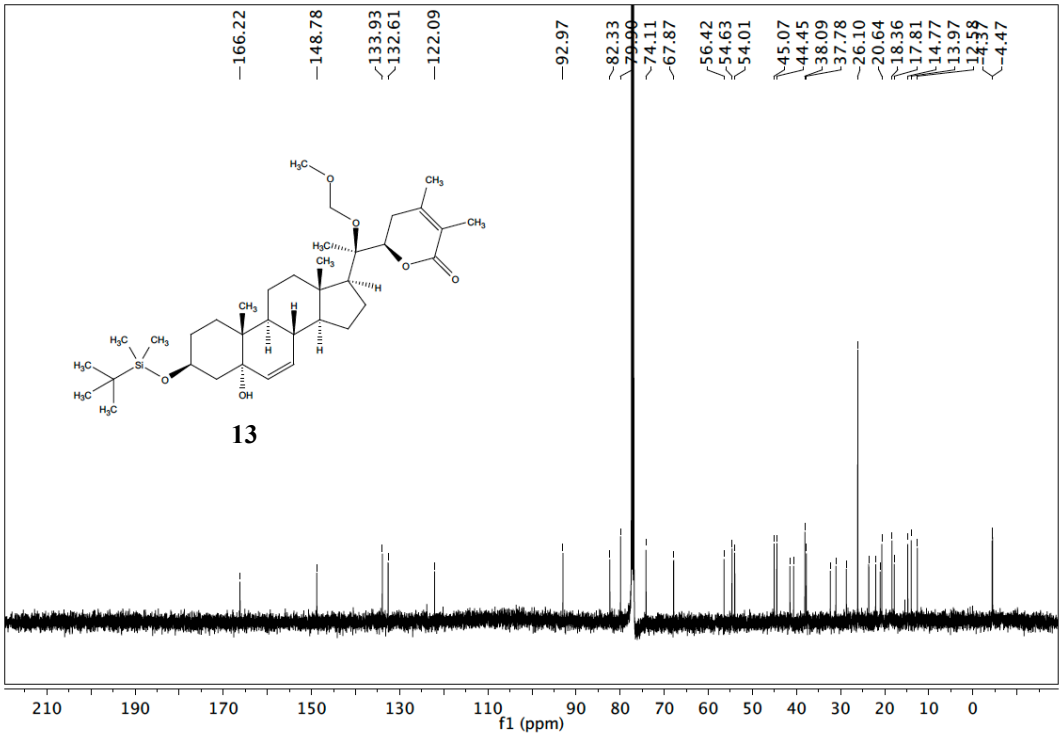
Total Synthesis of Withanolide A (**Scheme 2**)



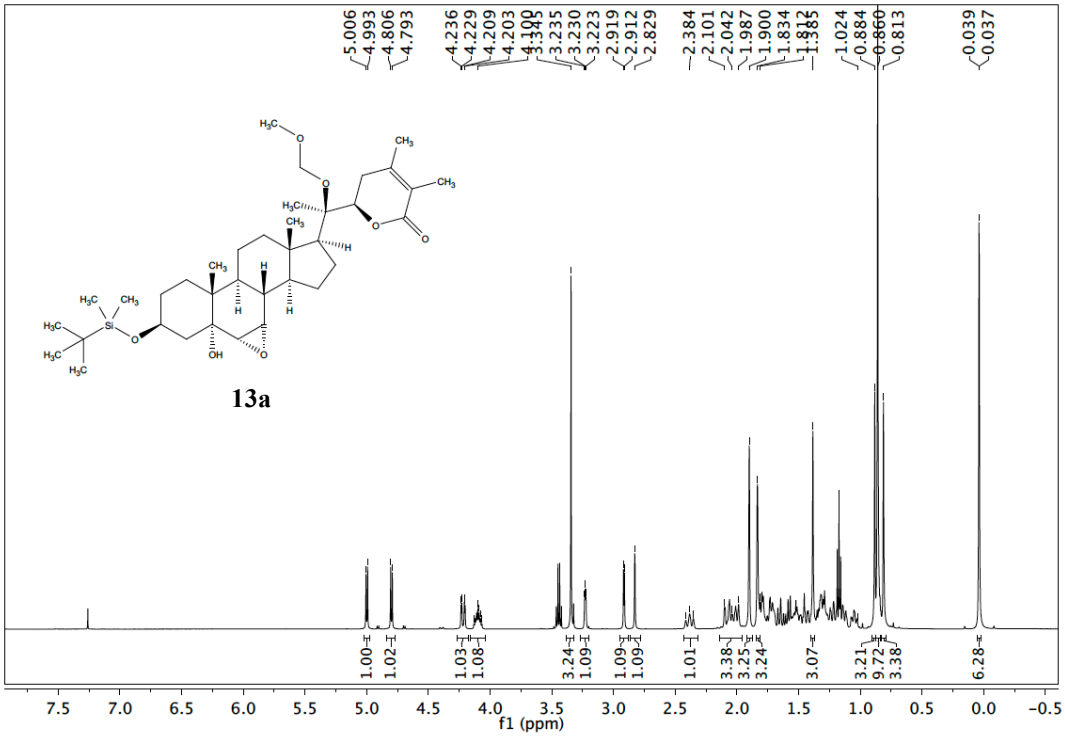


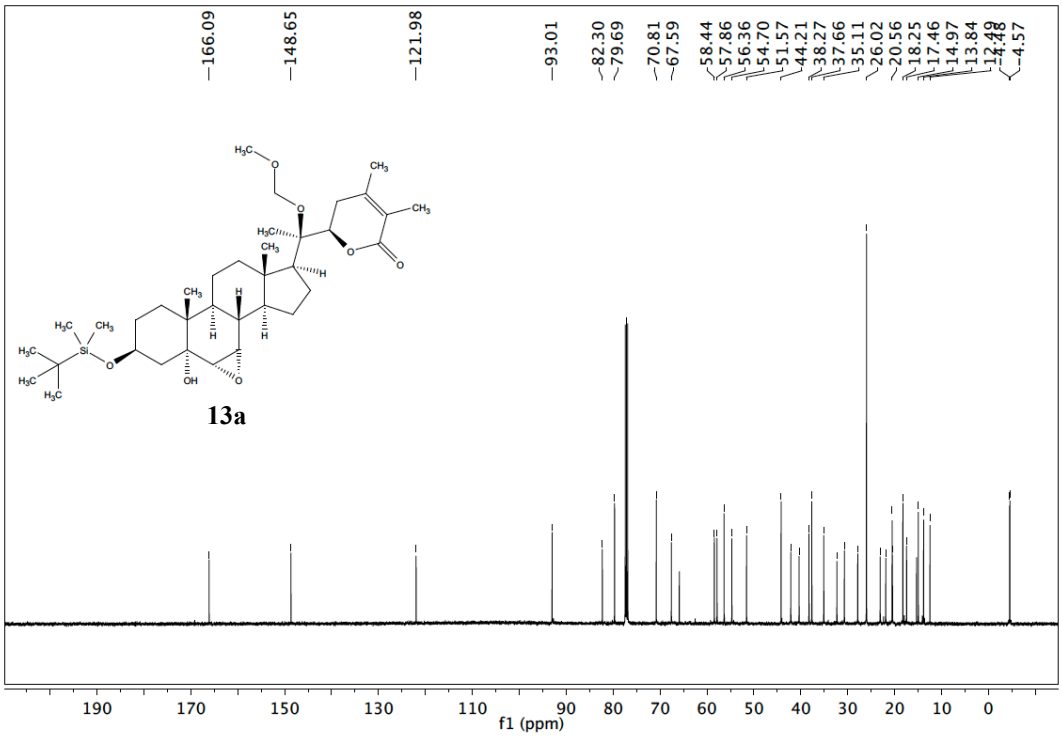

5.610
5.589
5.569
5.565
5.550
5.546
5.009
4.995
4.833
4.820
4.265
4.258
4.238
4.232
4.090
4.078
4.066
3.372
2.448
2.418
2.129
2.125
2.095
2.090
1.974
1.953
1.924
1.865
1.753
1.645
1.585
1.432
1.411
1.381
1.355
1.190
0.905
0.896
0.883
0.857
1.00
1.05
1.00
1.03
1.05
1.02
3.17
1.01
1.03
2.12
1.44
3.31
3.15
5.36
5.53
3.10
6.04
0.99
3.22
3.49
9.59
6.02
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

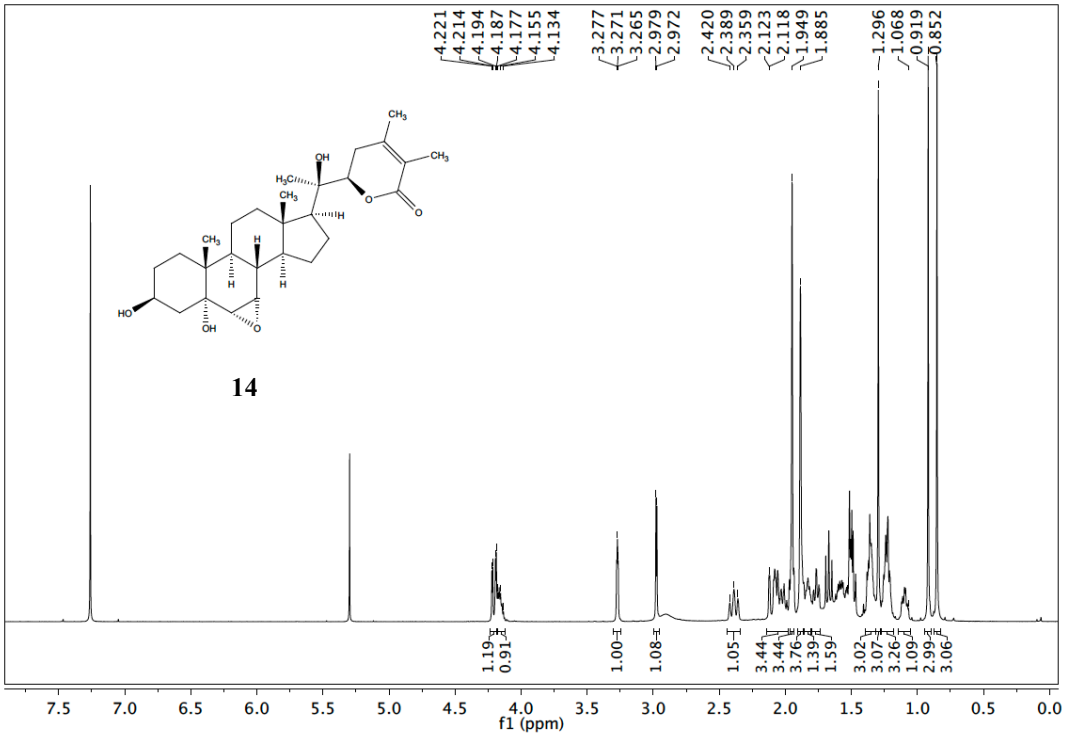
13


166.22
148.78
133.93
132.61
122.09
92.97
82.33
79.90
74.11
67.87
56.42
54.63
54.01
45.07
44.45
38.09
37.78
26.10
20.64
18.36
17.81
14.77
13.97
12.58
-4.37
-4.47
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

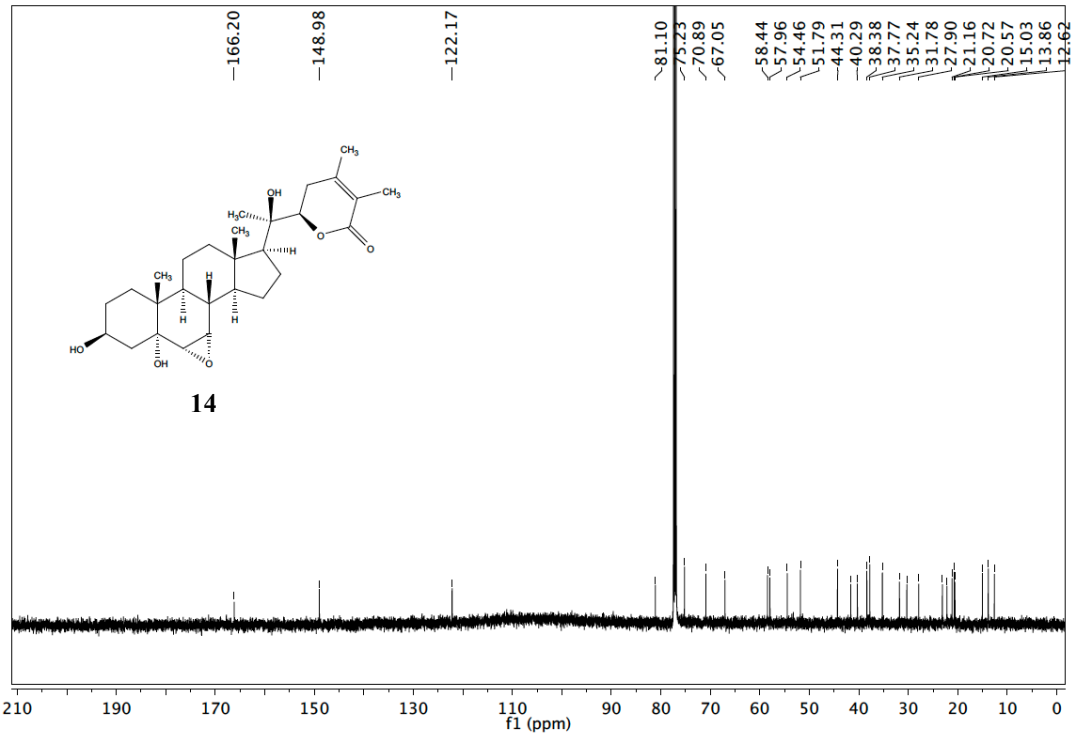
13


5.006
4.993
4.806
4.793
4.236
4.229
4.209
4.203
4.100
3.345
3.235
3.230
3.223
2.919
2.912
2.829
2.384
2.101
2.042
1.987
1.900
1.834
1.812
1.385
1.024
0.884
0.860
0.813
0.039
0.037
13a
1.00
1.02
1.03
1.08
3.24
1.09
1.09
1.09
1.01
3.38
3.25
3.24
3.07
3.21
9.72
3.38
6.28
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

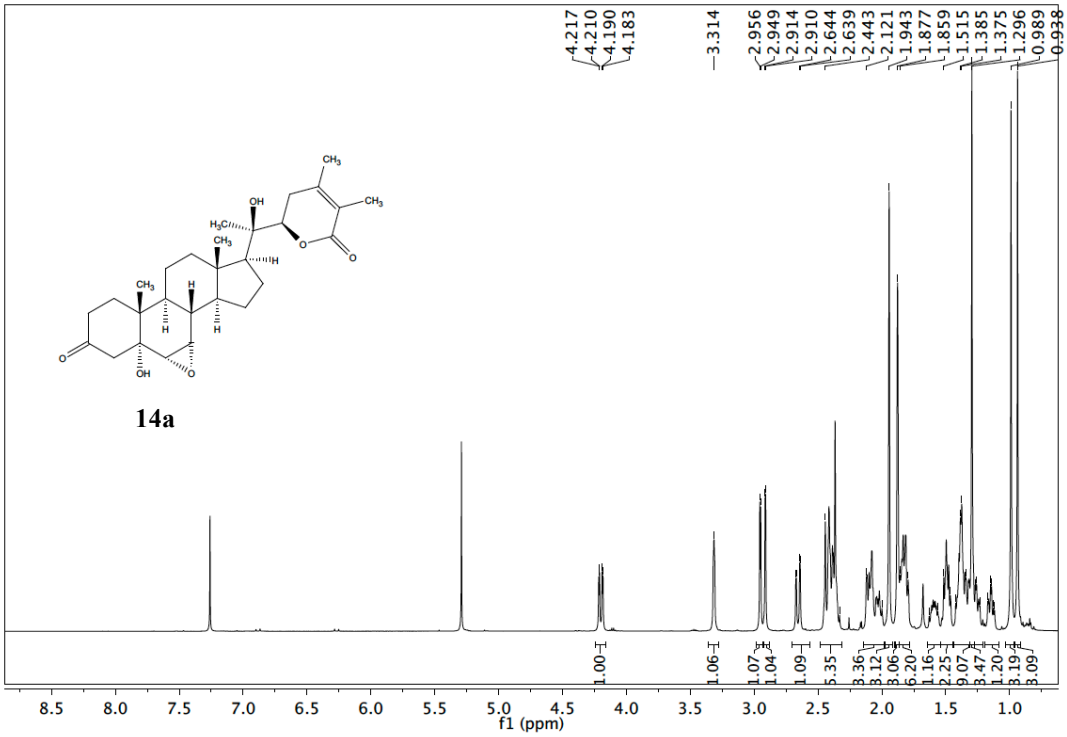

166.09
148.65
121.98
93.01
82.30
79.69
70.81
67.59
58.44
57.86
56.36
54.70
51.57
44.21
38.27
37.66
35.11
26.02
20.56
18.25
17.46
14.97
13.84
12.49
4.57
13a
190 170 150 130 110 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


4.221
4.214
4.194
4.187
4.177
4.155
4.134
3.277
3.271
3.265
2.979
2.972
2.420
2.389
2.359
2.123
2.118
1.949
1.885
1.296
1.068
0.919
0.852
1.19
0.91
1.00
1.08
1.05
3.44
3.44
3.76
1.39
1.59
3.02
3.07
3.26
1.09
2.99
3.06
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

