

## Two-directional synthesis and biological evaluation of alkaloid 5-*epi-cis*-275B'

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### Supplementary Information

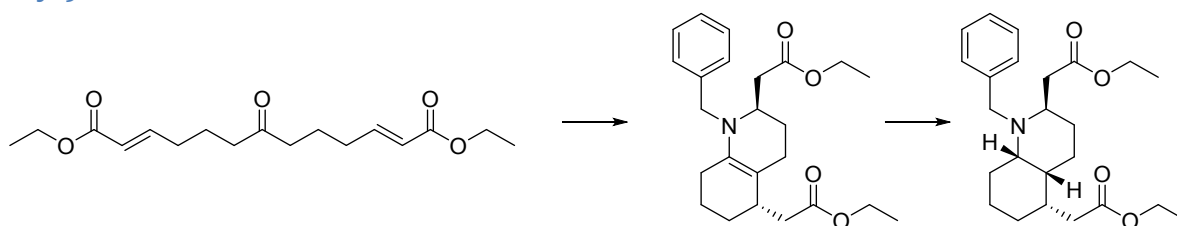
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## General Remarks

Unless otherwise stated, reagents were purchased from commercial sources and used without further purification. Anhydrous reactions were carried out in flame-dried glassware under an inert argon or nitrogen atmosphere. Dry solvents were obtained from in-house purification towers or according to accepted procedures. Tetrahydrofuran was distilled from sodium/benzophenone immediately prior to use. Column chromatography was carried out either manually using silica gel Fluka 60 or on a Biotage SP4 using either Biotage SNAP KP-Sil or GraceResolv silica cartridges and petroleum ether (40-60 °C)/ethyl acetate as eluent, whilst monitoring by thin layer chromatography: UV (254 nm) and an aqueous alkaline solution of potassium permanganate as stain. All NMR spectra were obtained in CDCl<sub>3</sub> at room temperature using Bruker DPX300, Bruker DPX400, Bruker AV400, Bruker AVIII400, Bruker AVIII500 and Jeol 270 spectrometers for which chemical shifts are expressed in ppm relative to the solvent and coupling constants are expressed in Hz. Infrared spectroscopic data were recorded using a Bruker Tensor27 FTIR spectrometer. Mass spectral data (and HRMS) were obtained using a Bruker MicroTOF spectrometer. Yields refer to isolated material (homogeneous by TLC or NMR) unless otherwise stated and names are assigned according to IUPAC nomenclature.

## Compounds

### Diethyl 2,2'-((2*R*,4*aR*,5*S*,8*aS*)-1-benzyldecahydroquinoline-2,5-diyl)diacetate



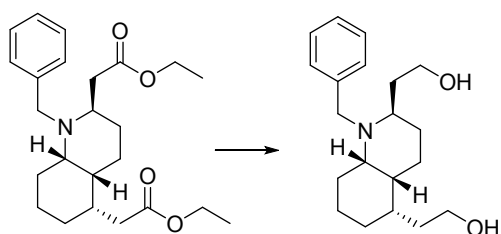
A solution of (2*E*,11*E*)-diethyl-7-oxotrideca-2,11-dienedioate (200 mg, 0.644 mmol) in anhydrous dichloromethane (2 mL) was charged with titanium (IV) chloride (1 M in CH<sub>2</sub>Cl<sub>2</sub>) (2 mL) slowly at room temperature and stirred under an inert atmosphere of argon. Benzylamine (84  $\mu$ L, 0.773 mmol) was then charged and the resulting orange mixture stirred overnight. This was subsequently quenched by the careful addition of methanol and then concentrated *in vacuo*. The resulting residue was purified by column chromatography (silica gel), eluting at 5:1 petroleum ether/ethyl acetate followed by 4:1 ethyl acetate/methanol (and 5% triethylamine). Upon evaporation of the eluent, a white solid was afforded, which was slurried in diethyl ether, decanted and the solvent removed *in vacuo* to give the unsaturated intermediate, which was hydrogenated immediately.

Data for the unsaturated intermediate:  $\nu_{\text{max}}$  (CHCl<sub>3</sub>)/cm<sup>-1</sup> 2930, 1731, 1153;  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 7.38-7.18 (5H, m), 4.24-3.99 (6H, m), 3.52-3.44 (1H, m), 2.59-2.21 (3H, m), 2.04-1.93 (2H, m), 1.87-1.75 (2H, m), 1.74-1.63 (3H, m), 1.62-1.52 (3H, m), 1.29 (3H, t, *J* 7) and 1.21 (3H, t, *J* 7), 0.97-0.87 (2H, m);  $\delta_{\text{C}}$  (100 MHz, CDCl<sub>3</sub>) 173.7, 172.4, 140.6, 135.6, 128.2, 127.5, 126.7, 109.6, 60.3, 60.2, 54.0, 52.8, 39.1, 37.2, 35.4, 27.6, 23.9, 21.9, 19.4, 14.3 and 14.2; HRMS calculated for [C<sub>24</sub>H<sub>34</sub>NO<sub>4</sub>]<sup>+</sup>: 400.2482, found 400.2484.

