Supporting information

The Total Synthesis of (-)-Callystatin A

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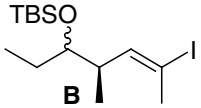
Vinyl iodide **B**:



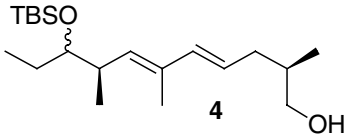
[368.0]

The Schwartz reagent (1.5 g, 5.84 mmol) was suspended in THF/benzene (20 mL) and acetylene **3** (700 mg, 2.92 mmol) was added at room temperature. The reaction was monitored via TLC and after the starting material was consumed I_2 (742 mg, 2.92 mmol) was added. The reaction was allowed to stir for 1h and was then quenched with water. The aqueous layer was extracted with MTB-ether (3x100 mL) and the combined organic layers were washed with sat. $Na_2S_2O_3$ solution (2x100 mL). The organic layer was washed once with 100 mL brine, dried over $MgSO_4$, concentrated under vacuum and purified via flash chromatography (hexanes) to yield the desired vinyl iodide **B** in 60% yield (645 mg, 1.75 mmol).

^{1}H NMR (500 MHz, $CDCl_3$)(major isomer resonances): 6.05 (dq, J = 10.0, 1.5 Hz, 1H), 3.44 (q, J = 5.5 Hz, 1H), 2.49 (qdd, J = 5.5, 6.8, 10.0 Hz, 1H), 2.38 (d, J = 1.5 Hz, 3H), 1.37-1.54 (m, 2H), 0.93 (d, J = 6.8 Hz, 3H), 0.90 (s, 9H), 0.85 (t, J = 5.8 Hz, 3H), 0.02 (s, 3H), 0.03 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): 145.04, 92.97, 76.21, 39.76, 27.76, 27.40, 25.91, 18.14, 15.10, 9.14, -4.25.

Alcohol **4:**



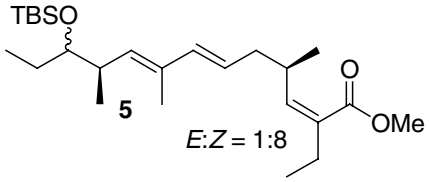
[340.62]

$Pd(OAc)_2$ (30 mg, 0.13 mmol), AgOAc (300 mg, 1.79 mmol) and alcohol **C**[1] (190 mg, 1.9 mmol) were dissolved in DMF (5 mL). Vinyl iodide **B** (500 mg, 1.36 mmol), dissolved in DMF (0.5 mL) was added over 20 min at room temperature. The reaction was stirred for 2h and then directly put on a silica gel column. The product was purified by flash chromatography (hexanes/ethyl acetate, 5:1) to yield 65% (300 mg, 88.3 mmol) of the desired product.

^{1}H NMR (500 MHz, $CDCl_3$)(major isomer resonances): 6.05 (d, J = 15.6 Hz, 1H), 5.54 (dt-like, J = 7.3, 15.6 Hz, 1H), 5.23 (d, J = 9.8 Hz, 1H), 3.41-3.53 (m, 3H), 3.07 (dq, J = 6.9, 10.0 Hz, 1H), 2.54-2.64 (m, 1H), 2.15-2.23 (m, 1H), 1.95-2.04 (m, 1H), 1.73 (d, J = 1.3 Hz, 3H), 1.37-1.52 (m, 3H), 0.93 (d, J = 6.8 Hz, 3H), 0.92 (d, J = 6.8 Hz, 3H), 0.90 (s, 9H), 0.84 (t, J = 7.4 Hz, 3H), 0.02 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): 137.12, 135.25, 132.39, 125.56, 77.56, 77.46, 68.39, 37.21, 36.67, 27.96, 26.32, 18.57, 16.88, 16.59, 13.12, 9.38, -4.11.