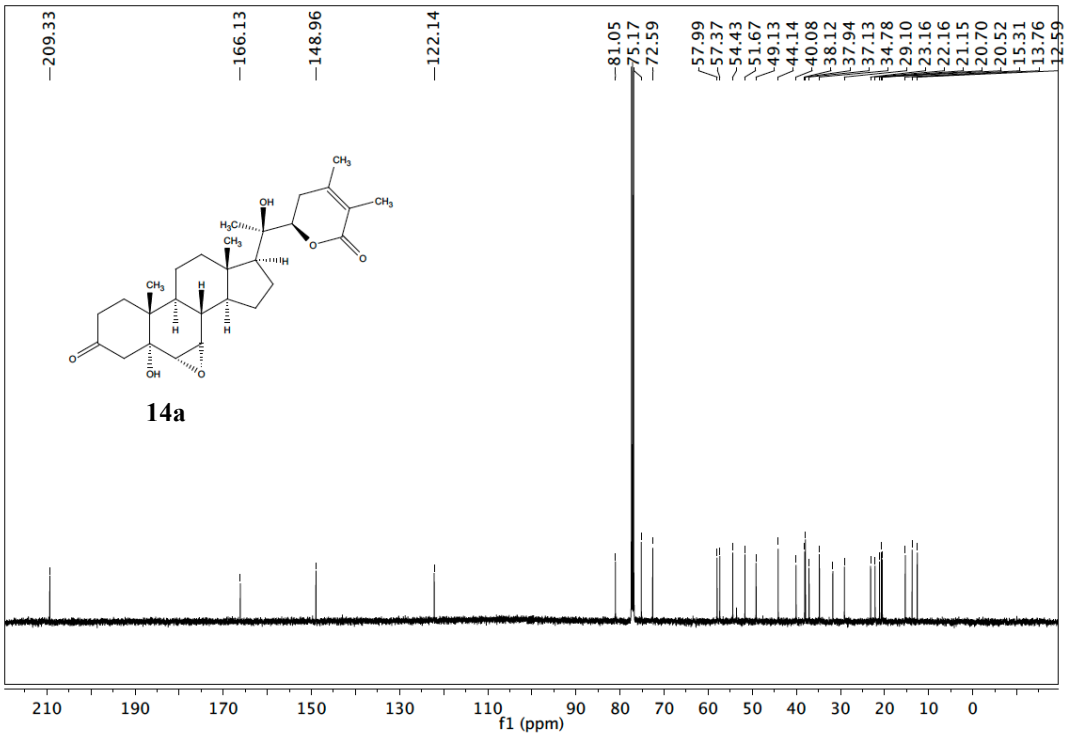
14


166.20
148.98
122.17
81.10
75.23
70.89
67.05
58.44
57.96
54.46
51.79
44.31
40.29
38.38
37.77
35.24
31.78
27.90
21.16
20.72
20.57
15.03
13.86
12.62
210 190 170 150 130 110 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

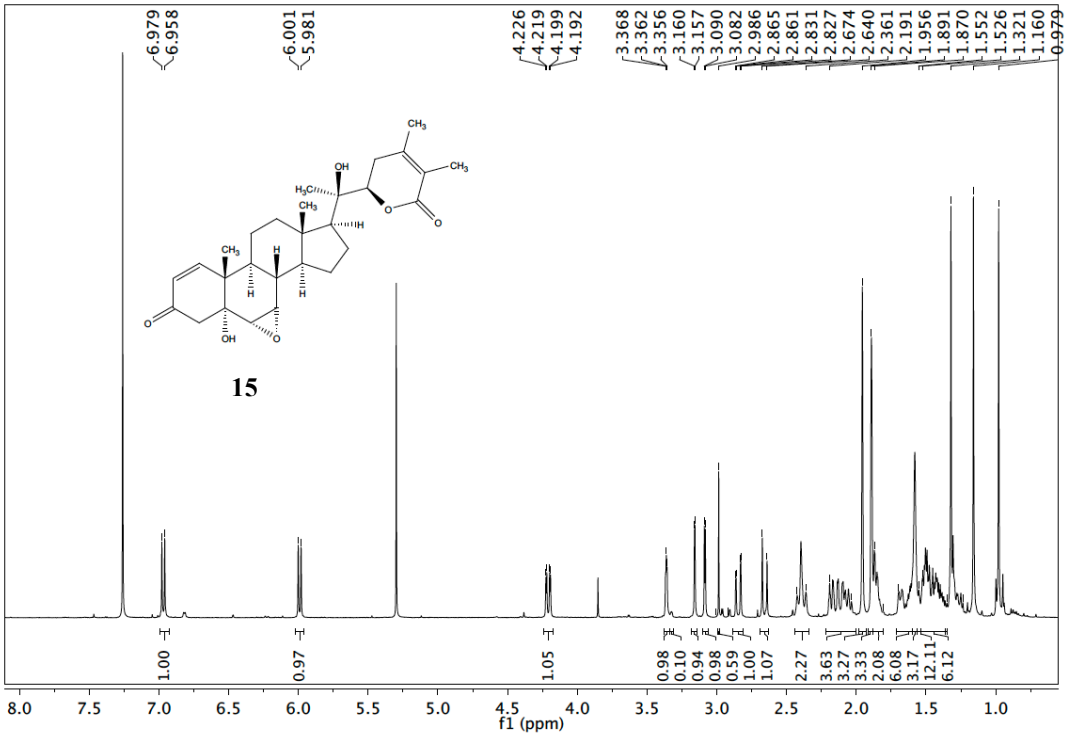
14


4.217
4.210
4.190
4.183
3.314
2.956
2.949
2.914
2.910
2.644
2.639
2.443
2.121
1.943
1.877
1.859
1.515
1.385
1.375
1.296
0.989
0.938
1.00
1.06
1.07
1.04
1.09
5.35
3.36
3.12
3.06
6.20
1.16
2.25
9.07
3.47
1.20
3.19
3.09
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
f1 (ppm)

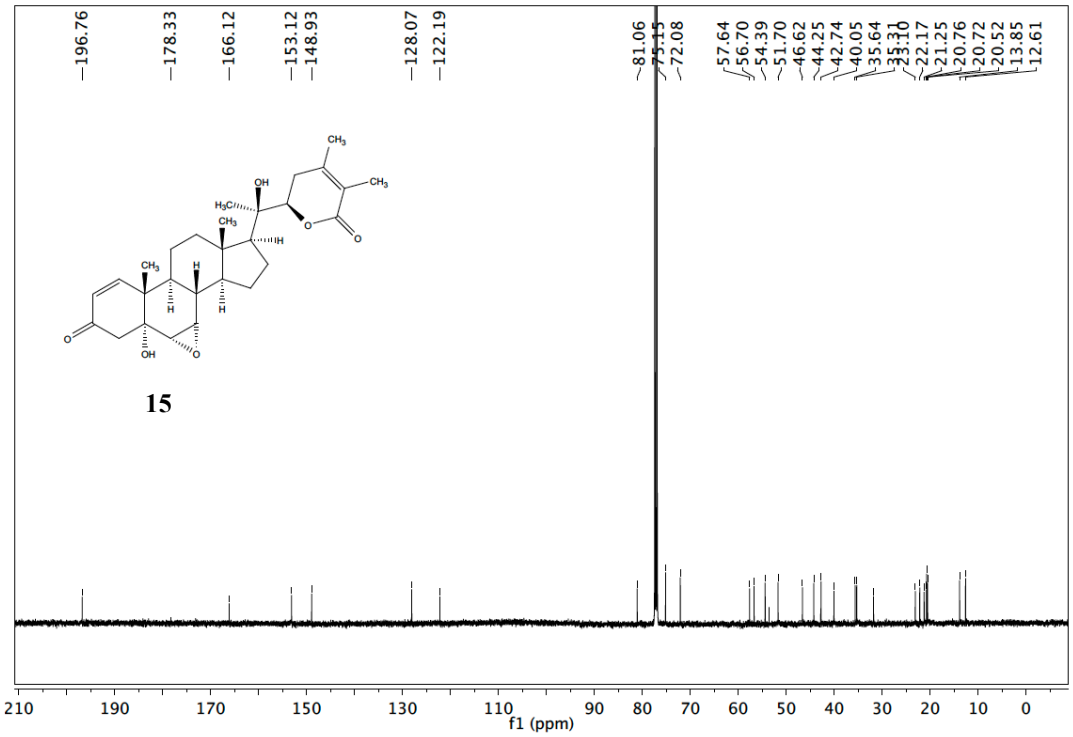
14a


209.33
166.13
148.96
122.14
81.05
75.17
72.59
57.99
57.37
54.43
51.67
49.13
44.14
40.08
38.12
37.94
37.13
34.78
29.10
23.16
22.16
21.15
20.70
20.52
15.31
13.76
12.59
210 190 170 150 130 110 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

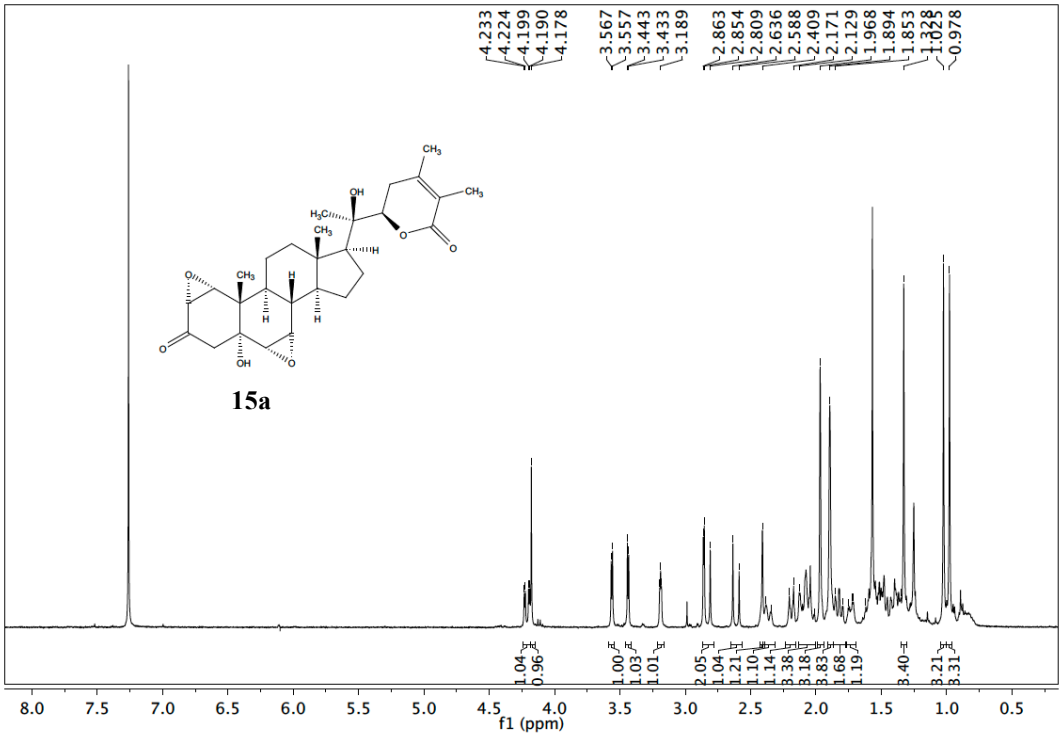
14a

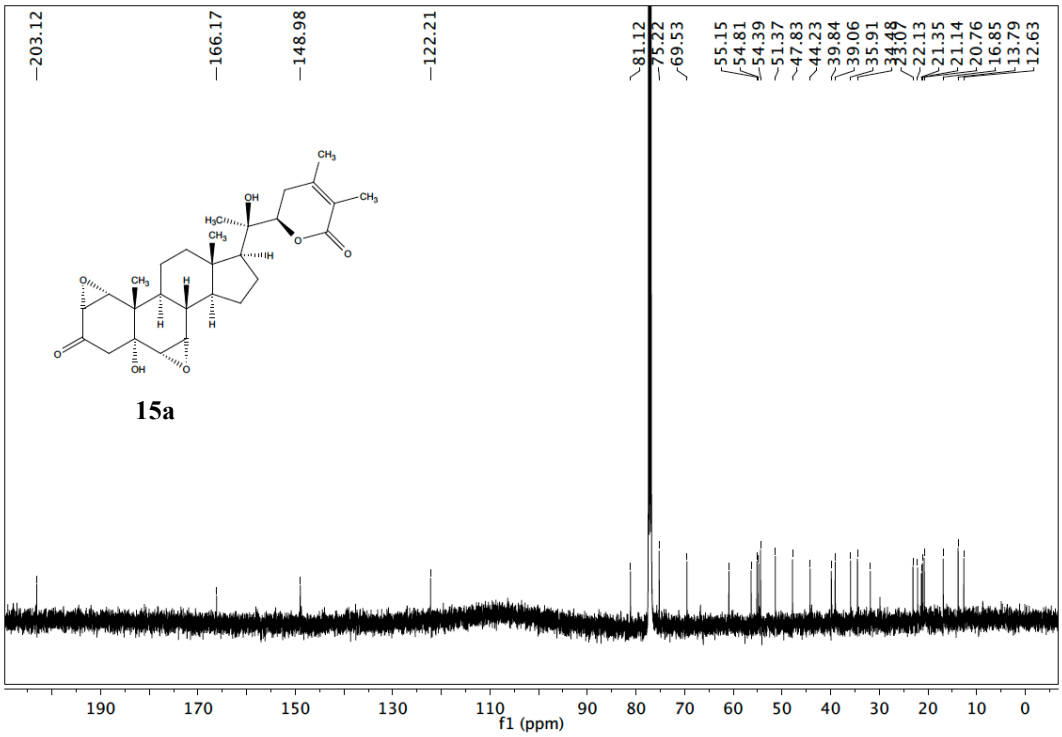

6.979
6.958
6.001
5.981
4.226
4.219
4.199
4.192
3.368
3.362
3.356
3.160
3.157
3.090
3.082
2.986
2.865
2.861
2.831
2.827
2.674
2.640
2.361
2.191
1.956
1.891
1.870
1.552
1.526
1.321
1.160
0.979
1.00
0.97
1.05
0.98
0.10
0.94
0.98
0.59
1.00
1.07
2.27
3.63
3.27
3.33
2.08
6.08
3.17
12.11
6.12
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

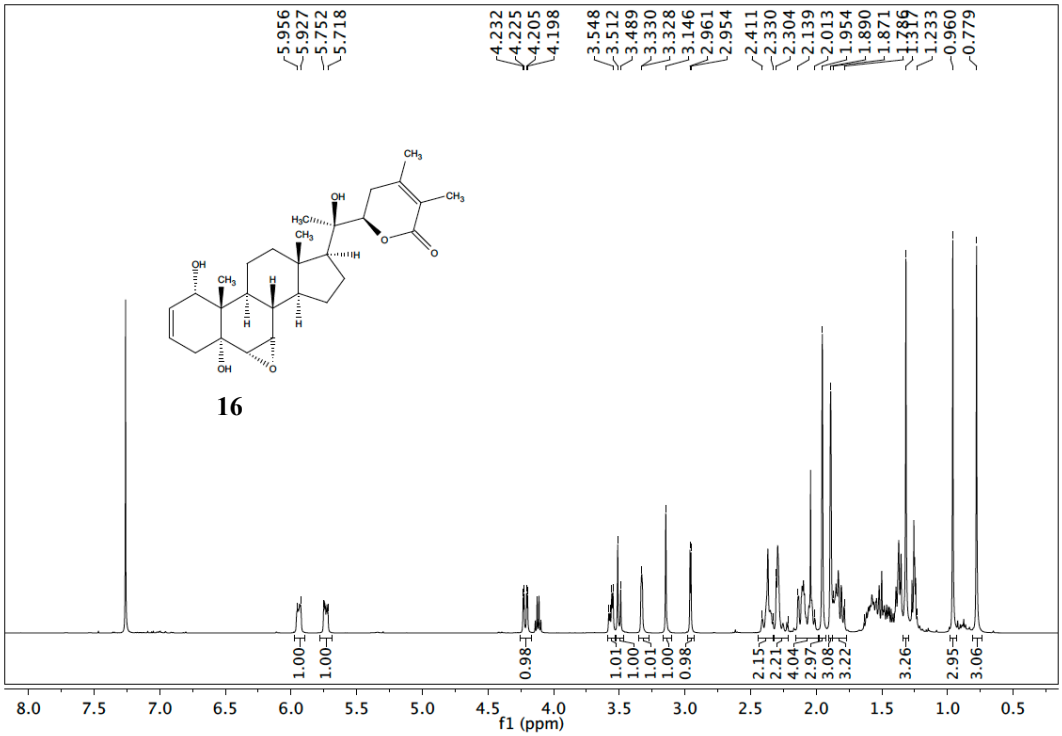
15


196.76
178.33
166.12
153.12
148.93
128.07
122.19
81.06
75.15
72.08
57.64
56.70
54.39
51.70
46.62
44.25
42.74
40.05
35.64
33.10
22.17
21.25
20.76
20.72
20.52
13.85
12.61
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

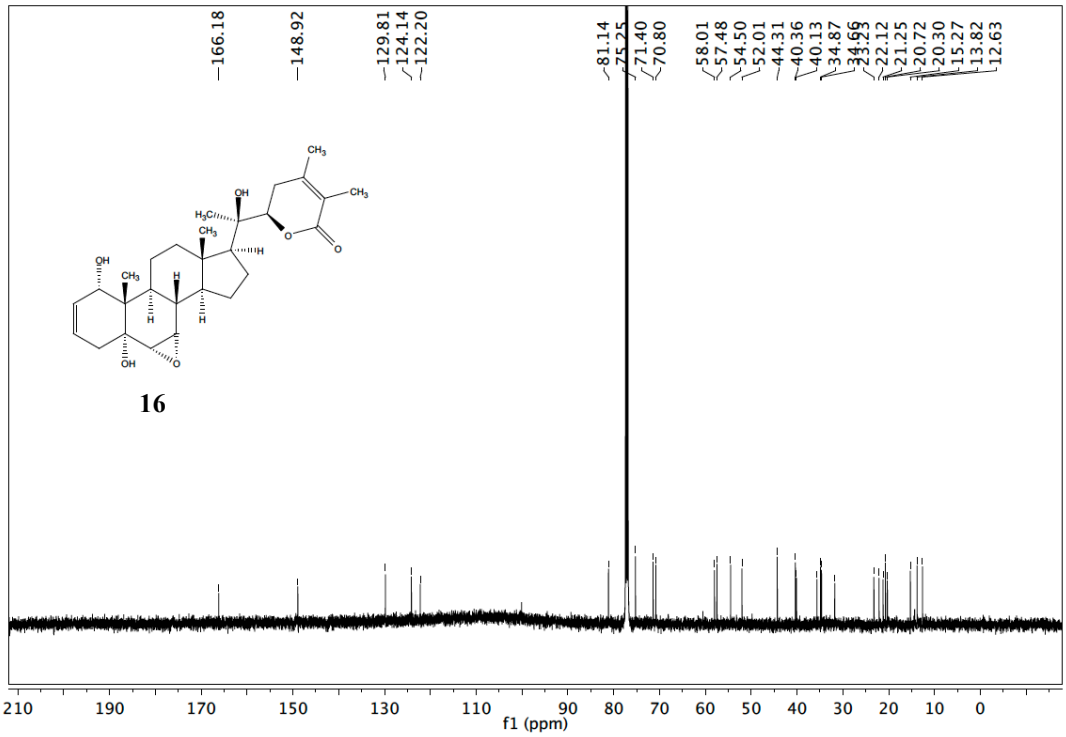
15


4.233
4.224
4.199
4.190
4.178
3.567
3.557
3.443
3.433
3.189
2.863
2.854
2.809
2.636
2.588
2.409
2.171
2.129
1.968
1.894
1.853
1.328
1.025
0.978
15a
1.04
0.96
1.00
1.03
1.01
2.05
1.04
1.21
1.10
1.14
3.38
3.18
3.83
1.68
1.19
3.40
3.21
3.31
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