The resulting yellow oil was dissolved in ethyl acetate (5 mL) and charged with platinum (IV) oxide (10 mg, 0.0042 mmol) and hydrogenated at 1 atm overnight, at room temperature. The catalyst was subsequently removed by filtering through celite and the solvent was removed by concentrating *in vacuo*. The resulting residue was then purified by chromatography (silica, started eluting at 25:1 petroleum ether/ethyl acetate) to give the product (153 mg, 59%) as a yellow oil. Data for the major diastereomer shown.

$\nu_{\max}$  (CHCl<sub>3</sub>)/cm<sup>-1</sup> 2932, 1724;  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 7.41-7.20 (5H, m), 4.20-4.06 (4H, m), 3.86-3.76 (2H, m), 3.38-3.31 (1H, m), 2.77-2.63 (2H, m), 2.45-2.14 (3H, m), 2.06-1.34 (11H, m), 1.33-1.21 (7H, m);  $\delta_{\text{C}}$  (100 MHz, CDCl<sub>3</sub>) 173.5, 171.2, 128.7, 128.2, 128.0, 126.6, 60.4, 60.3, 60.2, 53.4, 51.9, 43.5, 40.9, 32.8, 32.5, 29.7, 23.8, 21.1, 20.6, 14.3 and 14.2; HRMS calculated for [C<sub>24</sub>H<sub>36</sub>NO<sub>4</sub>]<sup>+</sup>: 402.2639, found 402.2566.

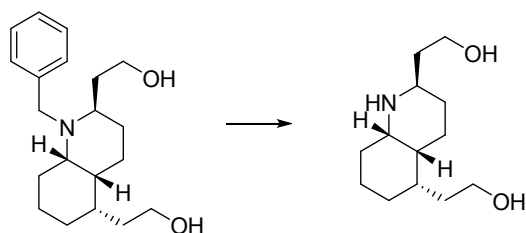
### 2,2'-((2*R*,4*aR*,5*S*,8*aS*)-1-Benzyldecahydroquinoline-2,5-diyl)diethanol



A solution of diethyl 2,2'-((2*R*,4*aR*,5*S*,8*aS*)-1-benzyldecahydroquinoline-2,5-diyl)diacetate (140 mg, 0.349 mmol) in anhydrous tetrahydrofuran (5 mL) was charged with lithium aluminium hydride solution (1 M in THF) (1.4 mL, 1.40 mmol) at room temperature and stirred under an inert atmosphere of nitrogen for 20 minutes. After carefully quenching with a saturated aqueous solution of Rochelle's salt and stirring until a clear solution persisted, the mixture was extracted thrice with ethyl acetate and concentrated *in vacuo* to give an oil that was dissolved in dichloromethane and passed through a phase separator, then concentrated *in vacuo* to give the product (110 mg, 99%) as a yellow oil.

$\nu_{\max}$  (CHCl<sub>3</sub>)/cm<sup>-1</sup> 3666, 3434, 2932, 1250, 1046;  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 7.38-7.19 (5H, m), 3.94-3.50 (7H, m), 2.94-2.59 (2H, m), 2.09-1.74 (4H, m), 1.74-1.17 (13H, m);  $\delta_{\text{C}}$  (100 MHz, CDCl<sub>3</sub>) 129.2, 128.8, 128.4, 127.1, 60.5, 57.2, 56.4, 53.8, 53.0, 45.1, 39.7, 37.1, 35.9, 34.7, 34.1, 26.9, 22.2 and 21.1; HRMS calculated for [C<sub>20</sub>H<sub>32</sub>NO<sub>2</sub>]<sup>+</sup>: 318.2428, found 318.2393.

### 2,2'-((2*R*,4*aR*,5*S*,8*aS*)-Decahydroquinoline-2,5-diyl)diethanol

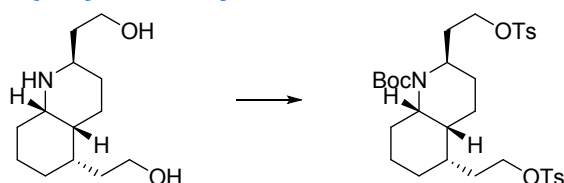


A solution of 2,2'-((2*R*,4*aR*,5*S*,8*aS*)-1-benzyldecahydroquinoline-2,5-diyl)diethanol (110 mg, 0.346 mmol) in anhydrous methanol (10 mL) was charged with palladium on activated charcoal (10% Pd basis) (110 mg) and ammonium formate (109 mg, 1.73 mmol) and heated to 65 °C under an inert

argon atmosphere, for 30 minutes. After allowing the mixture to cool to room temperature, it was filtered over celite (under nitrogen), washed with copious methanol and concentrated *in vacuo* to give the product (69 mg, 88%) as a yellow oil, which was used without further purification due to its highly polar nature.

$\nu_{\max}$  (CHCl<sub>3</sub>)/cm<sup>-1</sup> 3691, 3607, 3012, 1602, 1261, 1097, 1014;  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 3.75-3.71 (2H, m), 3.67 (2H, t, *J* 6.5), 2.47-2.17 (2H, m), 1.80-1.51 (10H, m), 1.48-1.23 (9H, m); HRMS calculated for [C<sub>13</sub>H<sub>25</sub>NO<sub>2</sub>]<sup>+</sup>: 228.1958, found 228.1952.

