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Enantioselective Total Synthesis of the Polycyclic Guanidine Containing Marine Alkaloid, (–)-Batzelladine D

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General. The chemical shifts of the ^{1}H-NMR and ^{13}C-NMR spectra were all recorded relative to chloroform or methanol. Multiplicities were determined with the aid of an APT sequence, separating methylene and quaternary carbons = e (even), from methyl and methine = o (odd). GC and HPLC analysis was carried out using an HP 5890 GC Series 2 and HP 1100 HPLC respectively. All compounds were purified using flash chromatography, and gave spectroscopic data consistent with being ≥95% the assigned structure. Analytical t.l.c. was carried out on pre-coated 0.2 mm thick Merck 60 F_{254} silica plates. Flash chromatography was carried out using Merck Silica Gel 60 (230-400 mesh).

(3*R*,4*R*,4a*S*,7*R*)-Methyl-2-[(7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)methylsulfonyl]-3,7-dimethyl-1-oxooctahydro-pyrrolo[1,2-c]pyrimidine-4-carboxylate (7a). The alkyl bromide **6** (110 mg, 0.21 mmol, azeotroped with anhydrous benzene) was dissolved in anhydrous benzene (20 ml) and heated at reflux under an atmosphere of nitrogen. Tributyltin hydride (68 μl, 0.25 mmol) and 2,2'-azobis(2-methylpropionitrile) (3.46 mg, 0.021 mmol) were then added as separate solutions in anhydrous benzene (2 x 5.0 ml) *via* syringe pump over *ca*. 5 hours (t.l.c. control). The reaction mixture was then cooled to room temperature and concentrated *in vacuo* to afford the crude reaction mixture. Purification by flash chromatography (eluting with 50% ethyl acetate/hexane) furnished the *bicyclic pyrimidine* **7a** (80.8 mg, 86%) as a white solid: $[\alpha]_D^{20}$ –6.7 (*c* 1.1, $CHCl_3$); ^{1}H-NMR Analysis (by 400 MHz on the crude reaction mixture) *ds* ≥19:1; IR (neat) 2964 (s), 1740 (vs), 1683 (vs), 1436 (m), 1416 (s), 1350 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.55 (dq, *J* = 6.4, 6.1 Hz, 1H), 4.45 (d, A of AB, J_{AB} = 15.0 Hz, 1H), 4.14-4.06 (m, 1H), 3.94 (dt, *J* = 7.5, 5.5 Hz, 1H) 3.72 (s, 3H), 3.25 (dd, *J* = 5.5, 5.5 Hz, 1H), 3.16 (d, B of AB, J_{AB} =

15.0 Hz, 1H), 2.48 (ddd, *J* = 14.8, 10.8, 4.0 Hz, 1H), 2.39 (ddd, *J* = 18.7, 4.3, 3.5 Hz, 1H), 2.20 (ddt, *J* = 13.0, 7.3, 5.8 Hz, 1H), 2.07-1.92 (m, 4H), 1.89 (d, *J* = 18.3 Hz, 1H), 1.74-1.59 (m, 2H), 1.56-1.27 (m, 2H), 1.42 (d, *J* = 6.7 Hz, 3H), 1.28 (d, *J* = 6.4 Hz, 3H), 1.17 (s, 3H), 0.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.46 (e), 169.85 (e), 150.67 (e), 59.42 (e), 55.13 (o), 54.33 (o), 54.10 (e), 52.27 (o), 52.12 (o), 48.60 (o), 47.44 (e), 43.51 (o), 42.60 (e), 30.49 (e), 28.55 (e), 26.69 (e), 26.62 (e), 21.05 (o), 20.18 (o), 20.03 (o), 17.75 (o); HRMS (EI, M+H$^+$) calcd for $C_{21}H_{33}N_2O_6S$ 441.2059, found 441.2079.

Methyl-(4*R*)-3-{[(7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-yl)methyl]sulfonyl}-4-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (10a). The dihydropyrimidin-2(3*H*)-one **9** (13.69 g, 80.53 mmol) was dissolved in anhydrous tetrahydrofuran (500 ml) and stirred at room temperature under an atmosphere of nitrogen. Lithium bis(trimethylsilyl)amide (161 ml, 161 mmol, 1M in tetrahydrofuran) was added dropwise to form the dianion over *ca*. 30 minutes. (1*S*)-(+)-10-camphorsulfonyl chloride (20.19 g, 80.53 mmol; recrystallized) was then added portionwise and the resulting mixture was stirred for an additional *ca*. 30 minutes (t.l.c. control). The reaction was then quenched with saturated aqueous NH_4Cl solution and partitioned between ethyl acetate and water. The combined organic phases were dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford a crude oil as a 1:1 mixture of diastereoisomers. Purification by flash chromatography (eluting with 40% ethyl acetate/hexane) furnished the *N-sulfonyl pyrimidine* **10a** (10.85 g, 35%) as a colorless oil: Rf_{10a} = 0.30 Rf_{10b} = 0.34; (3:7 ethyl acetate/hexane); $[\alpha]_D^{23}$ +6.9 (*c* 2.65, $CHCl_3$); IR (neat) 3307 (s), 3165 (s), 2959 (s), 1748(s), 1695 (s), 1652 (s), 1440 (s), 1392 (s), 1359 (s), 1167 (s), 914 (s), 733 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J* = 5.2 Hz, 1H), 7.25 (d, *J* = 5.2 Hz, 1H), 5.27 (q, *J* = 6.4 Hz, 1H), 4.26 (d, A of AB, J_{AB} = 14.8 Hz, 1H), 3.74 (s, 3H), 3.26 (d, B of AB, J_{AB} = 14.8 Hz, 1H), 2.46 (ddd, *J* = 10.8, 10.8, 3.6 Hz, 1H), 2.37 (ddd, *J* = 18.4, 3.6, 3.6 Hz, 1H), 2.15-2.00 (m, 2H), 1.92 (d, *J* = 18.4 Hz, 1H), 1.69-1.61 (m, 1H), 1.49-1.38 (m, 4H), 1.13 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.41 (e), 164.48 (e), 150.95 (e), 133.74 (o), 109.21 (e), 58.96 (e), 52.15 (e), 51.75 (o), 51.24 (o), 48.19 (e), 42.79 (o), 42.50 (e), 26.90 (e), 25.50 (e), 21.90 (o), 19.79 (o); HRMS (CI, M+H$^+$) calcd for $C_{17}H_{25}N_2O_6S$ 385.1433, found 385.1434.

(3*R*,5*S*)-Tetradec-1-ene-3,5-diol (12). Octylmagnesium chloride (3.3 ml, 6.6 mmol, 2M in tetrahydrofuran) was added to a stirred suspension of copper cyanide (80 mg, 0.90 mmol) in anhydrous tetrahydrofuran (30 ml) at –78 °C and stirred for *ca*. 30 minutes under an atmosphere of nitrogen. Boron

trifluoride etherate (0.83 ml, 6.6 mmol) was added followed by the dropwise addition of the *bis*-epoxide **11** (600 mg, 6.0 mmol) *via* tared syringe, and the resulting mixture stirred for *ca*. 1.5 hours (t.l.c. control). The reaction was quenched with saturated aqueous NH_4Cl solution at –78 °C and partitioned between dichloromethane and water. The combined organic phases were dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford a crude oil. Purification by flash chromatography (eluting with 10-60% ethyl acetate/hexane) afforded the *epoxy alcohol* (912 mg, 71%) as a colorless oil: $[\alpha]_D^{22}$ +24.9 (*c* 0.65, $CHCl_3$); IR (neat) 3403 (m), 2955 (s), 2922 (s), 2853 (s), 1466 (m), 1134 (w), 826 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.83-3.75 (m, 1H), 3.15-3.10 (m, 1H), 2.80 (t, *J* = 4.7 Hz, 1H), 2.59 (dd, *J* = 4.8, 2.8 Hz, 1H), 1.97 (br s, 1H), 1.80 (ddd, *J* = 14.5, 8.9, 4.2 Hz, 1H), 1.59 (ddd, *J* = 14.5, 6.3, 3.4 Hz, 1H), 1.50-1.15 (m, 16H), 0.85 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 69.18 (o), 50.16 (o), 46.88 (e), 39.10 (e), 37.56 (e), 31.81 (e), 29.52 (e), 29.48 (e), 29.23 (e), 25.49 (e), 22.59 (e), 14.01 (o); HRMS (CI, $M+H^+$) calcd for $C_{13}H_{27}O_2$ 215.2011, found 215.2009.

*n*Butyllithium (5.14 ml, 12.8 mmol, 2.5 M in hexane) was added to a stirred suspension of trimethylsulfonium triflate (2.96 g, 13.1 mmol) in anhydrous tetrahydrofuran (30 ml) at –10 °C under an atmosphere of nitrogen to form a homogeneous solution. The epoxy alcohol (400 mg, 1.87 mmol) in anhydrous tetrahydrofuran (10 ml) was then added *via* Teflon® cannula maintaining the internal temperature at –10 °C, and the resulting mixture allowed to slowly warm to room temperature over *ca*. 2 hours (t.l.c. control). The reaction was quenched with saturated aqueous NH_4Cl solution and partitioned between dichloromethane and water. The combined organic phases were dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford a crude oil. Purification by flash chromatography (eluting with 10-60% ethyl acetate/hexane) afforded the *anti-diol* **12** (404 mg, 95%) as a colorless oil: $[\alpha]_D^{23}$ –4.7 (*c* 0.55, $CHCl_3$); IR (neat) 3290 (s), 2918 (s), 2849 (s), 1469 (m), 1404 (m), 1135 (m), 1078 (m), 1044 (m), 987 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.91 (ddd, *J* = 17.0, 10.5, 5.5 Hz, 1H), 5.27 (d, *J* = 17.2 Hz, 1H), 5.12 (d, *J* = 10.5 Hz, 1H), 4.50-4.40 (m, 1H), 3.96-3.85 (m, 1H), 2.22 (s, 2H), 1.75-1.60 (m, 2H), 1.56-1.14 (m, 16H), 0.86 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.70 (o), 114.14 (e), 70.35 (o), 69.05 (o), 42.14 (e), 37.47 (e), 31.82 (e), 29.59 (e), 29.55 (e), 29.50 (e), 29.25 (e), 25.61 (e), 22.59 (e), 14.02 (o); HRMS (CI, $M+H^+$) calcd for $C_{14}H_{29}O_2$ 229.2168, found 229.2168.