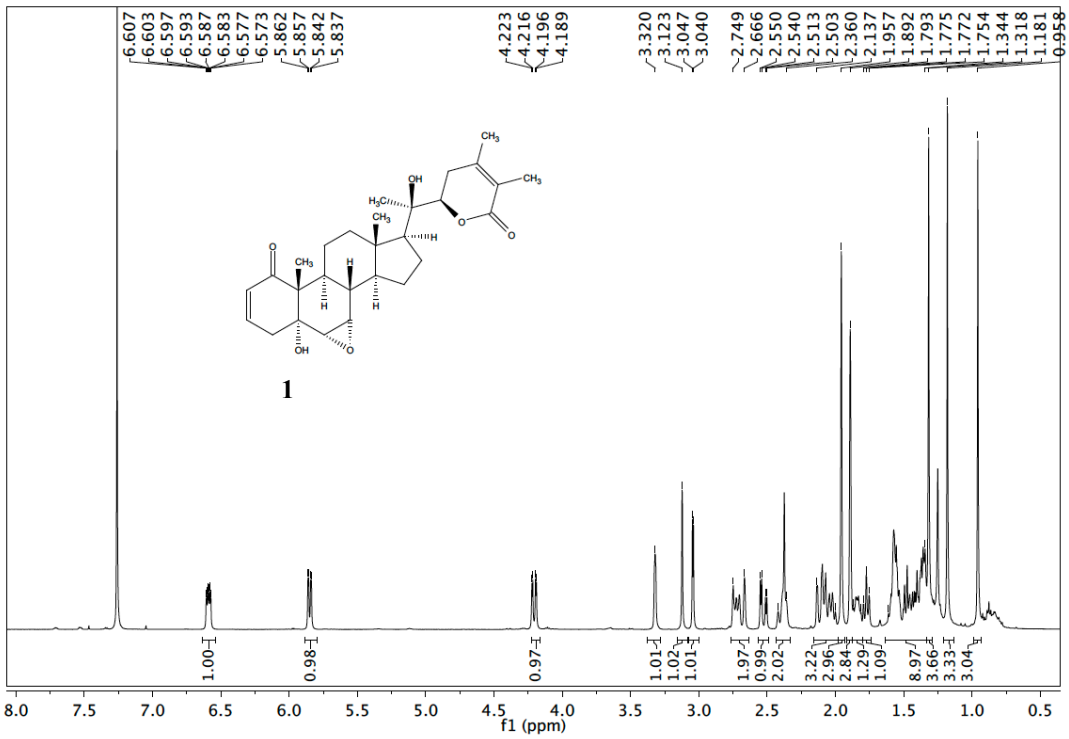

203.12
166.17
148.98
122.21
81.12
75.22
69.53
55.15
54.81
54.39
51.37
47.83
44.23
39.84
39.06
35.91
34.48
33.07
22.13
21.35
21.14
20.76
16.85
13.79
12.63
15a
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


5.956
5.927
5.752
5.718
4.232
4.225
4.205
4.198
3.548
3.512
3.489
3.330
3.328
3.146
2.961
2.954
2.411
2.330
2.304
2.139
2.013
1.954
1.890
1.871
1.786
1.317
1.233
0.960
0.779
1.00
1.00
0.98
1.01
1.00
1.01
1.00
0.98
2.15
2.21
4.04
2.97
3.08
3.22
3.26
2.95
3.06
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

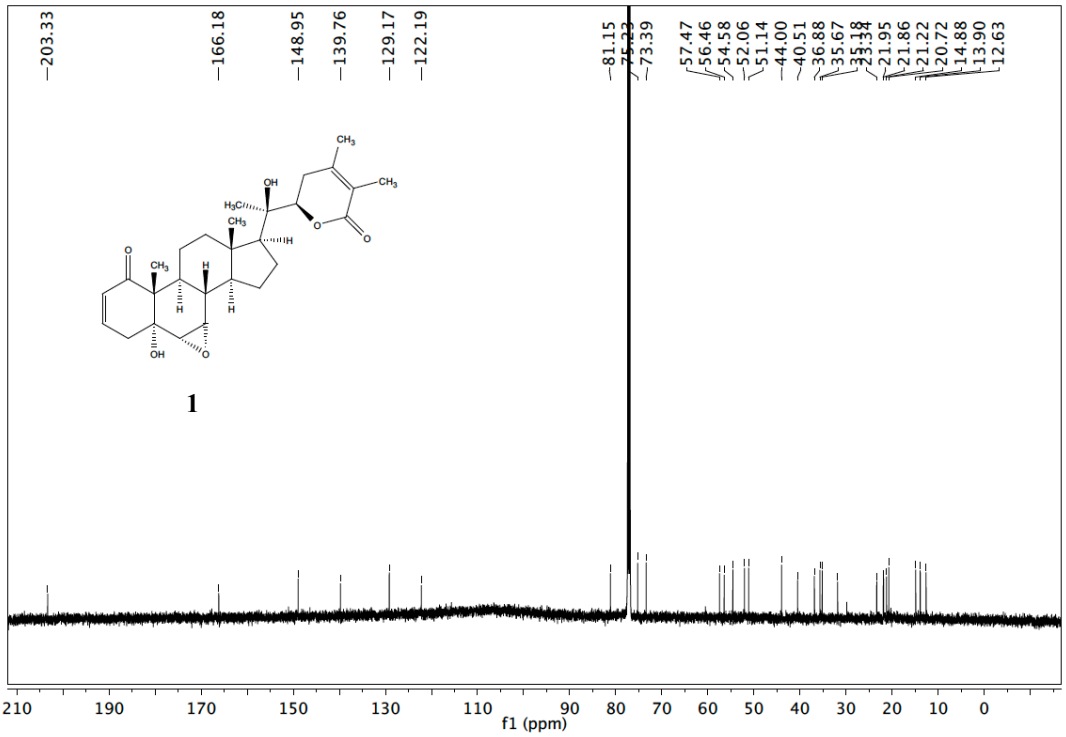
16


166.18
148.92
129.81
124.14
122.20
81.14
75.25
71.40
70.80
58.01
57.48
54.50
52.01
44.31
40.36
40.13
34.87
34.66
33.23
22.12
21.25
20.72
20.30
15.27
13.82
12.63
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

16

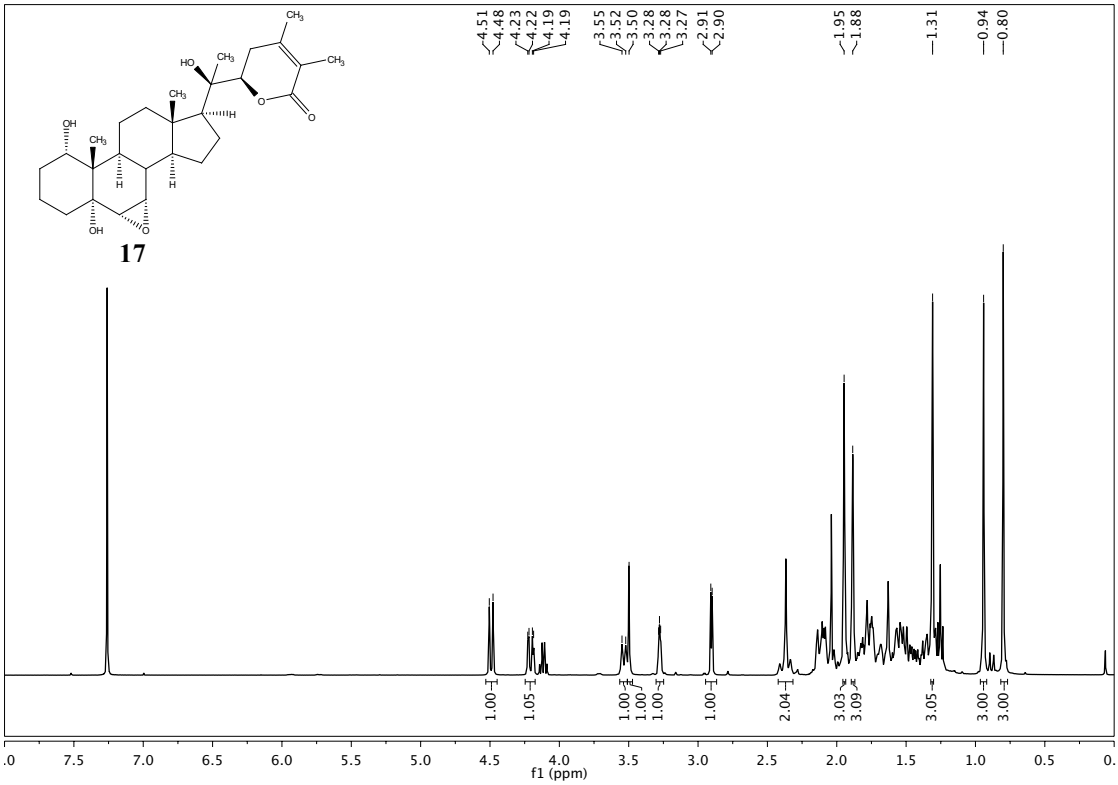

6.607
6.603
6.597
6.593
6.587
6.583
6.577
6.573
5.862
5.857
5.842
5.837
4.223
4.216
4.196
4.189
3.320
3.123
3.047
3.040
2.749
2.666
2.550
2.540
2.513
2.503
2.360
2.137
1.957
1.892
1.793
1.775
1.772
1.754
1.344
1.318
1.181
0.958
1.00
0.98
0.97
1.01
1.02
1.01
1.97
0.99
2.02
3.22
2.96
2.84
1.29
1.09
8.97
3.66
3.33
3.04
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

1

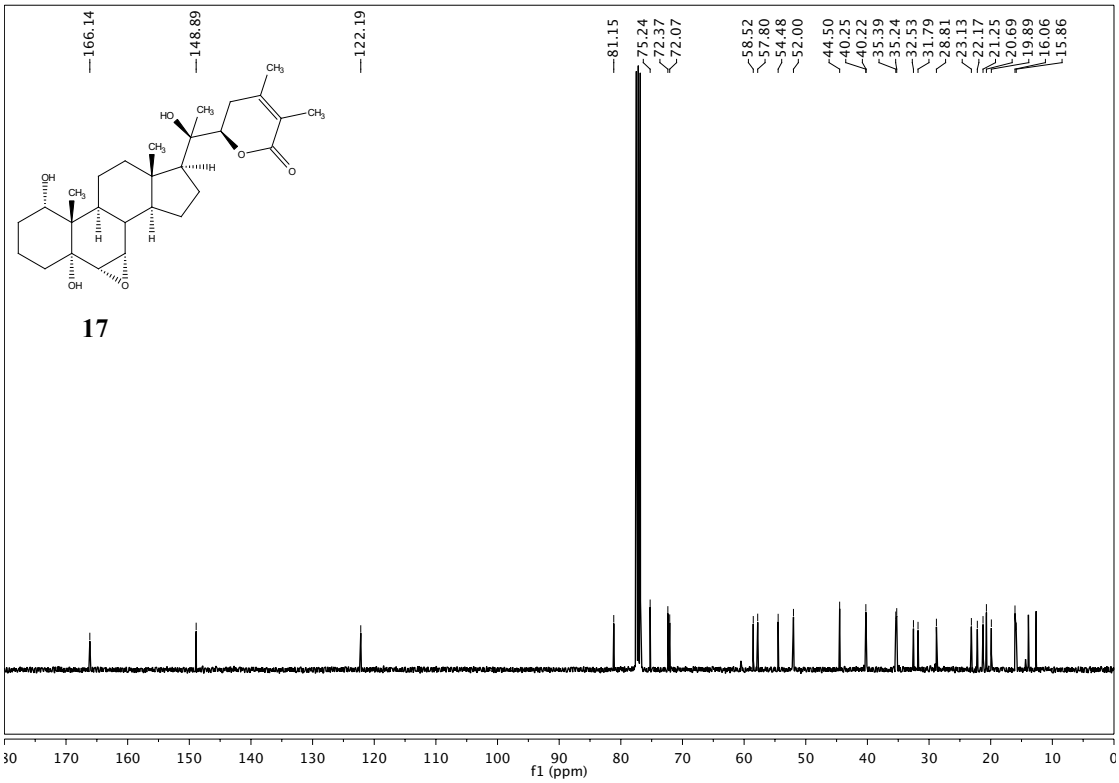

203.33
166.18
148.95
139.76
129.17
122.19
81.15
75.33
73.39
57.47
56.46
54.58
52.06
51.14
44.00
40.51
36.88
35.67
33.18
31.34
21.95
21.86
21.22
20.72
14.88
13.90
12.63
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

1

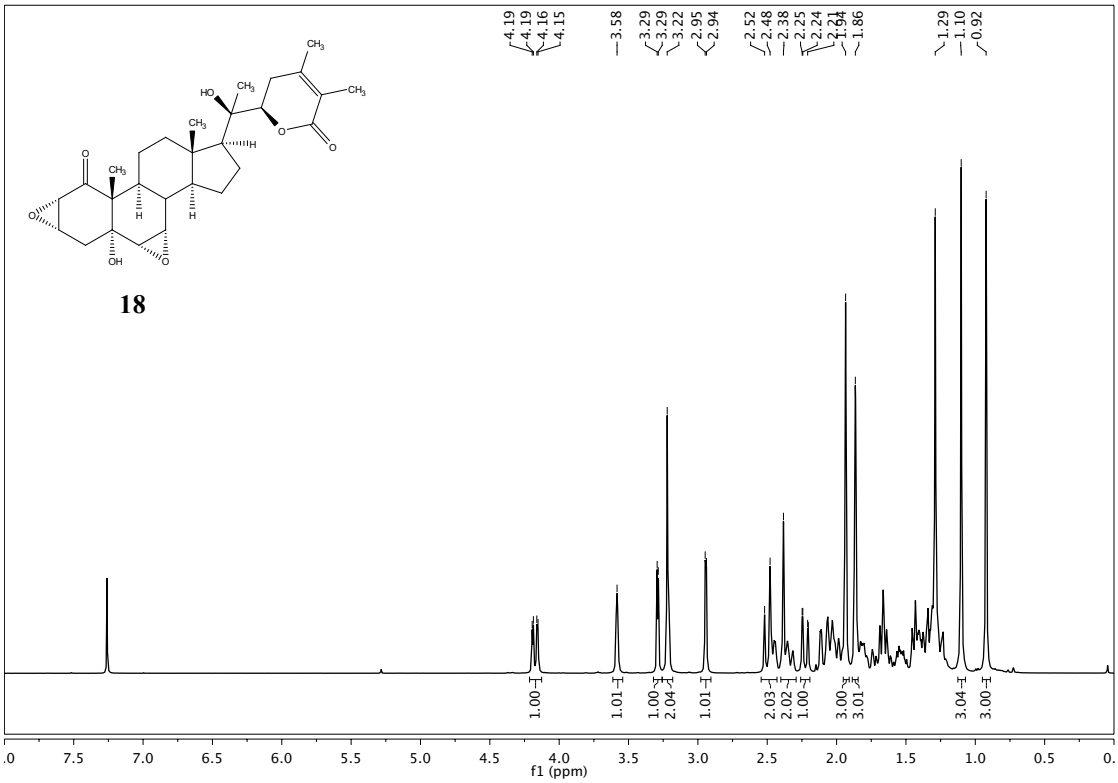
Semi-Synthesis (**Scheme 3, Scheme 4, Scheme 5, Scheme 6**)