### (2*R*,4*aR*,5*S*,8*aS*)-*tert*-Butyl 2,5-bis(2-(tosyloxy)ethyl)octahydroquinoline-1(2*H*)-carboxylate

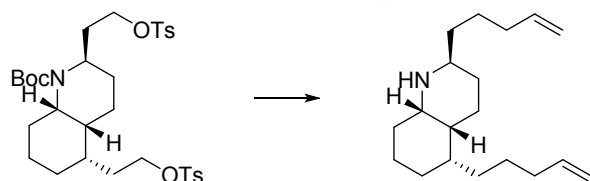


A solution of 2,2'-((2*R*,4*aR*,5*S*,8*aS*)-decahydroquinoline-2,5-diyl)diethanol (80 mg, 0.352 mmol) in water (5 mL) was charged with potassium carbonate (243 mg, 1.76 mmol) and di-*tert*-butyl dicarbonate (384 mg, 1.76 mmol) and heated at 35 °C overnight. The resulting residue was charged with ethyl acetate and separated, then extracted twice more (ethyl acetate) and the combined organic extracts then concentrated *in vacuo*. The resulting residue was then washed with copious petroleum ether and dried. The yellow oil afforded was used directly in the next step without further purification.

A solution of unpurified (2*R*,4*aR*,5*S*,8*aS*)-*tert*-butyl 2,5-bis(2-hydroxyethyl)octahydroquinoline-1(2*H*)-carboxylate (115 mg, 0.351 mmol) in chloroform (2 mL) was cooled to 0 °C, to which pyridine (57  $\mu$ L, 0.702 mmol) and *p*-toluenesulfonyl chloride (141 mg, 0.737 mmol) were added and stirred at this temperature for 10 hours then at room temperature overnight. The mixture was concentrated *in vacuo* then purified by column chromatography (silica, eluting at 10:1 to 5:1 petroleum ether/ethyl acetate) to give the product (308 mg, 68%) as a yellow oil.

$\nu_{\max}$  (CHCl<sub>3</sub>)/cm<sup>-1</sup> 3011, 2360, 1707, 1601, 1365, 1176;  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 7.86-7.76 (4H, m), 7.37 (4H, d, *J* 7.9), 4.10-3.98 (5H, m), 3.65-3.52 (1H, m), 2.47 (6H, s), 2.10-1.95 (3H, m), 1.91-1.84 (1H, m), 1.80-1.69 (3H, m), 1.68-1.55 (4H, m), 1.50 (9H, s), 1.31-1.11 (5H, m);  $\delta_{\text{C}}$  (100 MHz, CDCl<sub>3</sub>) 171.2, 144.8, 140.5, 133.0, 129.8, 82.0, 80.1, 77.3, 60.4, 40.8, 35.9, 33.8, 33.0, 31.4, 30.2, 28.4, 27.8, 25.0, 21.7; HRMS calculated for [C<sub>32</sub>H<sub>45</sub>NNaO<sub>8</sub>S<sub>2</sub>]<sup>+</sup>: 658.2479, found 658.2478.

### (2*S*,4*aR*,5*R*,8*aS*)-2,5-Di(pent-4-enyl)decahydroquinoline



Preparation of Li<sub>2</sub>CuCl<sub>4</sub> catalyst solution (0.1 M in THF): A slurry of CuCl<sub>2</sub> (10 mg, 0.074 mmol) in THF (0.74 mL) was charged with LiCl (6.3 mg, 0.149 mmol) at 0 °C and stirred under nitrogen for 5 mins. at room temperature.

