Enantioselective Synthesis of 2,6-Dideoxy Carbasugars based on a Desymmetrizing Hydroformylation/Carbonyl ene Cylization Process.

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Supporting Information

(33 pages)

I General

All reactions were carried out in dried glassware under an Argon atmosphere (Argon 5.0 from Sauerstoffwerke Friedrichshafen). All reagents were obtained commercially unless otherwise noted. All solvents were dried and distilled by standard procedures. Chromatographic purification of products was accomplished using flash chromatography[1] on Macherey-Nagel silica gel 60 (230-400 mesh) unless otherwise noted. Melting points were measured on a Büchi melting point apparatus using open glass capillaries, and the values are uncorrected. Nuclear magnetic resonance spectra were acquired on a Bruker Avance 400 (400 MHz, 160 MHz and 100 MHz for ^{1}H, ^{11}B and ^{13}C respectively) and a Bruker DRX 500 (500 MHz and 125 MHz for ^{1}H and ^{13}C respectively) and are referenced internally according to residual protio solvent signals. Data for ^{1}H-NMR are recorded as follows: chemical shift (δ in ppm),

multiplicity (s, singlet; br, broad signal; d, doublet; t, triplet; q, quartet; quint, quintet; hept, heptet; oct, octet; m, multiplet; m_c, symmetrical multiplet), integration, coupling constant (Hz). Data for ^{13}C-NMR and ^{11}B-NMR are reported in terms of chemical shift (δ in ppm), integration, coupling constant (Hz). Low-resolution mass spectra were recorded on Thermo Finnigan MAT 8200 and TSQ 7000 spectrometers (EI: 70 eV; CI/NH_3: 110 eV). High-resolution mass spectra were obtained on a Finnigan MAT 8200 instrument (EI: 70 eV; CI/NH_3: 110 eV). Elemental analyses: Elementar Vario EL (Elementar-Analysensysteme GmbH). Optical rotations were measured on a Perkin-Elmer 241 polarimeter in 1.0 dm, 1.0 mL cells. The concentration in g/100 mL and the solvent are given in parentheses. The enantiomeric excess (*ee*) of the products was determined by HPLC Chiralcel OD-H columns (wavelengths 238 and 273 nm) with *i*-propanol/heptane as the eluent. Hydroformylation experiments were performed in stainless steel tube autoclaves with Synthesis gas (CO 3.7, H_2 4.3, 1:1, Messer-Griessheim). The following compounds were prepared according to literature procedure: (1*R*, 2*S*)-1-Isopropenyl-2-methyl-4-oxobutyl (S_p)-2-(diphenylphosphinyl)ferrocene carboxylate (**2**),[2] 2,4-dimethylpenta-1,4-dien-3-ol (**5**),[3] *o*-DPPFA.[4]

Caution: All operations involving carbon monoxide must be carried out in a well-ventilated fume hood. Use of a gas-leak detector for carbon monoxide is highly recommended.

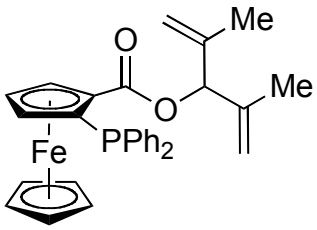
List of abbreviations:
BOP (benzotriazol-1-yloxy)-tris-(dimethylamino)-phosphoniumhexafluoro-phosphate (FLUKA)
DCE 1,2-dichloroethane
$NaBH(O\textit{i}\text{-Val})_3$ sodium tris[(3-methylbutanoyl)oxy]borohydride
o-DPPFA ***o****rtho*-(**d**iphenyl**p**hosphanyl)-**f**errocenecarboxylic **a**cid[4]
PE petrol ether (bp. 40-65°C)

II Experimental procedures and characterizations

1 Synthesis of bis-2-propenyl carbinol *o*-DPPF esters 1

Bis-2-propenyl carbinol *o*-DPPF esters **1** were prepared following a modified literature procedure.[2]

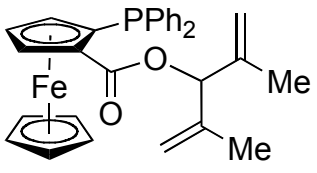
(S_p)-(2,4-Dimethyl-penta-1,4-dien-3-yl)-2-(diphenylphosphanyl)ferrocenecarboxylate (–)-1