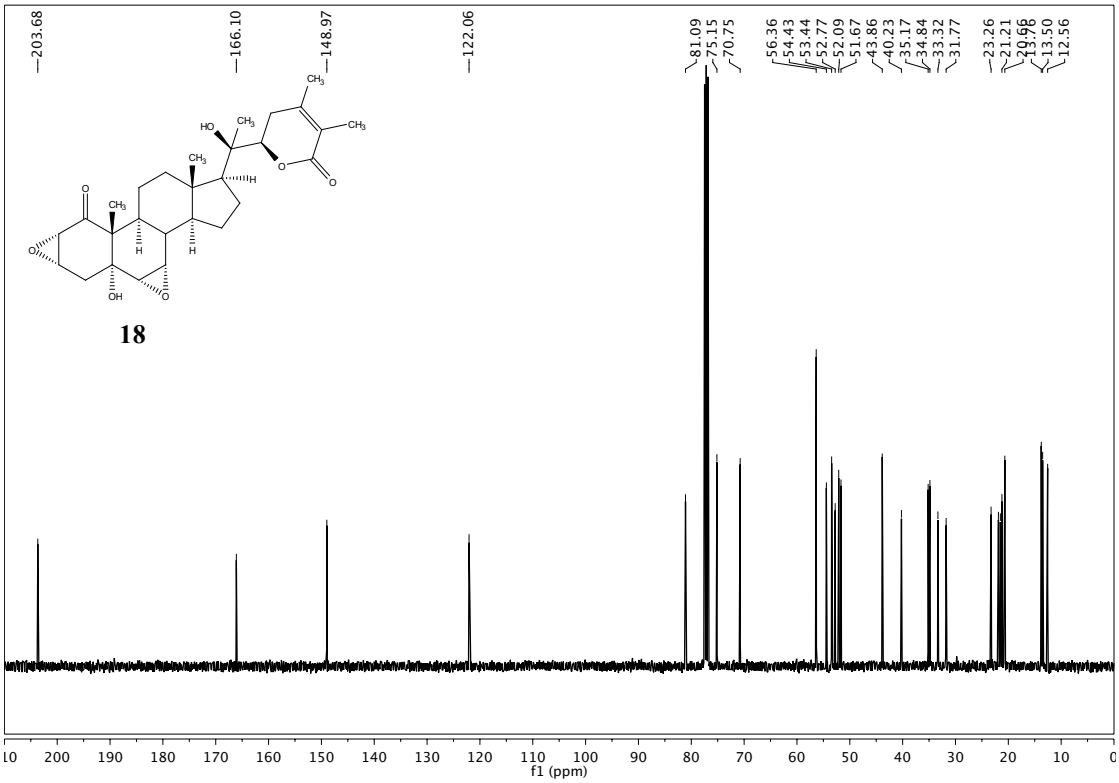
17



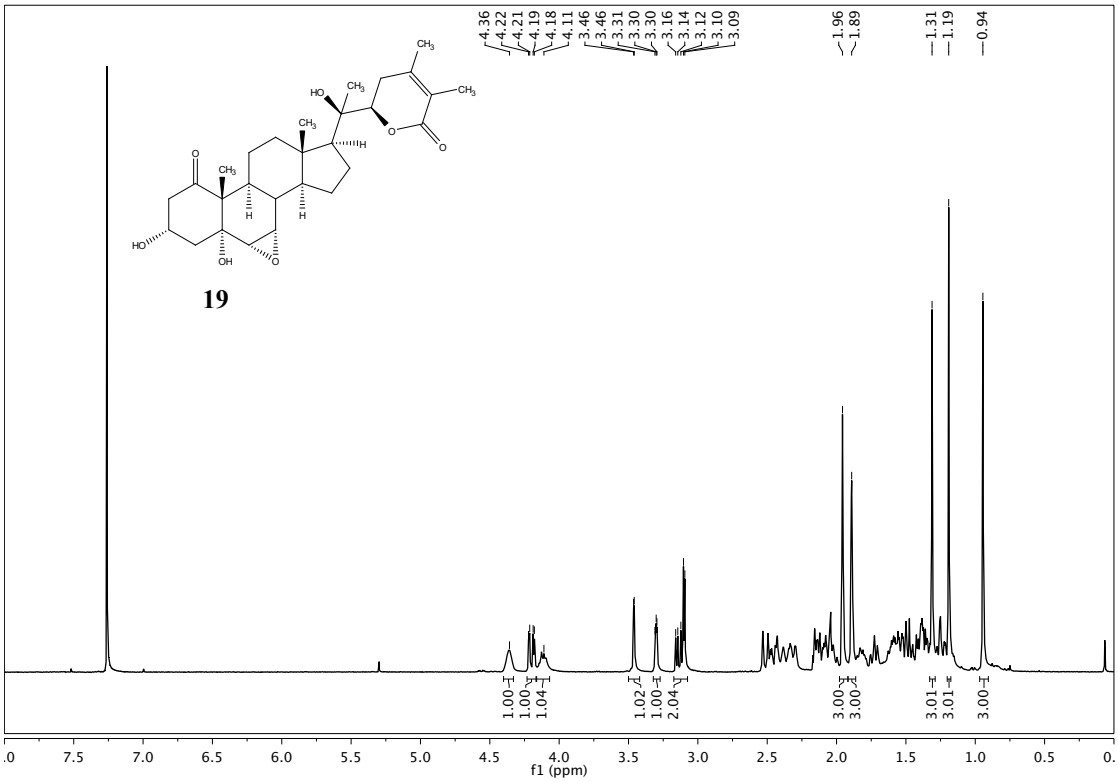
17


4.19
4.19
4.16
4.15
3.58
3.29
3.29
3.22
2.95
2.94
2.52
2.48
2.38
2.25
2.24
1.94
1.86
1.29
1.10
0.92
1.00
1.01
1.00
2.04
1.01
2.03
2.02
1.00
3.00
3.01
3.04
3.00
f1 (ppm)

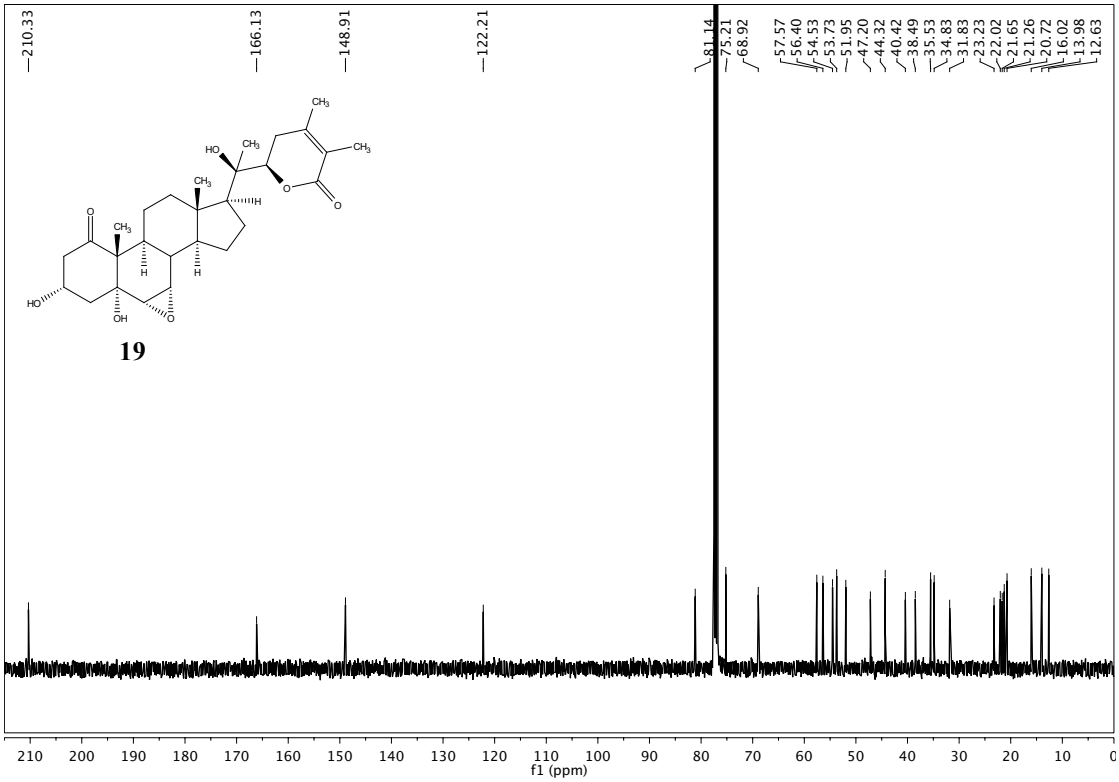
18


203.68
166.10
148.97
122.06
81.09
75.15
70.75
56.36
54.43
53.44
52.77
52.09
51.67
43.86
40.23
35.17
34.84
33.32
31.77
23.26
21.21
20.66
13.76
13.50
12.56
f1 (ppm)

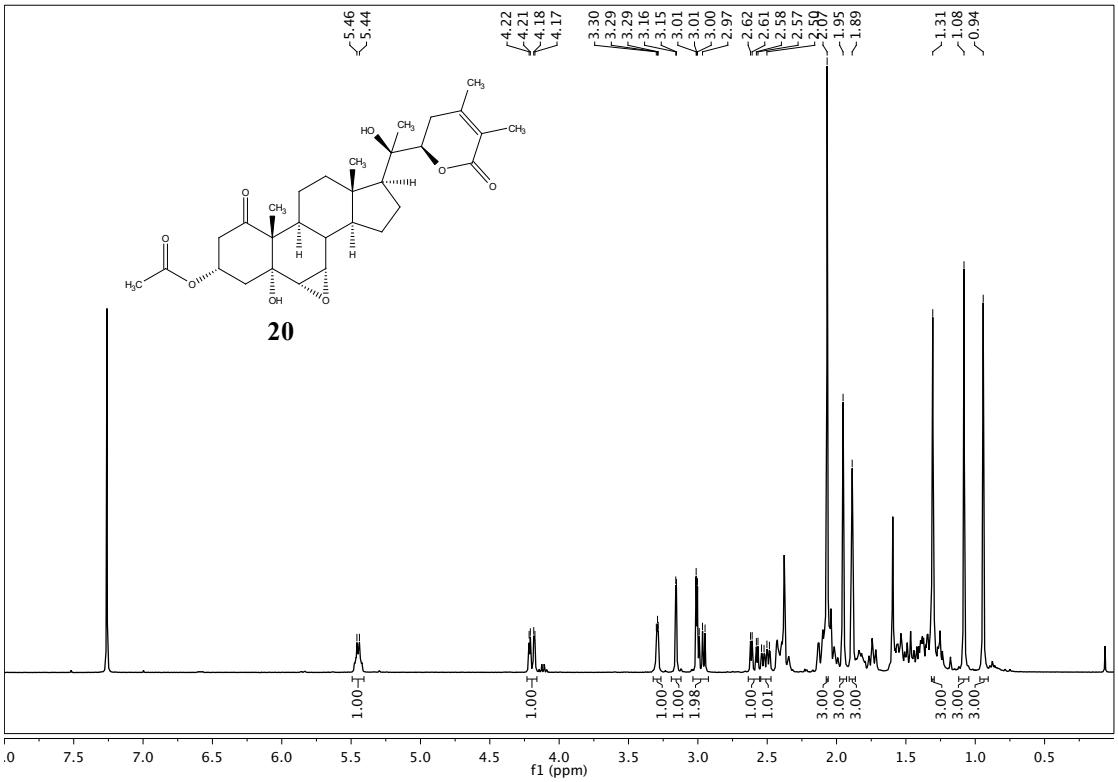
18


4.36
4.22
4.21
4.19
4.18
4.11
3.46
3.46
3.31
3.30
3.30
3.16
3.14
3.12
3.10
3.09
1.96
1.89
1.31
1.19
0.94
1.00
1.00
1.04
1.02
1.00
2.04
3.00
3.00
3.01
3.01
3.00
f1 (ppm)

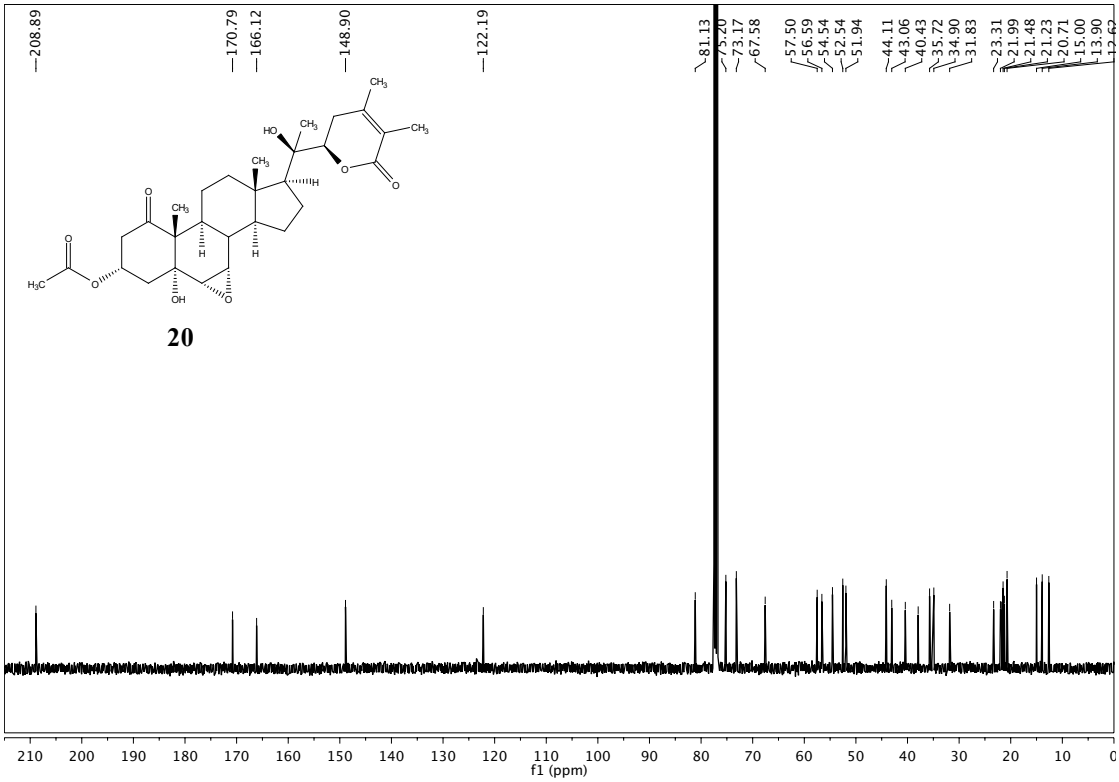
19


210.33
166.13
148.91
122.21
81.14
75.21
68.92
57.57
56.40
54.53
53.73
51.95
47.20
44.32
40.42
38.49
35.53
34.83
31.83
23.23
22.02
21.65
21.26
20.72
16.02
13.98
12.63
f1 (ppm)

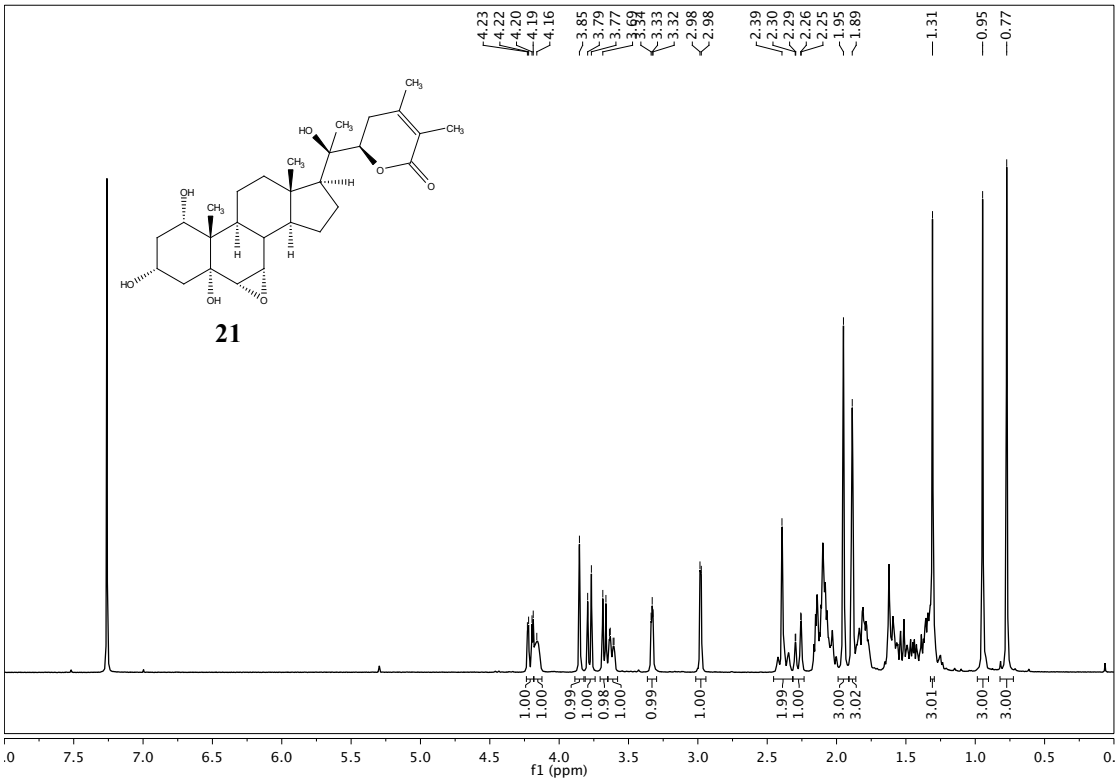
19

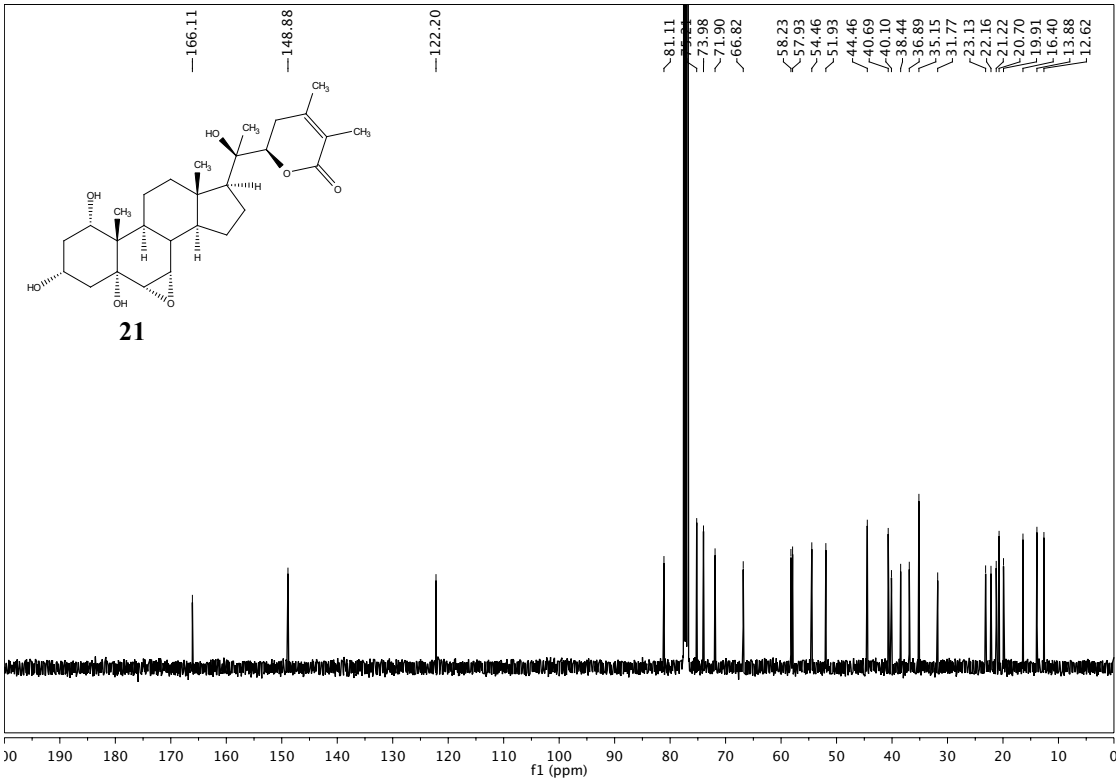

5.46
5.44
4.22
4.21
4.18
4.17
3.30
3.29
3.29
3.16
3.15
3.01
3.01
3.00
2.97
2.62
2.61
2.58
2.57
2.50
2.09
1.95
1.89
1.31
1.08
0.94
1.00
1.00
1.00
1.00
1.98
1.00
1.01
3.00
3.00
3.00
3.00
3.00
3.00
f1 (ppm)