(4*R*,6*S*)-4-Ethenyl-6-nonyl-1,3-dioxan-2-one (13). *N,N'*-Carbonyldiimidazole (3.13 g, 19.3 mmol) and pyridine (2.12 ml, 26.31 mmol) were sequentially added to a stirred solution of the *anti*-1,3-diol **12** (4.00

g, 17.54 mmol) in anhydrous dichloromethane (50 ml) at room temperature under an atmosphere of nitrogen. The reaction mixture was stirred at this temperature for *ca*. 12 hours, then additional *N,N'*-carbonyldiimidazole (427 mg, 2.63 mmol) was added and the reaction mixture was heated at reflux for *ca*. 8 hours (t.l.c. control). The reaction mixture was concentrated *in vacuo* to afford a crude oil. Purification by flash chromatography (eluting with 10-60% ethyl acetate/hexane) afforded the *cyclic carbonate* **13** (4.00 g, 90%) as a colorless oil: $[\alpha]_D^{23}$ –68.1 (*c* 1.7, $CHCl_3$); IR (neat) 2926 (s), 2856 (s), 1748 (s), 1467 (s), 1384 (s), 1248 (s), 1195 (s), 1140 (s), 929 (s), 767 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.81 (ddd, *J* = 17.2, 10.7, 4.6 Hz, 1H), 5.38-5.26 (m, 2H), 5.02-4.95 (m, 1H), 4.44-4.34 (m, 1H), 2.04-1.89 (m, 2H), 1.75-1.64 (m, 1H), 1.58-1.10 (m, 15H), 0.81 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.76 (e), 134.41 (o), 117.79 (e), 76.20 (o), 75.78 (o), 34.71 (e), 31.67 (e), 30.79 (e), 29.27 (e), 29.24 (e), 29.08 (e), 24.47 (e), 22.47 (e), 13.92 (o); HRMS (CI, $M+H^+$) calcd for $C_{15}H_{27}O_3$ 255.1960, found 255.1967.

Methyl-(4*R*)-3-{[(7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-yl)methyl]sulfonyl}-1-{(1*R*)-1-[(2*S*)-2-hydroxyundecyl]prop-2-en-1-yl}-4-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (14a). Trimethyl phosphite (0.24 ml, 2.05 mmol) was added directly to a red suspension of Wilkinson's catalyst (475 mg, 0.51 mmol) in anhydrous tetrahydrofuran (10 ml) under an atmosphere of argon, and the resulting mixture stirred at room temperature for *ca*. 10 minutes to afford a light yellow homogeneous solution. In a separate flask, lithium bis(trimethylsilyl)amide (10.7 ml, 10.7 mmol, 1.0 M solution in tetrahydrofuran) was added dropwise to the *N*-sulfonyl pyrimidine **10a** (3.75 g, 9.74 mmol) in anhydrous tetrahydrofuran (30 ml) at room temperature, and the anion allowed to form over *ca*. 20 minutes. The catalyst solution and cyclic carbonate **13** (1.24 g, 4.87 mmol) in anhydrous tetrahydrofuran (10 ml) were sequentially added *via* Teflon® cannula to the nucleophile, and the resulting reaction mixture heated at 30 °C for *ca*. 4 hours, (t.l.c. control). The reaction mixture was then quenched with saturated aqueous NH_4Cl solution (40 ml) and partitioned between diethyl ether and saturated aqueous NH_4Cl solution. The aqueous phase was washed with diethyl ether, and the organic phases were combined, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford a crude oil. Purification by flash chromatography (eluting with 25-60% ethyl acetate/hexane) furnished the amination adduct **14a** (2.46 g, 84%) as a pale yellow oil: HPLC analysis (Zorbax® Rx-Sil Column) *2°:1°* ≥50:1, *ds* ≥30:1; $[\alpha]_D^{23}$ +27.3 (*c* 4.9, $CHCl_3$); IR (neat) 3516 (s), 2928 (s), 2855 (s), 1748 (s), 1716 (s), 1668 (s), 1455 (s), 1394 (s), 1359 (s), 1165 (s), 911 (s),

733 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.05 (s, 1H), 5.82 (ddd, *J* = 17.3, 10.6, 4.7 Hz, 1H), 5.30-5.18 (m, 4H), 4.26 (d, A of AB, J_{AB} = 15.3 Hz, 1H), 3.74 (s, 3H), 3.44-3.36 (m, 1H), 3.19 (d, B of AB, J_{AB} = 15.3 Hz, 1H), 2.38-2.24 (m, 2H), 2.10-1.96 (m, 2H), 1.86 (d, *J* = 18.5 Hz, 1H), 1.78-1.66 (m, 3H), 1.46-1.32 (m, 6H), 1.28-1.12 (m, 14H), 1.25 (s, 3H), 0.88-0.80 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.48 (e), 164.17 (e), 151.70 (e), 136.39 (o), 133.40 (o), 118.05 (e), 110.79 (e), 66.65 (o), 59.05 (e), 53.08 (o), 52.21 (e), 51.85 (o), 50.56 (o), 48.49 (e), 42.79 (o), 42.56 (e), 39.69 (e), 36.83 (e), 31.83 (e), 29.59 (e), 29.47 (e), 29.26 (e), 27.01 (e), 26.09 (e), 25.81 (e), 22.60 (e), 22.18 (o), 19.70 (o), 19.63 (o), 14.06 (o); HRMS (CI, $M+H^+$) calcd for $C_{31}H_{51}N_2O_7S$ 595.3417, found 595.3419.

4-Azidobutyl(4*R*)-1-((1*R*,3*R*)-3-azido-1-{2-[dimethyl(phenyl)silyl]ethyl}dodecyl)-3-{[(7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-yl)methyl]sulfonyl}-4-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (15). Platinum(IV) oxide (120 mg, 0.53 mmol) was added to the terminal alkene **14a** (1.50 g, 2.52 mmol) in dimethylphenylsilane (20 ml) at 0 °C under an atmosphere of nitrogen, and the resulting mixture was allowed to warm up to room temperature and stirred for *ca*. 12 hours (t.l.c. control). The reaction was then filtered through a short pad of silica gel column with ethyl acetate and the filtrate concentrated *in vacuo* to afford a crude oil. Purification by flash chromatography (eluting with 10-60% ethyl acetate/hexane) afforded the *primary silane* (1.68 g, 91%) as a colorless oil: $[\alpha]_D^{23}$ +25.4 (*c* 12.3, $CHCl_3$); IR (neat) 3511 (w), 2927 (s), 2855 (s), 1749 (s), 1715 (s), 1691 (s), 1660 (s), 1357 (s), 1254 (s), 1165 (s), 1113 (s), 822 (s), 702 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46-7.38 (m, 2H), 7.36-7.26 (m, 3H), 6.99 (s, 1H), 5.21 (q, *J* = 6.4 Hz, 1H), 4.58-4.42 (m, 1H), 4.22 (d, A of AB, J_{AB} = 15.3 Hz, 1H), 3.73 (s, 3H), 3.37-3.27 (m, 1H), 3.19 (d, B of AB, J_{AB} = 15.3 Hz, 1H), 2.38-2.22 (m, 2H), 2.10-1.94 (m, 2H), 1.84 (d, *J* = 18.5 Hz, 1H), 1.71 (ddd, *J* = 14.1, 9.4, 4.7 Hz, 1H), 1.62-1.07 (m, 24H), 1.04 (s, 3H), 0.88-0.80 (m, 6H), 0.78-0.60 (m, 2H), 0.23 (s, 3H), 0.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.44 (e), 164.23 (e), 152.21 (e), 138.09 (e), 133.41 (o), 129.09 (o), 127.89 (o), 111.08 (e), 66.97 (o), 59.09 (e), 52.22 (e), 51.86 (o), 50.38 (o), 48.48 (e), 42.84 (o), 42.58 (e), 41.39 (e), 36.81 (e), 31.86 (e), 29.61 (e), 29.49 (e), 29.29 (e), 29.07 (e), 27.04 (e), 26.09 (e), 25.87 (e), 22.63 (e), 22.40 (o), 19.69 (o), 14.08 (o), 12.55 (e), -3.11 (o), -3.38 (o); HRMS (CI, $M+H^+$) calcd for $C_{39}H_{63}N_2O_7SSi$ 731.4125, found 731.4127.

4-Azidobutan-1-ol (95 mg, 0.82 mmol) and bis(dibutylchlorotin(IV)) oxide (45 mg, 0.082 mmol) were sequentially added to a stirred solution of the methyl ester (60 mg, 0.082 mmol) in anhydrous toluene (1 ml) at room temperature under an atmosphere of nitrogen. The resulting mixture was heated at

reflux for *ca*. 24 hours (t.l.c. control), and then concentrated *in vacuo* to afford the crude reaction mixture. Purification by flash chromatography (eluting with 10-60% ethyl acetate/hexane) afforded the *azido ester* (64 mg, 95%) as a colorless oil: $[\alpha]_D^{26}$ +27.4 (*c* 2.75, $CHCl_3$); IR (neat) 3511 (m), 2928 (s), 2855 (s), 2097 (s), 1749 (s), 1711 (s), 1656 (s), 1455 (m), 1357 (s), 1253 (s), 1164 (s), 820 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47-7.39 (m, 2H), 7.36-7.27 (m, 3H), 7.01 (s, 1H), 5.23 (q, *J* = 6.4 Hz, 1H), 4.60-4.42 (m, 1H), 4.27-4.10 (m, 3H), 3.48 (br s, 1H), 3.38-3.20 (m, 4H), 2.42-2.25 (m, 2H), 2.13-1.98 (m, 2H), 1.87 (d, *J* = 18.4 Hz, 1H), 1.82-1.12 (m, 29H), 1.07 (s, 3H), 0.90-0.80 (m, 6H), 0.79-0.62 (m, 2H), 0.24 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.38 (e), 163.73 (e), 152.16 (e), 138.07 (e), 133.39 (o), 129.09 (o), 127.87 (o), 111.08 (e), 66.99 (o), 64.13 (e), 59.09 (e), 52.25 (e), 50.84 (e), 50.30 (o), 48.42 (e), 42.83 (o), 42.55 (e), 41.34 (e), 36.79 (e), 31.84 (e), 29.64 (e), 29.59 (e), 29.47 (e), 29.27 (e), 29.05 (e), 27.00 (e), 26.05 (e), 25.92 (e), 25.88 (e), 25.45 (e), 22.61 (e), 22.39 (o), 19.71 (o), 19.68 (o), 14.06 (o), 12.53 (e), –3.18 (o), –3.34 (o); HRMS (CI, $M+H^+$) calcd for $C_{42}H_{68}N_5O_7SSi$ 814.4609, found 814.4616.

