Electronic Supplementary Material (ESI) for Chemical Communications

Supporting Information

Aziridine-based Concise Synthesis of (±)-Alstonerine

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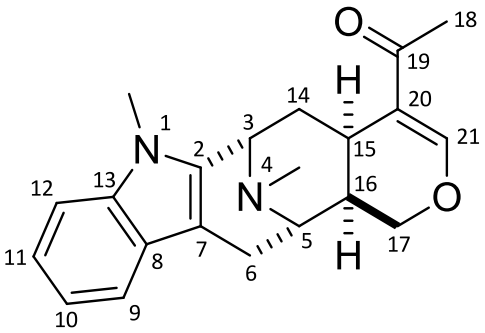
Macroline skeletal numbering

A brief overview of the skeletal numbering of macroline according to LeMen and Taylor[1] is depicted below (***Figure 1.***). For the purposes of reporting nmr data, all compounds herein reported are numbered such that the skeletal numbering corresponds to the final position of each carbon atom in the final natural product (±)-alstonerine **1**.



1

Figure 1. *Illustration of macroline skeletal numbering according to LeMen and Taylor.*

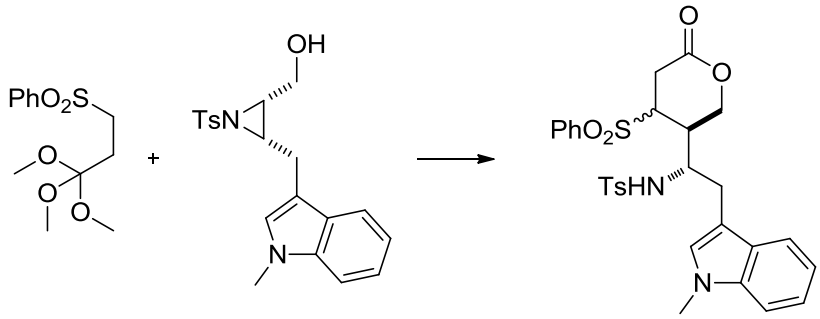
General experimental

Standard laboratory techniques were employed when handling air-sensitive reagents. All reactions were performed under a nitrogen atmosphere unless otherwise stated. Melting points were determined using a Stuart Scientific SMP1 or Büchi B-545 melting point apparatus and are uncorrected. Infrared spectra were recorded on Perkin–Elmer Spectrum RX FT-IR or Spectrum One FT-IR spectrometers. All ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Ultra-Shield AV-400 spectrometer. Chemical shifts (δH and δC) are expressed in parts per million (ppm), referenced to the appropriate residual solvent peak. Mass spectra (CI, EI and FAB) were recorded using a Micromass AutoSpec-Q, Micromass Platform II or Micromass AutoSpec Premier spectrometer. Elemental analyses were performed at the microanalytical laboratories of the London Metropolitan University. Thin-layer chromatography was performed on aluminium plates pre-coated with silica gel (0.2 mm, Merck Kieselgel 60 F254), which were developed using standard visualising agents: ultraviolet fluorescence (254 nm) and/or potassium permanganate and/or vanillin. Chromatography refers to flash column chromatography performed using BDH flash chromatography silica gel (40-63 μm) unless otherwise stated. Standard solvents were distilled under nitrogen prior to use: THF was distilled from sodiumbenzophenone ketyl, CH_2Cl_2, Et_3N and Hünig's base from CaH_2 and MeOH from Mg/MeOH. Hexane refers to the fraction of petroleum boiling between 67–70 °C. All other solvents and reagents were used as received from the supplier unless otherwise noted.

[1] J. LeMen, W. I. Taylor, *Experientia* **1965**, *21*, 508.

Experimental procedures

4-Methyl-*N*-((*R)-2-(1-methylindol-3-yl)-1-((3*S**,4*S**)-6-oxo-4-(phenylsulfonyl)tetrahydro-2*H*-pyran-3-yl)ethyl)benzenesulfonamide (8a) and 4-methyl-*N*-((*R**)-2-(1-methylindol-3-yl)-1-((3*S**,4*R**)-6-oxo-4-(phenylsulfonyl)tetrahydro-2*H*-pyran-3-yl)ethyl)benzenesulfonamide (8b)**



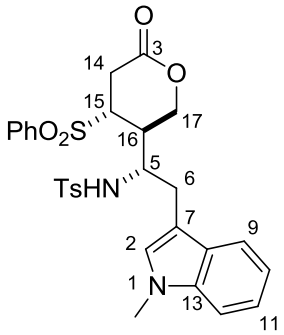
6 **7** **8**

To a solution of trimethyl 3-(phenylsulfonyl)orthopropionate **6** (7.43g, 27.08 mmol, 1.5 equiv.) in THF (30 mL) at –78 °C was added *n*BuLi (2.48 M in hexanes; 12.01 mL, 29.79 mmol, 1.7 equiv.) and the solution stirred for 1h at –78 °C.

Meanwhile, *n*BuLi (2.48 M in hexanes; 8.01 mL, 19.86 mmol, 1.1 equiv.) was added to a solution of (hydroxymethyl)aziridine **7** (6.69 g, 18.05 mmol, 1.0 equiv.) in THF (10.0 mL) at –78 °C and the solution stirred for 1 h at –78 °C.

The dark red solution of deprotonated **6** was added dropwise *via* cannula to the dark green solution of *O*-lithio (hydroxymethyl)aziridine **7**, maintaining both solutions at –78 °C throughout the addition. The reaction mixture was allowed to warm to rt slowly overnight. Aqueous HCl (2 M; 50 mL) was added and the solution stirred for 3 h. The aqueous layer was extracted with EtOAc (3×200 mL) and CH_2Cl_2 (3×100 mL), and the combined organic layers washed with brine, dried over $MgSO_4$ and filtered. Concentration under reduced pressure and chromatography (50% EtOAc–hexane) yielded a 2:1 mixture of lactones **8a** and **8b** (8.18 g, 80%).

4-Methyl-*N*-((*R)-2-(1-methylindol-3-yl)-1-((3*S**,4*S**)-6-oxo-4-(phenylsulfonyl)tetrahydro-2*H*-pyran-3-yl)ethyl)benzenesulfonamide (8a)**



8a

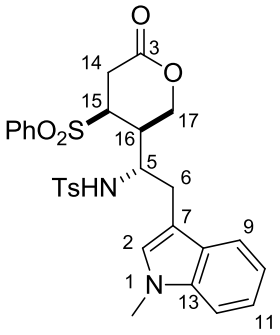
R_f 0.25 (50 % EtOAc–hexane); m.p. 226.0–226.5°C

δ_H (400 MHz, $CDCl_3$) 7.84 (2H, dd, *J* 8.0, 1.0 Hz, *ortho*-**Ph**SO_2), 7.66 (1H, tt, *J* 7.5, 1.0 Hz, *para*-**Ph**SO_2), 8.00 (2H, dd, *J* 8.0, 1.0 Hz, *meta*-**Ph**SO_2), 7.45 (2H, d, *ortho*-**Ts**), 7.24–7.22 (2H, m, **9** and **11**), 7.11–7.01 (4H, m, *meta*-**Ts**, **12** and **10**), 6.72 (1H, s, **2**), 4.70 (1H, d, *J* 7.5, N_4***H***), 4.49 (1H, dd, *J* 12.5, 4.0 Hz, **17**), 4.31 (1H, dd, *J* 12.5, 4.0 Hz, **17**), 3.81–3.76 (1H, m, **15**), 3.69 (3H, s, N_1**Me**), 3.66–3.60 (1H, m, **5**), 2.97 (1H, dd, *J* 15.0, 5.0 Hz, **6**), 2.82–2.74 (2H, m, **6** and **14**), 2.61 (1H, dd, *J* 16.0, 7.0 Hz, **14**), 2.36 (3H, s, *Ts***Me**).

δ_C (100 MHz, $CDCl_3$) 168.7 (**C3**), 143.5 (*para*-**Ts**), 137.0 (**C13**), 136.2 (*ipso*-**Ph**SO_2), 135.6 (*ipso*-**Ts**), 134.5 (*para*-**Ph**SO_2), 129.6 (*ortho*-**Ph**SO_2), 129.5 (*meta*-**Ts**), 129.1 (*meta*-**Ph**SO_2), 127.8 (**C8**), 127.4 (**C2**), 126.7 (*ortho*-**Ts**), 122.1 (**C11**), 119.6 (**C10**), 118.2 (**C12**), 109.5 (**C9**), 107.2 (**C7**), 66.5 (**C17**), 56.8 (**C15**), 53.7 (**C5**), 36.6 (**C16**), 32.7 (N_1**Me**), 29.0 (**C14**), 28.1 (**C6**), 21.6 (*Ts***Me**).

FTIR (film) υ_{max}: 3297, 2921, 1739, 1599 cm^{-1}; *m/z* (CI) 567 $[M+H]^+$ (Found $[M+H]^+$, 567.1614. $C_{29}H_{30}N_2O_6S_2$ requires $[M+H]^+$, 567.1624) (Found C, 61.38; H, 5.40; N, 5.05%. $C_{29}H_{30}N_2O_6S_2$ requires C, 61.46; H, 5.34; N, 4.94%).

4-Methyl-*N*-((*R)-2-(1-methylindol-3-yl)-1-((3*S**,4*R**)-6-oxo-4-(phenylsulfonyl)tetrahydro-2*H*-pyran-3-yl)ethyl)benzenesulfonamide (8b)**



8b

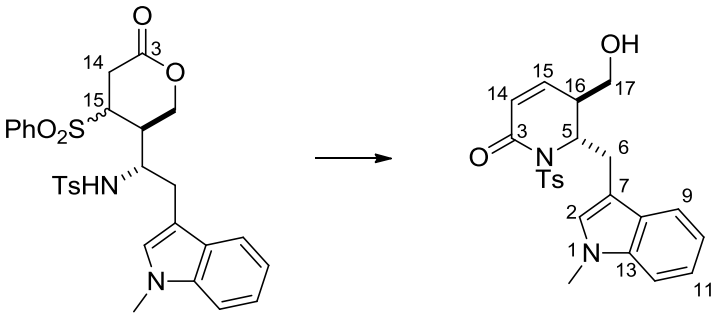
R_f 0.15 (50 % EtOAc–hexane); m.p. 214.0–215.0 °C

δ_H (400 MHz, $CDCl_3$) 8.03–7.98 (2H, m, *ortho*-**Ph**SO_2), 7.71 (1H, tt, *J* 7.5, 1.0 Hz, *para*-**Ph**SO_2), 7.61 (2H, t, *J* 8.0 Hz, *meta*-**Ph**SO_2), 7.42–7.35 (3H, m, *ortho*-**Ts** and **12**), 7.17 (2H, d, *J* 4.0 Hz, **9** and **11**), 7.01–6.95 (1H, m, **10**), 6.92 (2H, *J* 8.0 Hz, *meta*-**Ts**), 6.71 (1H, s, **2**), 5.35 (1H, d, *J* 6.5, N_4***H***), 5.03 (1H, dd, *J* 12.0, 8.0 Hz, **17**), 4.43–4.21 (2H, m, **17** and **5**), 4.03–3.96 (1H, m, **15**), 3.63 (3H, s, N_1**Me**), 3.18–3.02 (2H, m, **6** and **16**), 2.92–2.74 (2H, m, **6** and **14**), 2.51 (1H, dd, *J* 18.0, 7.0 Hz, **14**), 2.29 (3H, s, *Ts***Me**).

δ_C (100 MHz, $CDCl_3$) 166.9 (**C3**), 143.2 (*para*-**Ts**), 137.7 (*para*-**Ph**SO_2), 137.0 (**C13**), 135.8 (*ipso*-**Ts**), 134.7 (*ipso*-**Ph**SO_2), 129.8 (*ortho*-**Ph**SO_2), 129.2 (*meta*-**Ts**), 128.8 (*meta*-**Ph**SO_2), 127.4 (**C8**), 127.2 (**C2**), 126.7 (*ortho*-**Ts**), 121.9 (**C11**), 119.4 (**C10**), 118.6 (**C12**), 109.3 (**C9**), 108.3 (**C7**), 68.8 (**C17**), 57.3 (**C15**), 52.7 (**C4**), 38.9 (**C16**), 32.6 (N_1**Me**), 31.6 (**C14**), 28.1(**C6**), 21.6 (*Ts***Me**).

FTIR (film) υ_{max}: 3297, 2921, 1739, 1599 cm^{-1}; *m/z* (CI) 567 $[M+H]^+$ (Found $[M+H]^+$, 567.1614. $C_{29}H_{30}N_2O_6S_2$ requires $[M+H]^+$, 567.1624) (Found C, 61.38; H, 5.40; N, 5.05%. $C_{29}H_{30}N_2O_6S_2$ requires C, 61.46; H, 5.34; N, 4.94%).