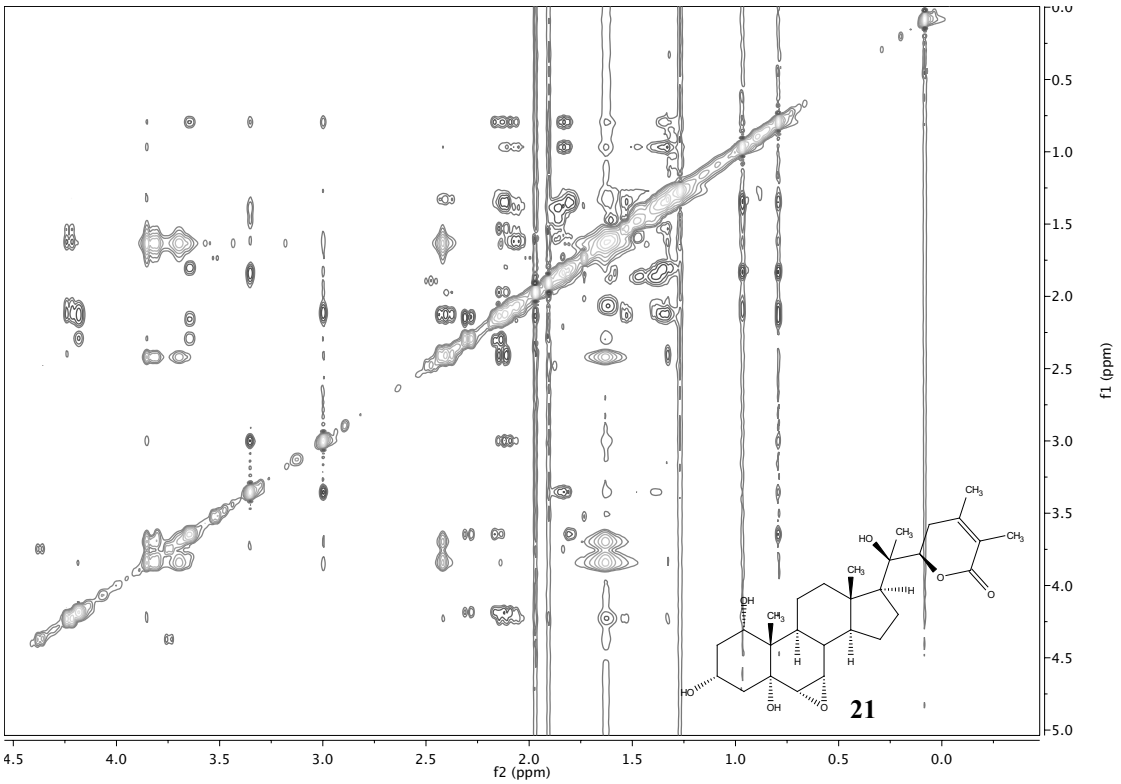
20

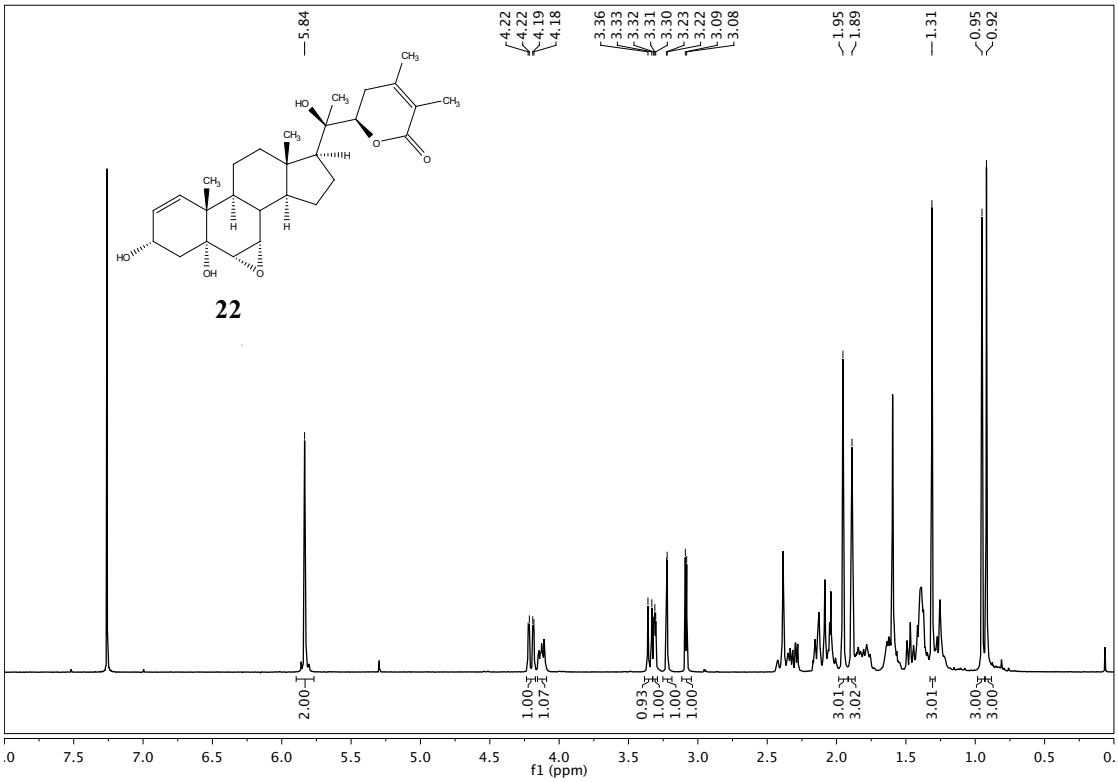

208.89
170.79
166.12
148.90
122.19
81.13
75.20
73.17
67.58
57.50
56.59
54.54
52.54
51.94
44.11
43.06
40.43
35.72
34.90
31.83
23.31
21.99
21.48
21.23
20.71
15.00
13.90
12.62
f1 (ppm)

20

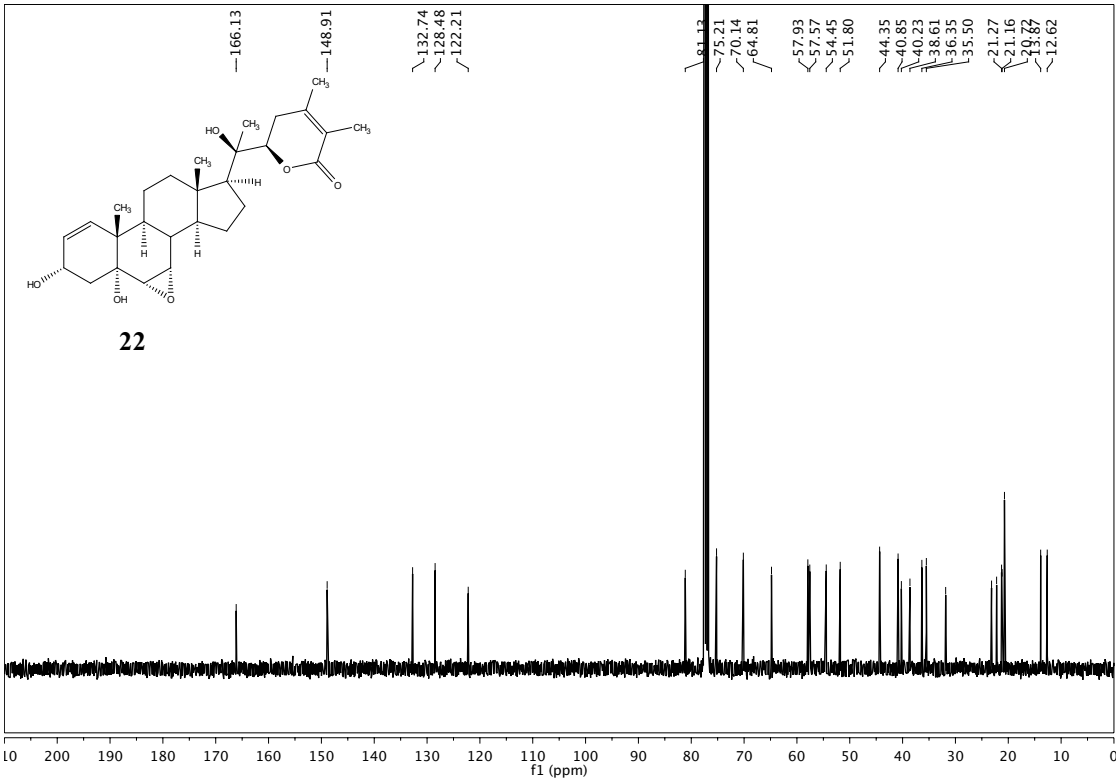

4.23
4.22
4.20
4.19
4.16
3.85
3.79
3.77
3.69
3.54
3.33
3.32
2.98
2.98
2.39
2.30
2.29
2.26
2.25
1.95
1.89
1.31
0.95
0.77
1.00
1.00
0.99
1.00
0.98
1.00
0.99
1.00
1.99
1.00
3.00
3.02
3.01
3.00
3.00
21
f1 (ppm)


166.11
148.88
122.20
81.11
73.98
71.90
66.82
58.23
57.93
54.46
51.93
44.46
40.69
40.10
38.44
36.89
35.15
31.77
23.13
22.16
21.22
20.70
19.91
16.40
13.88
12.62
21
f1 (ppm)

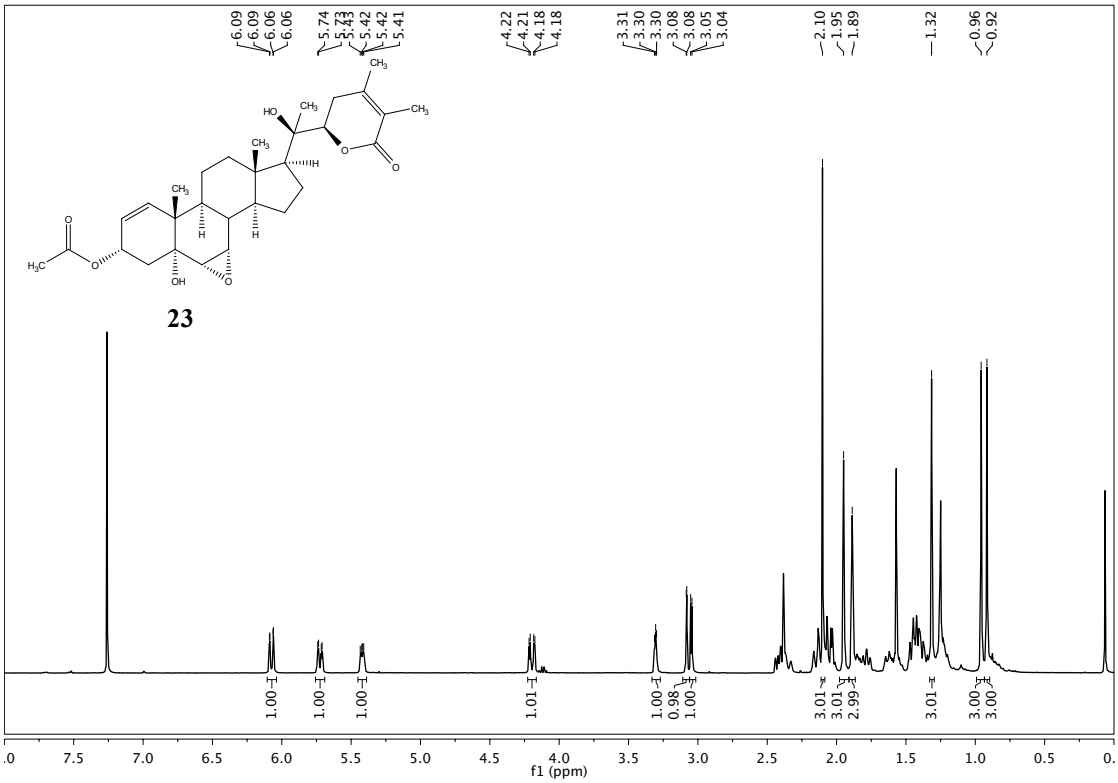



5.84
4.22
4.22
4.19
4.18
3.36
3.33
3.32
3.31
3.30
3.23
3.22
3.09
3.08
1.95
1.89
1.31
0.95
0.92
2.00
1.00
1.07
0.93
1.00
1.00
1.00
3.01
3.02
3.01
3.00
3.00
f1 (ppm)

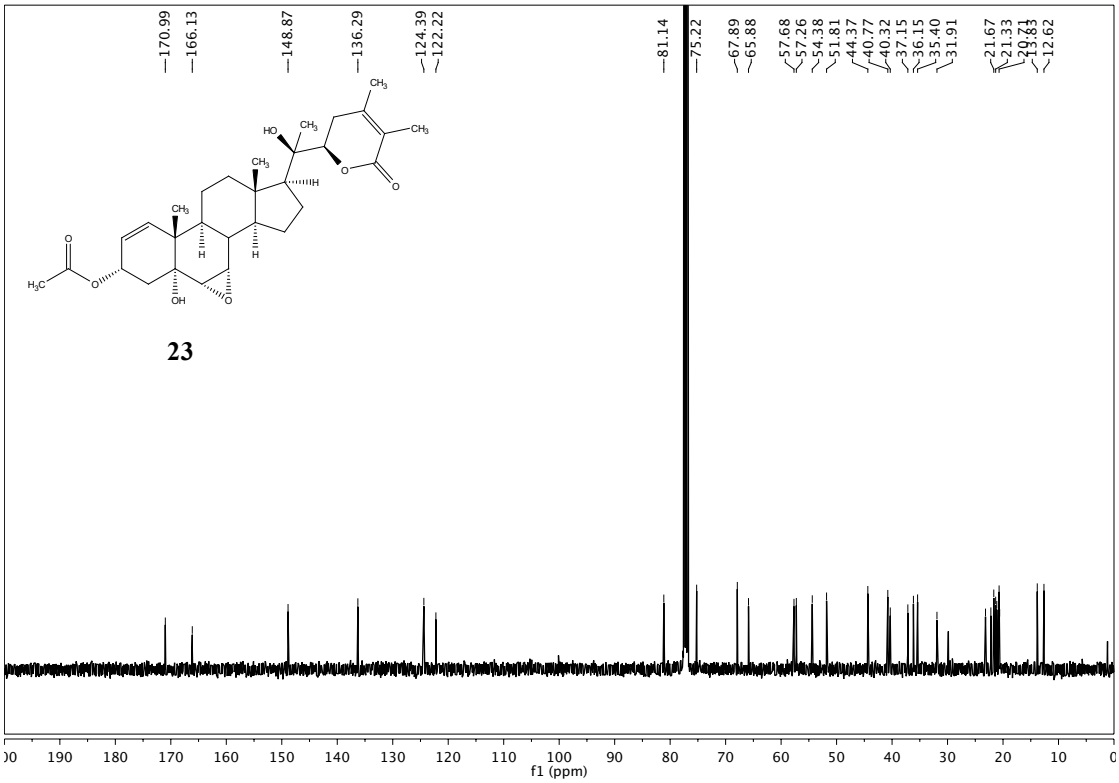
22


166.13
148.91
132.74
128.48
122.21
81.12
75.21
70.14
64.81
57.93
57.57
54.45
51.80
44.35
40.85
40.23
38.61
36.35
35.50
21.27
21.16
19.47
18.87
12.62
f1 (ppm)

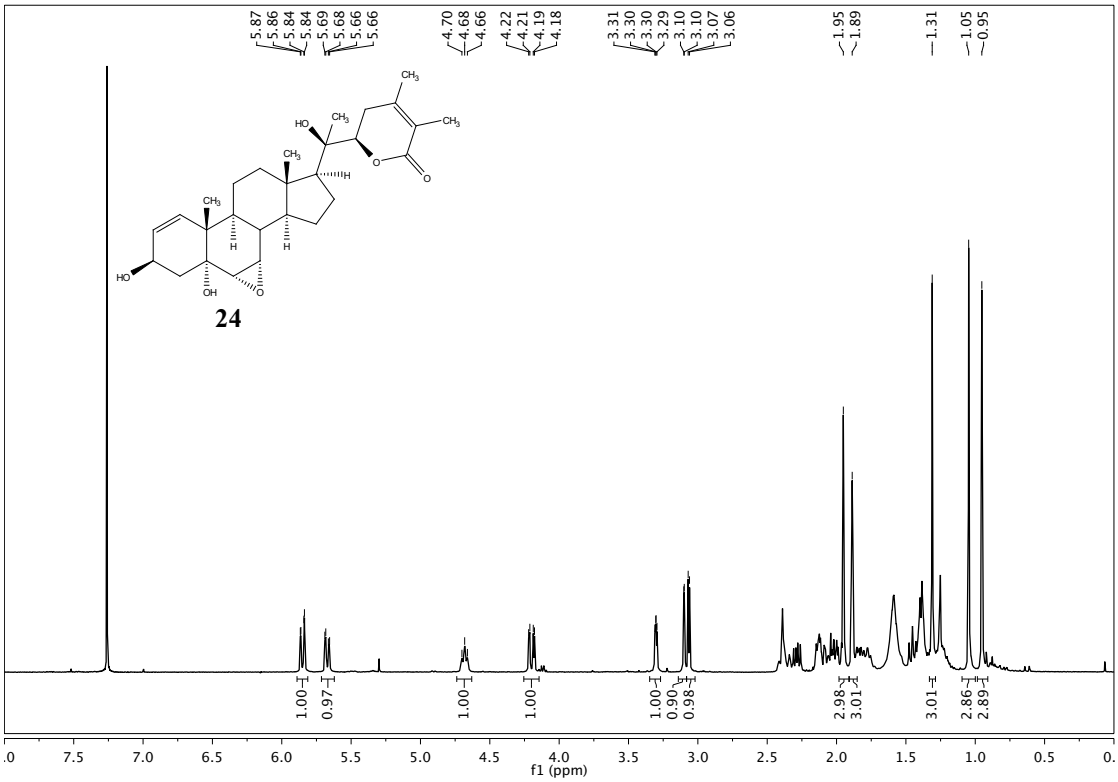
22


6.09
6.09
6.06
6.06
5.74
5.43
5.43
5.42
5.42
5.41
4.22
4.21
4.18
4.18
3.31
3.30
3.30
3.08
3.05
3.04
2.10
1.95
1.89
1.32
0.96
0.92
1.00
1.00
1.00
1.01
1.00
0.98
1.00
3.01
3.01
2.99
3.01
3.00
3.00
f1 (ppm)