Diisopropyl azodicarboxylate (197 μl, 1.0 mmol) was added to triphenylphosphine (262 mg, 1 mmol) in anhydrous benzene (4 ml) at room temperature and stirred for *ca*. 15 minutes under an atmosphere of nitrogen. Hydrazoic acid (186 μl, 0.186 mmol, 1M in benzene) and the diisopropyl azodicarboxylate/triphenylphosphine solution (372 μl, 0.093 mmol, 0.25 M in benzene) were then added sequentially to the secondary alcohol (50 mg, 0.062 mmol) in anhydrous benzene (1.5 ml) at room temperature. The resulting mixture was stirred at room temperature for *ca*. 2 hours (t.l.c. control), and then concentrated *in vacuo* to afford the crude reaction mixture. Purification by flash chromatography (eluting with 10-60% ethyl acetate/hexane) afforded the secondary azide **15** (49 mg, 95%) as a colorless oil: $[\alpha]_D^{23}$ +35.2 (*c* 2.2, $CHCl_3$); IR (neat) 3049 (w), 2928 (s), 2856 (s), 2100 (s), 1749 (s), 1714 (s), 1694 (s), 1661 (s), 1455 (s), 1376 (s), 1355 (s), 1251 (s), 1165 (s), 1113 (s), 837 (s), 702 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46-7.40 (m, 2H), 7.35-7.29 (m, 3H), 7.06 (s, 1H), 5.22 (q, *J* = 6.4 Hz, 1H), 4.50-4.34 (m, 1H), 4.26-4.12 (m, 3H), 3.35-3.22 (m, 4H), 2.43 (ddd, *J* = 12.6, 12.6, 3.6 Hz, 1H), 2.34 (ddd, *J* = 18.4, 4.0, 4.0 Hz, 1H), 2.10-1.96 (m, 2H), 1.86 (d, *J* = 18.4 Hz, 1H), 1.83-1.72 (m, 3H), 1.72-1.53 (m, 6H), 1.53-1.16 (m, 20H), 1.09 (s, 3H), 0.90-0.82 (m, 6H), 0.75-0.61 (m, 2H), 0.25 (s, 3H), 0.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.03 (e), 163.77 (e), 150.63 (e), 137.96 (e), 133.34 (o), 129.04 (o), 127.82 (o), 110.12 (e), 63.96 (e), 59.85 (o), 58.90 (e), 51.89 (e), 50.78 (e), 50.12 (o), 48.18 (e), 42.78 (o), 42.47 (e), 37.60 (e), 34.18 (e), 31.76 (e), 29.37 (e), 29.30 (e), 29.17 (e), 28.54 (e), 26.90 (e), 25.86 (e),

25.81 (e), 25.63 (e), 25.38 (e), 22.55 (e), 22.38 (o), 19.72 (o), 19.70 (o), 14.00 (o), 12.10 (e), –3.24 (o), –3.40 (o); HRMS (CI, M+H$^+$) calcd for $C_{42}H_{67}N_8O_6SSi$ 839.4674, found 839.4652.

4-Azidobutyl(4*R*)-1-[(1*R*,3*R*)-3-azido-1-(2-iodoethyl)dodecyl]-3-{[(7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-yl)methyl]sulfonyl}-4-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (16). The primary silane **15** (400 mg, 0.48 mmol) was dissolved in acetic acid (9 ml) and stirred at room temperature. Mercury(II) acetate (212 mg, 0.67 mmol) was added and the resulting mixture stirred at room temperature for *ca*. 10 minutes. Hydrogen peroxide (0.853 ml, 8.88 mmol, 30% solution in water), peracetic acid (1.84 ml, 8.88 mmol, 32% in dilute acetic acid) and mercury(II) acetate (212 mg, 0.67 mmol) were then added sequentially, and the resulting mixture was stirred at room temperature for *ca*. 1 hour (t.l.c. control). The reaction mixture was then diluted with dichloromethane (6 ml) and cooled to 0 °C before being *slowly* quenched by the portionwise addition of $Na_2S_2O_3$ (2.81 g, 17.76 mmol). The resulting mixture was stirred vigorously for 30 minutes, then filtered through a short pad of celite and washed with dichloromethane, and the filtrate concentrated *in vacuo* to afford a crude oil. Purification by flash chromatography (eluting with 10-60% ethyl acetate/hexane) afforded the *primary alcohol* (226 mg, 66%) as a colorless oil: $[\alpha]_D^{23}$ +16.5 (*c* 2.0, $CHCl_3$); IR (neat) 3522 (m), 2928 (s), 2856 (s), 2100 (s), 1749 (s), 1689 (s), 1661 (s), 1456 (m), 1377 (s), 1356 (s), 1260 (s), 1164 (s), 746 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (s, 1H), 5.20 (q, *J* = 6.4 Hz, 1H), 4.70-4.55 (m, 1H), 4.26-4.12 (m, 3H), 3.69-3.54 (m, 2H), 3.37-3.21 (m, 4H), 2.42 (ddd, *J* = 12.8, 12.8, 4.0 Hz, 1H), 2.32 (ddd, *J* = 18.4, 4.0, 4.0 Hz, 1H), 2.10-1.48 (m, 14H), 1.46-1.15 (m, 18H), 1.08 (s, 3H), 0.90-0.80 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.27 (e), 163.88 (e), 150.53 (e), 110.14 (e), 64.08 (e), 59.95 (o), 58.96 (e), 58.91 (e), 52.01 (e), 50.85 (e), 50.28 (o), 48.27 (e), 42.83 (o), 42.54 (e), 37.78 (e), 36.11 (e), 34.32 (e), 31.80 (e), 29.43 (e), 29.35 (e), 29.22 (e), 26.93 (e), 25.91 (e), 25.88 (e), 25.68 (e), 25.44 (e), 22.60 (e), 22.41 (o), 19.75 (o), 14.04 (o); HRMS (CI, M+H$^+$) calcd for $C_{34}H_{57}N_8O_7S$ 721.4071, found 721.4079.

The primary alcohol (354 mg, 0.49 mmol) in anhydrous dichloromethane (7 ml) was added to a stirred solution of imidazole (170 mg, 2.5 mmol), triphenylphosphine (262 mg, 1.0 mmol) and iodine (253 mg, 1.0 mmol) in anhydrous dichloromethane (2 ml) at room temperature under nitrogen. The reaction mixture was then stirred at room temperature for *ca*. 30 min. (t.l.c. control) and concentrated *in vacuo* to afford a crude oil. Purification by flash chromatography (eluting with 10-60% ethyl acetate/hexane) afforded the *alkyl iodide* **16** (350 mg, 86%) as a colorless oil: $[\alpha]_D^{23}$ +12.6 (*c* 2.2, $CHCl_3$);

IR (neat) 2955 (s), 2928 (s), 2855 (s), 2100 (s), 1749 (s), 1690 (s), 1662 (s), 1455 (m), 1356 (s), 1281 (s), 1165 (s), 1112 (s), 746 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.17 (s, 1H), 5.20 (q, *J* = 6.8 Hz, 1H), 4.60-4.35 (m, 1H), 4.30-4.10 (m, 3H), 3.37-3.27 (m, 3H), 3.24-3.09 (m, 2H), 3.06-2.97 (m, 1H), 2.46-2.18 (3H), 2.16-1.47 (m, 13H), 1.46-1.14 (m, 18H), 1.07 (s, 3H), 0.90-0.80 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.19 (e), 163.75 (e), 150.26 (e), 110.56 (e), 64.16 (e), 59.78 (o), 58.94 (e), 52.06 (e), 50.85 (e), 50.22 (o), 48.32 (e), 42.86 (o), 42.56 (e), 37.25 (e), 34.32 (e), 31.82 (e), 29.43 (e), 29.35 (e), 29.23 (e), 26.97 (e), 25.93 (e), 25.88 (e), 25.77 (e), 25.46 (e), 22.61 (e), 22.50 (o), 19.79 (o), 19.73 (o), 14.06 (o); HRMS (CI, $M+H^+$) calcd for $C_{34}H_{56}IN_8O_6S$ 831.3088, found 831.3076.