Ester **5**:



[422.72]

Alcohol **4** (380 mg, 1.12 mmol) was dissolved in CH_2Cl_2 (5 mL) and cooled to 0 °C. At this temperature the Dess-Martin periodinane (475 mg, 1.12 mmol) was added and the reaction was stirred for 30 min. Then sat. $NaHCO_3$ solution (10 mL) and $Na_2S_2O_3$ (1g) were added. The aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The Dess-Martin reagent was precipitated by the addition of light petroleum and the crude product was directly used in the next transformation. Still-Gennari reagent (581 mg, 1.68 mmol) and 18-c-6 (1.48 g, 5.6 mmol) were dissolved in 20 mL THF. At 0 °C KHMDS (0.5 M in toluene, 2.24 mL, 1.12 mmol) was added and the solution was cooled to –78 °C. After 15 min the crude aldehyde prepared above (377 mg, 1.12 mmol) dissolved in THF (0.5 mL) was added and the reaction was stirred at that temperature for 15 min. The reaction was then allowed to warm to room temperature. After 1.5h the

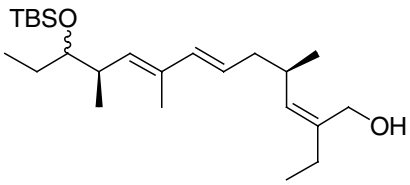
[1] a) Overman, L. E; Robinson, L. A.; Zablocki, J. *J. Am. Chem. Soc.* **1992**, *114*, 368; b) Schinzer, D.; Bauer, A.; Schieber, J. *Synlett* **1998**, 861.

reaction was quenched with brine, extracted with MTB-ether (3x100 mL) and dried over $MgSO_4$. After purification via flash chromatography (hexanes/ethyl acetate, 60:1) ester **5** was obtained in 65% yield (307 mg, 0.728 mmol).

^{1}H NMR (500 MHz, $CDCl_3$)(major isomer resonances): 5.99 (d, J = 14.7 Hz, 1H), 5.62 (d, J = 10.0 Hz, 1H), 5.47 (dt-like, J = 7.0, 15.6 Hz, 1H), 5.21 (d, J = 9.1 Hz, 1H), 3.73 (s, 3H), 3.44 (q-like, J = 5.5 Hz, 1H), 3.07 (dq, J = 6.9, 10.0 Hz, 1H), 2.56 (m, 1H), 2.25 (q, J = 7.1 Hz, 2H), 2.01-2.14 (m, 2H), 1.71 (d, J = 1.1 Hz, 3H), 1.37-1.51 (m, 2H), 1.01 (t, J = 7.4 Hz, 3H), 0.99 (d, J = 6.6 Hz, 3H), 0.93 (d, J = 6.8 Hz, 3H), 0.89 (s, 9H), 0.84 (t, J = 7.4 Hz, 3H), 0.02 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): 169.12, 146.06, 136.07, 134.98, 132.64, 132.54, 125.42, 77.36, 51.45, 40.83, 37.20, 34.20, 27.97, 27.95, 26.33, 20.47, 18.57, 16.52, 14.16, 13.07, 9.36, -4.11.

Alcohol:

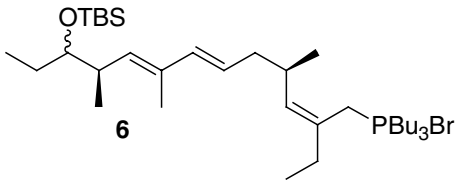


[394.71]

Ester **5** (200 mg, 0.474 mmol) was dissolved in CH_2Cl_2 (10 mL) and cooled to –78 °C. At this temperature Dibal-H (948 μL, 948 mmol) was added drop-wise. The reaction was stirred for 1.5 h and then quenched with MeOH (10 mL). The reaction mixture was warmed to room temperature and then diluted with sat. NH_4Cl solution. The organic layer was extracted with MTB-ether, the layers were separated and the organic layer was dried over $MgSO_4$. After flash chromatography (hexanes/ethyl acetate, 5:1) the alcohol was obtained in 96% yield (179 mg, 0.455 mmol).