(5*R,6*S**)-5-(Hydroxymethyl)-6-((1-methylindol-3-yl)methyl)-1-tosyl-5,6-dihydropyridin-2(1*H*)-one (5)**



8 **5**

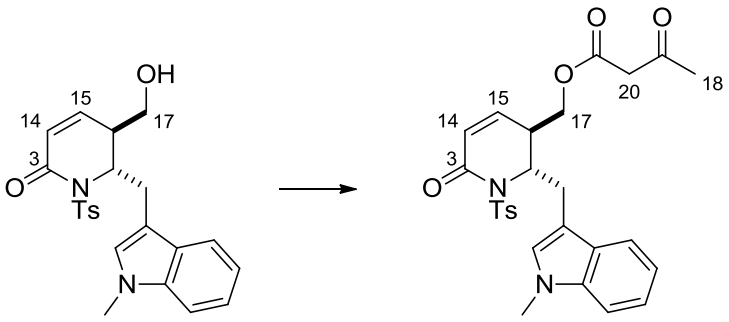
To a solution of lactones **8** (7.76 g, 13.71 mmol, 1.0 equiv.) in toluene (50 mL) was added trimethylaluminum (2.0 M in hexanes; 10.5 mL, 21.0 mmol, 1.5 equiv.) and the reaction mixture heated under reflux at 120 °C for 2 h. The reaction mixture was cooled to rt before saturated aqueous Rochelle salt (10 mL) and EtOAc (10 mL) were added, and the resulting suspension was stirred vigorously at rt overnight. Saturated aqueous $NaHCO_3$ (1 mL) was added and the aqueous layer extracted with EtOAc (3×100 mL) and CH_2Cl_2 (3×100 mL). The organic layers were washed with brine, dried over $MgSO_4$ and filtered. Concentration under reduced pressure and chromatography (33% EtOAc–hexane) yielded the title compound **5** as a colourless, amorphous solid (5.66 g, 94%); R_f 0.25 (66% EtOAc–hexane).

δ_H (400 MHz, $CDCl_3$) 7.99 (2H, d, *J* 8.0 Hz, *meta*-**Ts**), 7.68 (1 H, d, *J* 8.0 Hz, **12**), 7.33–7.21 (4H, m, *ortho*-**Ts**, **9** and **11**), 7.15 (1H, t, *J* 8.0 Hz, **10**), 6.90 (1H, s, **2**), 6.57 (1H, ddd, *J* 10, 8.0, 1.5 Hz, **15**), 5.94 (1H, d, *J* 10.0 Hz, **14**), 5.16 (1H, dd, *J* 11.0, 4.0 Hz, **5**), 3.75 (3H, s, N_1**Me**), 3.57 (1H, dd, *J* 11.0, 6.0 Hz, **17**), 3.38 (1H, t, *J* 9.0 Hz, **17**), 3.31 (1H, dd, *J* 14.0, 4.0 Hz, **6**), 3.14 (1H, dd, *J* 14.0, 11.0 Hz, **6**), 2.69 (1H, dt, *J* 7.5, 6.0 Hz, **16**), 2.42 (3H, s, *Ts***Me**), 1.59 (1H, br s, O***H***).

δ_C (100 MHz, $CDCl_3$) 161.6 (**C3**), 144.7 (*para*-**Ts**), 142.4 (**C15**), 137.0 (**C13**), 136.4 (*ipso*-**Ts**), 129.3 (*meta*-**Ts**), 129.1 (*ortho*-**Ts**), 127.94 (**C2**), 127.85 (**C8**), 125.9 (**C14**), 121.9 (**C11**), 119.4 (**C10**), 118.9 (**C12**), 109.5 (**C7**), 109.4 (**C9**), 62.9 (**C17**), 57.0 (**C5**), 39.9 (**C16**), 32.7 (N_1**Me**), 29.9 (**C6**), 21.7 (*Ts***Me**).

FTIR (film) υ_{max}: 3530, 3056, 2917, 1687 cm^{-1}; *m/z* (CI) 425 $[M+H]^+$ (Found $[M+H]^+$, 425.1530. $C_{23}H_{24}N_2O_4S$ requires $[M+H]^+$, 425.1535) Found C, 64.94; H, 5.63; N, 6.57%. $C_{23}H_{24}N_2O_4S$ requires C, 65.07; H, 5.70; N, 6.60%.

((2*R,3*S**)-2-((1-Methylindol-3-yl)methyl)-6-oxo-1-tosyl-1,2,3,6-tetrahydropyridin-3-yl)methyl 3-oxobutanoate**



5

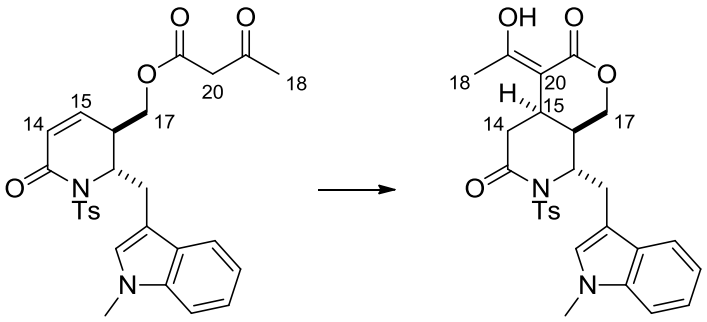
A solution of alcohol **5** (360.0 mg, 0.85 mmol, 1.0 equiv.) and 4*H*-2,2,6-trimethyl-1,3-dioxin-4-one **4** (0.23 mL, 1.70 mmol, 2.0 equiv.) in toluene (3 mL) was heated to 150 °C in the microwave for 20 min in a sealed tube. On cooling to rt, saturated aqueous NH_4Cl (10 mL) was added and the aqueous layer extracted with EtOAc (3×30 mL) and CH_2Cl_2 (3×30 mL). The organic layers were washed with brine, combined, dried over $MgSO_4$ and filtered. Concentration under reduced pressure and chromatography (20→50% EtOAc–hexane) yielded the title compound (399.0 mg, 96%) as a colourless, amorphous solid; R_f 0.63 (66% EtOAc–hexane).

δ_H (400 MHz, $CDCl_3$) 8.03 (2 H, app d *J* 8.4 Hz, *meta*-**Ts**), 7.79 (1 H, app d *J* 8.0 Hz, **12**), 7.38–7.23 (4H, m, *ortho*-**Ts**, **9**, and **11**), 7.17 (1H, t, *J* 7.4 Hz, **10**), 6.88 (1H, s, **2**), 6.49 (1H, ddd, *J* 9.8, 6.2, 1.5 Hz, **15**), 5.98 (1H, d, *J* 10.0 Hz, **14**), 5.14 (1H, dd, *J* 11.5, 4.1 Hz, **5**), 4.08 (1H, dd, *J* 11.3, 4.4 Hz, **17**), 3.84 (1H, dd, *J* 11.3, 8.4 Hz, **17**), 3.76 (3H, s, N_1**Me**), 3.36 (1H, dd, *J* 14.1, 4.1 Hz, **6**), 3.23–3.03 (3H, m, 2 × **20** and **6**), 2.83 (**16**), 2.43 (3H, s, *Ts***Me**), 2.10 (3H, s, **18**).

δ_C (100 MHz, $CDCl_3$) 200.3 (**C19**), 166.6 (**C21**), 161.2 (**C3**), 145.0 (*para*-**Ts**), 140.0 (**C15**), 137.2 (**C13**), 136.2 (*ipso*-**Ts**), 129.4 (*meta*-**Ts**), 129.2 (*ortho*-**Ts**), 127.9 (**C2**), 127.5 (**C8**), 126.7 (**C14**), 122.0 (**C11**), 119.5 (**C10**), 119.1 (**C12**), 109.5 (**C9**), 109.3 (**C7**), 63.6 (**C17**), 56.9 (**C5**), 49.2 (**C20**), 36.6 (**C16**), 32.9 (N_1**Me**), 30.3 (**C6**), 30.1 (**C18**), 21.7 (*Ts***Me**).

FTIR (film) υ_{max}: 2923, 1747, 1717, 1690, 1596, 1351 cm^{-1}; (New C=O, no OH); *m/z* (CI) 509 $[M+H]^+$ (Found $[M+H]^+$, 509.1735. $C_{27}H_{28}N_2O_6S$ requires $[M+H]^+$, 509.1746) Found C, 63.80; H, 5.63; N, 5.37%. $C_{27}H_{28}N_2O_6S$ requires C, 63.76; H, 5.55; N, 5.51%.

(8*R,8a*S**,*Z*)-4-(1-Hydroxyethylidene)-8-((1-methylindol-3-yl)methyl)-7-tosyltetrahydro-1*H*-pyrano[3,4-*c*]pyridine-3,6(4*H*,7*H*)-dione (11)**



11

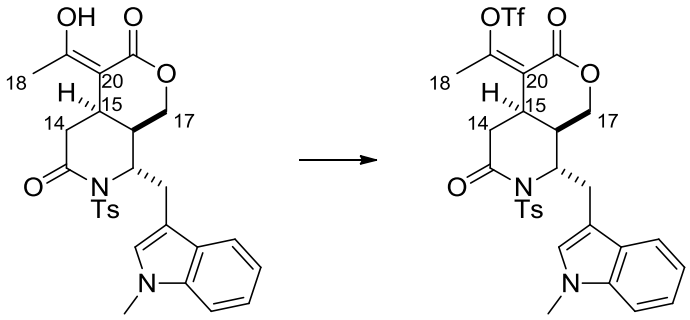
To a solution of malonate ester (3.48 g, 6.85 mmol, 1.0 equiv.) in THF (23 mL) at rt was added DBU (2.0 mL, 13.7 mmol, 2.0 equiv.). The reaction mixture was allowed to stir at rt for 24 h, saturated aqueous NH_4Cl (2 mL) was added and the aqueous layer extracted with EtOAc (3×30 mL) and CH_2Cl_2 (2×50 mL). The organic layers were washed with brine, combined, dried over $MgSO_4$ and filtered. Concentration under reduced pressure and chromatography (33% EtOAc–hexane) yielded the title compound **11** (3.34 g, 93%) as an amorphous solid; R_f 0.24 (33% EtOAc–hexane).

δ_H (400 MHz, $CDCl_3$) 13.72 (1H, s, **19**-O***H***), 7.94 (2H, d, *J* 8.5 Hz, *meta*-**Ts**), 7.72 (1H, d, *J* 8.0 Hz, **9**), 7.38–7.30 (3H, m, *ortho*-**Ts** and **12**), 7.27 (1H, t, *J* 8.0 Hz, **11**),7.17 (1H, t, *J* 8.0 Hz, **10**), 6.94 (1H, s, **2**), 4.78 (1H, ddd, *J* 8.0, 3.0, 2.0 Hz, **5**), 4.21 (1H, ddd, *J* 11.5, 4.5 1.5 Hz, **17**), 4.03 (1H, t, *J* 12.0 Hz, **17**), 3.78 (3H, s, (*N*$_1$**Me**), 3.54 (1H, dd, *J* 15.0, 4.0 Hz, **6**), 3.21 (1H, dd, 15.0, 10.0 Hz, **6**), 3.16–3.07 (1H, m, **15**), 2.61–2.46 (2H, m, **14**, **16**), 2.45 (3H, s, *Ts***Me**), 2.17 (1H, dd, *J* 19.0, 10. 5 Hz, **14**), 1.74 (3H, s, **18**).

δ_C (100 MHz, $CDCl_3$) 177.3 (**C19**), 171.0 (**C21**), 167.4 (**C3**), 145.4 (*para*-**Ts**), 137.0 (**C13**), 135.7 (*ipso*-**Ts**), 129.5 (*meta*-**Ts**), 129.1 (*ortho*-**Ts**), 128.2 (**C2**), 127.7 (**C8**), 122.3 (**C11**), 119.8 (**C10**), 118.6 (**C12**), 109.7 (**C9**), 108.3 (**C7**), 96.2 (**C20**), 66.9 (**C17**), 57.3 (**C5**), 36.6 (**C14**), 32.9 (*N*$_1$**Me**), 31.5 (**C6**), 26.0 (**C15**), 21.7 (*Ts***Me**), 18.0 (**C18**).

FTIR (film) υ_{max}: 3058, 2923, 2855, 2252, 1690, 1636, 1612, 1597 cm^{-1}; *m/z* (CI) 509 $[M+H]^+$ (Found $[M+H]^+$, 509.1741. $C_{27}H_{28}N_2O_6S$ requires $[M+H]^+$, 509.1746).

(*Z*)-1-((8*R,8a*S**)-8-((1-Methylindol-3-yl)methyl)-3,6-dioxo-7-tosyl-1*H*-pyrano[3,4-*c*]pyridin-4(3*H*,4a*H*,5*H*,6*H*,7*H*,8*H*,8a*H*)ylidene)ethyl trifluoromethanesulfonate**



11

To a solution of enol **11** (31.0 mg, 0.061 mmol, 1.0 equiv.) in THF (1 mL) at –78 °C was added KHMDS (0.5 M in toluene; 0.15 mL, 0.073 mmol, 1.2 equiv.) and the solution stirred at –78 °C for 1 h. A solution of $PhNTf_2$ (0.13 M in THF; 0.5 mL, 0.067 mmol, 1.1 equiv.) was added and the solution allowed to warm slowly from –78°C to rt overnight. The reaction was quenched with wet Et_2O (2 mL), 10% aqueous citric acid (5 mL) was added and the aqueous layer extracted with CH_2Cl_2 (3×30 mL) and EtOAc (3×30 mL). The organic layers were washed with brine, combined, dried over $MgSO_4$ and filtered. Concentration under reduced pressure and chromatography (25→50% EtOAc–hexane) yielded the title compound (28.8 mg, 74%) as an amorphous solid; R_f 0.65 (50% EtOAc–hexane).