$C_{30}H_{29}FeO_2P$
Mol.Wt.: 508.38

(S_p)-*o*-DPPFA (500 mg, 1.20 mmol, *ee* >99%) was dissolved in THF (12 mL) and a solution of prewashed NaH[5] (60% in mineral oil, 78 mg, 1.92 mmol, 1.6 eq.) in THF (1 mL) was slowly added at 25°C. In a separate flask under light-protection, BOP (587 mg, 1.32 mmol, 1.1 eq.) was dissolved in THF (12 mL) and the carboxylate mixture was added during 30 min at 25°C and the mixture was stirred for 60 min. In a separate flask, the alcohol **5** (203 mg, 1.81 mmol, 1.5 eq.) was dissolved in THF (5.5 mL), cooled at 0°C, the NaH (97 mg, 2.41 mmol, 2 eq.) in THF (1.2 mL) was added and the alcoholate mixture was then slowly dropped to the solution of the activated ester and the mixture was again stirred for 4 h. The reaction mixture was quenched with water (2 eq.), silica was added (300 mg) and all volatile material was removed in *vacuo*. Flash chromatography (PE/AcOEt 20:1) (the product fraction was collected in a flask under argon and the solvents were removed in an argon-purged rotary-evaporator due to the air-sensibility of the *o*-DPPF-ester) furnished the title compound (–)-**1** (496 mg, 0.97 mmol, 81%, *ee* >99%) as an orange solid after being dried at 60°C/0.1 mbar overnight. Analytical data are in accordance with the literature.[2] **HPLC** (OD-H, heptane/ *i*-propanol 100:1, 25°C, 0.5 ml/min, 238 nm): t_R [(+)-**1**]: 10.25 min, t_R [(–)-**1**]: 12.17 min.

(R_p)-(2,4-Dimethyl-penta-1,4-dien-3-yl)-2-(diphenylphosphanyl)ferrocenecarboxylate (+)-1



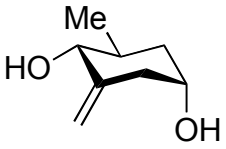
$C_{30}H_{29}FeO_2P$
Mol.Wt.: 508.38

Following the same procedure, (R_p)-*o*-DPPFA (1.0 g, 2.41 mmol, *ee* >99%), alcohol **5** (406 mg, 3.62 mmol, 1.5 eq.), BOP (1.17 g, 26.56 mmol, 1.1 eq.) and NaH (60% in mineral oil, 346 mg, 8.68 mmol, 3.6 eq.) gave after flash chromatography (PE/AcOEt 20:1) the title compound (+)-**1** (1.05 g, 2.06 mmol, 86%, *ee* >99%)

as an orange solid. Analytical data are in accordance with the literature.[2]

2 One pot desymmetrizing hydroformylation/carbonyl ene cyclization process: synthesis of carbocyclic diols 6

(1*R*,2*S*,4*S*) 2-Methyl-6-methylene-cyclohexane-1,4-diol (+)-6

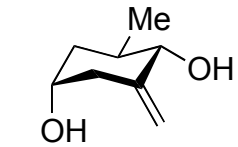


$C_8H_{14}O_2$
Mol.Wt.: 142.20

The *o*-DPPF ester (–)-**1** (375 mg**,** 0.73 mmol, *ee* >99%) was dissolved in freshly distilled THF (5 mL) under argon and [$Rh(CO)_2$acac] (3.4 mg, 13.1 μmol, 0.018 eq.) was added (a gas evolution was observed). After addition of the co-ligand $P(OPh)_3$ (13.8 μL, 0.053 mmol, 0.072 eq.) the orange solution was transferred via syringe into an oven dried stainless-steel tube autoclave; the flask and the syringe were rinsed two times with THF (2×1.2 mL). The argon atmosphere in the autoclave was removed by a pressurizing/depressurizing cycle (three times 10 bar H_2/CO), and finally the autoclave was pressurized with 40 bar H_2/CO (1:1) and heated in an oil bath to 70°C for 48 h. Subsequently, the autoclave was cooled to 25°C, depressurized, opened, the Lewis acid $SnCl_4(THF)_2$[6] (59.7 mg, 0.14 mmol, 0.02 eq.). was quickly added under argon atmosphere and after re-closing the autoclave, the whole was heated to 70°C for 2 h. The mixture was then transferred in an oven-dried flask under argon, cooled to 0°C then $LiAlH_4$ (112 mg, 2.95 mmol, 4 eq.) was carefully added and the whole was allowed to warm to 25°C and stirred overnight. The reaction was quenched by the dropwise addition of water (0.11 mL) then NaOH (3.75 M, 0.11 mL) and water (0.33 mL) at 0°C and the whole was further stirred 2 h at 25°C. The reaction mixture was filtered through Celite and concentrated in *vacuo*. The residue was purified by flash chromatography (Et_2O pure to Et_2O/AcOEt 8:2) to afford the title compound (+)-**6** (67 mg, 0.47 mmol, 64%, *ee* >99%, see chapter **3**) as a colorless oil which crystallizes upon standing at 25°C. Analytical data for the title compound: $\mathbf{R_f}$ (Et_2O) 0.20; **mp** 63°C; **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 1.05 (d, 3H, *J* = 6.5 Hz), 1.42 (ddd, 1H, *J* = 13.8, 11.1, 2.7 Hz), 1.65 (brs, 1H), 1.78 (m_c, 1H), 1.83 (brs, 1H), 1.88 (dddd, 1H, *J* = 13.9, 4.4, 3.5, 2.6 Hz), 2.35 (pd, 1H, *J* = 13.7 Hz), 2.44 (ddd, 1H, *J* = 13.8, 3.7, 2.4 Hz), 3.65 (d, 1H, *J* = 9.2 Hz), 4.00 (brs, 1H), 4.91 (ddd, 1H, *J* = 3.7, 1.5, 0.6 Hz), 5.14 (q, 1H, *J* = 1.5 Hz); **^{13}C-NMR** (125 MHz, $CDCl_3$): δ 18.4, 36.2, 39.7, 41.6, 66.8, 77.4, 109.3, 146.53; **MS** (EI, M = 142.20 g/mol, 70 eV): *m*/*z* (%) = 142 $[M]^+$, 12), 125