^{1}H NMR: (500 MHz, $CDCl_3$)(major isomer resonances): 5.98 (dd, J = 0.6, 5.5 Hz, 1H), 5.47 (dt, J = 7.3, 15.5 Hz, 1H), 5.23 (d, J = 9.9 Hz, 1H), 5.06 (d, J = 9.8 Hz, 1H), 4.02-4.18 (m, 2H), 3.43 (q-like, J = 5.5 Hz, 1H), 2.40-2.67 (m, 2H), 1.90-2.20 (m, 4H), 1.71 (d, J = 1.3 Hz, 3H), 1.04-1.06 (m, 2H), 1.03 (t, J = 6.8 Hz, 3H), 0.97 (d, J = 7.0 Hz, 3H), 0.95 (d, J = 6.3 Hz, 3H), 0.89 (s, 9H), 0.83 (t, J = 6.7 Hz, 3H), 0.03 (s, 6H).

Wittig salt **6**:



[659.92]

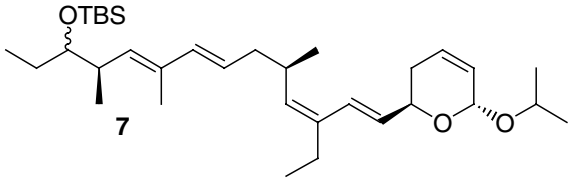
a) Transformation into the bromide:

The alcohol (158 mg, 0.4 mmol) from the previous reaction was dissolved in CH_3CN (5 mL) and PPh_3 and CBr_4 were added. The reaction was stirred for 15 min at room temperature and then quenched with water. After extraction with MTB-ether, drying over $MgSO_4$ and concentration the product was directly used in the succeeding transformation. Any attempts at purifying the compound with the aid of chromatography resulted in decomposition of the material.

b) Transformation into the Wittig salt:

The crude material from the previous reaction was dissolved in CH_3CN and tributylphosphine (200 µL, 850 mmol) was added and stirred for 1.5 h at room temperature. The disappearance of the starting material could be monitored by TLC. After 1.5 h, the solvent was removed under reduced pressure to provide residue **6** which was used directly in the following reaction.

Fragment **7**.



[530.90]

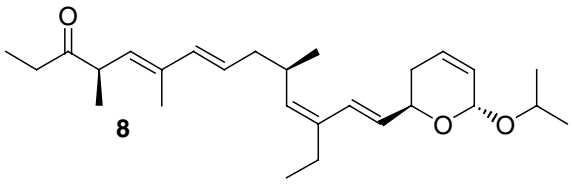
Residue **6** (~ 0.17 mmol) and aldehyde **D**[2] (0.17 mmol) were dissolved in toluene (2 mL) at 0 °C. KO*t*Bu (204 µL, 0.204 mmol, 1M in THF) was added over a period of 15 min and stirred for 30 min. After completion the reaction was quenched with water (10 mL), extracted with

[2] Quitschalle, M.; Christmann, M.; Bhatt, U.; Kalesse, M. *Tetrahedron Lett.* **2001**, *42*, 1263.

MTB-ether (3x 50 mL), dried over $MgSO_4$ and concentrated. Flash chromatography (hexanes/ethyl acetate, 5:1) gave 72 % (64.98 mg, 0.122 mmol) of the desired product.

^{1}H NMR (500 MHz, $CDCl_3$)(major isomer resonances): 6.60 (d, J = 5.6 Hz, 1H), 5.90-6.10 (m, 2H), 5.60-5.80 (m, 2H), 5.35-5.55 (m, 1H), 5.05-5.30 (m, 3H), 4.40-4.60 (m, 1H), 4.05 (heptet, J = 6.1 Hz, 1H), 3.45 (q, J = 5.5 Hz, 1H), 2.50-2.75 (m, 2H), 1.90-2.30 (m, 6 H), 1.70 (d, J = 1.0 Hz, 3H), 1.26 (d, J = 6.2 Hz, 3H), 1.18 (d, J = 6.1 Hz, 3H), 1.04-1.05 (m, 2H), 1.04 (t, J = 7.4 Hz, 3H), 0.97 (d, J = 6.7 Hz, 3H), 0.93 (d, J = 6.8 Hz, 3H), 0.89 (s, 9H), 0.83 (t, J = 7.5 Hz, 3H), 0.02 (s, 3H), 0.01 (s, 3H).