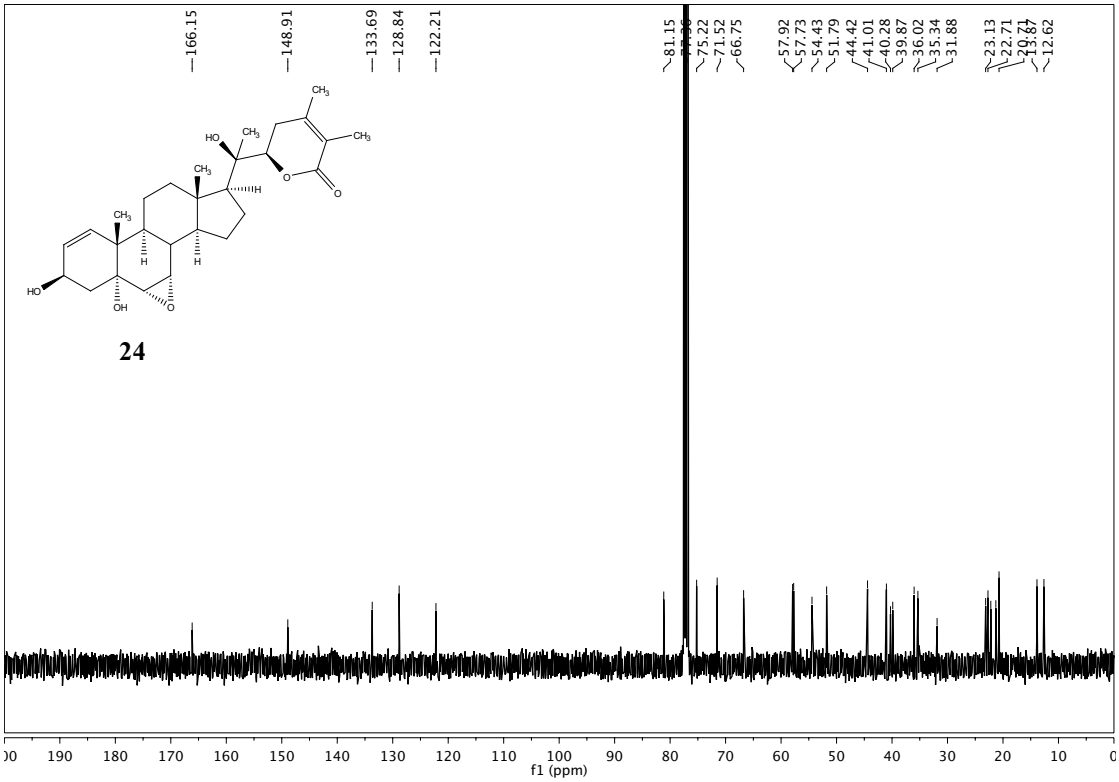
23


170.99
166.13
148.87
136.29
124.39
122.22
81.14
75.22
67.89
65.88
57.68
57.26
54.38
51.81
44.37
40.77
40.32
37.15
36.15
35.40
31.91
21.67
21.33
19.71
13.83
12.62
f1 (ppm)

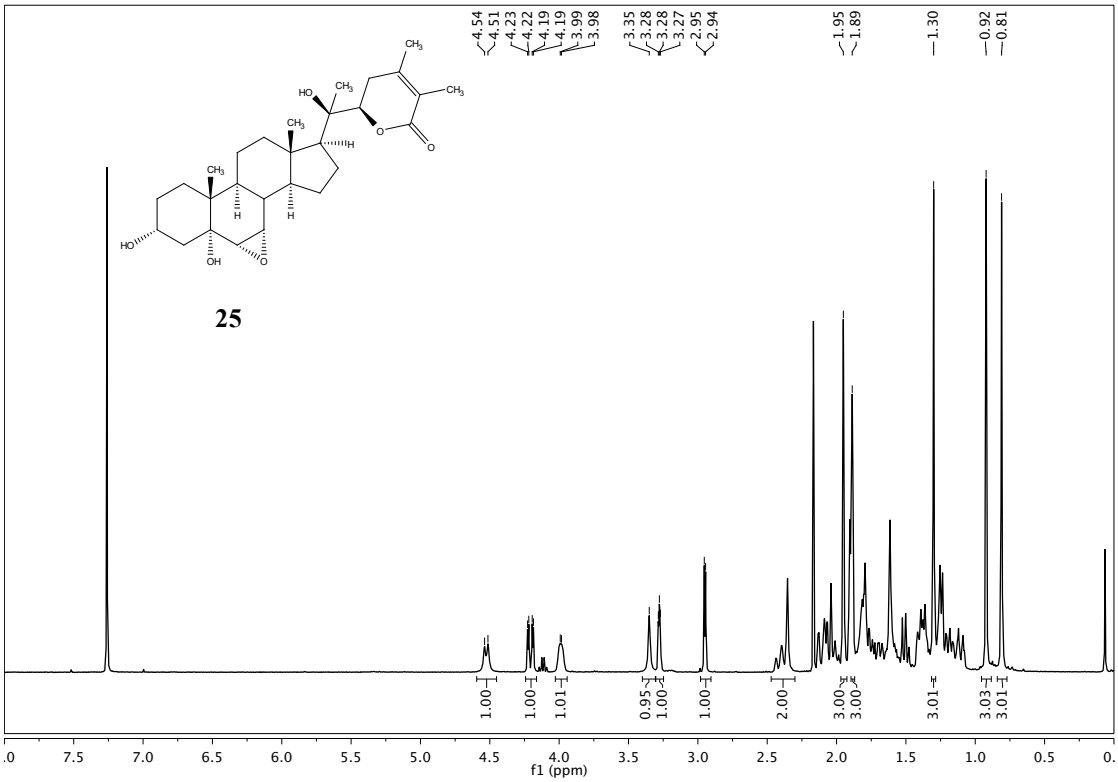
23


5.87
5.86
5.84
5.84
5.69
5.68
5.66
5.66
4.70
4.68
4.66
4.22
4.21
4.19
4.18
3.31
3.30
3.30
3.29
3.10
3.10
3.07
3.06
1.95
1.89
1.31
1.05
0.95
1.00
0.97
1.00
1.00
1.00
0.90
0.98
2.98
3.01
3.01
2.86
2.89
f1 (ppm)

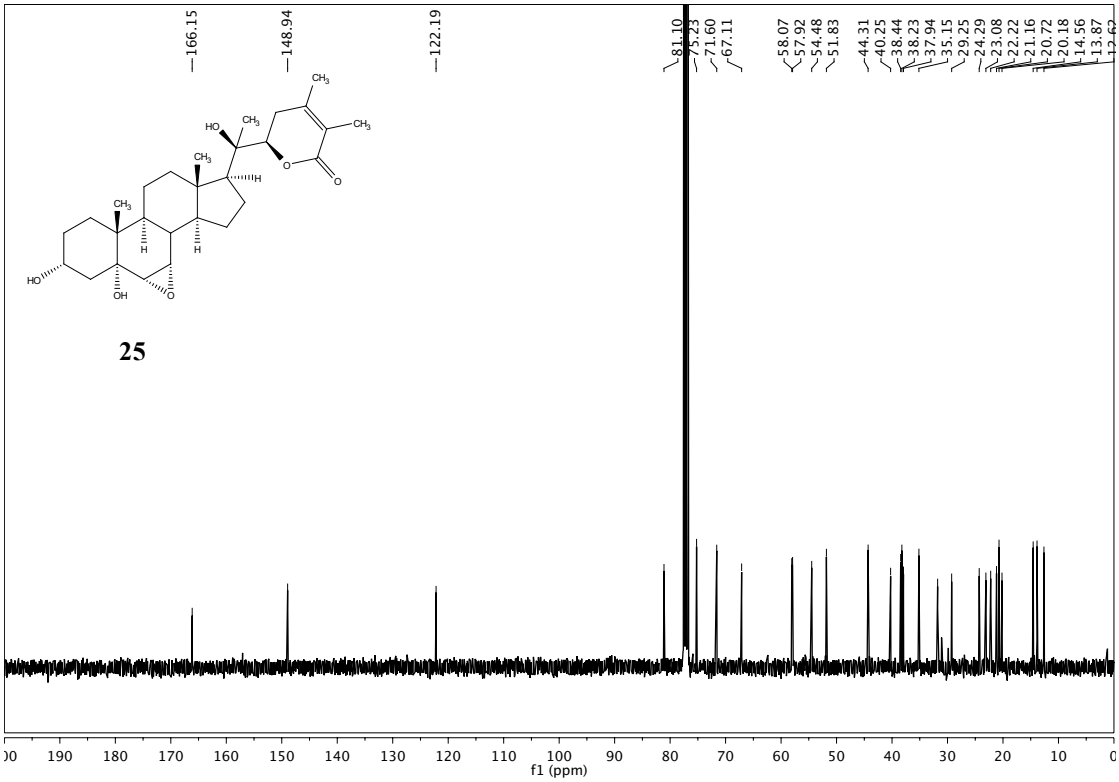
24


166.15
148.91
133.69
128.84
122.21
81.15
75.22
71.52
66.75
57.92
57.73
54.43
51.79
44.42
41.01
40.28
39.87
36.02
35.34
31.88
23.13
22.71
20.71
19.87
12.62
f1 (ppm)

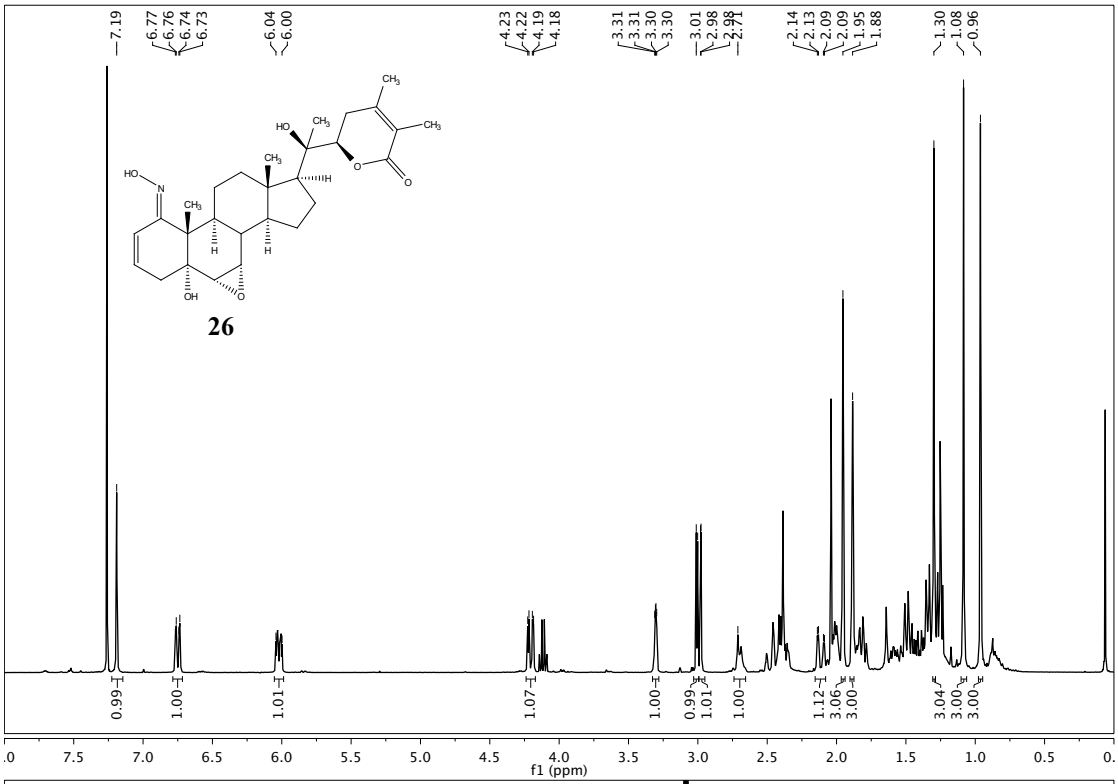
24


4.54
4.51
4.23
4.22
4.19
4.19
3.99
3.98
3.35
3.28
3.28
3.27
2.95
2.94
1.95
1.89
1.30
0.92
0.81
1.00
1.00
1.01
0.95
1.00
1.00
2.00
3.00
3.00
3.01
3.03
3.01
f1 (ppm)

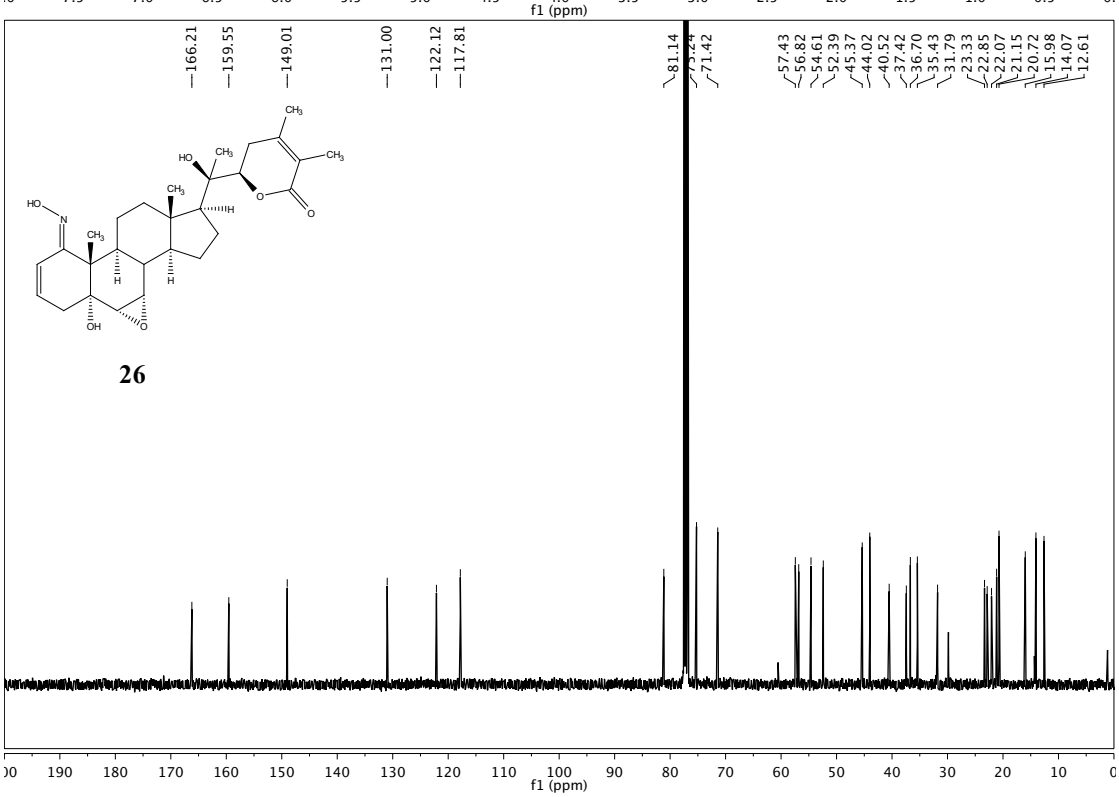
25


166.15
148.94
122.19
81.10
75.23
71.60
67.11
58.07
57.92
54.48
51.83
44.31
40.25
38.44
38.23
37.94
35.15
29.25
24.29
23.08
22.22
21.16
20.72
20.18
14.56
13.87
f1 (ppm)

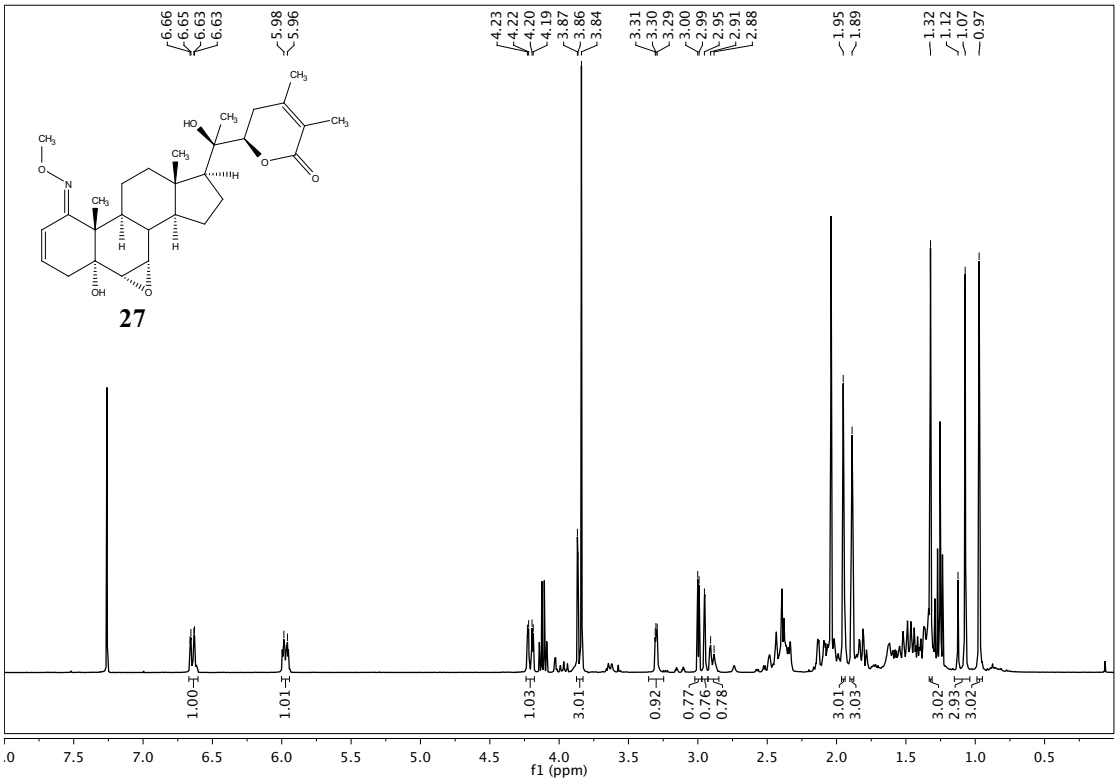
25


7.19
6.77
6.76
6.74
6.73
6.04
6.00
4.23
4.22
4.19
4.18
3.31
3.31
3.30
3.30
3.01
2.98
2.98
2.91
2.14
2.13
2.09
2.09
1.95
1.88
1.30
1.08
0.96
0.99
1.00
1.01
1.07
1.00
0.99
1.01
1.00
1.12
3.06
3.00
3.04
3.00
3.00
f1 (ppm)