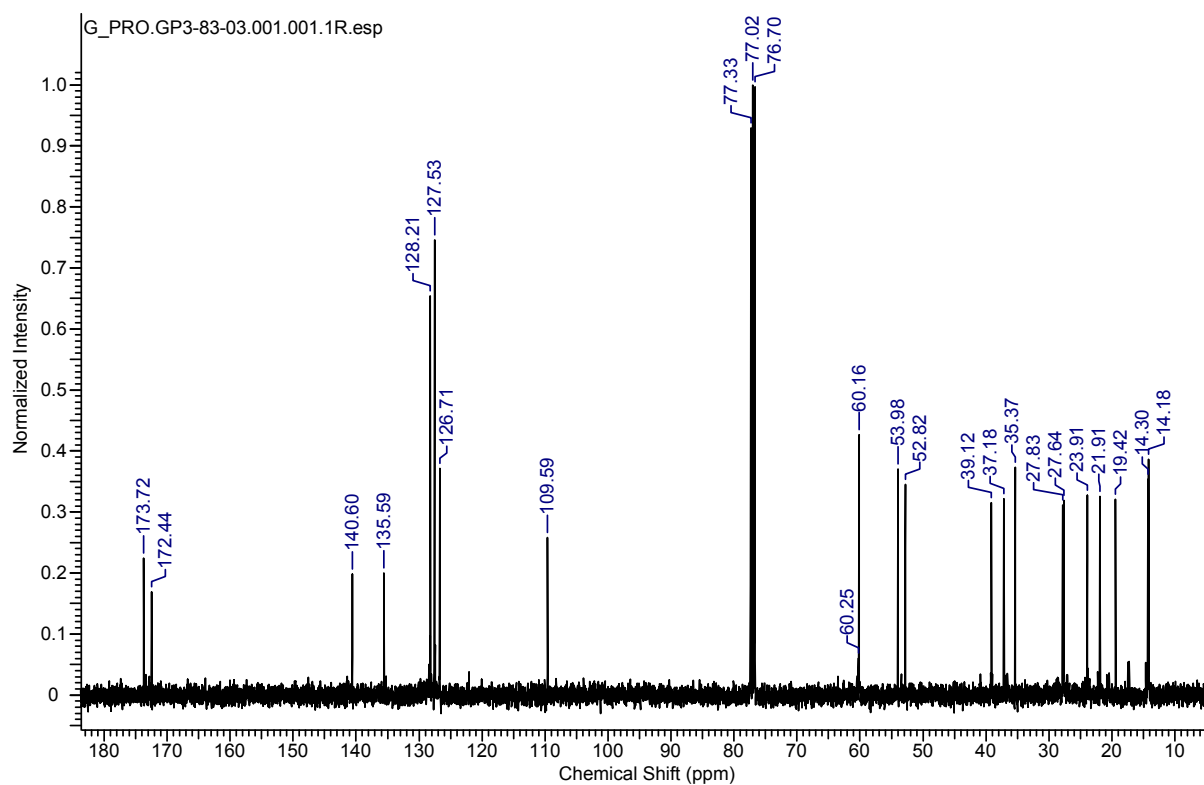
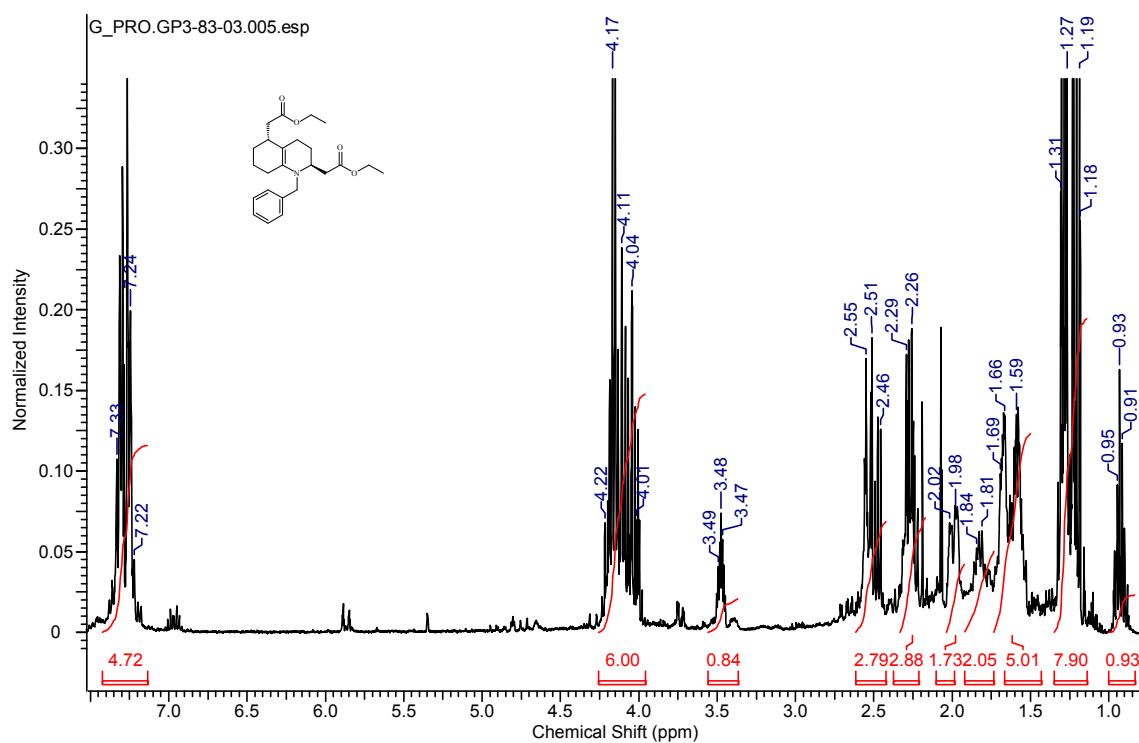
Allylic displacement: A solution of (2*R*,4*aR*,5*S*,8*aS*)-*tert*-butyl 2,5-bis(2-(tosyloxy)ethyl) octahydroquinoline-1(2*H*)-carboxylate (9 mg, 0.0142 mmol) in THF (100  $\mu$ L) was charged with freshly prepared Li<sub>2</sub>CuCl<sub>4</sub> catalyst solution (0.1 M in THF) (14  $\mu$ L, 0.0014 mmol) and allylmagnesium bromide (1 M in diethyl ether) (60  $\mu$ L, 0.056 mmol), upon which the solution immediately turned from orange to black. The resulting mixture was heated at 30 °C for 2 hours, then at 65 °C for a further 6 hours. The mixture was subsequently charged with water, extracted thrice with ethyl acetate and the resulting combined organic extracts dried over magnesium sulfate, concentrated *in vacuo* and purified by column chromatography (silica, started eluting with 6:1 petroleum ether/ethyl acetate). The resulting material was treated with formic acid (1 mL) and water (0.1 mL) and heated very gently. This was subsequently treated with ammonia (aqueous, 33%), and dichloromethane, extracted thrice with dichloromethane and concentrated *in vacuo*, to give the product (2.8 mg, 72%) as a yellow oil.