Ketone **8**:



8

[414.62]

Fragment **7** (65 mg, 0.123 mmol) was dissolved in THF (1 mL) and TBAF (615 µL, 0.615 mmol) was added at room temperature. The reaction was stirred for 24 h and then quenched with water and extracted with MTB-ether (3 x 50 mL). After drying over $MgSO_4$ and concentration under reduced pressure the material was directly used in the succeeding transformation.

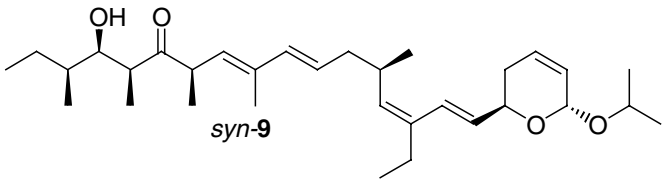
To a solution of oxalyl chloride (0.07 mL, 0.135 mmol) in CH_2Cl_2 (5 mL) was added at –78 °C dimethylsulfoxide (0.02 mL, 0.27 mmol). The reaction was stirred for 10 min and then the alcohol from the previous transformation dissolved in CH_2Cl_2 (1 mL) was added over 10 min. The mixture was stirred for additional 10 min and Et_3N (0.085 mL, 0.616 mmol) was added. After 5 min, the reaction was warmed to room temperature and concentrated under reduced pressure. Purification with flash chromatography (hexanes/ethyl acetate, 5:1) gave 73 % (37 mg, 0.09 mmol) of ketone **8**.

^{1}H NMR (500 MHz, D4-MeOH): 6.64 (dt-like, J = 1.0, 15.9 Hz, 1H), 6.02-6.10 (m, 2H), 5.78 (ddd, J = 0.7, 6.0, 15.9 Hz, 1H), 5.70-5.76 (m, 1H), 5.65 (dt-like, J = 7.0, 15.6 Hz, 1H), 5.18-5.27 (m, 2H), 5.14-5.17 (m, 1H), 4.46-4.53 (m, 1H), 4.03 (heptet, J = 6.2 Hz, 1H), 3.62 (dq, J = 6.8, 9.8 Hz, 1H), 2.69-2.79 (m, 1H), 2.54-2.59 (m,2H), 2.07-2.29 (m, 6H), 1.83 (d, J = 1.4

Hz, 3H), 1.25 (d, J = 6.3 Hz, 3H), 1.21 (d, J = 6.3, 3H), 1.15 (d, J = 6.8 Hz, 3H), 1.09 (t, J = 7.5Hz, 3H), 1.03 (d, J = 6.5 Hz, 3H),1.02 (t, J = 7.25, 3H).

^{13}C NMR (125 MHz, D4-MeOH): 214.96, 137. 98, 137.34, 136.86, 136.68, 130.48, 130.24, 129.73, 128.97, 128.59, 127.53, 95.22, 71.54, 68.83, 47.48, 42.33, 35.11, 33.72, 32.31, 27.99, 24.55, 22.82, 21.65, 17.25, 14.51, 13.39, 8.45.