4-Azidobutyl(3*R*,4*R*,4*aS*,7*S*)-7-[(2*R*)-2-azidoundecyl]-2-{[(7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-yl)methyl]sulfonyl}-3-methyl-1-oxooctahydropyrrolo[1,2-c]pyrimidine-4-carboxylate (17). The alkyl iodide **16** (339 mg, 0.41 mmol, azeotroped with anhydrous benzene) was dissolved in anhydrous benzene (80 ml), and stirred at room temperature under an atmosphere of dry air. Tributyltin hydride (0.17 ml, 0.61 mmol) and triethylborane (0.41 ml, 0.41 mmol, 1M in hexane) were added sequentially, and the resulting mixture was stirred at room temperature for *ca*. 5 minutes (t.l.c. control). The reaction mixture was then concentrated *in vacuo* to afford the crude reaction mixture. Purification by flash chromatography (eluting with 10-60% ethyl acetate/hexane) furnished the *bicyclic pyrimidine* **17** (230 mg, 80%) as a colorless oil: $[\alpha]_D^{23}$ –82.9 (*c* 1.2, $CHCl_3$); IR (neat) 2928 (s), 2856 (s), 2099 (s), 1739 (s), 1684 (s), 1415 (s), 1351 (s), 1158 (s), 1052 (m), 740 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.55 (app. qn, *J* = 6.2 Hz, 1H), 4.42 (d, A of AB, J_{AB} = 14.9 Hz, 1H), 4.21-4.11 (m, 3H), 3.94 (ddd, *J* = 7.6, 7.6, 5.6 Hz, 1H), 3.37-3.23 (m, 4H), 3.17 (d, B of AB, J_{AB} = 14.9 Hz, 1H), 2.50-2.34 (m, 2H), 2.26-2.14 (m, 2H), 2.09-1.94 (m, 3H), 1.89 (d, *J* = 18.4 Hz, 1H), 1.80-1.18 (m, 28H), 1.16 (s, 3H), 0.95 (s, 3H), 0.85 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.30 (e), 169.20 (e), 150.82 (e), 64.58 (e), 59.96 (o), 59.29 (e), 55.94 (o), 55.32 (o), 53.98 (e), 52.10 (o), 50.76 (e), 48.54 (o), 47.41 (e), 43.38 (o), 42.49 (e), 38.94 (e), 34.37 (e), 31.71 (e), 29.34 (e), 29.23 (e), 29.13 (e), 28.52 (e), 28.26 (e), 26.59 (e), 26.47 (e), 25.94 (e), 25.73 (e), 25.39 (e), 22.51 (e), 19.98 (o), 19.86 (o), 17.89 (o), 13.96 (o); HRMS (CI, $M+H^+$) calcd for $C_{34}H_{57}N_8O_6S$ 705.4122, found 705.4130.

4-Azidobutyl(3*R*,4*S*,4*aS*,7*S*)-7-[(2*R*)-2-azidoundecyl]-3-methyl-1-(methyloxy)-3,4,4*a*,5,6,7-hexahydropyrrolo[1,2-*c*]pyrimidine-4-carboxylate (18). Triflic acid (0.94 ml, 0.47 mmol, 0.5 M in

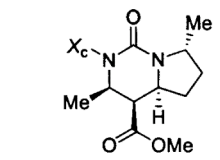
dichloromethane) was added to the *N*-sulfonyl bicyclic pyrimidine **17** (220 mg, 0.31 mmol) in anhydrous dichloromethane (30 ml) at room temperature under an atmosphere of nitrogen. The reaction was allowed to stir at this temperature for *ca*. 30 minutes (t.l.c. control), and then concentrated *in vacuo* to afford a crude oil. Purification by flash chromatography (eluting with 10-60% ethyl acetate/hexane) furnished the *bicyclic pyrimidine* (130 mg, 0.265 mmol, 85%) as a colorless oil: $[\alpha]_D^{23}$ –39.2 (*c* 0.6, $CHCl_3$); IR (neat) 3299 (m), 3208 (m), 3066 (m), 2928 (s), 2856 (s), 2100 (s), 1733 (s), 1661 (s), 1470 (s), 1455 (s), 1302 (s), 1253 (s), 1164 (s), 764 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.24 (s, 1H), 4.15-4.00 (m, 3H), 3.82-3.75 (m, 1H), 3.74-3.67 (m, 1H), 3.32-3.20 (m, 3H), 2.75 (t, *J* = 4.0 Hz, 1H), 2.23 (ddd, *J* = 13.9, 9.2, 4.7 Hz, 1H), 2.09-1.94 (m, 2H), 1.73-1.13 (m, 26H), 0.82 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.24 (e), 155.58 (e), 63.77 (e), 60.29 (o), 57.75 (o), 55.41 (o), 50.83 (e), 48.08 (o), 45.85 (o), 39.19 (e), 34.60 (e), 31.74 (e), 29.67 (e), 29.39 (e), 29.32 (e), 29.15 (e), 28.58 (e), 25.99 (e), 25.83 (e), 25.34 (e), 22.53 (e), 18.51 (o), 13.98 (o); HRMS (CI, M+H^+) calcd for $C_{24}H_{43}N_8O_3$ 491.3458, found 491.3450.

Methyl triflate (13.4 μl, 0.122 mmol) was added to a stirred solution of the bicyclic pyrimidine (30 mg, 0.061 mmol) in anhydrous dichloromethane (4 ml) at room temperature under an atmosphere of nitrogen. The reaction was stirred at this temperature for *ca*. 3 days (t.l.c. control), and then concentrated *in vacuo* to afford the *methyl imidate* **18** (38 mg, 95%) as the triflate salt, which was used without further purification; $[\alpha]_D^{24}$ –41.2 (*c* 0.75, $CHCl_3$); IR (neat) 3244 (m), 3141 (m), 2928 (s), 2856 (s), 2101 (s), 1732 (s), 1635 (s), 1589 (s), 1464 (m), 1285 (s), 1245 (s), 1166 (s), 1031 (s), 638 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.49 (bs, 1H), 4.24-4.00 (m, 8H), 3.32 (t, *J* = 6.6 Hz, 2H), 3.17-3.04 (m, 2H), 2.30-2.04 (m, 3H), 1.79-1.16 (m, 26H), 0.86 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.65 (e), 156.37 (e), 64.71 (e), 59.51 (o), 59.19 (o), 58.56 (o), 57.92 (o), 50.83 (e), 49.90 (o), 43.13 (o), 38.75 (e), 34.75 (e), 31.83 (e), 29.59 (e), 29.43 (e), 29.31 (e), 29.24 (e), 27.79 (e), 26.00 (e), 25.86 (e), 25.46 (e), 22.64 (e), 17.02 (o), 14.08 (o); HRMS (CI, M+H^+) calcd for $C_{25}H_{45}N_8O_3$ 505.3615, found 505.3615.

(–)-Batzelladine D (2). The methyl imidate **18** (38 mg, 0.058 mmol) was dissolved in methanol (3 ml) and stirred at room temperature. Palladium on charcoal (20 mg, 10% Pd/C) was added and the reaction mixture was stirred under an atmosphere of hydrogen for *ca*. 9 hours (t.l.c. control). The reaction mixture was filtered through celite to remove the Pd/C and the filtrate was concentrated *in vacuo* to afford a crude product. Purification by flash chromatography (eluting with MeOH:CH_2Cl_2:H_2O:HCOOH =

1:4:0.063:0.087) furnished the tricyclic guanidine, contaminated with silica gel. The product was dissolved in dichloromethane, filtered and then concentrated *in vacuo* to afford the *tricyclic guanidine* as the formic acid salt (25 mg, 83%) as colorless oil: $[\alpha]_D^{24}$ –32.5 (*c* 0.20, MeOH); IR (neat) 3298 (m), 3221 (m), 3142 (m), 2928 (s), 2856 (s), 1732 (s), 1645 (s), 1466 (m), 1379 (m), 1287 (s), 1244 (s), 1225 (s), 1165 (s) cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 8.54 (bs, 2H), 4.25-4.15 (m, 2H), 4.00-3.92 (m, 1H), 3.90-3.82 (m, 1H), 3.60-3.49 (m, 2H), 3.14 (dd, *J* = 4.6, 3.5 Hz, 1H), 2.99-2.93 (m, 2H), 2.38-2.32 (m, 1H), 2.28-2.17 (m, 2H), 1.80-1.20 (m, 26H), 0.90 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 170.52 (e), 151.49 (e), 65.24 (e), 57.75 (o), 57.32 (o), 53.23 (o), 49.89 (o), 45.59 (o), 40.44 (e), 37.03 (e), 34.21 (e), 33.04 (e), 31.41 (e), 30.65 (e), 30.44 (e), 29.36 (e), 26.75 (e), 26.22 (e), 25.58 (e), 23.72 (e), 18.46 (o), 14.41 (o); HRMS (CI, M-$C_2H_3O_4$) calcd for $C_{24}H_{45}N_4O_2$ 421.3543, found 421.3551.

1*H*-pyrazole-1-carboxamidine hydrochloride (34 mg, 0.31 mmol) and $^iPr_2NEt$ (0.17 ml, 0.98 mmol) were sequentially added to the *tricyclic guanidine* (11.5 mg, 0.022 mmol) in anhydrous dimethylformamide (0.3 ml) at room temperature under an atmosphere of nitrogen. The reaction mixture was stirred at this temperature for *ca*. 16 hours (t.l.c. control), and then partitioned between chloroform and 1M aqueous hydrochloric acid solution. The organic phases were combined and washed with 1M aqueous hydrochloric acid solution, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to afford a crude oil. Purification by flash chromatography (eluting with MeOH:CH_2Cl_2:H_2O:HCOOH=1:4:0.063:0.087) furnished the product contaminated with silica gel. The product was dissolved in dichloromethane, filtered and then concentrated *in vacuo* to afford *(–)-batzelladine D* **(2)** (10 mg, 80%) as colorless oil: $[\alpha]_D^{25}$ –37.5 (*c* 0.48, MeOH); IR (neat) 3281 (s), 3196 (m), 3141 (m), 2927 (s), 2856 (m), 1730 (m), 1644 (s), 1465 (w), 1345 (m), 1175 (m) cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 8.54 (bs, 2H), 4.18 (t, *J* = 6.0 Hz, 2H), 3.98-3.91 (m, 1H), 3.89-3.81 (m, 1H), 3.59-3.48 (m, 2H), 3.20 (t, *J* = 6.8 Hz, 2H), 3.13 (dd, *J* = 4.8, 3.6 Hz, 1H), 2.38-2.31 (m, 1H), 2.28-2.16 (m, 2H), 1.80-1.20 (m, 26H), 0.89 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 170.58 (e), 158.74 (e), 151.54 (e), 65.46 (e), 57.71 (o), 57.31 (o), 53.22 (o), 49.87 (o), 45.67 (o), 42.03 (e), 36.99 (e), 34.22 (e), 33.03 (e), 31.43 (e), 30.63 (e), 30.42 (e), 29.36 (e), 26.94 (e), 26.63 (e), 26.22 (e), 23.71 (e), 18.49 (o), 14.42 (o); HRMS (CI, M-$C_2H_3O_4$) calcd for $C_{25}H_{47}N_6O_2$ 463.3761, found 463.3762.