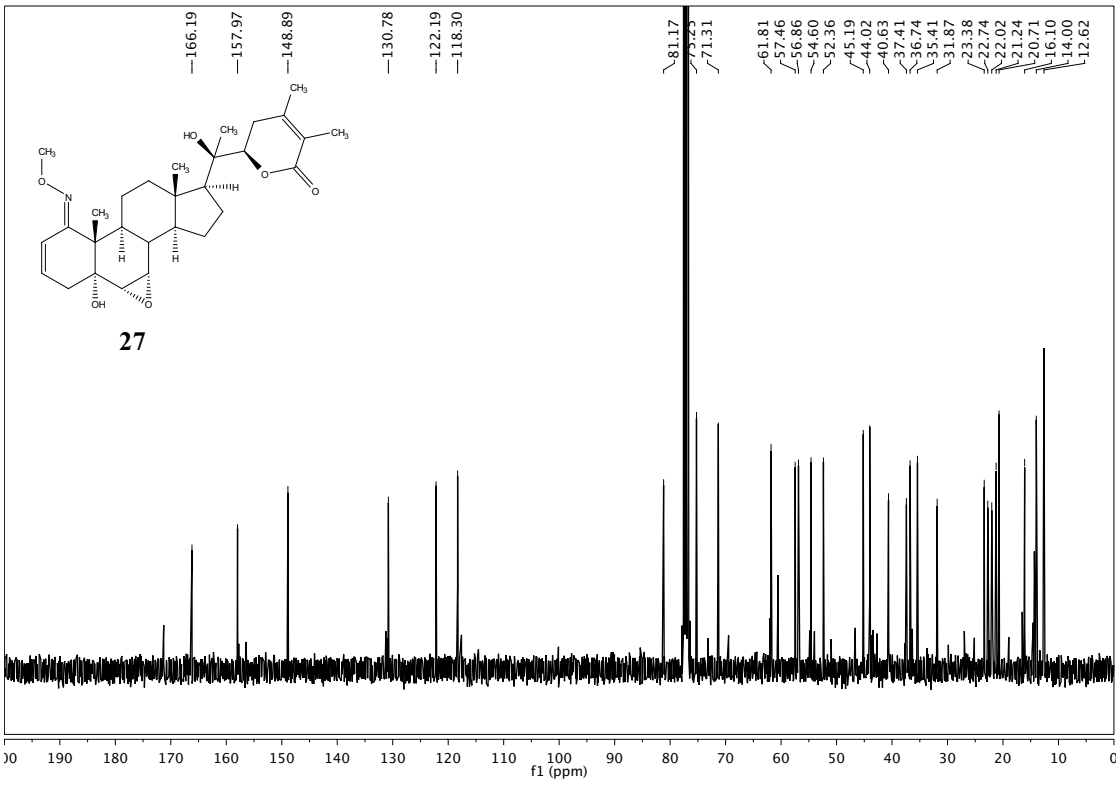
26


166.21
159.55
149.01
131.00
122.12
117.81
81.14
57.43
56.82
54.61
52.39
45.37
44.02
40.52
37.42
36.70
35.43
31.79
23.33
22.85
22.07
21.15
20.72
15.98
14.07
12.61
f1 (ppm)

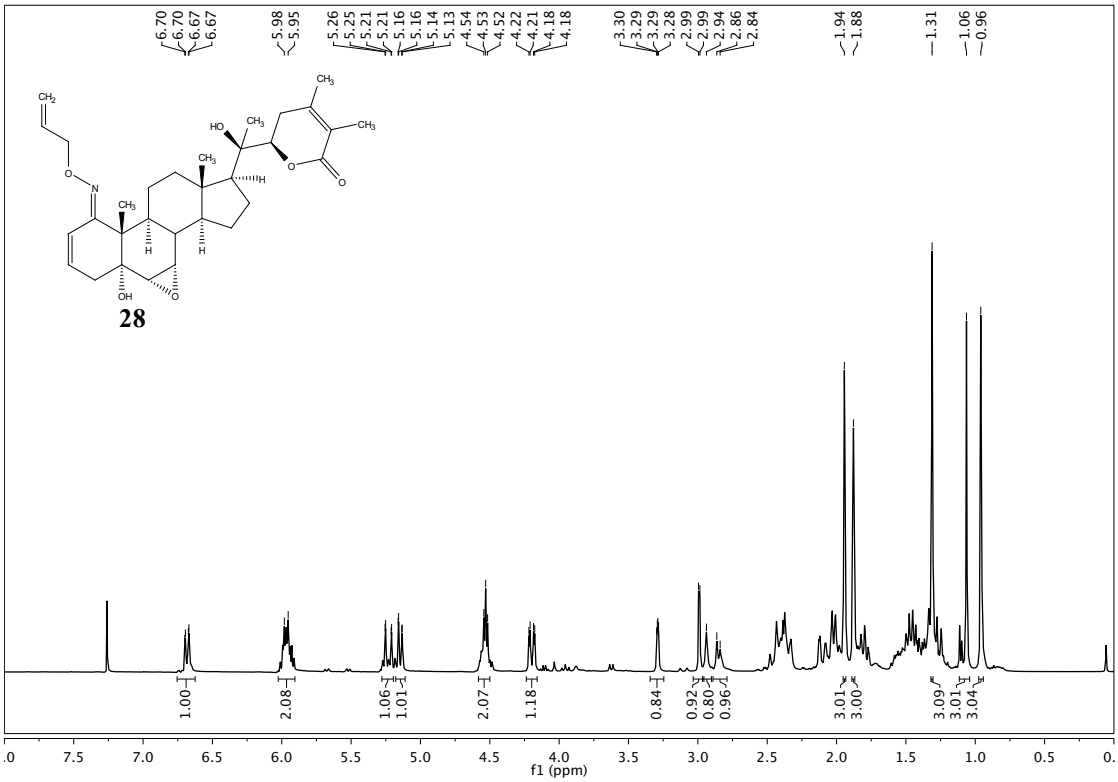
26


6.66
6.65
6.63
6.63
5.98
5.96
4.23
4.22
4.20
4.19
3.87
3.86
3.84
3.31
3.30
3.29
3.00
2.99
2.95
2.91
2.88
1.95
1.89
1.32
1.12
1.07
0.97
1.00
1.01
1.03
3.01
0.92
0.77
0.76
0.78
3.01
3.03
3.02
2.93
3.02
f1 (ppm)

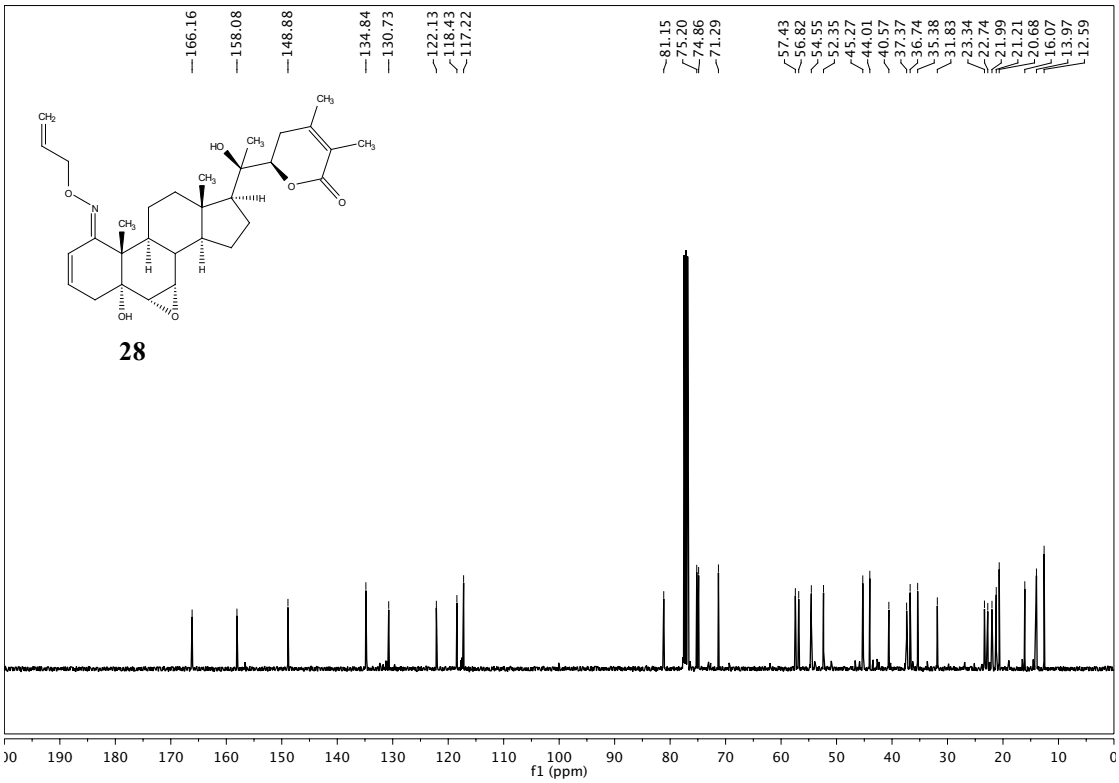
27


166.19
157.97
148.89
130.78
122.19
118.30
81.17
79.23
71.31
61.81
57.46
56.86
54.60
52.36
45.19
44.02
40.63
37.41
36.74
35.41
31.87
23.38
22.74
22.02
21.24
20.71
16.10
14.00
12.62
f1 (ppm)

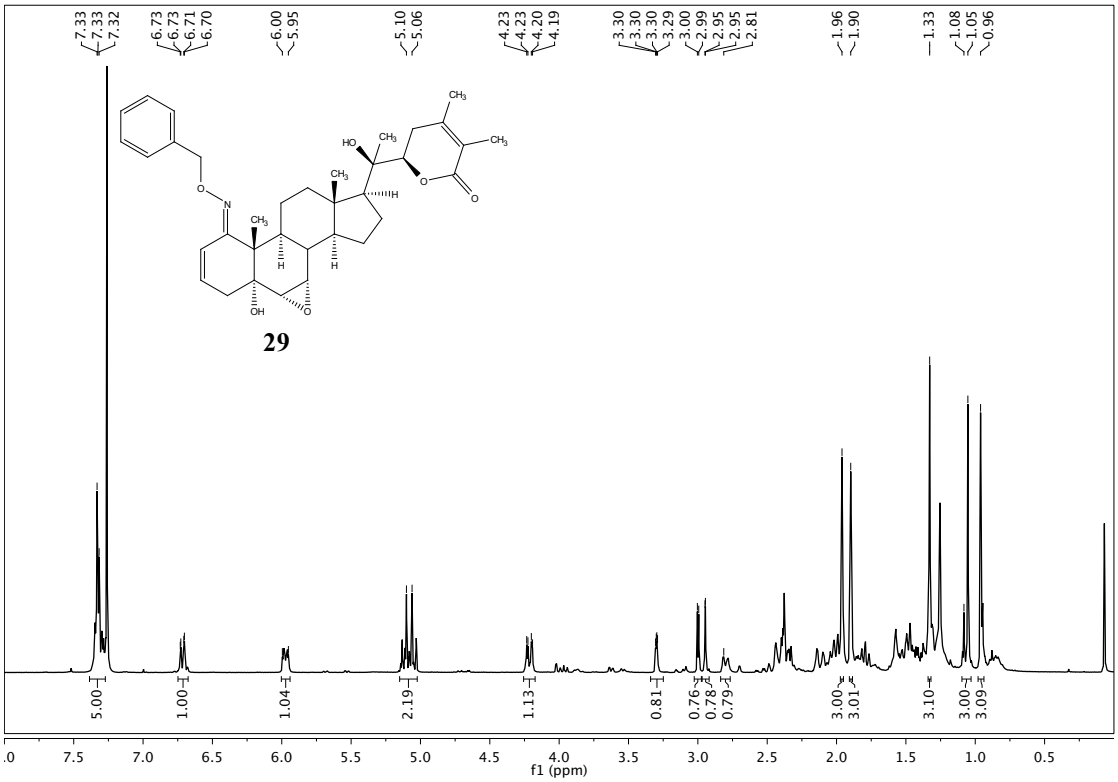
27


6.70
6.70
6.67
6.67
5.98
5.95
5.26
5.25
5.21
5.21
5.16
5.16
5.14
5.13
4.54
4.53
4.52
4.22
4.21
4.18
4.18
3.30
3.29
3.29
3.28
2.99
2.99
2.94
2.86
2.84
1.94
1.88
1.31
1.06
0.96
1.00
2.08
1.06
1.01
2.07
1.18
0.84
0.92
0.80
0.96
3.01
3.00
3.09
3.01
3.04
f1 (ppm)

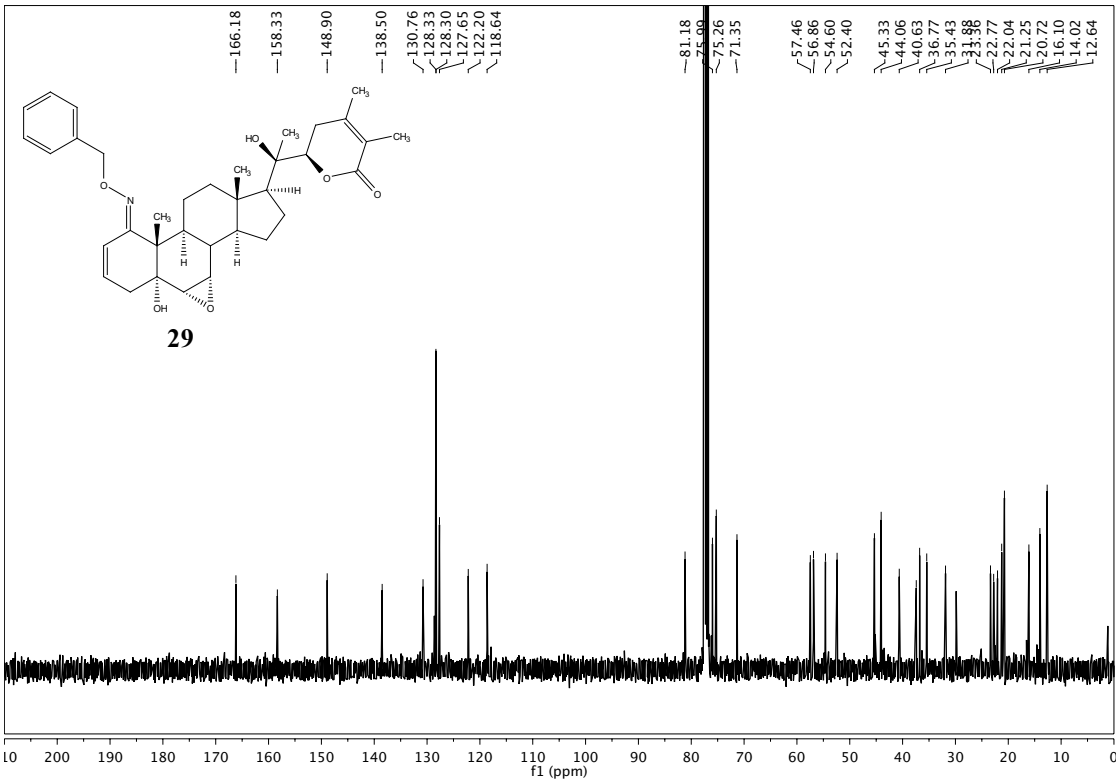
28


166.16
158.08
148.88
134.84
130.73
122.13
118.43
117.22
81.15
75.20
74.86
71.29
57.43
56.82
54.55
52.35
45.27
44.01
40.57
37.37
36.74
35.38
31.83
23.34
22.74
21.99
21.21
20.68
16.07
13.97
12.59
f1 (ppm)