*19,20-Syn-***9:**



*syn-***9**

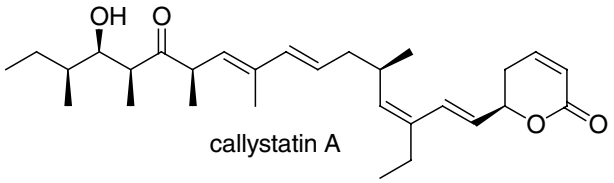
[500.75]

LiHMDS (80 µL, 0.08 mmol) was dissolved in THF (0.3 mL) and cooled to –78 °C. Ethyl ketone **8** (22 mg, 0.053 mmol, in 0.2 mL THF) was added over 5 min and stirred for additional 15 min. Then aldehyde **A** (9 mg, 0.106 mmol) was added and the reaction was quenched after 15 min with sat. NH_4Cl solution at –78 °C. The aqueous layer was extracted with MTB-ether (50 mL), the organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. After purification via flash chromatography (hexanes/ethyl acetate, 5:1) *all-syn* **9** (17 mg, 0.033 mmol) was obtained in 63 % yield.

^{1}H-NMR (500 MHz, D4-MeOH): 6.65 (d, J = 5.9 Hz, 1H), 6.00-6.10 (m, 2H), 5.62-5.82 (m, 3H), 5.09-5.25 (m, 3H), 4.50 (q, J = 6.7 Hz, 1H), 4.05 (heptet, J = 6.2 Hz, 1H), 3.79 (dd, J = 10.3, 6.7 Hz, 1H), 3.69 (dd, J = 7.65, 2.6 Hz, 1H), 2.90 (dd, J = 7.0, 8.6 Hz, 1H), 2.71-2.79 (m, 1H), 2.20-2.28 (m, 2H), 2.06-2.19 (m, 5H), 1.89 (d, 1.2 Hz, 3H), 1.26 (d, J = 6.2 Hz, 3H), 1.21 (d, J = 6.2 Hz, 3H), 1.17 (d, J = 7.0 Hz, 3H), 1.13 (d, J = 6.6 Hz, 3H), 1.09 (t, J = 7.4 Hz, 3H), 0.95-1.06 (m, 2H), 1.02 (d, J = 6.7 Hz, 3H), 0.91 (t, J = 7.1 Hz, 3H), 0.78 (d, J = 6.4 Hz, 3H).

^{13}C NMR (125 MHz, D4-MeOH): 216.68, 137.88, 137.75, 136.94, 136.72, 130.26, 129.99, 129.79, 129.19, 128.40, 127.50, 95.23, 75.56, 71.59, 68.83, 47.23, 42.32, 39.43, 33.53 32.32, 28.56, 27.97, 25.75, 24.57, 22.83, 21.47, 16.99, 14.94, 14.50, 13.72, 13.60, 12.33.

(-)-Callystatin A:



callystatin A

[456.66]

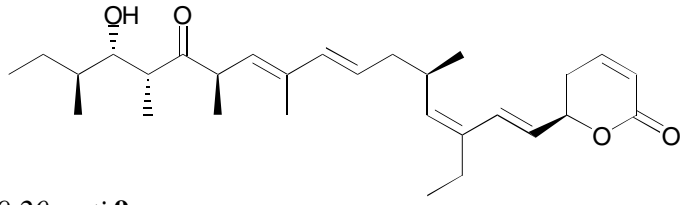
Acetal 19,20-*syn* **9** (12 mg, 0.02 mmol) was dissolved in a 3:1 mixture of acetone and water (0.5 mL). Pyridinium *p*-toluenesulfonate (PPTS) (5 mg) was added and the reaction mixture was stirred for 2h at room temperature. The reaction was then quenched with sat. $NaHCO_3$ solution and the aqueous layer was extracted with MTB-ether (3x 20 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Activated MnO_2 (100 mg) was suspended in CH_2Cl_2 (0.5 mL) containing pyridine (10 µL) and the crude lactol (dissolved in 0.5 mL CH_2Cl_2) was added at room temperature. After the reaction was allowed to stir for 30 min the MnO_2 was removed by filtration through a short plug of celite. After concentration the product was purified by flash chromatography (hexanes/ethyl acetate, 3:1) to yield 7 mg (0.015 mmol, 81 %) of synthetic callystatin A.