7a

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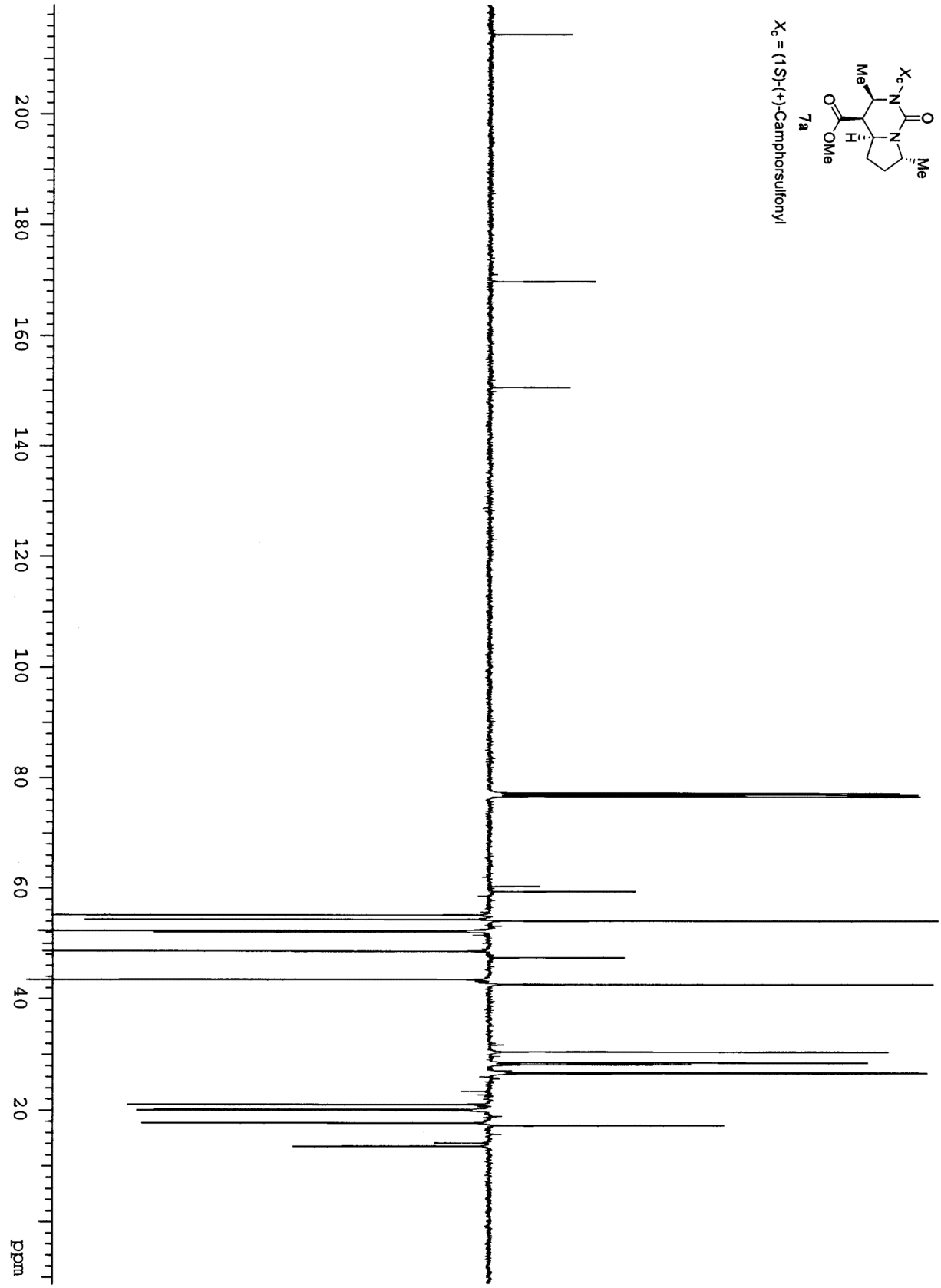
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O
OMe
H
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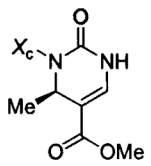

10a

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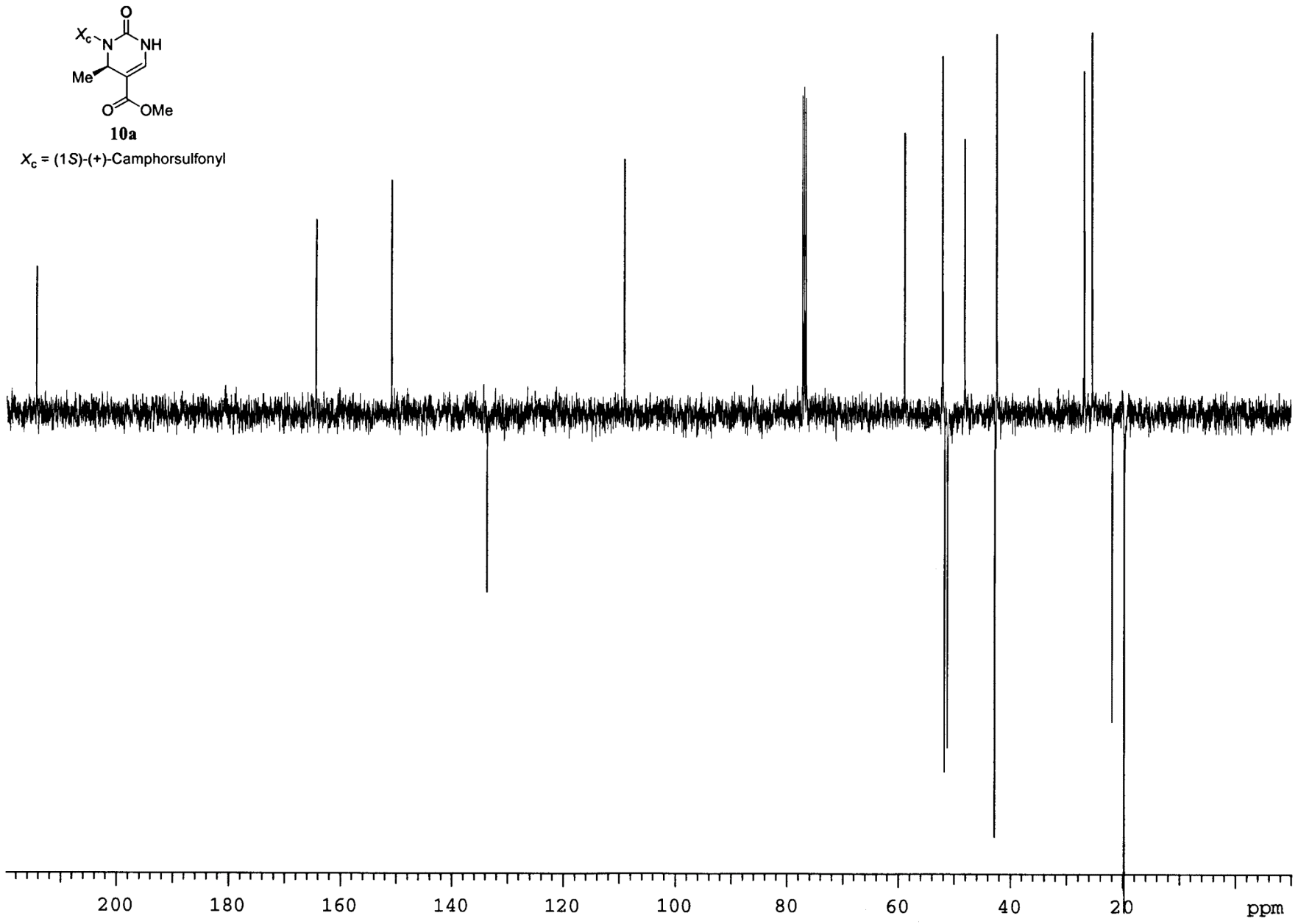
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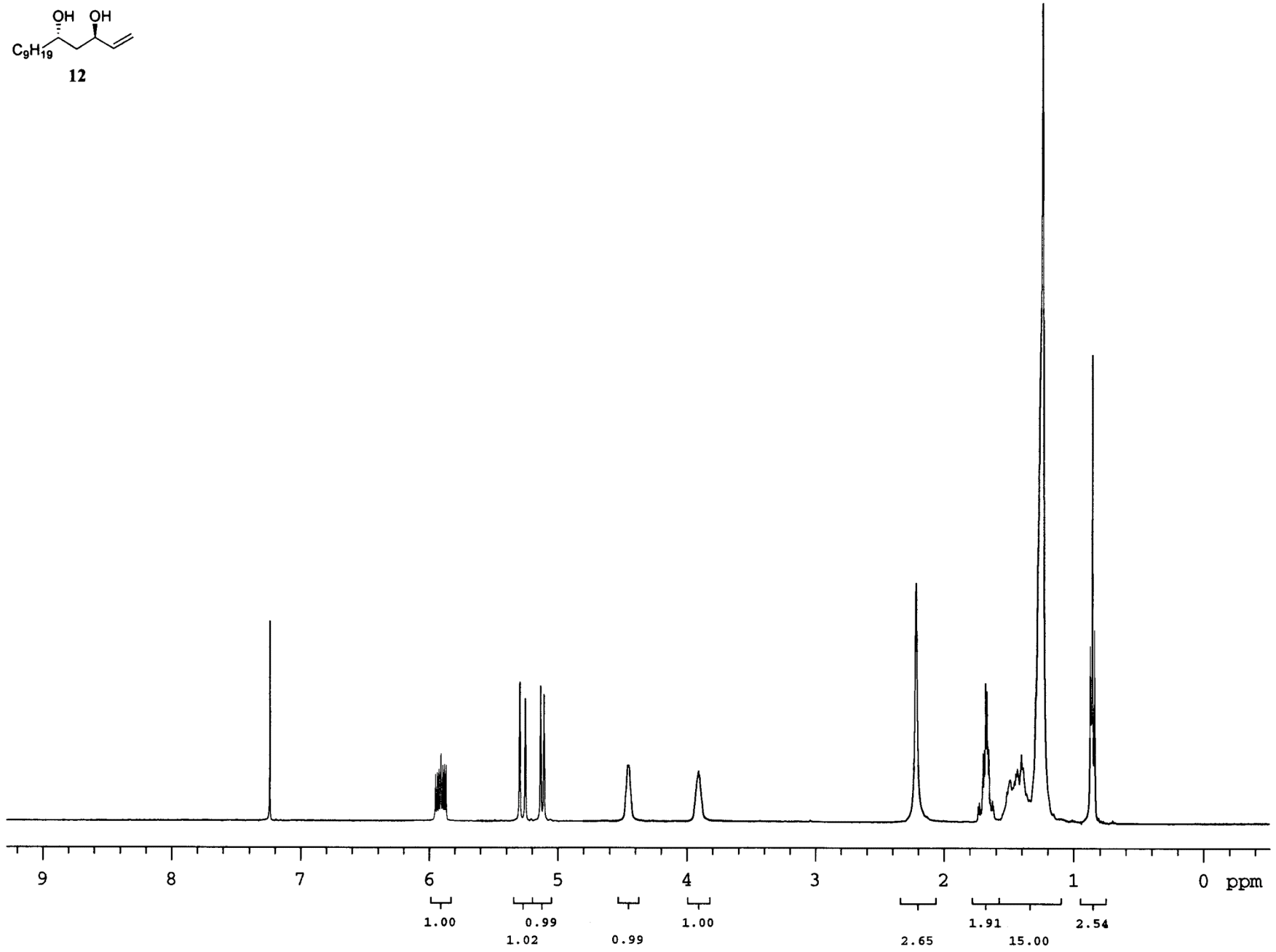
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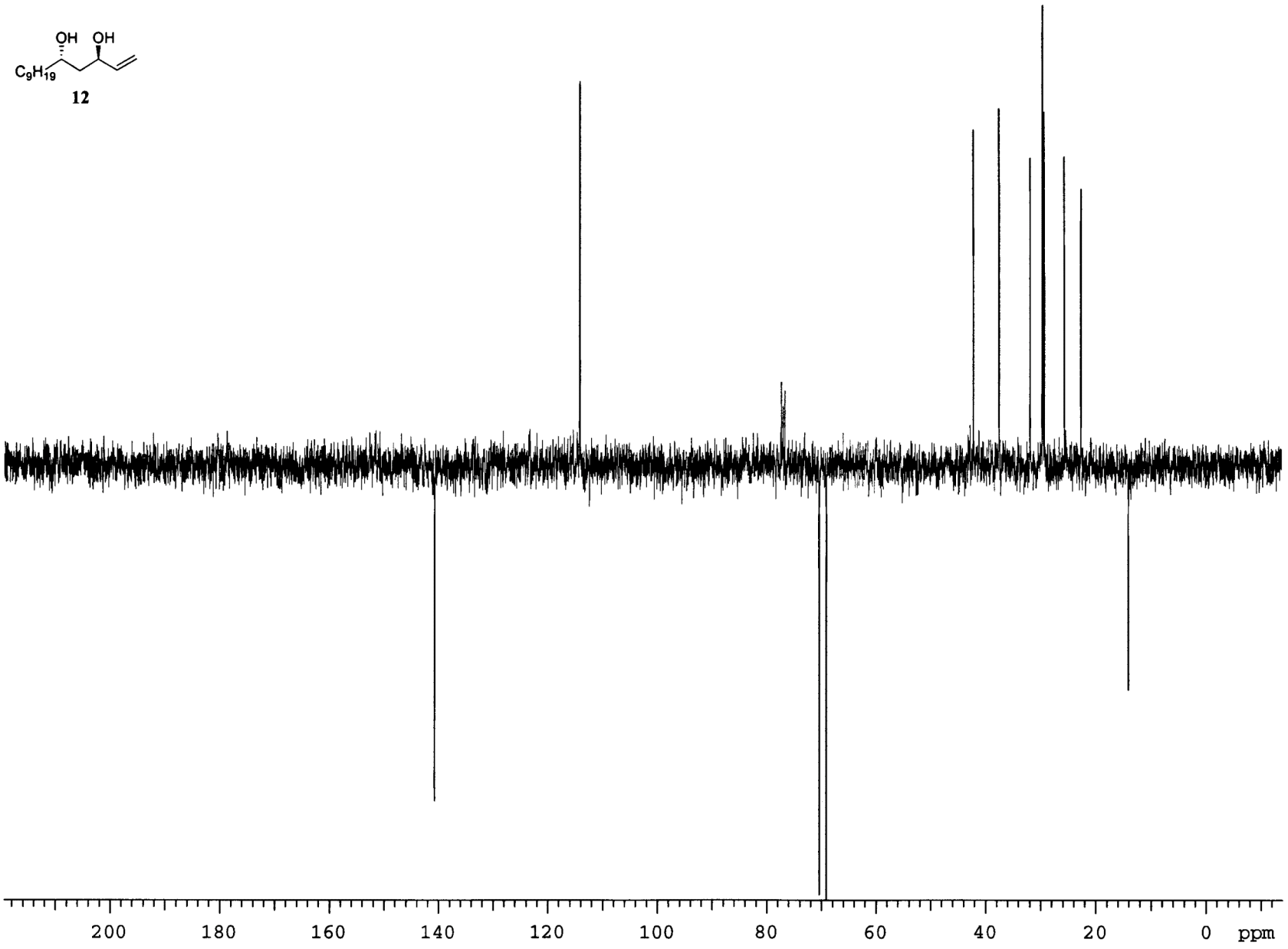
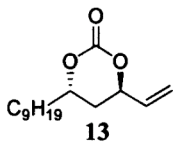