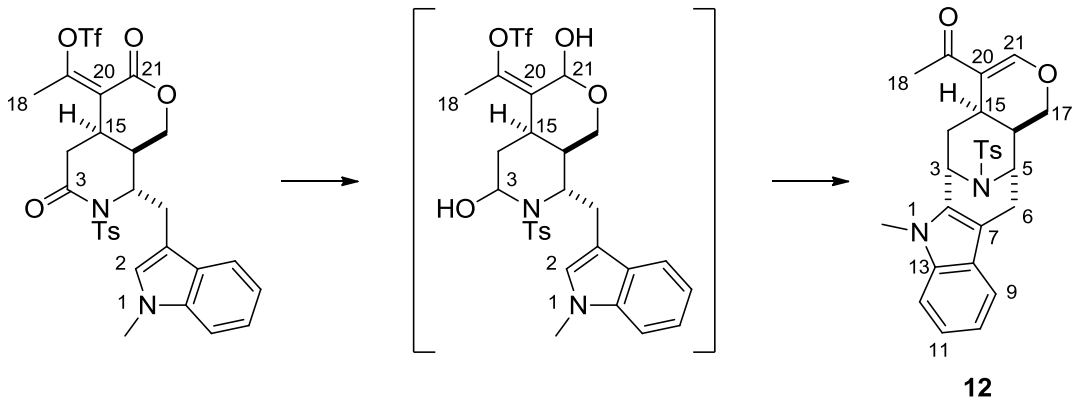
δ_H (400 MHz, $CDCl_3$) 7.98 (2H, d, *J* 8.5 Hz, *ortho*-**Ts**), 7.83 (1H, d, *J* 8.0 Hz, **12**), 7.37–7.32 (3H, m, *meta*-**Ts**, **9**), 7.29 (1H, t, *J* 8.0 Hz, **11**), 7.19 (1H, t, *J* 8.0 Hz, **10**), 6.99 (1H, s, **2**), 4.87 (1H, ddd, *J* 8.0, 3.0, 2.0 Hz, **5**), 4.20 (1H, ddd, *J* 11.5, 4.5 1.5 Hz, **17**), 4.15–4.06 (1H, m, **17**), 3.87–3.79 (1H, m, **15**), 3.78 (3H, s, N_1**Me**), 3.65 (1H, dd, *J* 15.0, 4.0 Hz, **6**), 3.00 (1H, dd, *J* 15.0, 10.0 Hz, **6**), 2.90 (1H, dd, *J* 19.0, 8.0 Hz, **14**), 2.55 (1H, m, **16**), 2.52 (3H, s, **18**), 2.45 (3H, s, *Ts***Me**), 2.34 (1H, dd, *J* 19.0, 9.5 Hz, **14**).

δ_C (100 MHz, $CDCl_3$) 166.5 (**C3**), 161.8 (**21**), 159.8 (**19**), 145.5 (*ipso*-**Ts**), 137.3 (**13**), 135.5 (*para*-**Ts**), 129.5 (*meta*-**Ts**), 129.3 (*ortho*-**Ts**), 128.0 (**C2**), 127.2 (**C8**), 122.3 (**C11**), 121.5 (**C20**), 119.7 (**C10**), 119.0 (**C12**), 109.6 (**C9**), 108.2 (**C7**), 67.8 (**17**), 57.1 (**5**), 34.2 (**14**), 32.8 (N_1**Me**), 31.9 (**6**), 28.2 (**15**), 21.8 (*Ts***Me**), 19.7 (**18**).

δ_F NMR (100 MHz, $CDCl_3$) –73.8 ($C\boldsymbol{F}_3$).

FTIR (film) υ_{max}: 2925, 1726, 1695, 1643, 1596, 1476, 1415, 1354 cm^{-1}; *m/z* (CI) 663 $[M+Na]^+$ (Found $[M+Na]^+$, 663.1062. $C_{28}H_{27}N_2O_8S_2F_3$ requires $[M+Na]^+$, 663.1059).

N_4-Demethyl-N_4-tosylalstonerine (12)



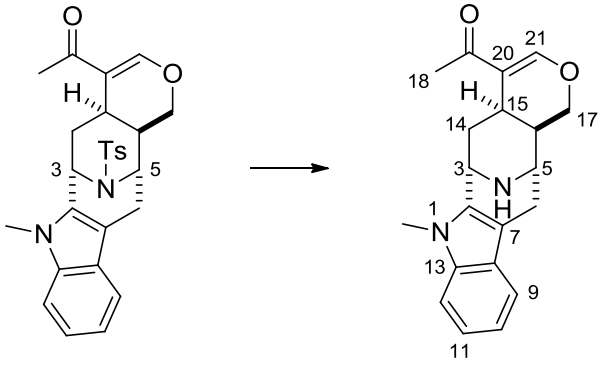
To a solution of the enol triflate derivative of **11** prepared as described above (200.0 mg, 0.312 mmol, 1.0 equiv.) in CH_2Cl_2 (2 mL) at –78 °C was added DIBAL-H (1.0 M in toluene; 0.78 mL, 0.781 mmol, 2.5 equiv.) and the solution stirred at –78 °C for 2.25 h. Wet Et_2O (5 mL) was added and the reaction mixture was allowed to warm slowly from –78 °C to rt. Saturated aqueous Rochelle salt (10 mL) and EtOAc (10 mL) were added, and the resulting suspension stirred vigorously at rt overnight. Saturated aqueous $NaHCO_3$ (10 mL) was then added, and the aqueous phase extracted with EtOAc (3×20 mL) and CH_2Cl_2 (2×20 mL). The organic phases were washed with brine (20 mL), combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield the intermediate lactol as an amorphous, colourless solid. This material was dissolved in wet CH_2Cl_2 (10 mL) and stirred at rt for 1 h. The dark brown solution was then filtered over basic alumina to give crude N_4-tosylalstonerine **12** as an amorphous, colourless solid. Purification by chromatography (50% EtOAc–hexane) yielded the title compound **12** (146.0 mg, 98%) as an amorphous solid; R_f 0.56 (50% EtOAc–hexane).

δ_H (400 MHz, $CDCl_3$) 7.55 (1H, s, **21**), 7.35 (2H, d, *J* 8.0 Hz, *ortho*-**Ts**), 7.25 (1H, d, *J* 8.0 Hz, **9**), 7.18–7.10 (2H, m, **12** and **11**), 6.99 (1H, td, *J* 8.0, 1.0 Hz, **10**), 6.79 (2H, d, *J* 8.0 Hz, *meta*-**Ts**), 5.24 (1H, br. t, *J* 3.0 Hz, **3**), 4.35–4.25 (3H, m, 2 × **17** and **5**), 3.67 (3H, s, N_1**Me**), 2.88 (1H, dd, *J* 16.5, 8.0 Hz, **6**), 2.84–2.76 (1H, m, **15**), 2.47 (1H, d, *J* 16.5, **6**), 2.17 (1H, ddd, *J* 12.0, 5.0, 3.0 Hz, **14**), 2.10 (3H, s, **18**), 2.00 (3H, s, *Ts***Me**), 1.98–1.85 (2H, m, **14** and **16**).

δ_C (100 MHz, $CDCl_3$) 195.2 (**C19**), 157.5 (**C21**), 143.4 (*para*-**Ts**), 136.9 (**C13**), 136.1 (*ipso*-**Ts**), 131.9 (**C2**), 128.8 (*meta*-**Ts**), 126.3 (*ortho*-**Ts**), 126.1 (**C8**), 121.5 (**C11**), 120.2 (**C20**), 119.0 (**C10**), 117.7 (**C12**), 108.9 (**C9**), 106.8 (**C7**), 66.2 (**C17**), 49.4 (**C5**), 48.5 (**C3**), 38.0 (**C15**), 32.3 (**C14**), 29.2 (N_1**Me**), 25.6 (**C6**), 25.0 (**C18**), 22.8 (**C16**), 21.1 (*Ts***Me**).

FTIR (film) υ_{max}: 2988, 2301, 1619, 1449, 2338, 2276, 1261 cm^{-1}; *m/z* (CI) 477 $[M+H]^+$ (Found $[M+H]^+$, 477.1838. $C_{27}H_{28}N_2O_4S$ requires $[M+H]^+$, 477.1848).

N_4-Demethylalstonerine



12

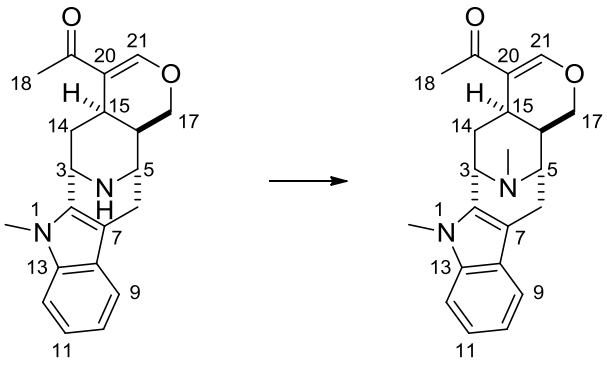
To a solution of naphthalene (200 mg, 1.6 mmol) in THF (16 mL) at rt was added sodium (40 mg, 1.6 mmol) and the reaction mixture stirred at rt for 1 h. The resulting dark green/blue solution was cooled to –78 °C and an aliquot (*ca.* 0.1 M in THF; 0.33 mL, 0.031 mmol, 5 equiv.) was added to a solution of **12** (31.3 mg, 0.066 mmol, 1.0 equiv.) in THF (3 mL) at –78 °C. The reaction mixture was stirred at –78 °C for 2 h. Saturated aqueous $NaHCO_3$ (3 mL) was added and the solution allowed to warm slowly from –78 °C to rt. The aqueous layer was then extracted with EtOAc (3× 30 mL) and CH_2Cl_2 (2× 50 mL), the organic layers were washed with brine, combined, dried over $MgSO_4$ and filtered. Concentration under reduced pressure and purification *via* chromatography (2→10% MeOH–CH_2Cl_2) yielded the title compound (17.6 mg, 83%) as a pale yellow oil; R_f 0.3 (3% MeOH–CH_2Cl_2).

δ_H (400 MHz, $CDCl_3$) 7.54 (1H, s, **21**), 7.47 (1H, d, *J* 8.0 Hz, **9**), 7.31 (1H, d, *J* 8.0 Hz, **9**), 7.21 (1H, t, *J* 7.5 Hz, **10**), 7.09 (1H, t, *J* 7.5 Hz, **10**), 4.45 (1H, t, *J* 11.5 Hz, **17**), 4.36–4.24 (2H, m, **17** and **5**), 3.64 (3H, s, N_1**Me**), 3.50 (1H, d, *J* 7.0 Hz, **6**), 3.27 (1H, dd, *J* 16.5, 7.0 Hz, **6**), 3.11 (1H, br. s, N_4**H**), 2.77–2.66 (2H, m, **15** and **6**), 2.16–2.04 (4H, s, **18** and **14**), 1.92 (1H, dt, *J* 12.0, 4.5 Hz, **16**), 1.81 (td, *J* 12.0, 4.5 Hz, **14**).

δ_C (100 MHz, $CDCl_3$) 195.4 (**C19**), 157.5 (**C21**), 136.9 (**C13**), 136.7 (**C2**), 126.8 (**C8**), 121.3 (**C20**), 121.1 (**C11**), 118.7 (**C10**), 117.8 (**C9**), 109.0 (**C12**), 107.1 (**C7**), 67.5 (**C17**), 48.3 (**C3**), 46.5 (**C5**), 37.4 (**C16**), 31.6 (**C14**), 29.0 (N_1**Me**), 28.9 (**C6**), 25.0 (**C18**), 23.6 (**C15**).

FTIR (film) υ_{max}: 2923, 1704, 1651, 1617, 1470 cm^{-1}; *m/z* (CI) 323 $[M+H]^+$ (Found $[M+H]^+$, 3323.1774. $C_{20}H_{22}N_2O_2$ requires $[M+H]^+$, 323.1760).