(100), 107 (4); **CHN** calcd. C: 67.57, H: 9.92 found C: 67.48, H: 10.10; $[\alpha]_D^{20}$: +54.4° (c = 0.50, $CHCl_3$, *ee* >99%).

(1*S*,2*R*,4*R*) 2-Methyl-6-methylene-cyclohexane-1,4-diol (–)-6

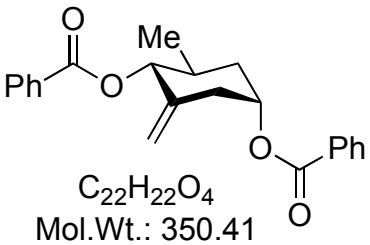


$C_8H_{14}O_2$
Mol.Wt.: 142.20

Following the same procedure, hydroformylation of (+)-**1** (820 mg, 1.61 mmol, *ee* >99%) was carried out with $[Rh(CO)_2acac]$ (7.4 mg, 29.0 μmol, 0.018 eq.) and $P(OPh)_3$ (30.2 μL, 0.11 mmol, 0.072 eq.) in THF (16.1 mL) at 70°C for 48 h. The subsequent cyclization was performed by addition of $SnCl_4(THF)_2$ (130.5 mg, 0.32 mmol, 0.02 eq.). Then reduction with $LiAlH_4$ (245 mg, 6.44 mmol, 4 eq.), subsequent quenching with water (0.24 mL), NaOH (3.75 M, 0.24 mL) and water (0.72 mL) and final flash chromatography (Et_2O pure to Et_2O/AcOEt 8:2) furnished the title compound (–)-**6** (138 mg, 0.97 mmol, 60%, *ee* >99% see chapter **3**). Spectroscopic data are identical to (+)-**6**. **CHN** calcd. C: 67.57, H: 9.92 found C: 67.31, H: 9.73; $[\alpha]_D^{20}$: –56.0° (c = 0.50, $CHCl_3$, *ee* >99%).

3 Determination of enantiomeric purity of carbocyclic diols 6: benzoylation for HPLC analysis

(1*R*,2*S*,4*S*) Benzoic acid 4-benzoyloxy-2-methyl-6-methylene-cyclohexyl ester (+)-12

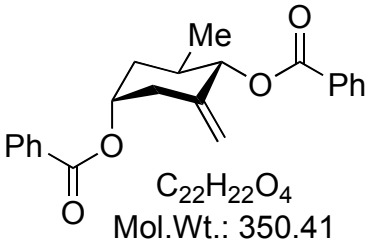


$C_{22}H_{22}O_4$
Mol.Wt.: 350.41

To a solution of (+)-**6** (10 mg, 0.070 mmol) in pyridine (0.7 mL) was added benzoyl chloride (49 μL, 0.42 mmol, 6 eq.) at 0°C. The ice bath was removed and the reaction mixture was stirred overnight at 25°C. The reaction was quenched with few drops of water, diluted with AcOEt (2 mL) and washed with HCl (3×1 mL, 1 M) and water (2 mL). The organic phase was dried over Na_2SO_4 before the solvent was removed under reduced pressure. Flash chromatography of the residue (PE/AcOEt 95:5) afforded the title compound (+)-**12** (19 mg, 0.054 mmol, 77%, *ee* >99%) as a colorless oil. Analytical data for the title compound: $\mathbf{R_f}$ (PE/AcOEt 9:1) 0.26; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 1.06 (d, 3H, *J* = 6.7 Hz), 1.74 (ddd, 1H, *J* = 14.2, 10.5, 3.0 Hz), 2.22 (dtd, 1H, *J* = 14.4, 4.6, 2.2 Hz), 2.32 (m_c, 1H), 2.59 (dd, 1H, *J* = 14.1, 3.4 Hz),