12



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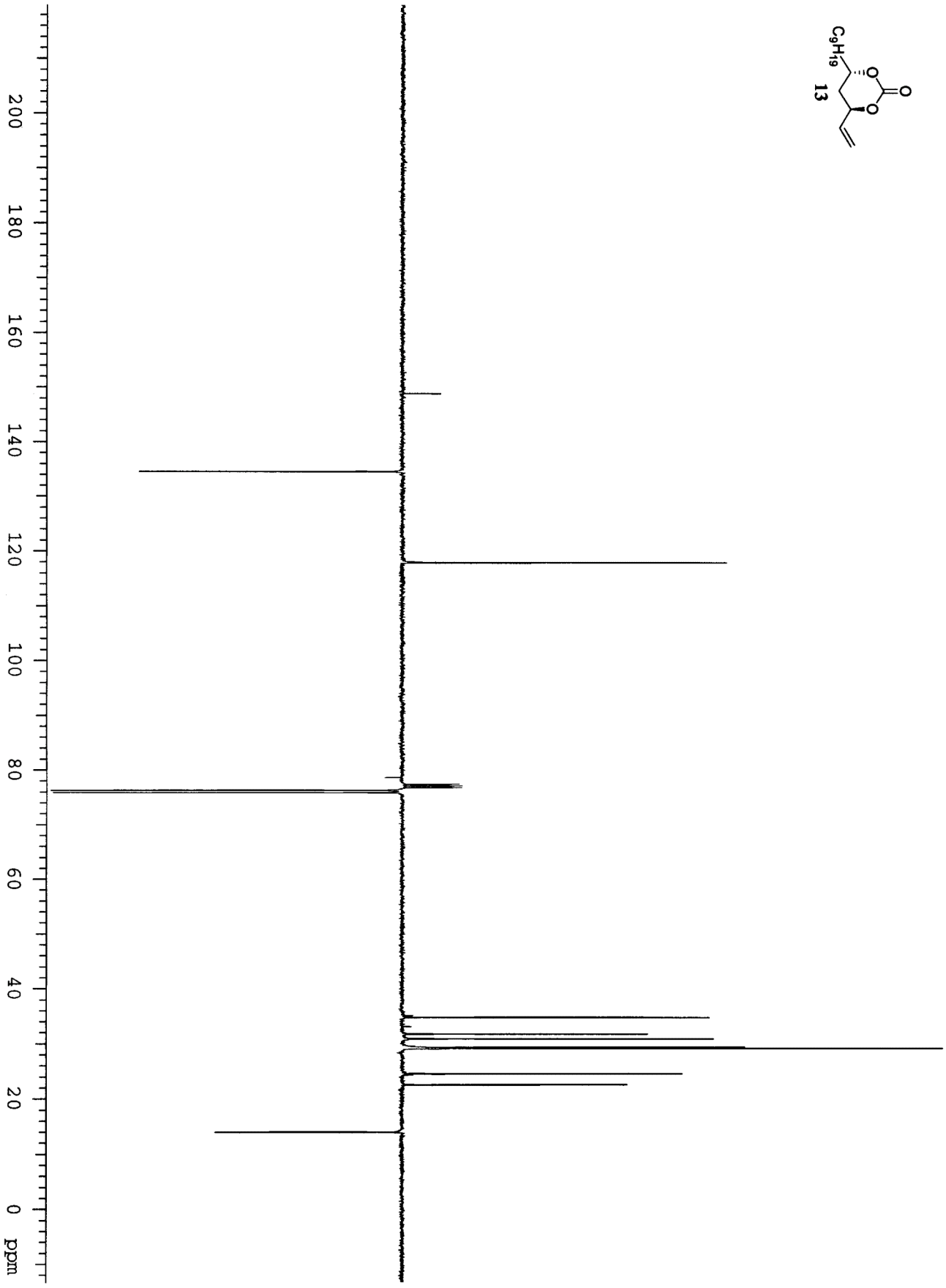
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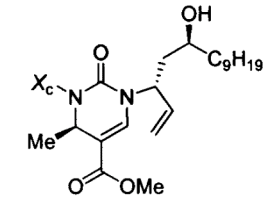