(±)-Alstonerine (1)



1

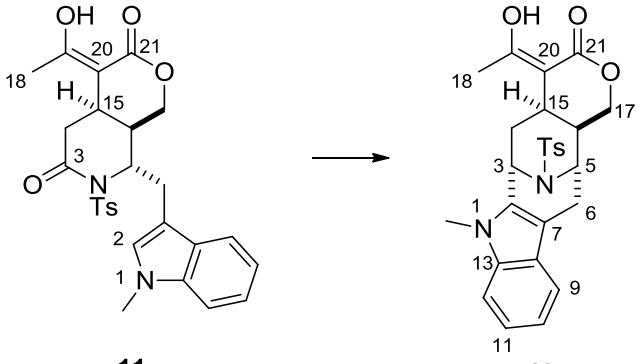
To a solution of N_4-demethylalstonerine (13 mg, 0.04 mmol, 1.0 equiv.) in THF (1 mL) at –78 °C was added Hünig's base (0.02 mL, 0.12 mmol, 3.0 equiv.) and iodomethane (0.005 mL, 0.08 mmol, 2.0 equiv.) and the solution allowed to warm slowly to rt overnight. To the resulting cloudy solution was added saturated aqueous $NaHCO_3$ (3 mL) and the aqueous phase extracted with CH_2Cl_2 (4×20 mL) and EtOAc (3×20 mL). The combined organic layers were dried over $MgSO_4$ and filtered. Concentration under reduced pressure and chromatography (50→75% EtOAc–hexane) yielded (±)-alstonerine **1** as a pale yellow oil (12.2 mg, 91%). R_f 0.3 (100% EtOAc).

δ_H (400 MHz, $CDCl_3$) 7.53 (1H, s, **21**), 7.48 (1H, d, *J* 8.0 Hz, **9**), 7.32 (1H, d, *J* 8.0 Hz, **9**), 7.20 (1H, t, *J* 7.5 Hz, **10**), 7.09 (1H, t, *J* 7.5 Hz, **10**), 4.41 (1H, t, *J* 11.0 Hz, **17**), 4.17 (1H, ddd, *J* 11.0, 4.0, 1.5 Hz, **17**), 3.89 (1H, br. t, *J* 3.5 Hz, **3**), 3.65 (3H, s, N_1**Me**), 3.33 (1H, dd, *J* 16.5, 7.0 Hz, **6**), 3.10 (1H, d, *J* 7.0 Hz, **5**), 2.66–2.58 (1H, m, **15**), 2.51 (*J* 16.5 Hz, **6**), 2.33 (3H, br. s, N_4**Me**), 2.15 (1H, dd, *J* 5.0, 3.0 Hz, **14**), 2.13–2.01 (4H, m, **14** then **18**), 1.91 (1H, dt, *J* 12.0, 4.5 Hz, **16**)**,** 1.81 (td, *J* 12.0, 4.5 Hz, **14**).

δ_C (100 MHz, $CDCl_3$) 195.5 (**C19**), 157.5 (**C21**), 137.1 (**C13**) 133.1 (**C2**), 126.6 (**C8**), 121.1 (**C10**), 120.8 (**C20**), 118.7 (**C11**), 117.9 (**C9**), 109.0 (**C12**), 105.9 (**C7**), 67.8 (**C17**), 54.7 (**C3**), 53.8 (**C5**), 41. 8 (**C16**), 38.5 (**C14**), 32.4 (**C15**), 29.1 (N_1**Me**), 25.1 (N_4**Me**), 22.9 (**C18**), 22.8 (**C6**).

FTIR (film) υ_{max}: 1652, 1618 cm^{-1}; *m/z* (CI) 337 $[M+H]^+$ (Found $[M+H]^+$, 337.1908. $C_{21}H_{24}N_2O_2$ requires $[M+H]^+$, 337.1916).

Pentacyclic lactone 13



To a solution of enol **11** (870.0 mg, 1.712 mmol, 1.0 equiv.) in THF (5.7 mL) at –78 °C was added DIBAL-H (1.0 M in toluene; 3.4 mL, 3.4 mmol, 2.0 equiv.). and the solution stirred at –78 °C for 3 h. Trifluoromethanesulfonic acid (0.4 mL, 4.28 mmol, 2.5 equiv.) was added and the reaction mixture was allowed to warm slowly from –78 °C to rt over 1 h. Saturated aqueous Rochelle salt (10 mL) and EtOAc (30 mL) were added, and the resulting suspension stirred vigorously at rt overnight. Saturated aqueous $NaHCO_3$ (10 mL) was added, and the aqueous phase extracted with EtOAc (3×50 mL) and CH_2Cl_2 (2×50 mL). The organic phases were washed with brine, combined, dried over $MgSO_4$, and filtered. Concentration under reduced pressure and chromatography (33% EtOAc–hexane) yielded the title compound **13** (766.8 mg, 91%) as an amorphous solid; R_f 0.60 (66% EtOAc–hexane).

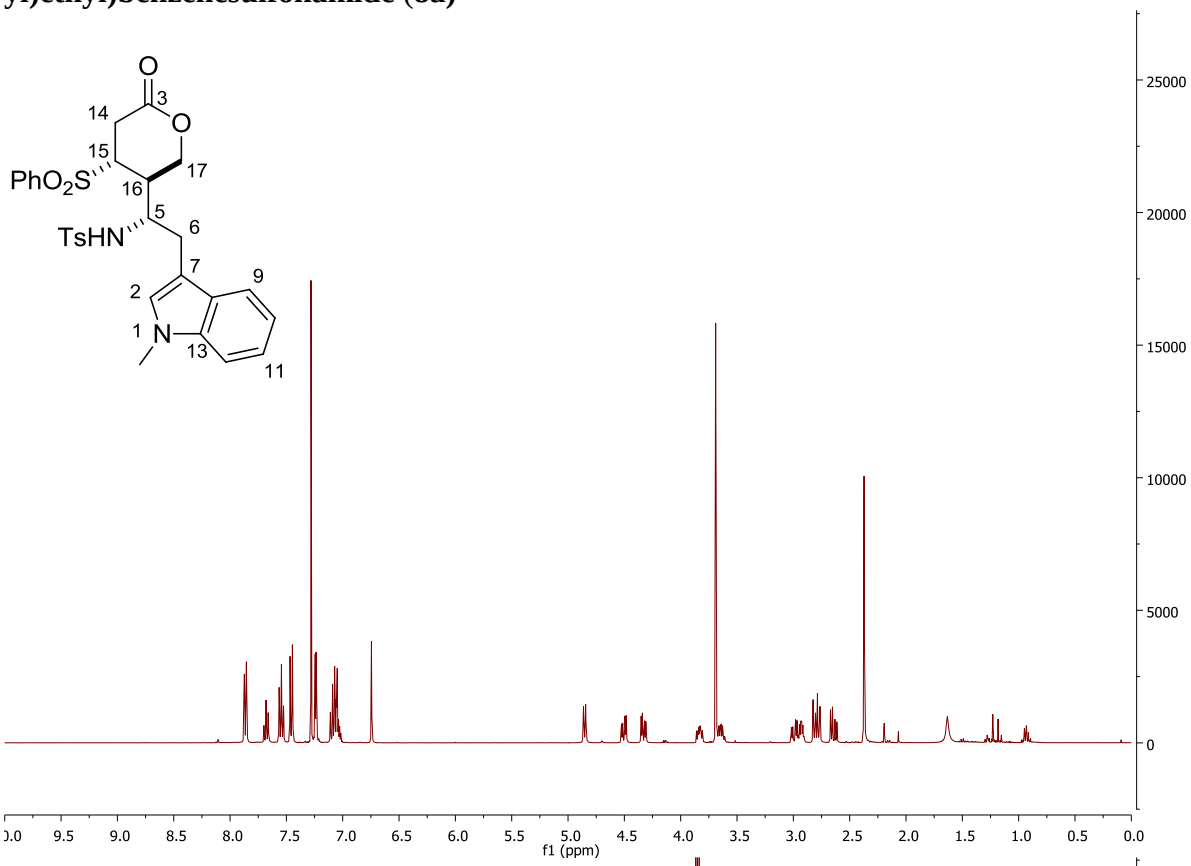
δ_H (400 MHz, $CDCl_3$) 14.04 (1H, s, **19**-O***H***), 7.36 (2H, ap. d, *J* 8.0 Hz, *ortho*-**Ts**), 7.28–7.15 (3H, m, **9**, **11** and **12**), 7.04 (1H, t, *J* 7.0 Hz, **10**), 6.81 (2H, ap. d, *J* 8.0 Hz, *meta*-**Ts**), 5.30 (1H, br. s, **3**), 4.70 (1H, t, *J* 12.0 Hz, **17**), 4.41 (1H, ddd, *J* 12.0, 4.5, 1.0 Hz, **17**), 4.32 (1H, br d, *J* 7.5, **5**), 3.68 (3H, s, N_1**Me**), 2.94 (1H, dd, *J* 16.5, 8.0 Hz, **6**), 2.75 (1H, dt, *J* 12.5 2.5 Hz, **15**), 2.50 (1H, d, *J* 16.5 Hz,**6**), 2.26–2.15 (2H, m, **14** and **16**), 2.03 (3H, s, *Ts***Me**), 1.74 (1H, ddd, 14.0, 4.5, 3.0 Hz, **14**), 1.65 (3H, s, **18**).

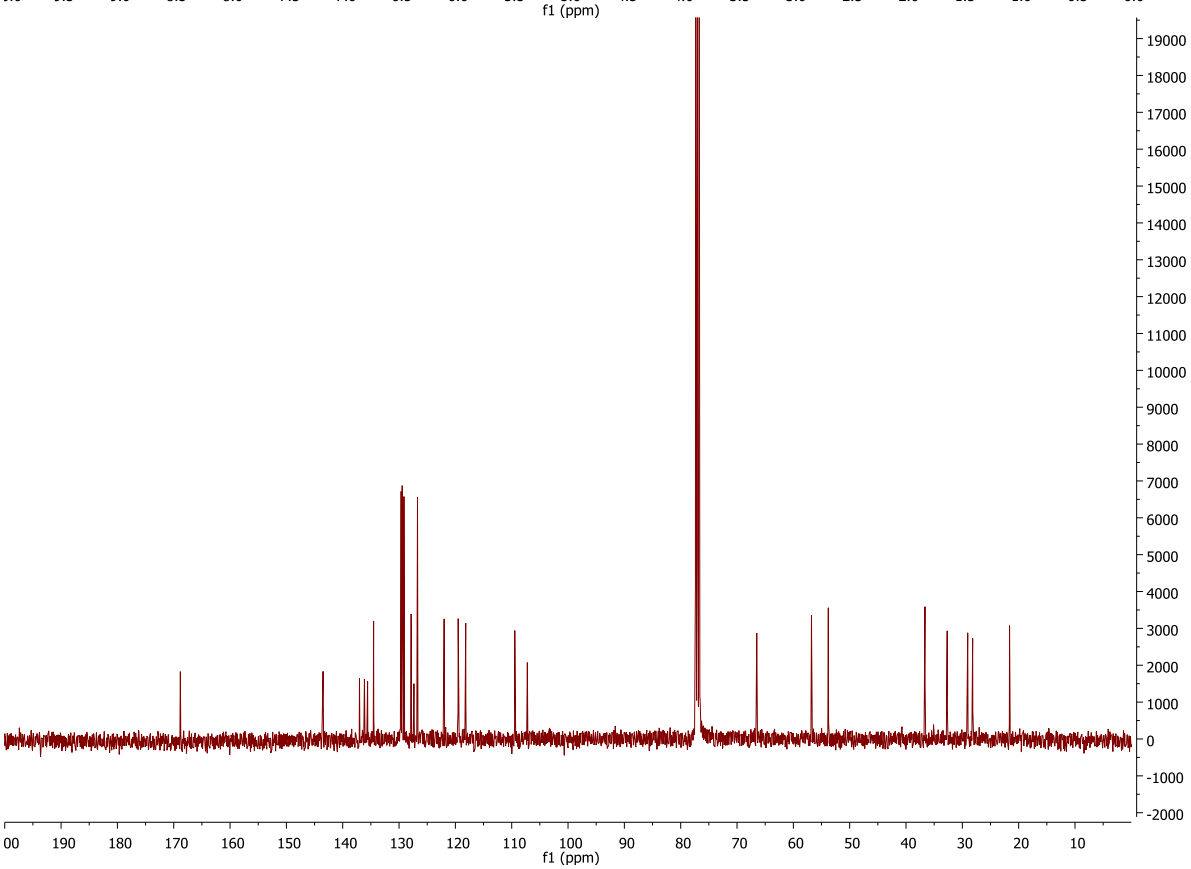
δ_C (100 MHz, $CDCl_3$) 176.8 (**C19**), 172.0 (**C21**), 143.7 (*para*-**Ts**), 136.9 (**C13**), 135.9 (*ipso*-**Ts**), 131.4 (**C2**), 128.9 (*meta*-**Ts**), 126.4 (*ortho*-**Ts**), 121.9 (**C11**), 119.4 (**C10**), 118.0 (**C12**), 109.0 (**C9**), 95.7 (**C20**), 67.5 (**C17**), 49.3 (**C3**), 48.1 (**C5**), 39.7 (**C16**), 32.7 (**C14**), 29.3 (N_1**Me**), 26.1 (**C15**), 25.3 (**C6**), 21.1 (*Ts***Me**), 18.1 (**C18**).

FTIR (film) υ_{max}: 3049, 2924, 2854, 1634, 1610, 1468 cm^{-1}; *m/z* (CI) 493 $[M+H]^+$ (Found $[M+H]^+$, 493.1779. $C_{27}H_{28}N_2O_5S$ requires $[M+H]^+$, 493.1797).