There is only very limited data available for 5-*epi-cis*-**275B'** in the original publication,<sup>2a</sup> where the structure is described as 'tentative'. However, there is quite detailed NMR data available for its stereoisomer, *cis*-**275B**, which corresponds quite well to our data.

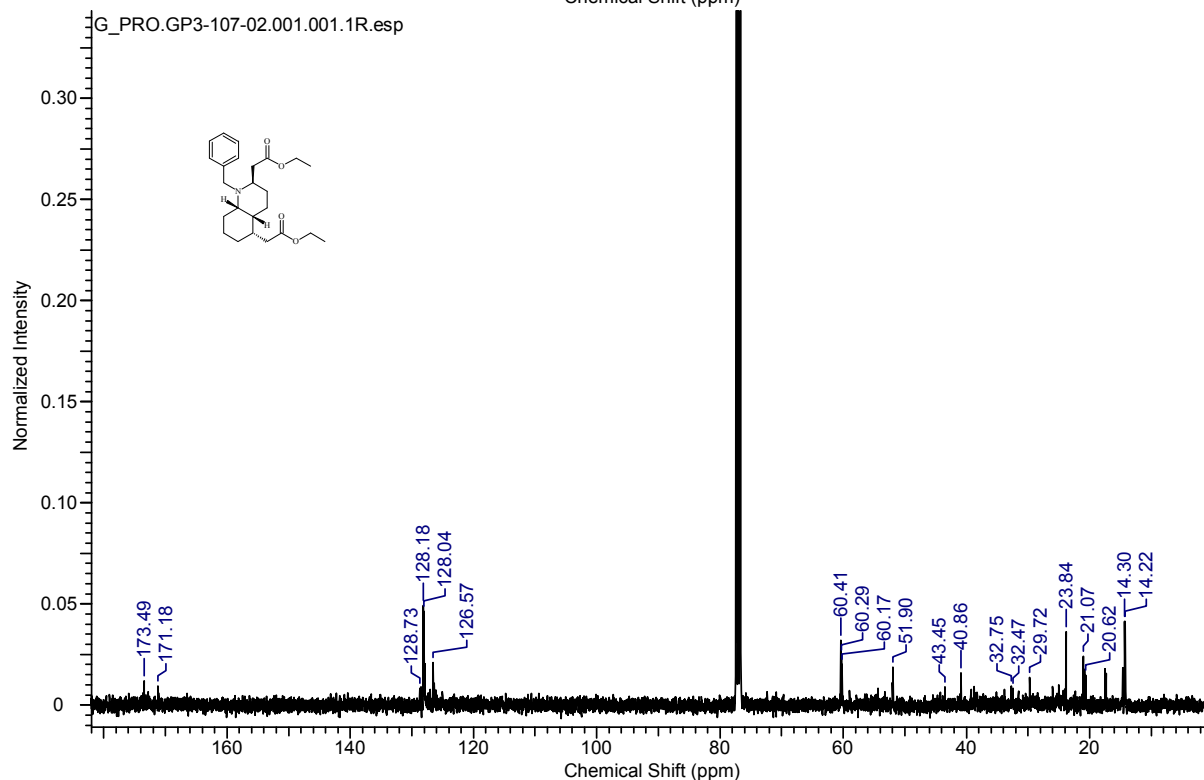
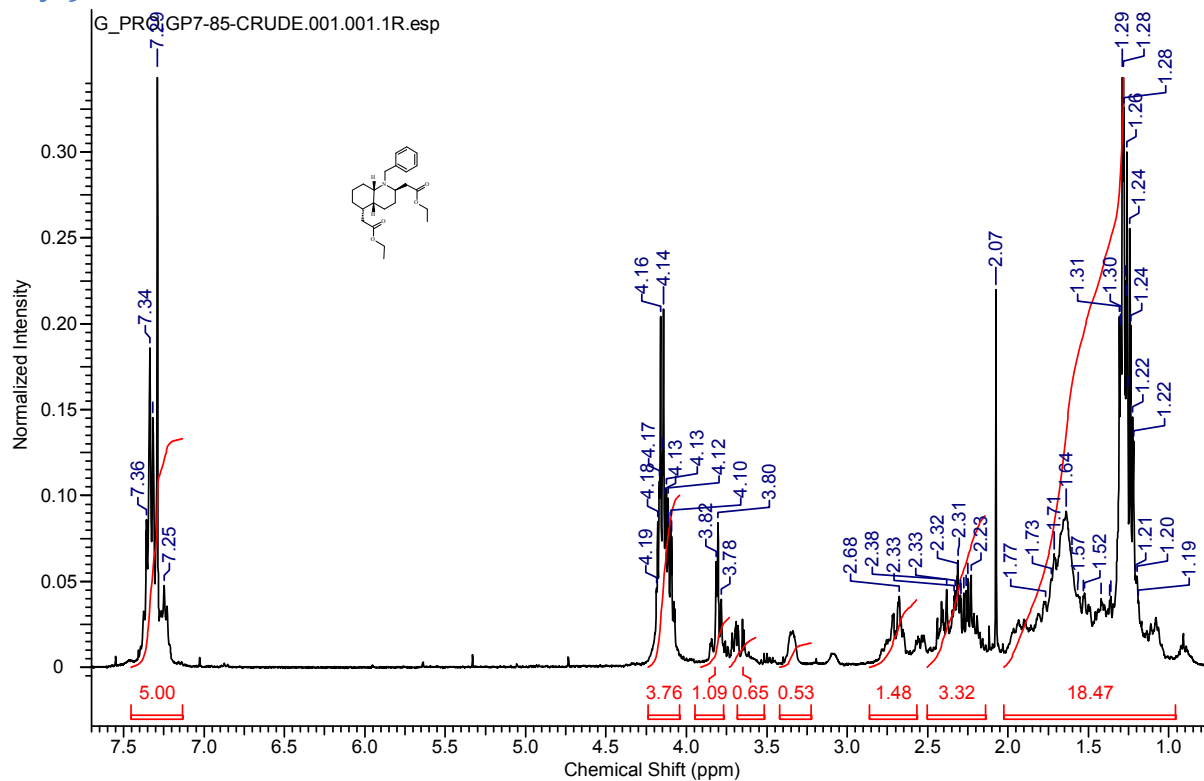
$\delta_{\text{H}}$  (500 MHz, CDCl<sub>3</sub>) 5.85 (1H, dddd, *J* 17.2, 10.4, 6.6), 5.79 (1H, dddd, *J* 17.2, 10.4, 6.6), 5.03 (2H, dd, *J* 17.2 and 1.6), 4.95 (2H, dd, *J* 10.1 and 1.0), 2.40-2.00 (6H, m), 1.48-1.21 (16H, m), 0.93-0.85 (5H, m);  $\delta_{\text{C}}$  (125 MHz, CDCl<sub>3</sub>) 139.3, 138.7, 114.7, 114.1, 58.3, 56.0, 39.5, 37.3, 34.3, 33.8, 31.9, 31.5, 30.2, 29.7, 29.4, 29.0, 26.7, 26.1, 22.7; HRMS calculated for [C<sub>19</sub>H<sub>34</sub>N]<sup>+</sup>: 276.2686, found 276.2675.