14a

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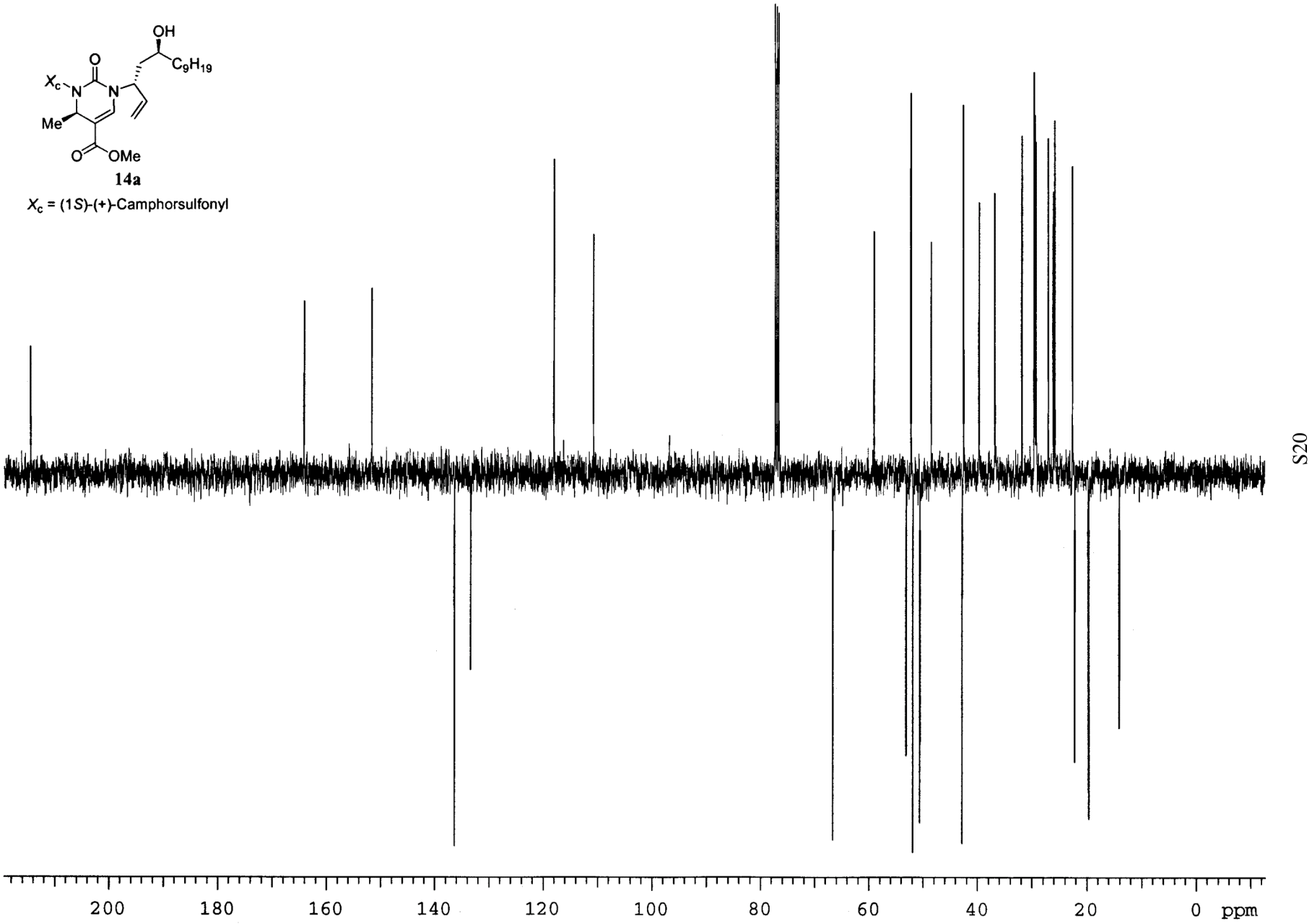

14a

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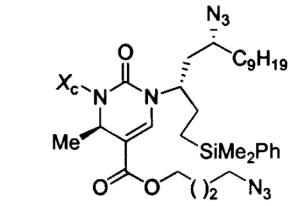

15

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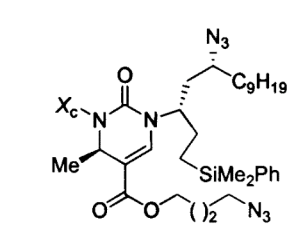
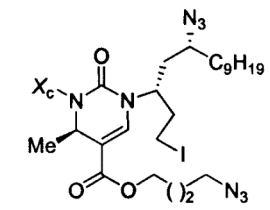