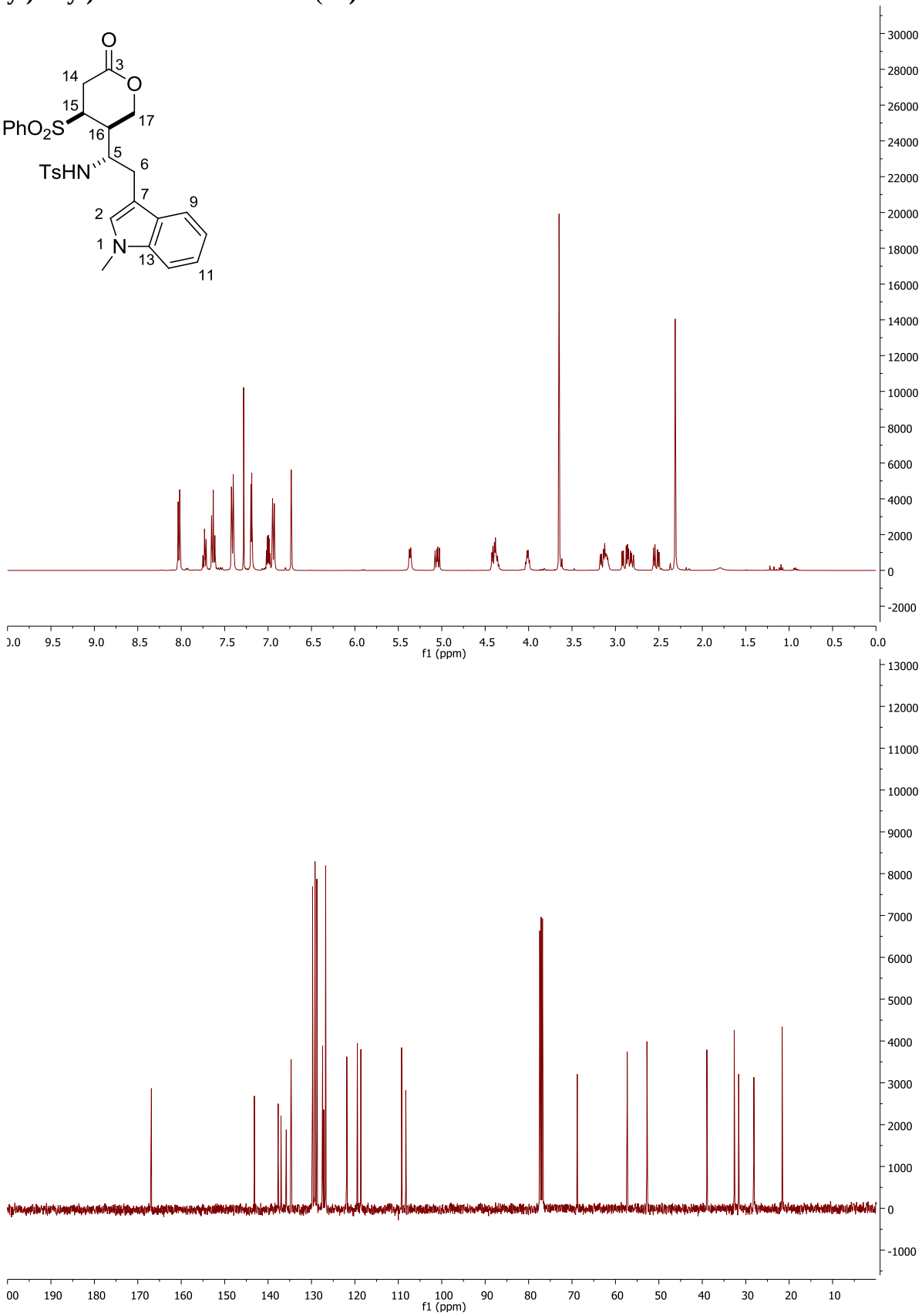
NMR Spectra

4-Methyl-*N*-((*R**)-2-(1-methylindol-3-yl)-1-((3*S**,4*S**)-6-oxo-4-(phenylsulfonyl)tetrahydro-2*H*-pyran-3-yl)ethyl)benzenesulfonamide (8a)

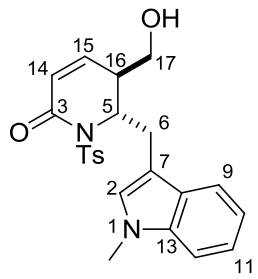


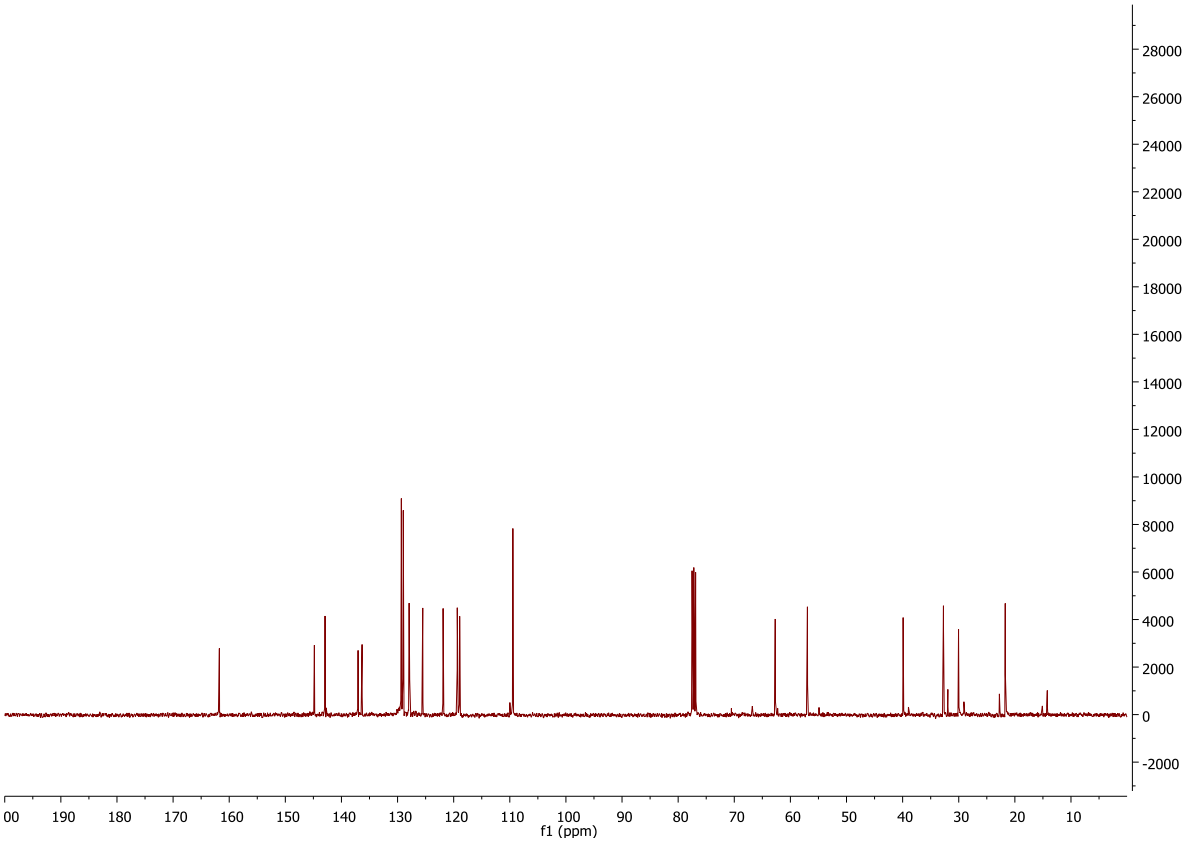


4-Methyl-*N*-((*R)-2-(1-methylindol-3-yl)-1-((3*S**,4*R**)-6-oxo-4-(phenylsulfonyl)tetrahydro-2*H*-pyran-3-yl)ethyl)benzenesulfonamide (8b)**

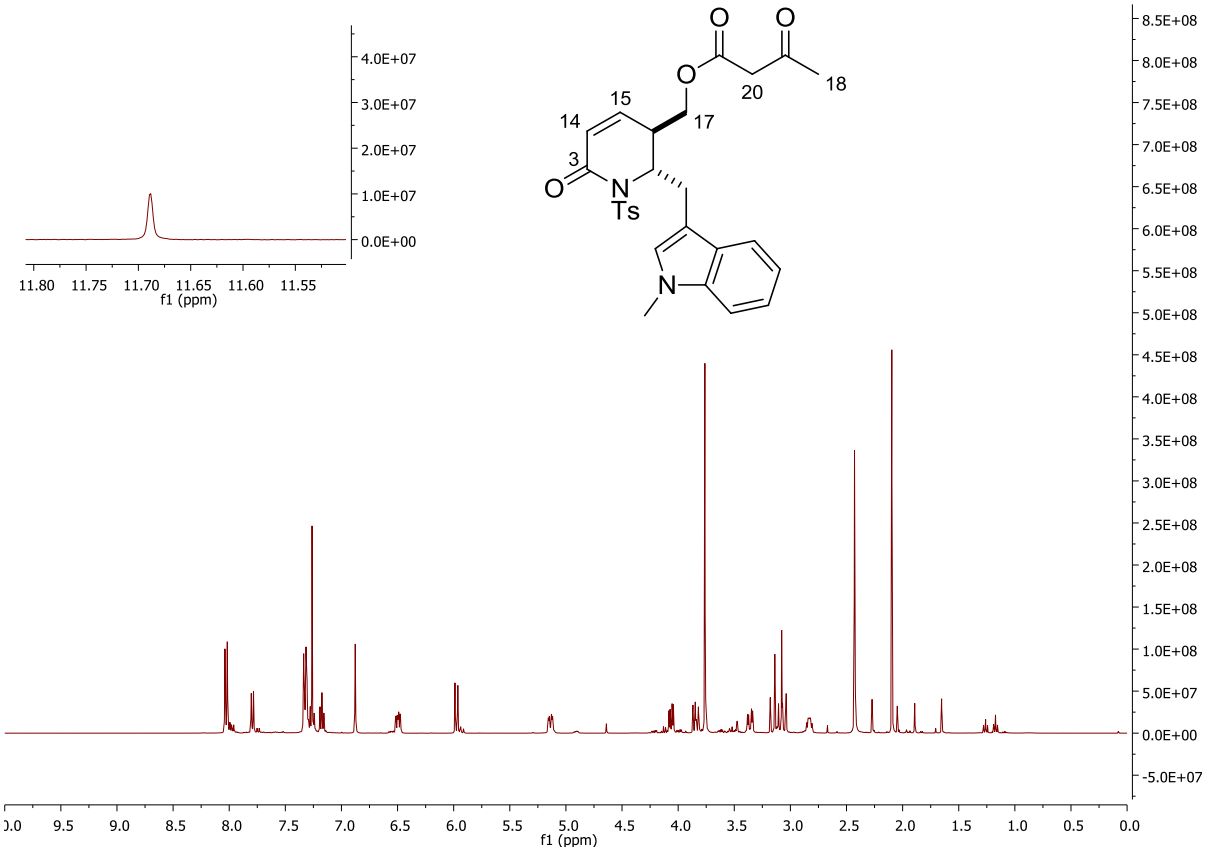


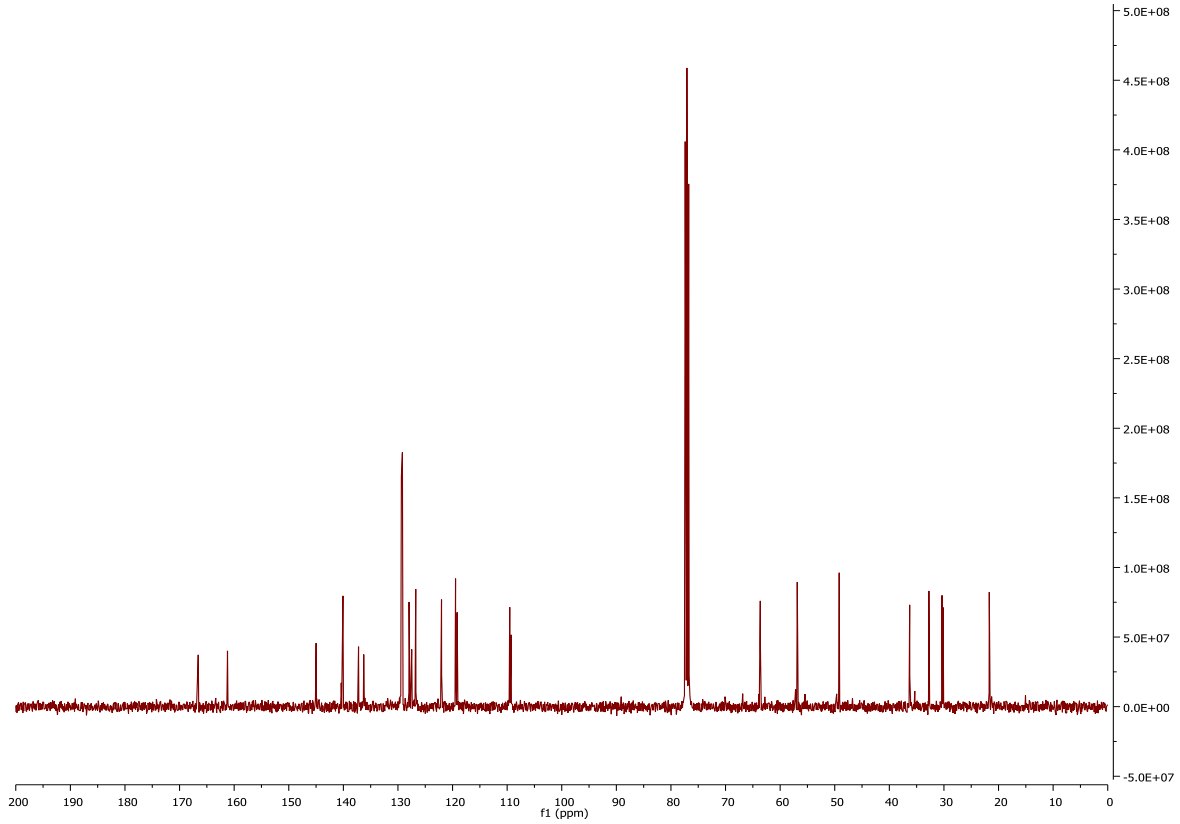
(5*R,6*S**)-5-(Hydroxymethyl)-6-((1-methylindol-3-yl)methyl)-1-tosyl-5,6-dihydropyridin-2(1*H*)-one (5)**