# NMR Spectra

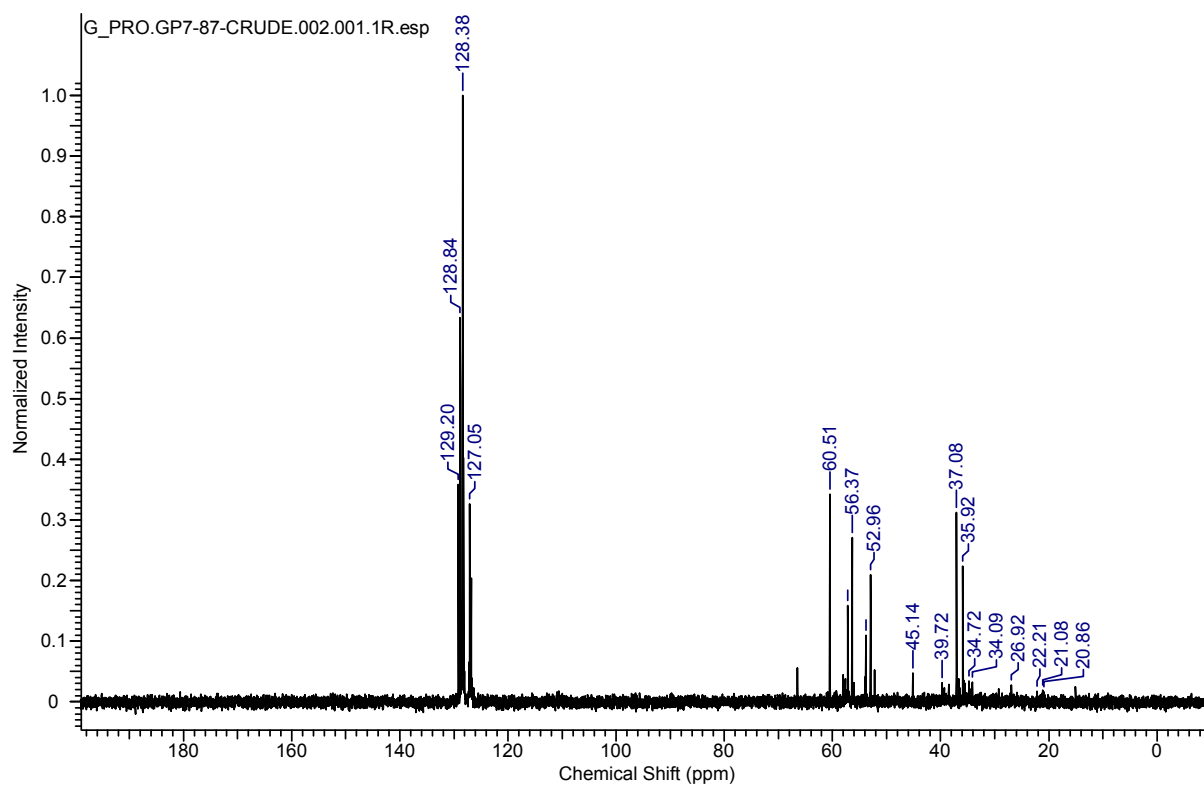
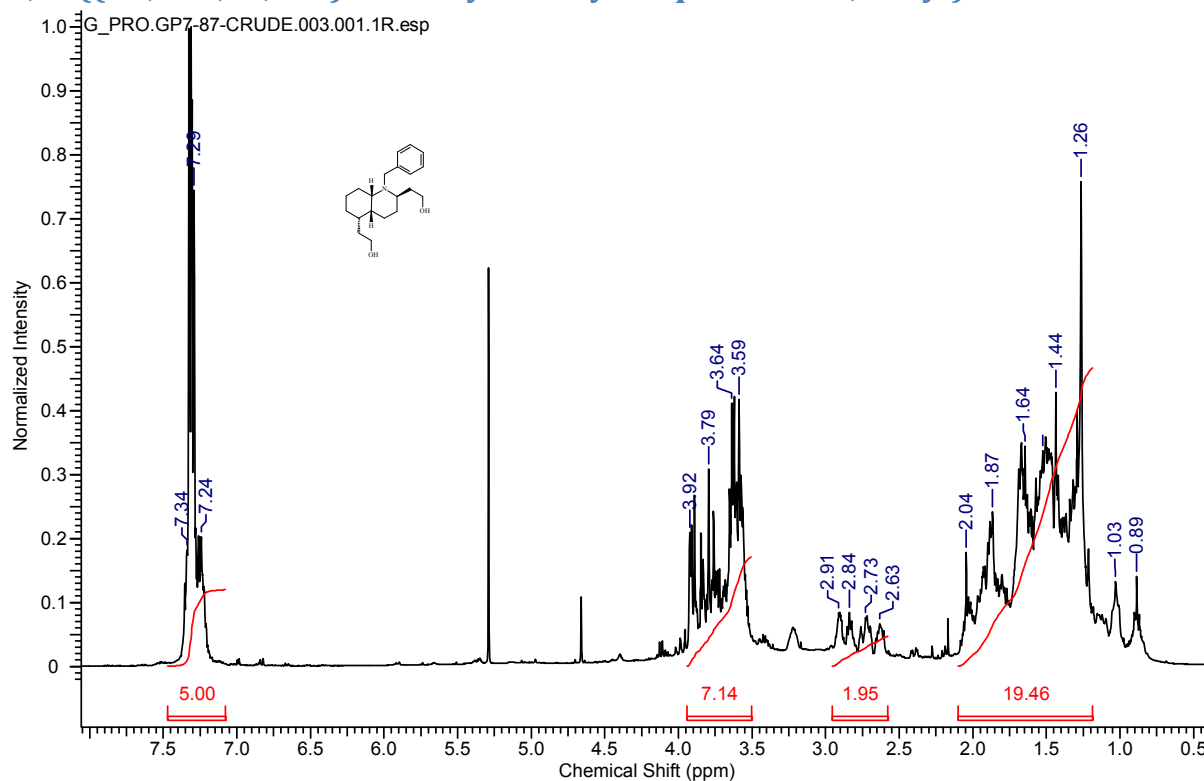
## Diethyl 2,2'-((2R,5S)-1-benzyl-1,2,3,4,5,6,7,8-octahydroquinoline-2,5-diyl)diacetate