$[\alpha]^{24}_D$ –105° (c = 0.1, MeOH); (Lit) –107° (c = 0.1, MeOH);

^{1}H NMR (500 MHz, $CDCl_3$): 6.90 (dt, J = 9.74, 4.25 Hz, 1H), 6.64 (d, J = 15.78 Hz, 1H), 6.06 (dt, J = 9.88, 1.85 Hz, 1H), 6.01 (d, J = 15.55 Hz, 1H), 5.76 (dd, J = 15.85, 6.77 Hz, 1H), 5.58 (dt, J = 15.51, 7.6 Hz, 1H), 5.25 (d, J = 9.74 Hz, 1H), 5.13 (d, J = 10.0 Hz, 1H), 4.98 (q-like, J = 7.1 Hz, 1H), 3.66 (dq, J = 10.0, 6.6 Hz, 1H), 3.58 (ddd, J = 6.6, 4.3, 3.43 Hz, 1H), 2.86 (dq, J = 7.3, 4.4 Hz, 1H), 2.64-2.70 (m, 1H), 2.62 (d, J = 3.43 Hz, 1H), 2.45-2.48 (m, 2H), 2.14-2.23 (m, 2H), 2.09 (t-like, J = 6.8 Hz, 2H), 1.82 (d, J = 1.2 Hz, 3H), 1.31-1.44 (m, 3H), 1.14 (d, J = 6.6 Hz, 3H), 1.12 (d, J = 7.13 Hz, 3H), 1.05 (t, J = 7.4 Hz, 3H), 0.97 (d, J = 6.7 Hz, 3H), 0.89 (d, J = 6.6 Hz, 3H), 0.85 (t, J = 7.4 Hz, 3H);

^{13}C NMR (125 MHz, D4-MeOH): 215.26, 165.79, 148.27, 138.43, 137.43, 137.31, 137.04, 130.98, 130.63, 129.02, 126.93, 121.85, 80.75, 76.99, 46.49, 42.26, 41.75, 39.66, 33.67, 31.25, 27.87, 25.74, 21.61, 16.93, 16.52, 14.43, 13.54, 11.94, 10.95.

(+)-epi-Callystatin A:

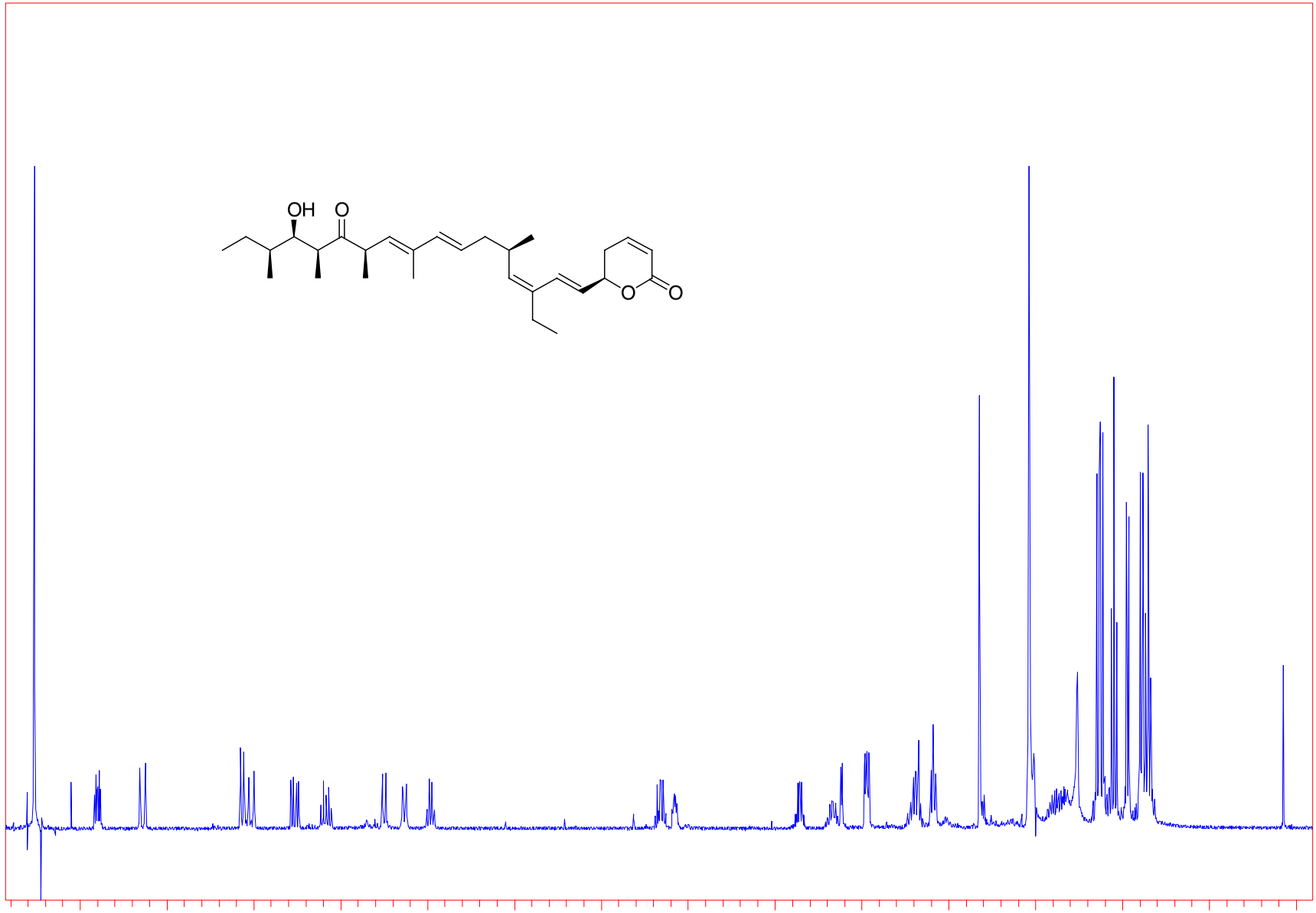


Prepared from *19,20-anti* **9**.

$[\alpha]^{24}_{D}$ +410° (c = 0.1, MeOH);

^{1}H NMR (500 MHz, $CDCl_3$): 6.89 (dt, J = 9.9, 4.4 Hz, 1H), 6.64 (d, J = 15.78 Hz, 1H), 6.06 (dt, J = 9.88, 1.85 Hz, 1H), 6.02 (d, J = 15.6 Hz, 1H), 5.76 (ddd, J = 15.85, 7.0, 0.7 Hz, 1H), 5.58 (dt, J = 15.6, 8.3 Hz, 1H), 5.22-5.26 (m, 2H), 4.98 (q-like, J = 7.1 Hz, 1H), 3.65 (dq, J = 9.7, 6.8 Hz, 1H), 3.48-3.52 (m, 1H), 2.88 (dq, J = 7.1, 2.9 Hz, 1H), 2.71 (d, J = 3.2 Hz, 1H), 2.64-2.70 (m, 1H), 2.45-2.48 (m, 2H), 2.14-2.24 (m, 2H), 2.08 (t-like, J = 6.8 Hz, 2H), 1.79 (d, J = 1.4 Hz, 3H), 1.31-1.44 (m, 3H), 1.16 (d, J = 6.9 Hz, 3H), 1.05 (t, J = 7.4 Hz, 3H), 1.04 (d, J = 7.0 Hz, 3H), 0.97 (d, J = 6.7 Hz, 3H), 0.90 (t, J = 7.6 Hz, 3H), 0.82 (d, J = 6.8 Hz, 3H).