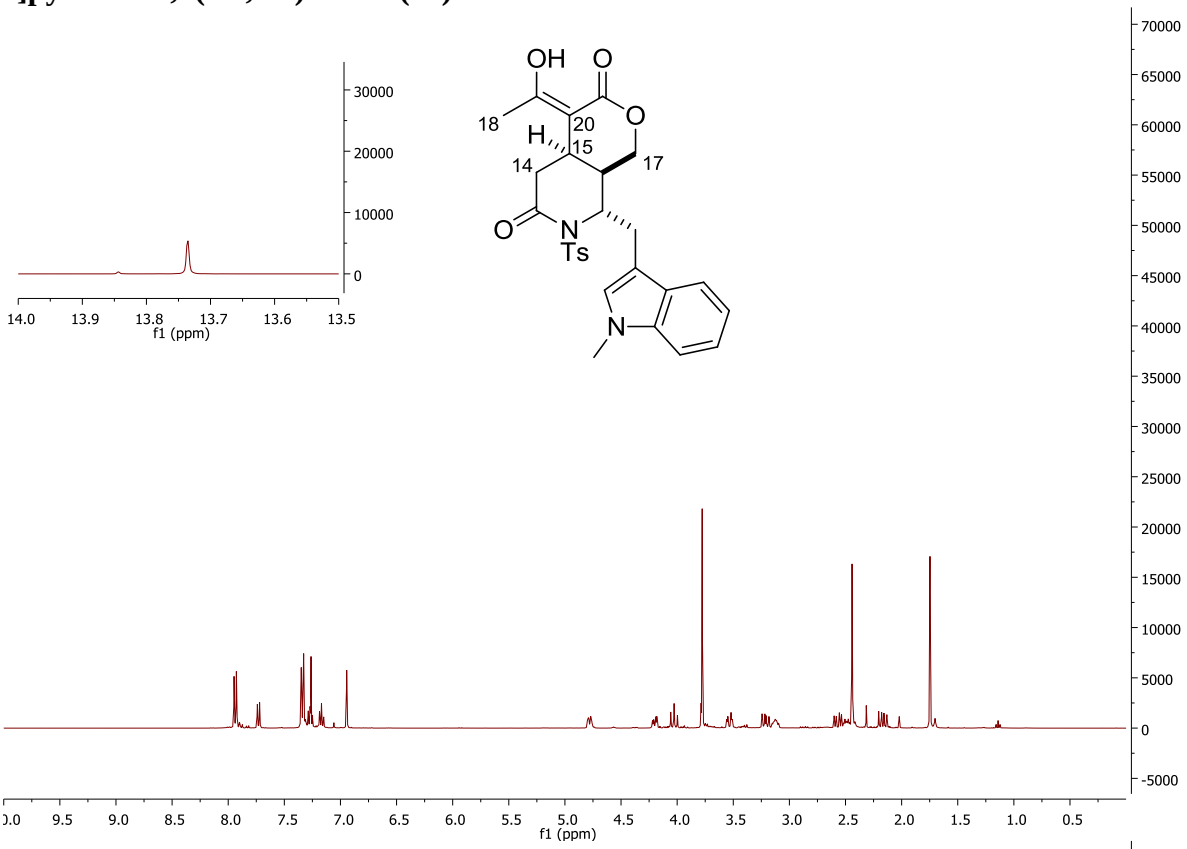


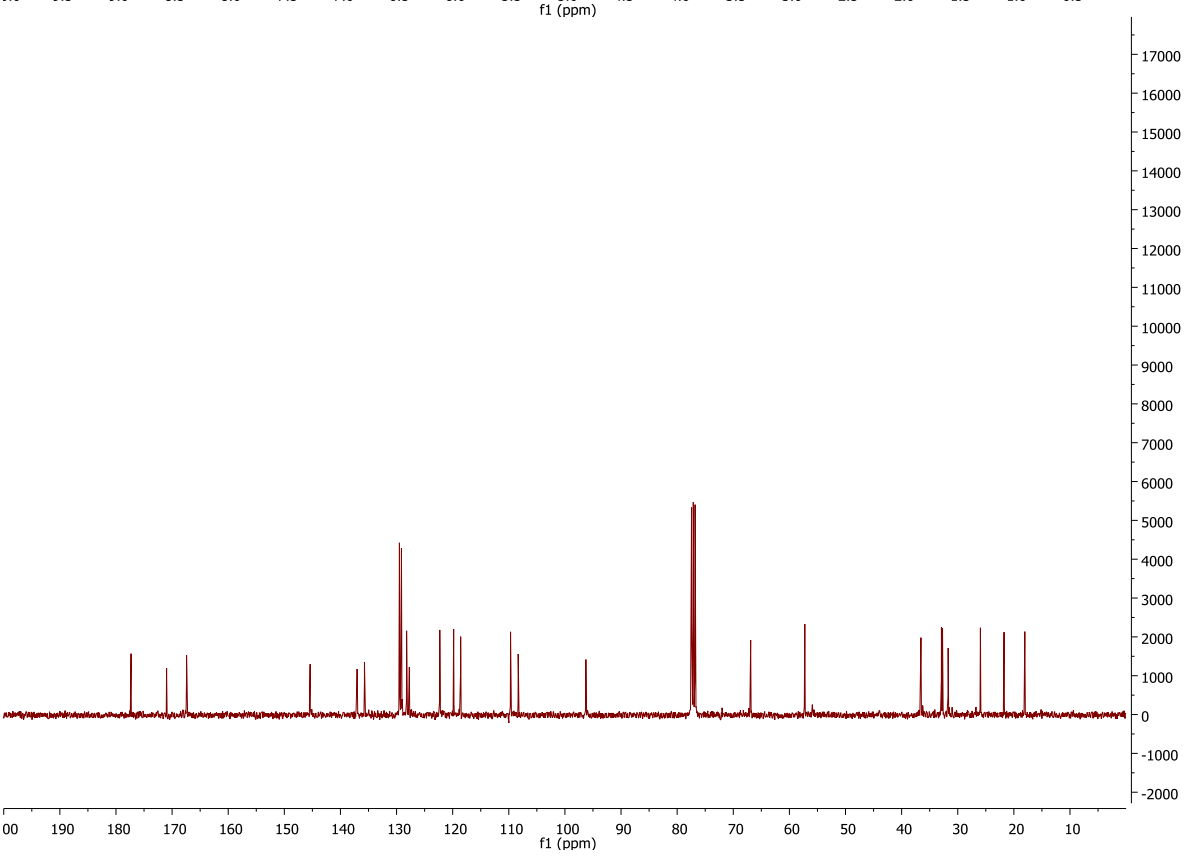
((2*R,3*S**)-2-((1-Methylindol-3-yl)methyl)-6-oxo-1-tosyl-1,2,3,6-tetrahydropyridin-3-yl)methyl 3-oxobutanoate**



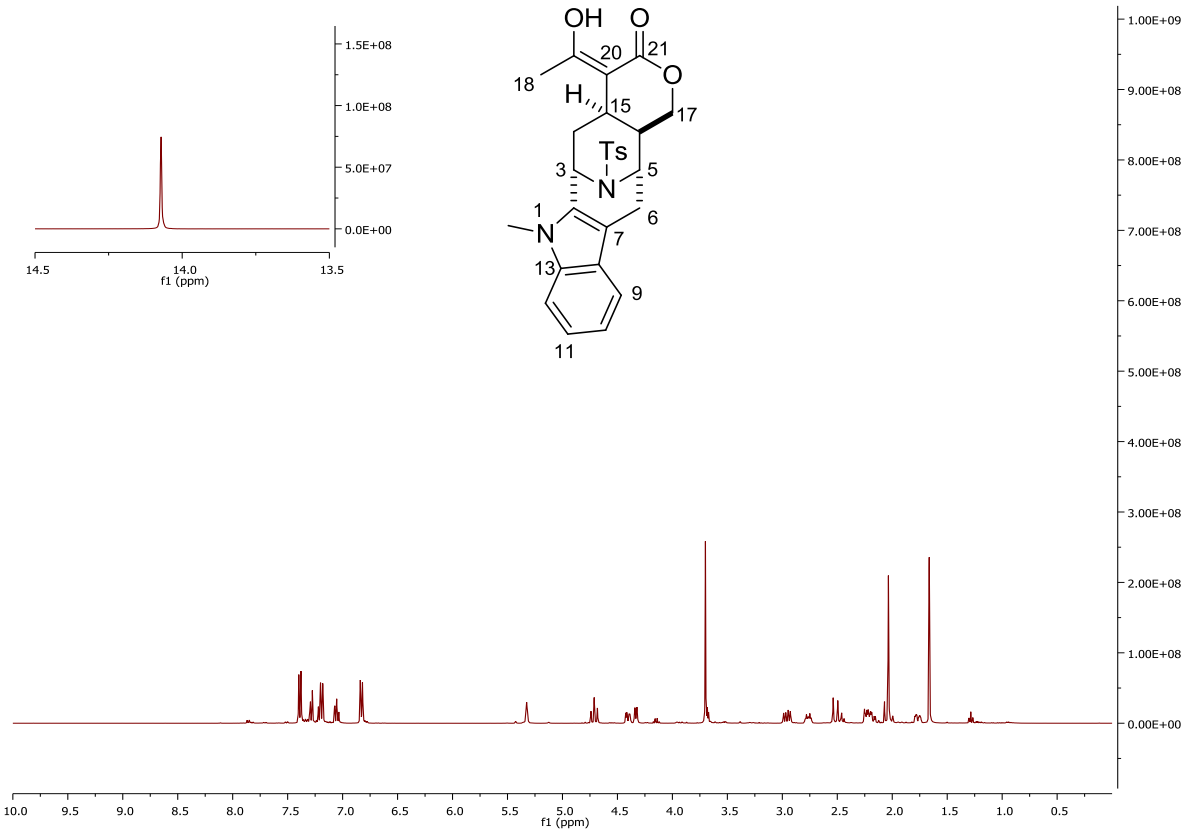


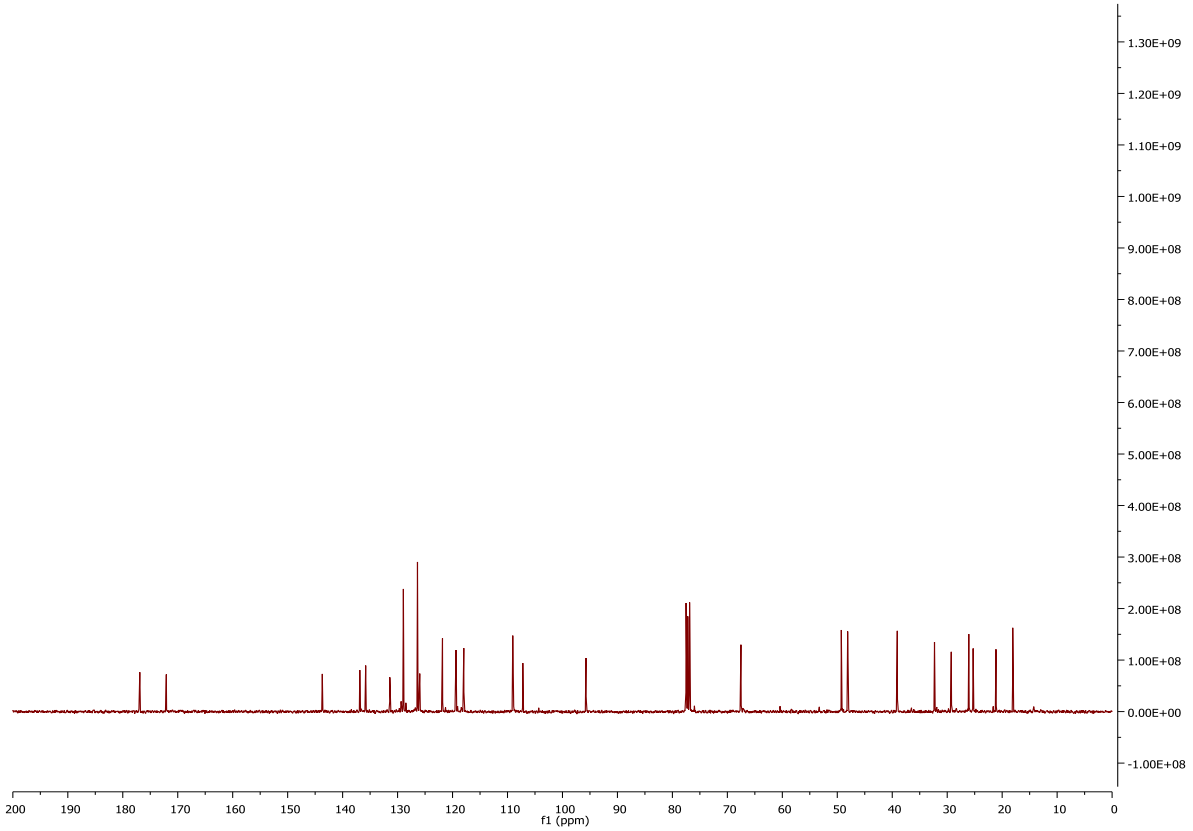
(8*R,8a*S**,*Z*)-4-(1-Hydroxyethylidene)-8-((1-methylindol-3-yl)methyl)-7-tosyltetrahydro-1*H*-pyrano[3,4-*c*]pyridine-3,6(4*H*,7*H*)-dione (11)**