# Diethyl 2,2'-((2R,4aR,5S,8aS)-1-benzyldecahydroquinoline-2,5-diyl)diacetate

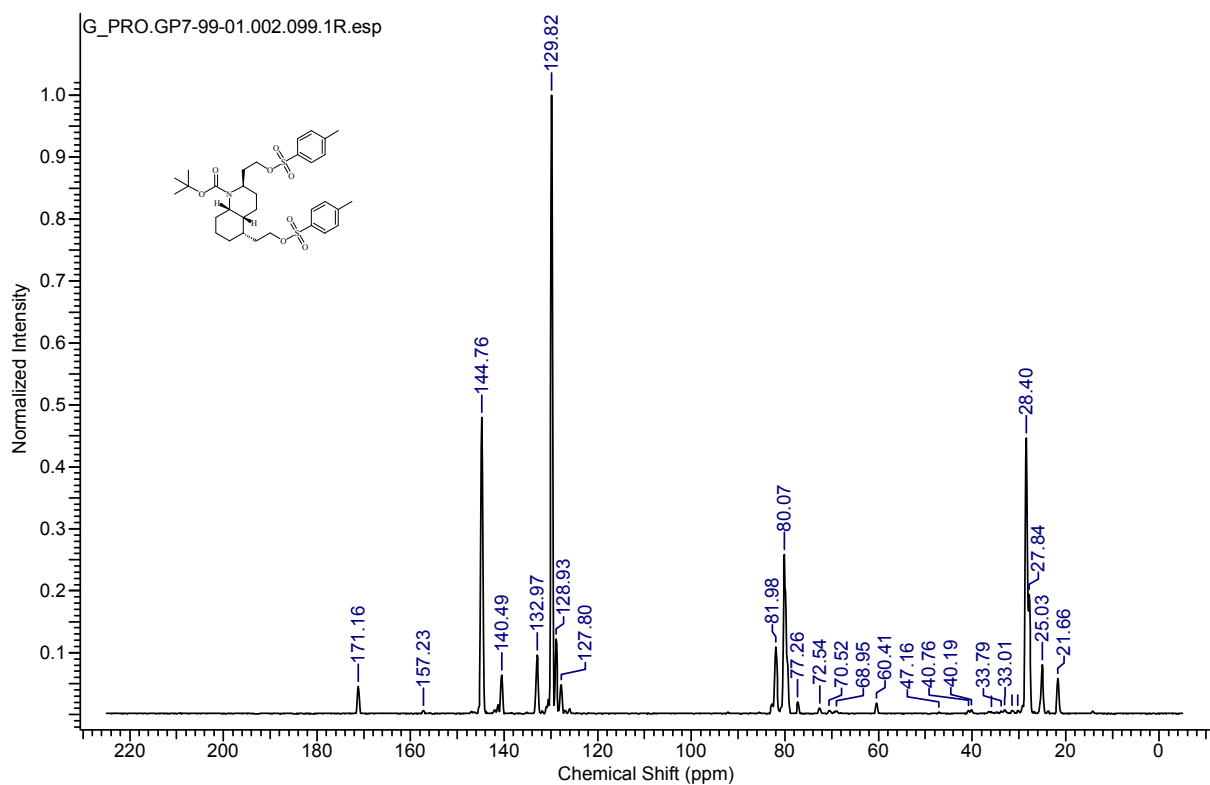
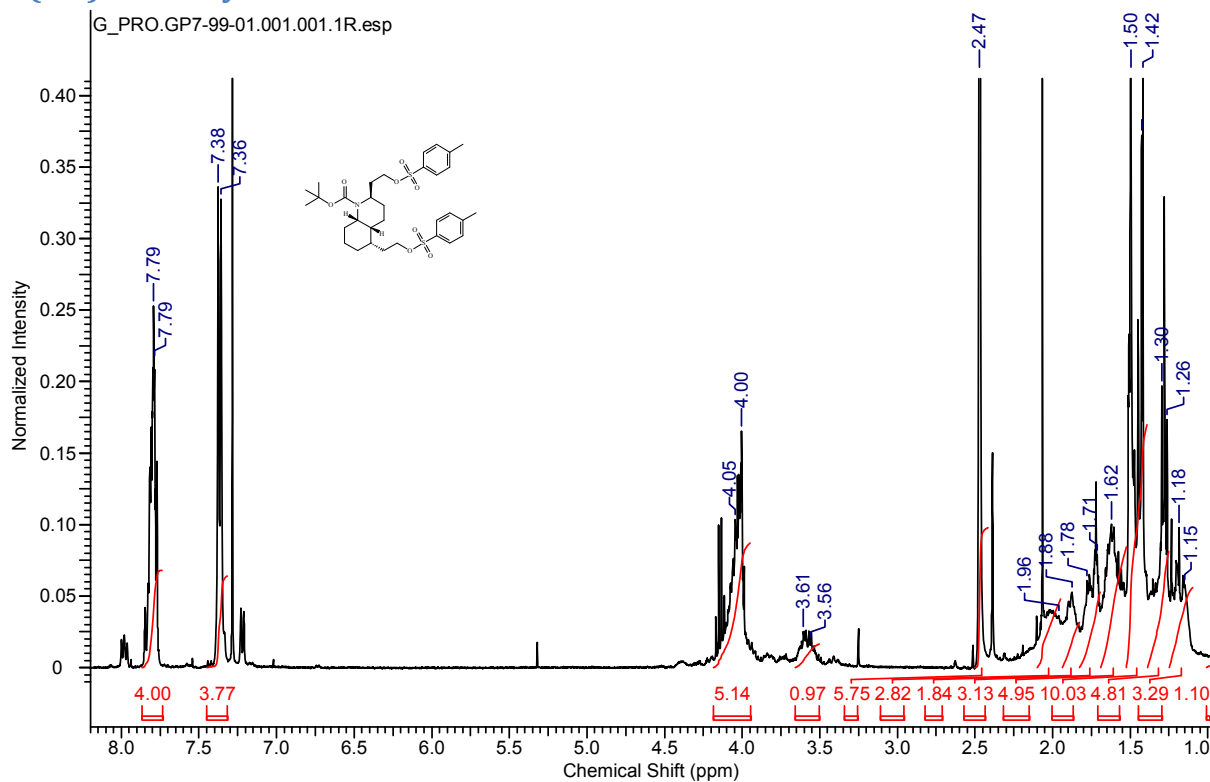


## 2,2'-((2R,4aR,5S,8aS)-1-Benzyldecahydroquinoline-2,5-diyl)diethanol





**(2*R*,4*aR*,5*S*,8*aS*)-*tert*-Butyl 2,5-bis(2-(tosyloxy)ethyl)octahydroquinoline-1(2*H*)-carboxylate**



**(2*S*,4*aR*,5*R*,8*aS*)-2,5-Di(pent-4-enyl)decahydroquinoline**