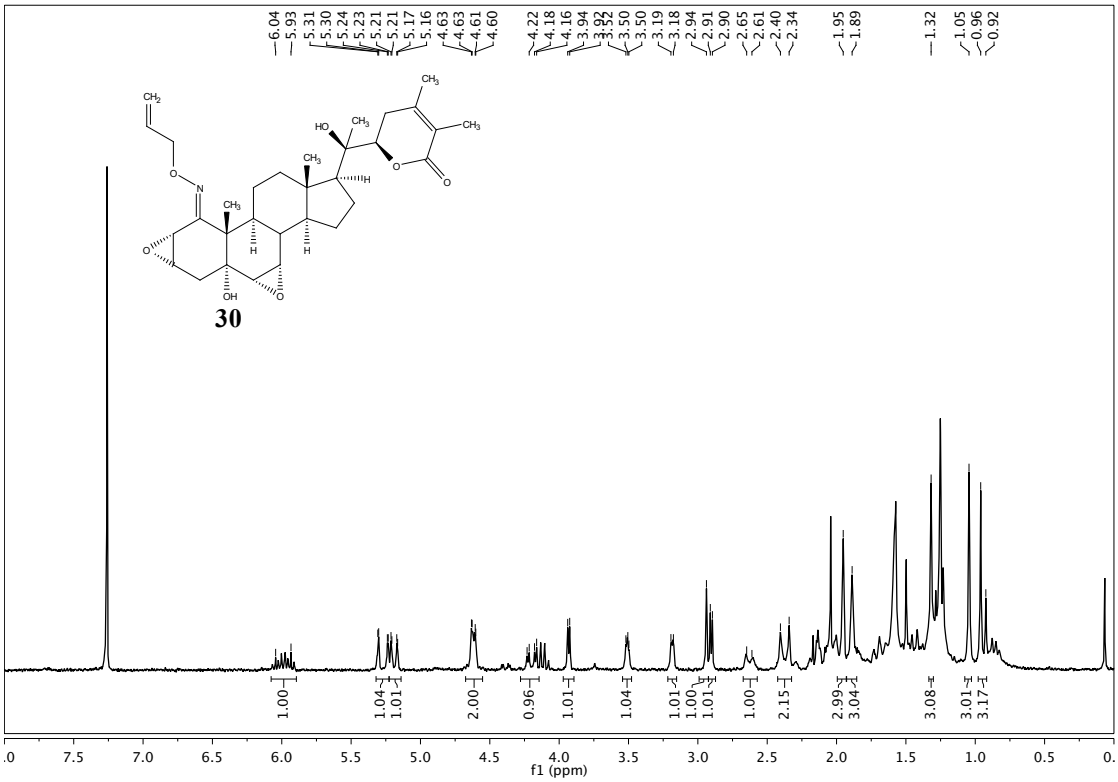
28

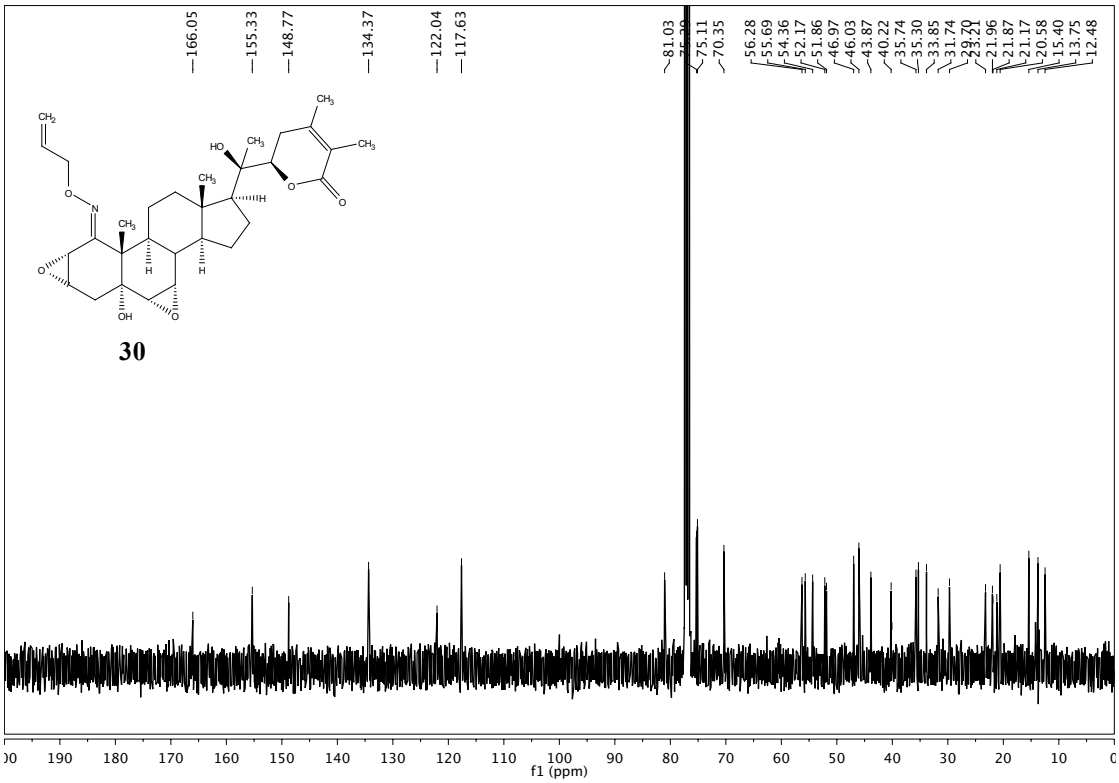

7.33
7.33
7.32
6.73
6.73
6.71
6.70
6.00
5.95
5.10
5.06
4.23
4.23
4.20
4.19
3.30
3.30
3.30
3.29
3.00
2.99
2.95
2.95
2.81
1.96
1.90
1.33
1.08
1.05
0.96
5.00
1.00
1.04
2.19
1.13
0.81
0.76
0.78
0.79
3.00
3.01
3.10
3.00
3.09
f1 (ppm)

29

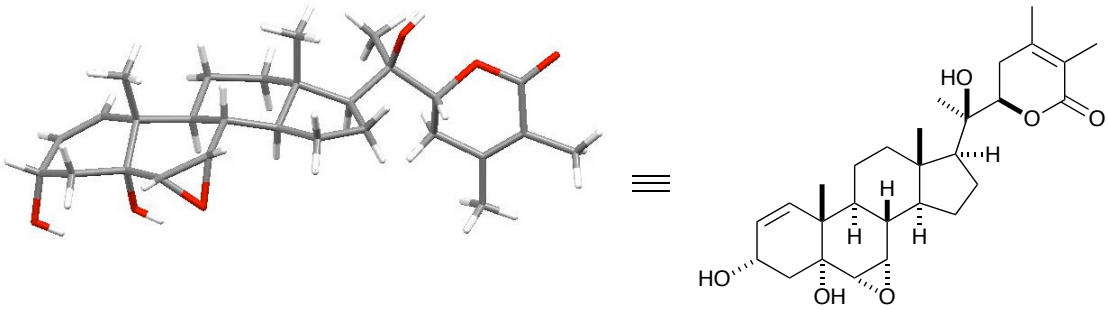

166.18
158.33
148.90
138.50
130.76
128.33
128.30
127.65
122.20
118.64
81.18
75.09
75.26
71.35
57.46
56.86
54.60
52.40
45.33
44.06
40.63
36.77
35.43
31.88
31.36
22.77
22.04
21.25
20.72
16.10
14.02
12.64
f1 (ppm)

29


6.04
5.93
5.31
5.30
5.24
5.23
5.21
5.21
5.17
5.16
4.63
4.63
4.61
4.60
4.22
4.18
4.16
3.94
3.92
3.52
3.50
3.50
3.19
3.18
2.94
2.91
2.90
2.65
2.61
2.40
2.34
1.95
1.89
1.32
1.05
0.96
0.92
30
1.00
1.04
1.01
2.00
0.96
1.01
1.04
1.01
1.00
1.01
1.00
2.15
2.99
3.04
3.08
3.01
3.17
f1 (ppm)


166.05
155.33
148.77
134.37
122.04
117.63
81.03
75.11
70.35
56.28
55.69
54.36
52.17
51.86
46.97
46.03
43.87
40.22
35.74
35.30
33.85
31.74
29.70
23.21
21.96
21.87
21.17
20.58
15.40
13.75
12.48
30
f1 (ppm)

IV. X-Ray Data



22

Table 1: Crystal data for allylic alcohol **22** (CCDC 924130).

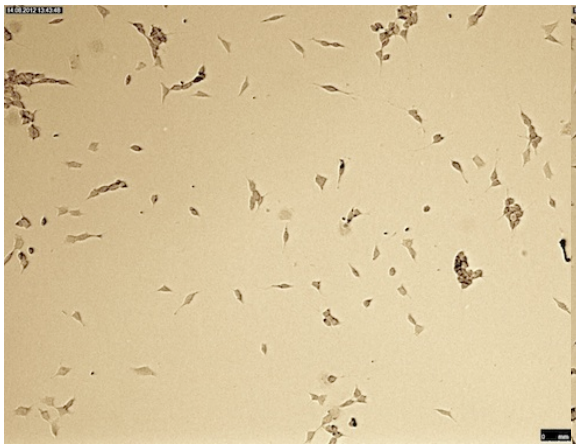
Formula	$C_{28}H_{40}O_6$
Formula weight	472.62
Z, calculated density	4, 1.256 Mg · m^{-3}
F(000)	1024
Description and size of crystal	colourless, 0.030·0.090·0.270 mm^3
Absorption coefficient	0.087 mm^{-1}
Min/max transmission	0.99 / 1.00
Temperature	123 K
Radiation(wavelength)	Mo K_α (λ = 0.71073 Å)
Crystal system, space group	orthorhombic, $P\ 2_1\ 2_1\ 2_1$
a	11.3881(10) Å
b	13.7611(13) Å
c	15.9461(16) Å
α	90°
β	90°
γ	90°
V	2499.0(4) $Å^3$
Min/max Θ	1.955° / 36.318°
Number of collected reflections	42220
Number of independent refections	6467 (merging r = 0.050)
Number of observed reflections	4541 (I>2.0σ(I))
Number of refined parameters	307
r	0.0394
rW	0.0673
Goodness of fit	1.1096

V. Neuritogenic Properties

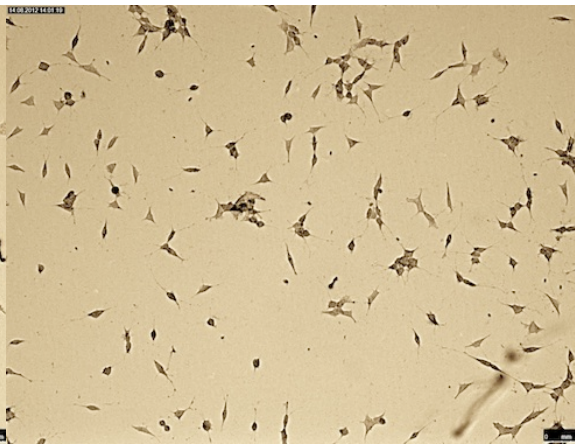
SH-SY5Y cells (obtained from DSMZ, Germany) were cultured either in *minimal essential medium* (MEM Glutamax, GIBCO, Invitrogen) containing 5% fetal bovine serum (FBS, GIBCO, Invitrogen) without antibiotics or in *Dulbecco's modified Eagle's medium* (DMEM, high glucose + L-glutamine, Sigma-Aldrich), containing 10% FBS and 1% of antibiotics in solution (10.000 units penicillin and 10 mg streptomycin/mL, Sigma-Aldrich). All experiments were conducted under strictly sterile conditions. Passage numbers 6 to 9 were used for the experiments. Cells were plated either on 24-well plates (Becton Dickinson Labware, Europe) or on collagen coated 24-well plates (Iwaki, Asahi Glass Co., Japan). After incubating for six days in the presence of the compounds, e.g. withanolide A (1 µM), vehicle solution (DMSO, 0.1%, negative control) or *all-trans* retinoic acid (1 µM, positive control, Sigma-Aldrich), cells were examined under a phase contrast microscope (Leica, Germany). Cells were examined in three randomly chosen areas per well (160x magnification). 18-21 wells were analyzed for withanolide A under different conditions (cond. A : MEM, uncoated wells; cond. B: DMEM, coated wells; cond. C : MEM, coated wells). More than 1500 cells were examined and ranked positive, if they had neurite processes of more than 50 µM length. Large cell aggregates were not counted. The ratio of neurite positive cells to total cells was calculated. Error bars are given as SEM. Under conditions C, negative control pictures could not be obtained randomly, as almost exclusively cell aggregates were found. Therefore, wells were scanned for areas that were appropriate for evaluation.

Representative micrographs:

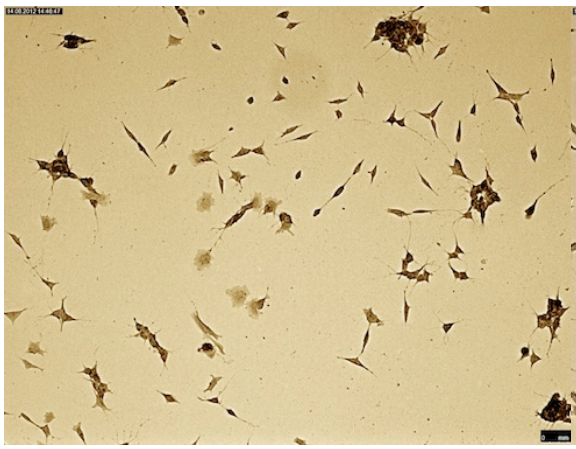
DMSO



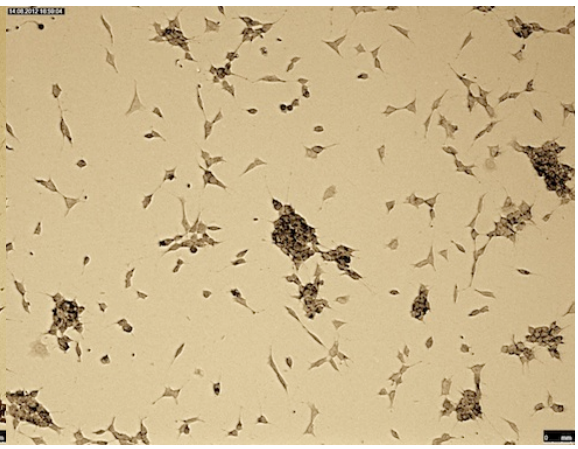
withanolide A **1**



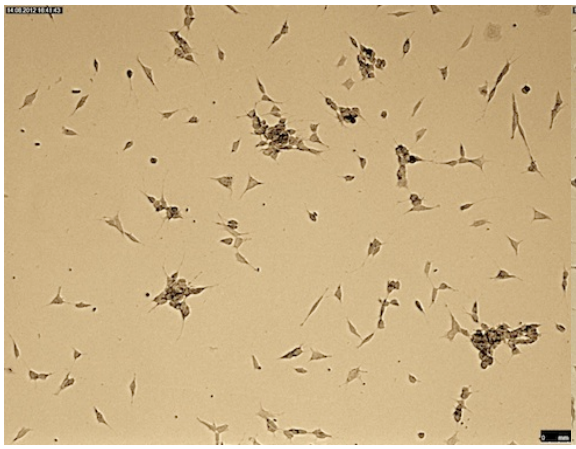
allyl alcohol **24**



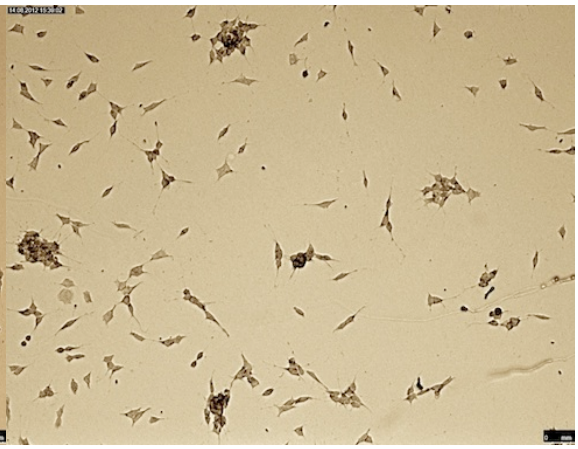
allyl alcohol **22**



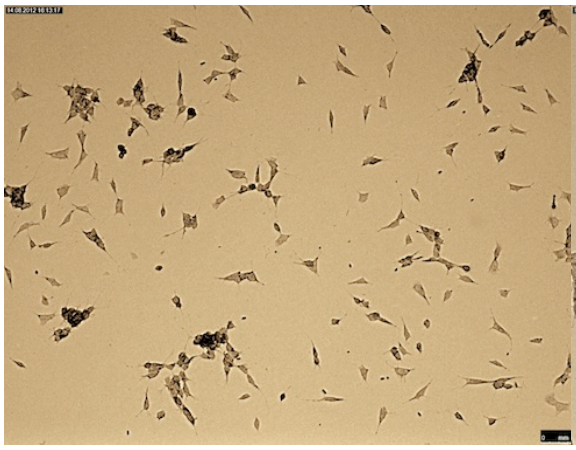
hydroxylamine **26**



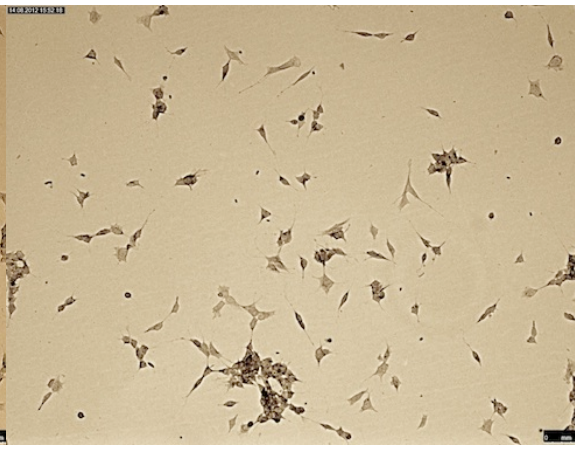
allyl alcohol **16**



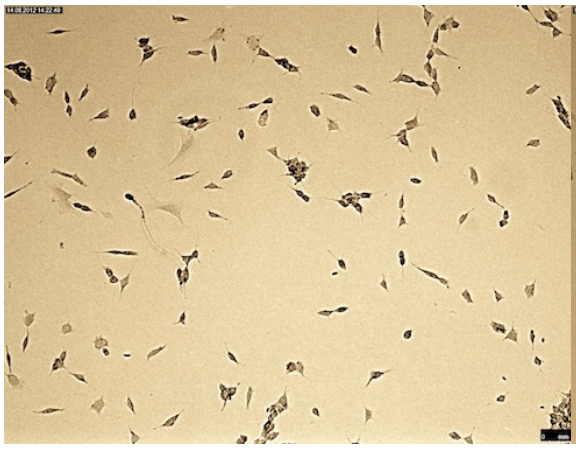
acetate **23**



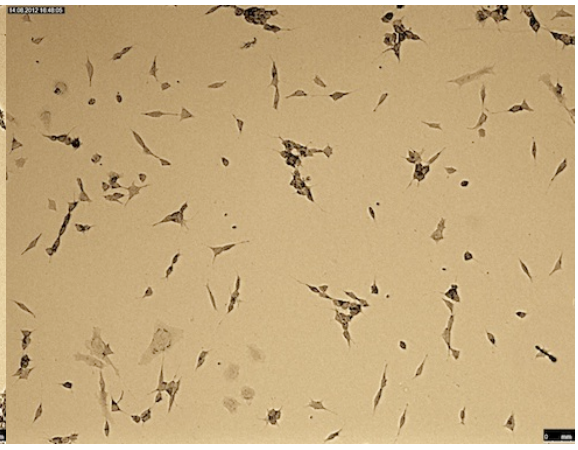
epoxy allyloxime **30**



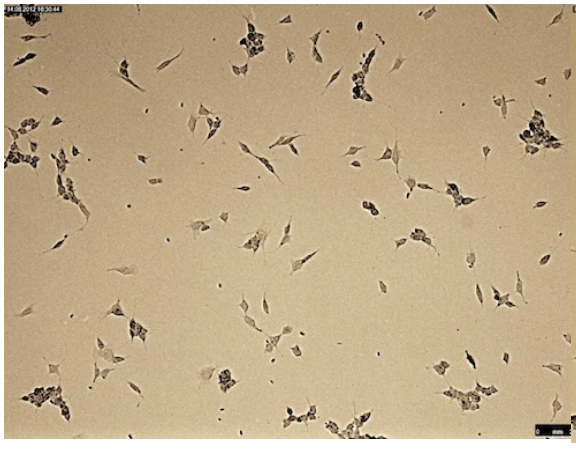
allyloxime **28**



epoxide **18**



benzyloxime **29**



methyloxime **27**