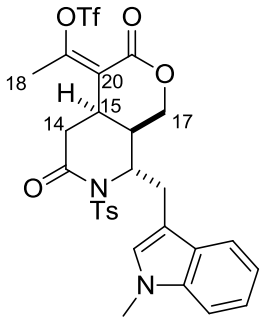


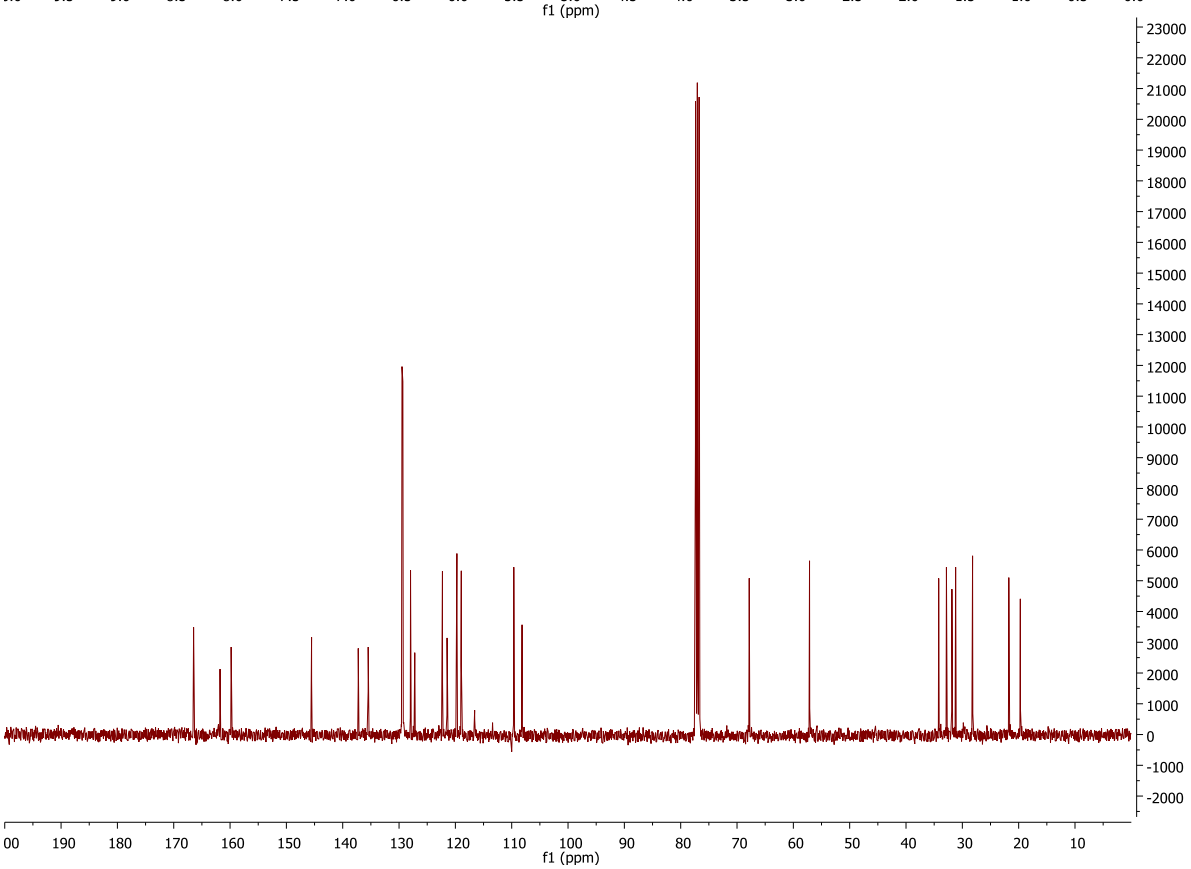
Pentacyclic lactone (13)



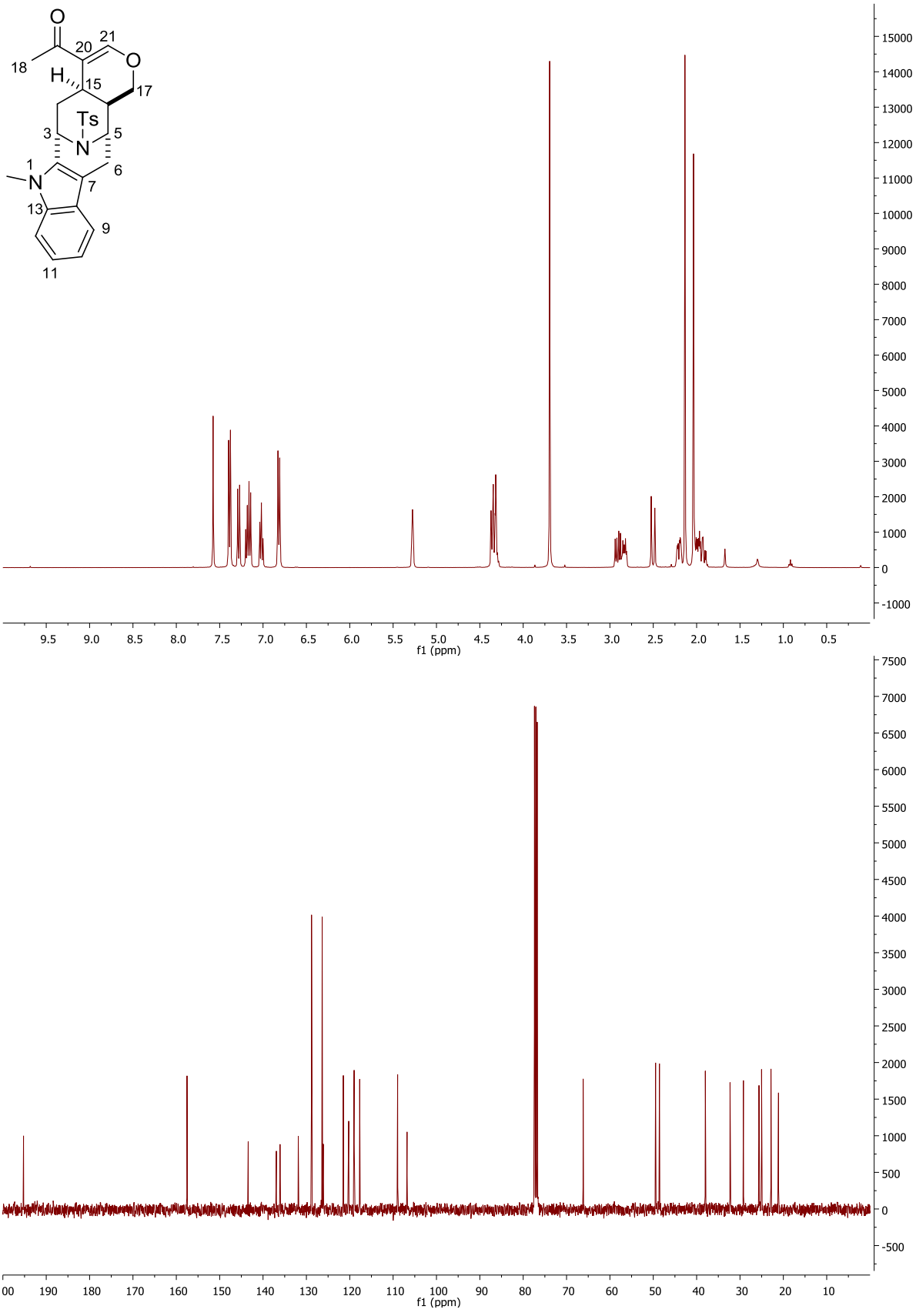


(*Z*)-1-((8*R,8a*S**)-8-((1-Methylindol-3-yl)methyl)-3,6-dioxo-7-tosyl-1*H*-pyrano[3,4-*c*]pyridin-4(3*H*,4a*H*,5*H*,6*H*,7*H*,8*H*,8a*H*)ylidene)ethyl trifluoromethanesulfonate**