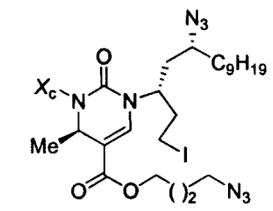
15

X_c = (1*S*)-(+)-Camphorsulfonyl



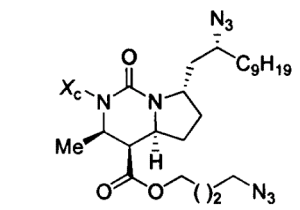
16

X_c = (1*S*)-(+)-Camphorsulfonyl



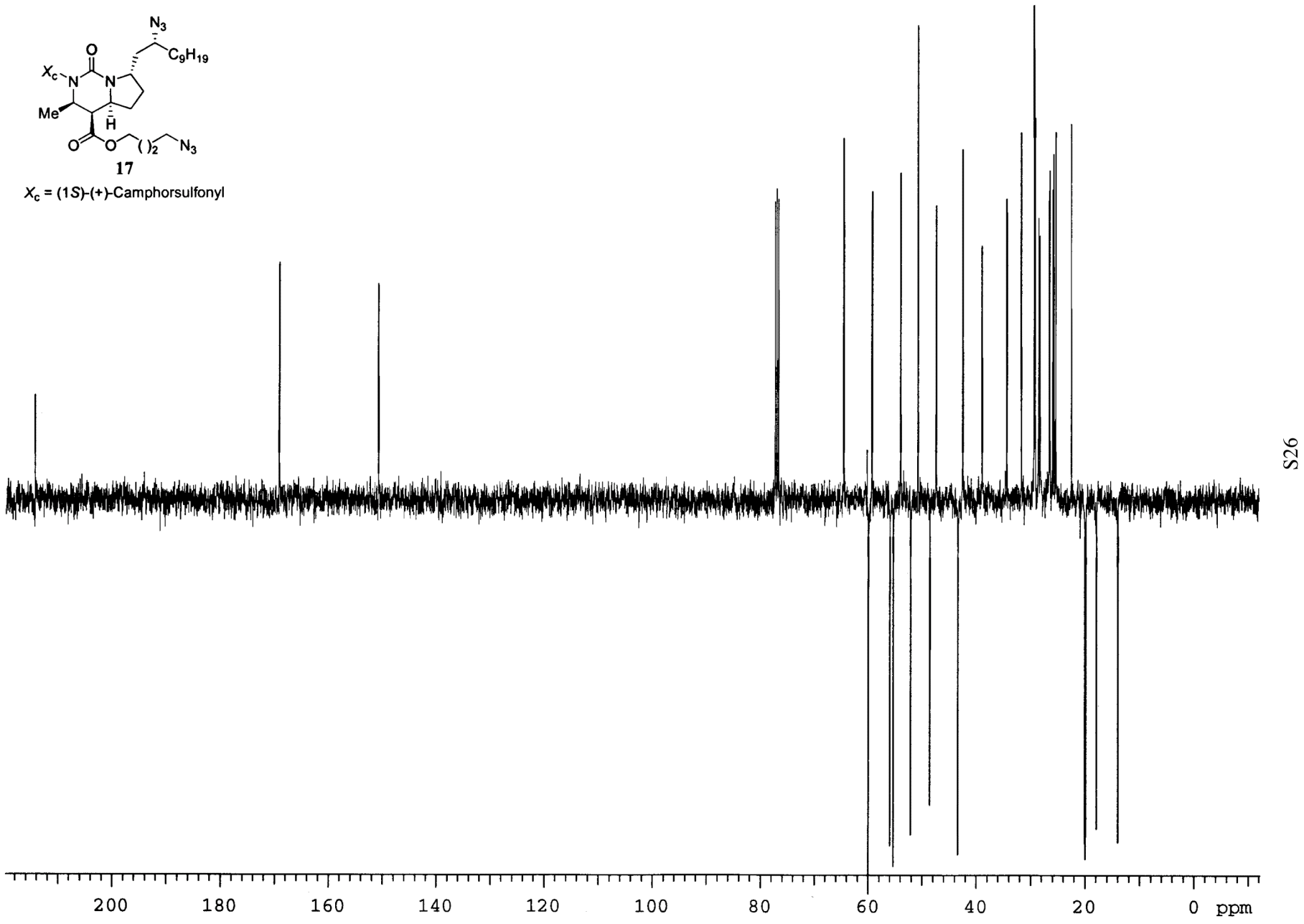
16

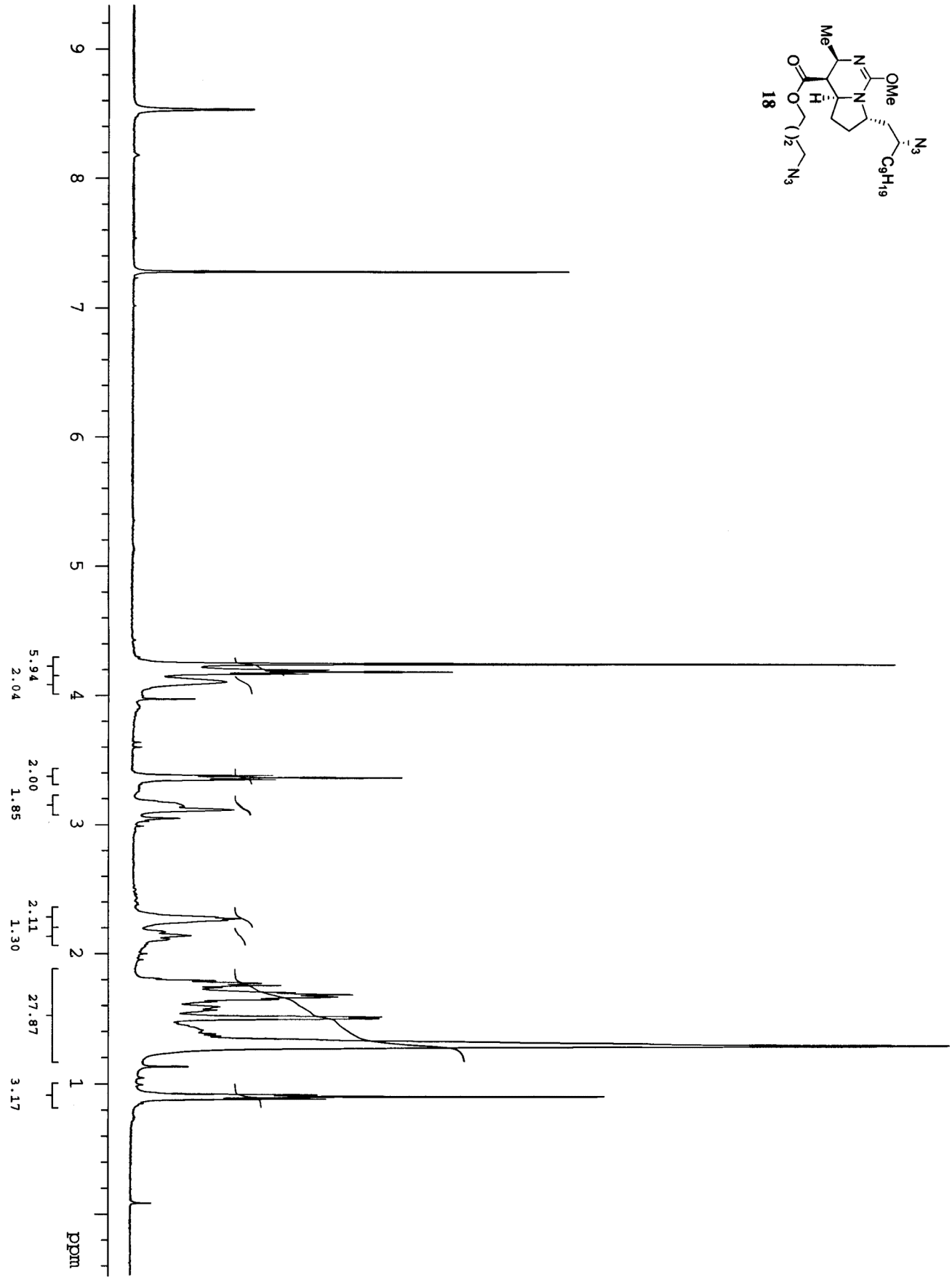
X_c = (1*S*)-(+)-Camphorsulfonyl

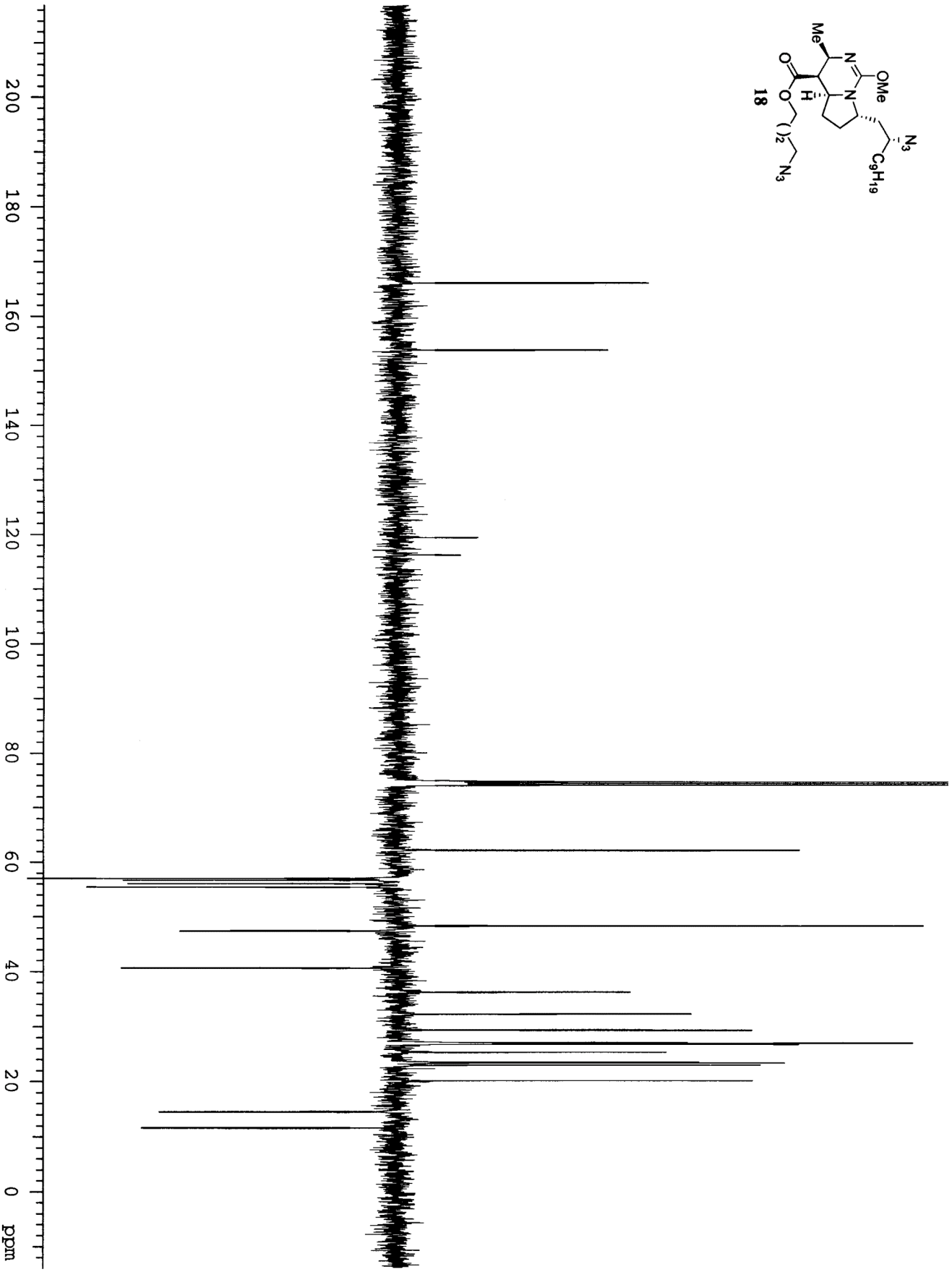


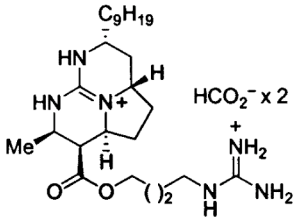
17

X_c = (1*S*)-(+)-Camphorsulfonyl

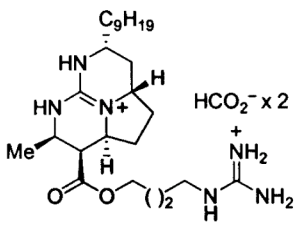

N3
C9H19
Xc
N
O
N
Me
H
O
O
( )2
N3
17
Xc = (1S)-(+)-Camphorsulfonyl
200
180
160
140
120
100
80
60
40
20
0 ppm


Me
N
OMe
N
H
O
O
( )2
N3
N3
C9H19
18
9
8
7
6
5
4
3
2
1
ppm
5.94
2.04
2.00
1.85
2.11
1.30
27.87
3.17


Me
OMe
N
N
H
O
O
( )2
N3
N3
C9H19
18
200
180
160
140
120
100
80
60
40
20
0
ppm



(–)-Batzelladine D (**2**)



(–)-Batzelladine D (**2**)

Indiana University Molecular Structure Center

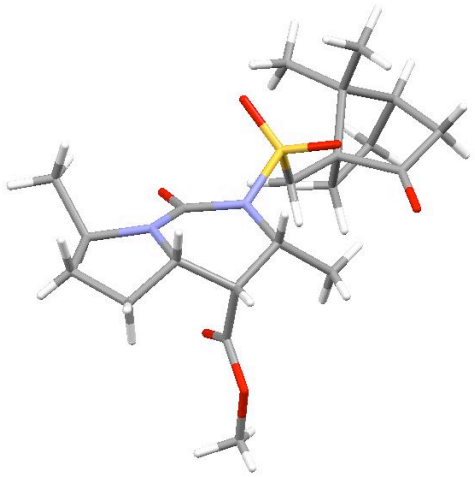
Report 02101

John C. Huffman

October 18, 2002

Overview

Empirical Formula:		$C_{21}H_{32}N_2O_6S$
Color of Crystal:		colorless
Crystal System:		monoclinic
Space Group:		$P2_1$
Cell Dimensions (at 114(2)K; 2744 data)		
a, Å =	6.7235(6)	
b, Å =	10.6124(10)	
c, Å =	15.7575(14)	
alpha, ° =	90.00	
beta, ° =	98.507(3)	
gamma, ° =	90.00	
Z (molecules/cell):		2
Volume, Å^3:		1111.97(17)
Calculated Density, g/cm^3:		1.316
Molecular Weight, g/mole:		440.55
Linear Absorption Coefficient, mm^{-1}:		0.185
Final residuals are:		
R(F) (observed data)	=	0.0446
$R_w(F^2)$ (refinement data)	=	0.1004



Summary

The sample was submitted by the research group of Prof. P.A. Evans, Department of Chemistry, Indiana University. The crystals grew as transparent prisms. A fragment of one of the prisms of approximate dimensions 0.40 × 0.32 × 0.20 mm was mounted on the tip of a 0.1 mm diameter glass fiber which was subsequently mounted on a SMART6000 (Bruker) and cooled to 114(2) K.

The data collection was carried out using graphite-monochromated Mo Kα radiation with a frame time of 10 seconds and a detector distance of 5.0 cm. A randomly oriented region of a sphere in reciprocal space was surveyed. Six sections of 606 frames were collected with 0.30° steps in ω at different ϕ settings with the detector set at –43° in 2θ. Final cell constants were calculated from the centroids of 2744 strong reflections observed during data collection.

Intensity statistics and systematic absences suggested the non-centrosymmetric monoclinic space group $P2_1$ and subsequent solution and refinement confirmed this choice. The structure was solved using SHELXS-97 and refined with SHELXL-97. All hydrogen atoms were refined isotropically.

Full Report and Supporting Information

http://bl-chem-iumsc110.chem.indiana.edu/recipnet/showsample.jsp?sampleId=35006925