^{13}C NMR (125 MHz, D4-MeOH): 215.26, 165.79, 148.27, 138.43, 137.43, 137.31, 137.04, 130.98, 130.63, 129.02, 126.93, 121.85, 80.75, 76.99, 46.49, 42.26, 41.75, 39.66, 33.67, 31.25, 27.87, 25.74, 21.61, 16.93, 16.52, 14.43, 13.54, 11.94, 10.95.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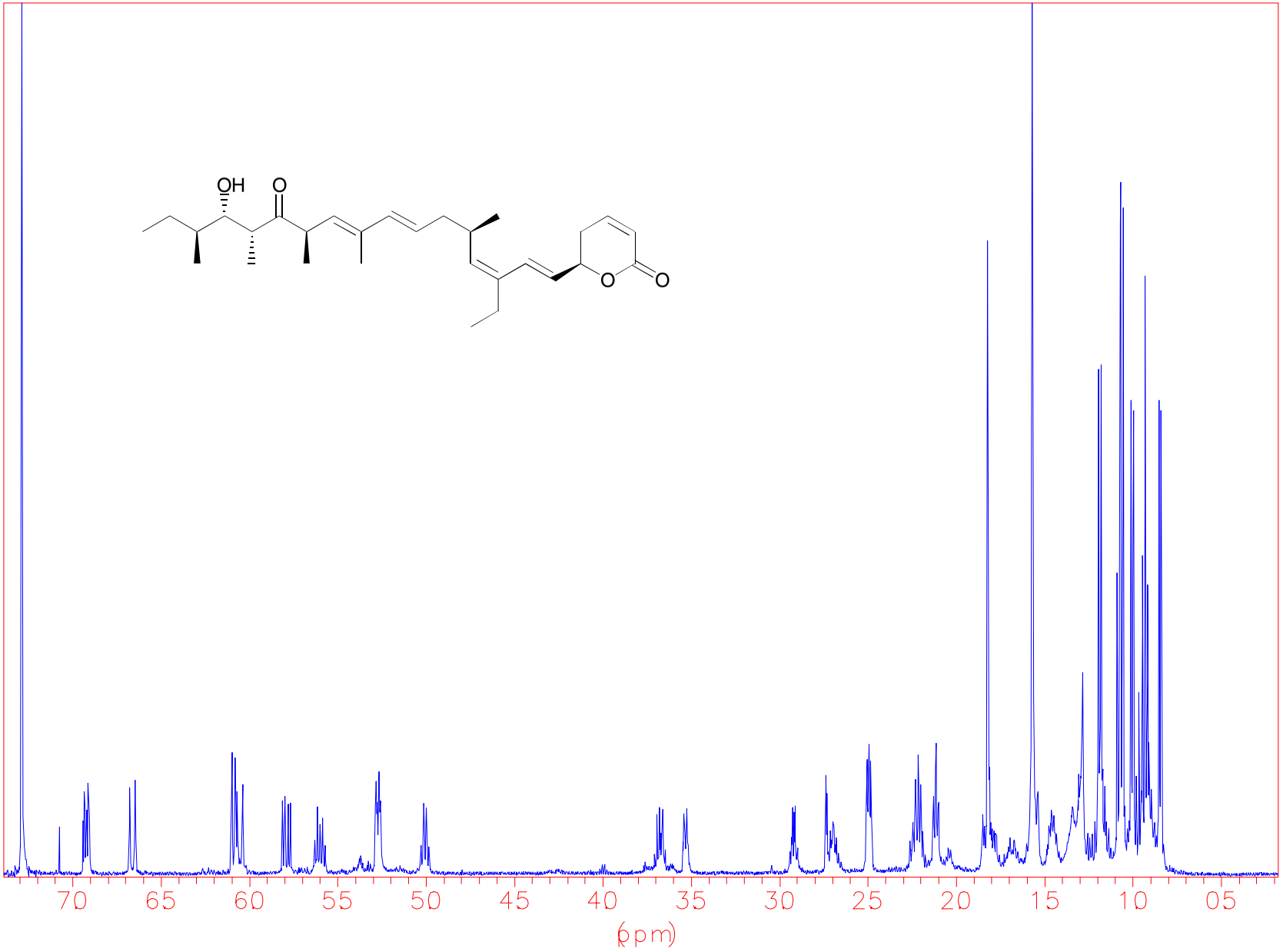
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