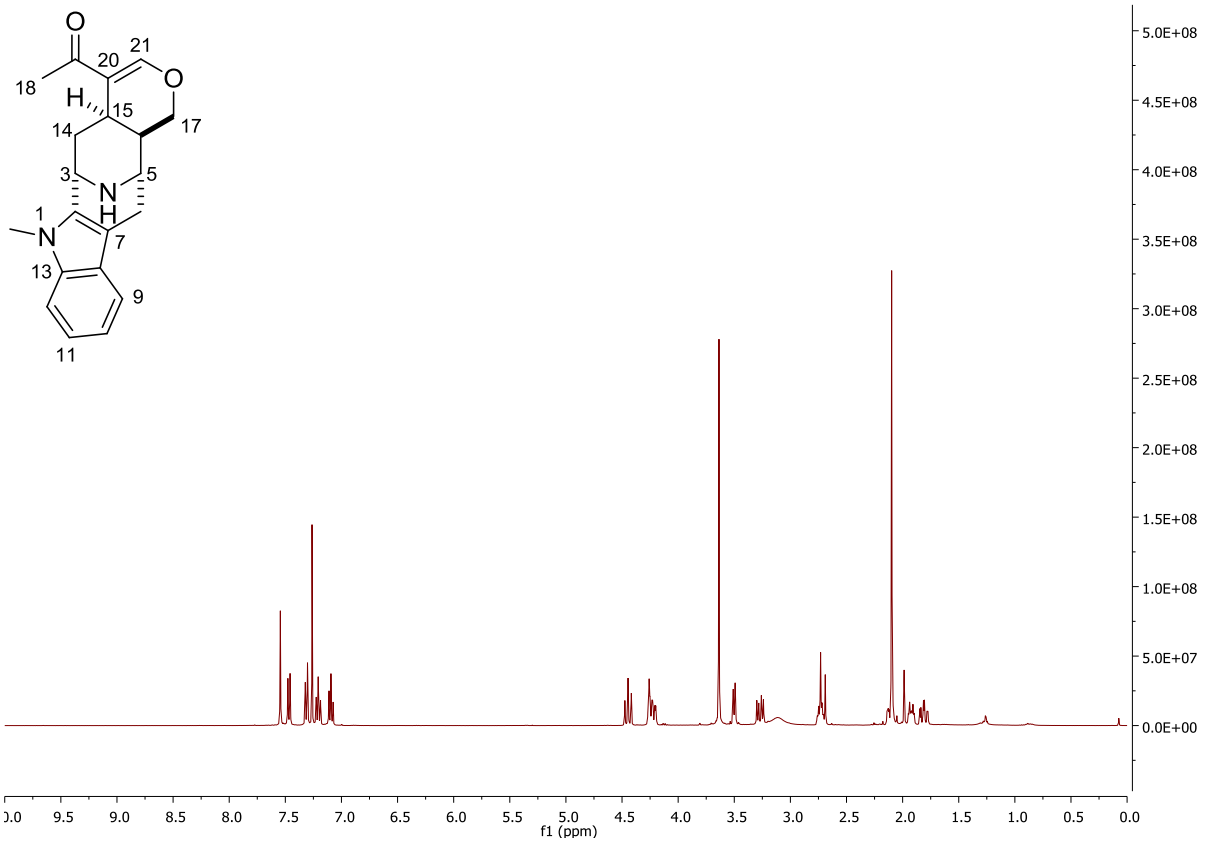


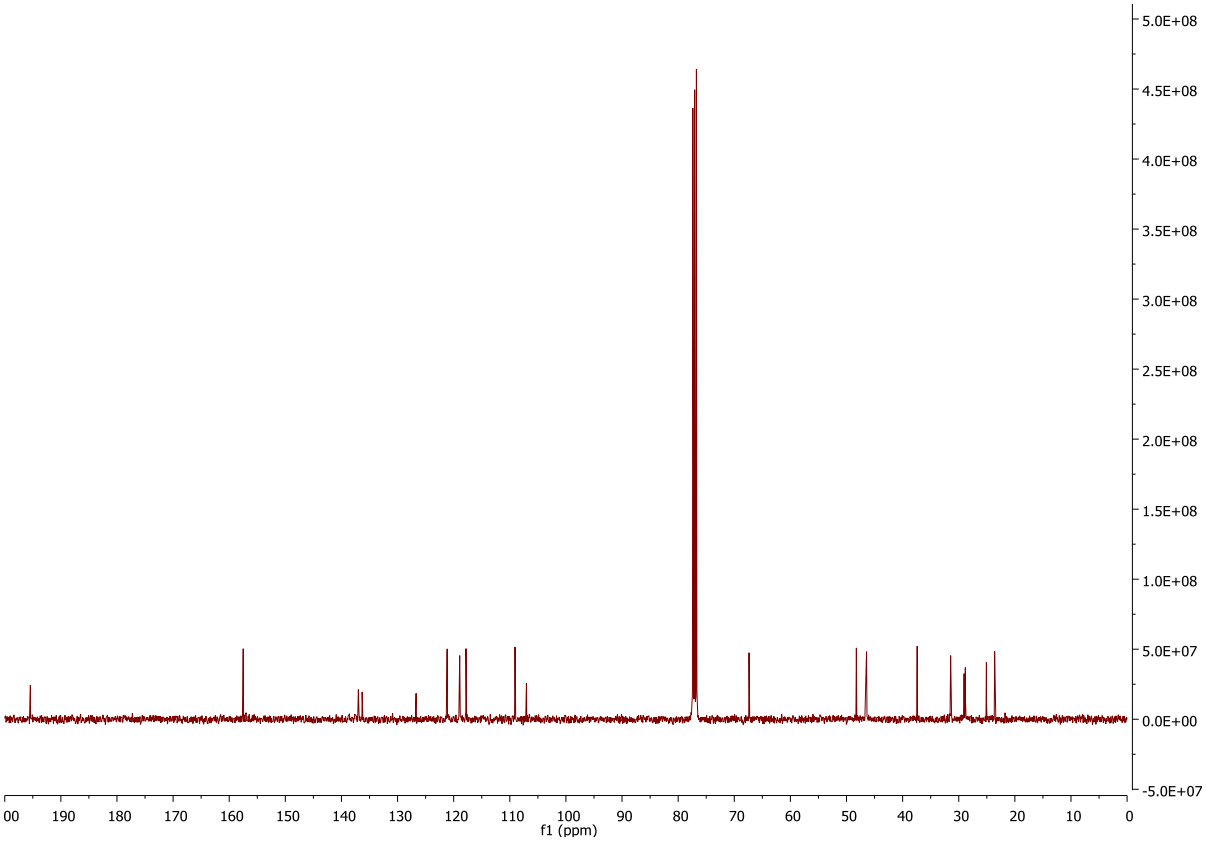


N_4-Tosylalstonerine (12)

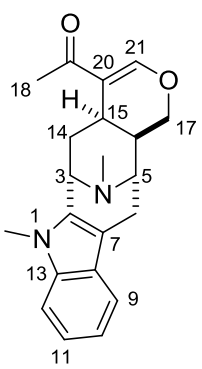


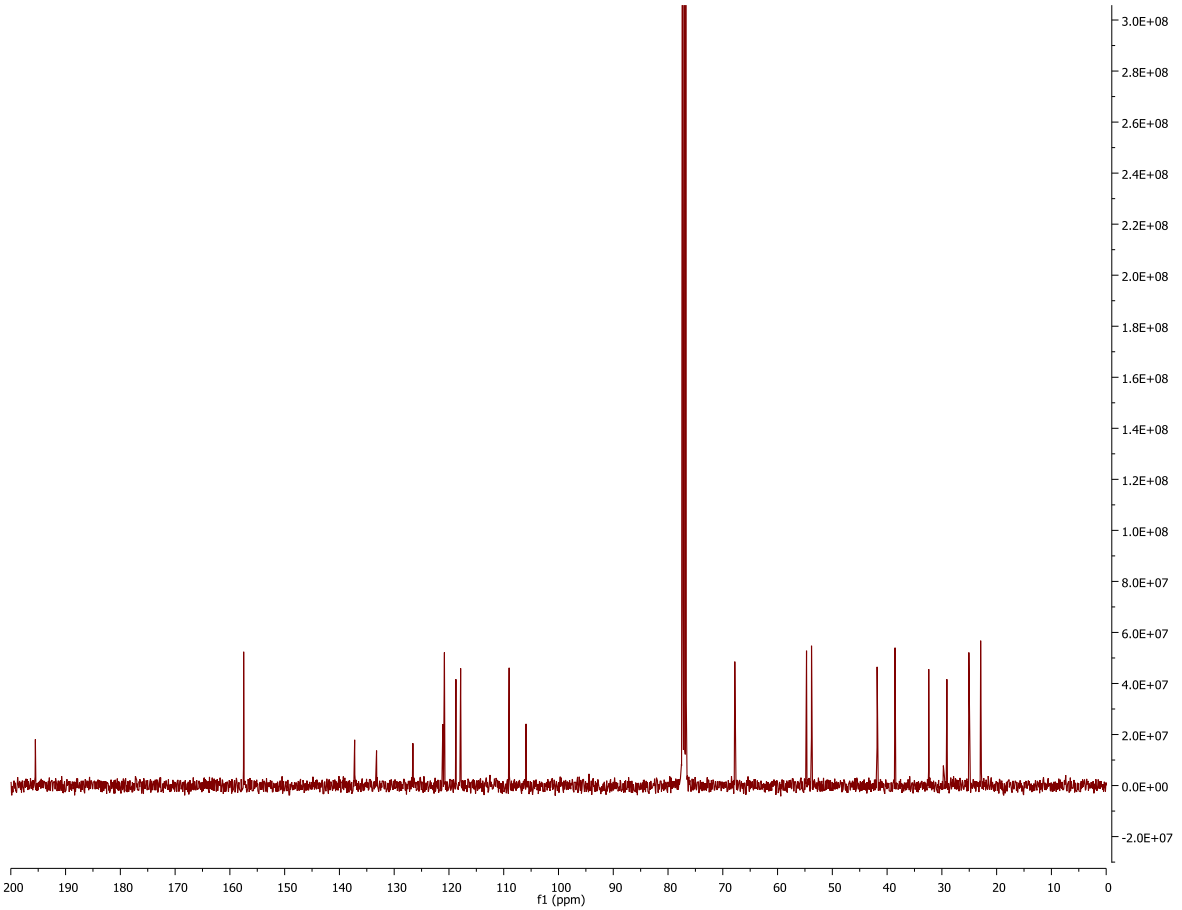
N_4-Demethylalstonerine





(±)-Alstonerine (1)





X-Ray crystal structures of 8a and 8b

The N–H hydrogen atoms in the structures of **8a** and **8b** were located from ΔF maps and refined freely, subject to an N–H distance constraint of 0.90 Å.

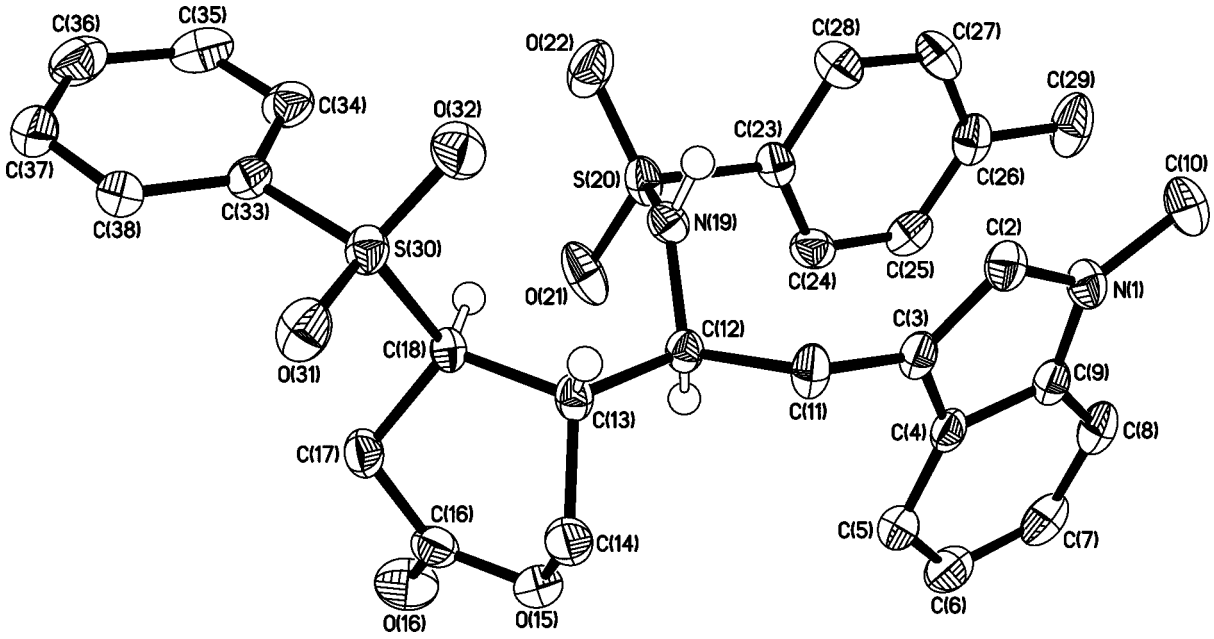


Fig. S1 The crystal structure of **8a** (50% probability ellipsoids).

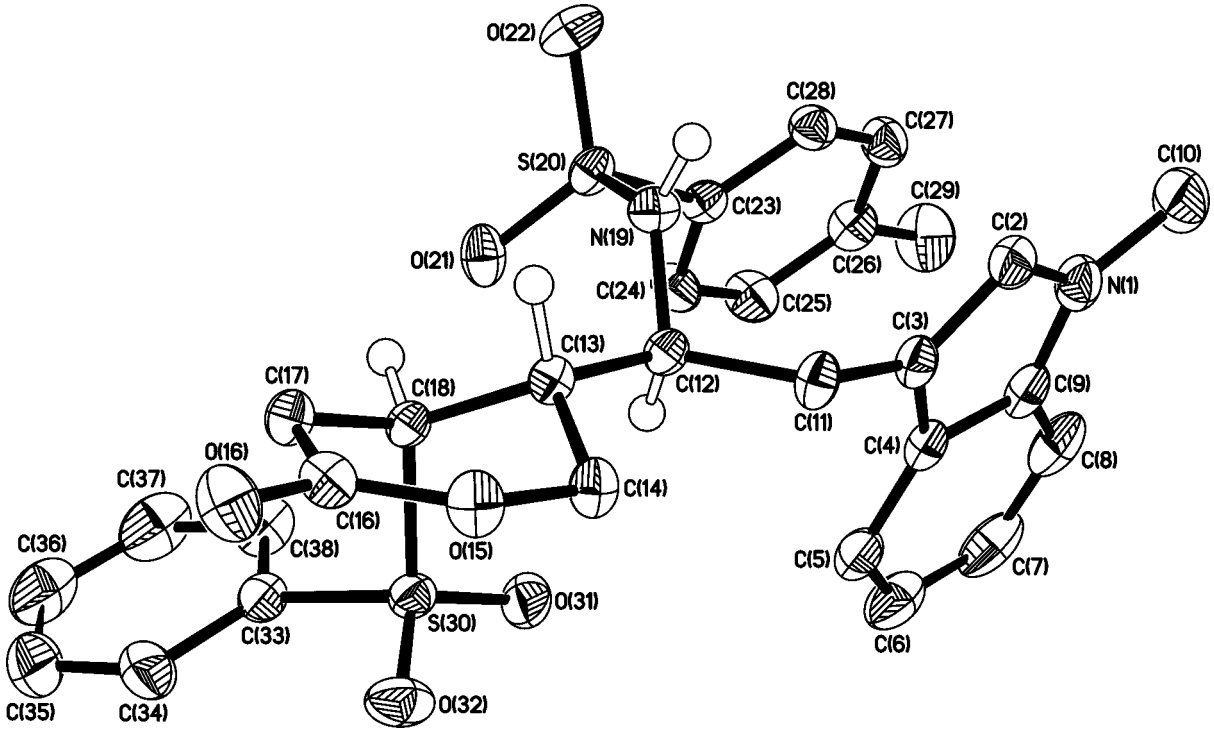


Fig. S2 The crystal structure of **8b** (50% probability ellipsoids).