2.75 (ddd, 1H, *J* = 14.3, 4.7, 2.2 Hz), 4.91 (s, 1H), 4.99 (q, 1H, *J* = 1.4 Hz), 5.27 (d, 1H, *J* = 9.1 Hz), 5.37 (pquint, 1H, *J* = 4.0 Hz), 7.42-7.50 (m, 4H), 7.54-7.61 (m, 2H), 8.03-8.06 (m, 2H), 8.13-8.16 (m, 2H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 18.0, 34.2, 36.5, 38.4, 70.0, 78.6, 110.4, 128.4 (2C), 128.5 (2C), 129.7 (2C), 129.8 (2C), 130.2, 130.7, 133.0, 133.1, 141.2, 165.9 (2C); **HRMS** (CI/NH_3, 110 eV, $[M+NH_4]^+$): *m*/*z* calcd. for $C_{22}H_{26}NO_4$: 368.1861; found: 368.1862 ; **HPLC** (OD-H, heptane/*i*-propanol 200:1, 30°C, 0.8 ml/min, 273 nm): t_R [(+)-**12**]: 16.70 min, t_R [(−)-**12**]: 21.17 min; $[\alpha]_D^{20}$: +9.0° (c = 0.70, $CHCl_3$, *ee* >99%).

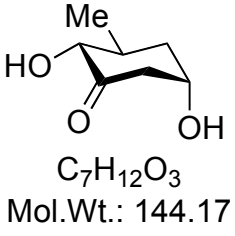
(1*S*,2*R*,4*R*) Benzoic acid 4-benzoyloxy-2-methyl-6-methylene-cyclohexyl ester (–)-12



Following the same procedure, benzoylchloride (49 µL, 0.42 mmol, 6 eq.) added to a solution of (−)-**6** (10 mg, 0.070 mmol) in pyridine (0.7 mL) afforded after work-up and flash chromatography (PE/AcOEt 95:5) the title compound (−)-**12** (21 mg, 0.059 mmol, 85%, *ee* >99%). Spectroscopic data are identical to (+)-**12**. $[\alpha]_D^{20}$: −9.4° (c = 0.35, $CHCl_3$, *ee* >99%).

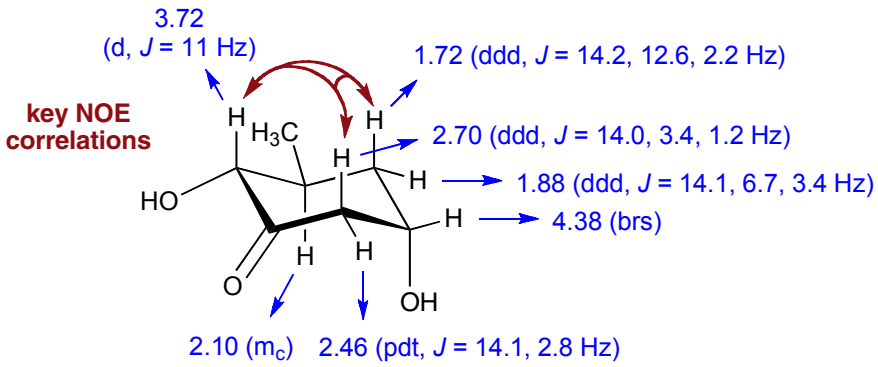
4 Ozonolysis of 6: preparation of dihydroxyketones 4

(2*R*,3*S*,5*S*) 2,5-dihydroxy-3-methyl-cyclohexanone (+)-4

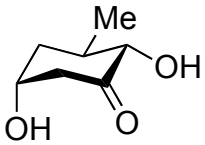


(+)-**6** (60 mg, 0.42 mmol) was dissolved in abs. CH_2Cl_2 (3.5 mL) and abs. MeOH (1.8 mL) and ozone was slowly bubbled into the mixture at -78°C until a strong blue color appeared (10 min). The whole was further stirred 20 min, then nitrogen was passed through the solution until decoloration and Me_2S (0.3 mL, 4.21 mmol, 10 eq.) was added dropwise. The mixture was allowed to warm to 0°C and further stirred for 2 h. The solvent was then removed under reduced pressure (temperature of the bath 20°C). Flash chromatography (FLORISIL®, Et_2O/EE 9:1 to 1:1) afforded the title compound (+)-**4** (49 mg, 0.34 mmol, 81%) as a white powder. Analytical data for the title compound: $\mathbf{R_f}$ (Et_2O) 0.15; **mp** 103°C; **^{1}H-NMR** (500 MHz, Acetone-D6): δ 1.10 (d, 3H, *J* = 6.6 Hz), 1.72 (ddd, 1H, *J* = 14.2, 12.6, 2.2 Hz), 1.88 (ddd, 1H, *J* = 14.1, 6.7, 3.4 Hz), 2.10 (m_c, 1H), 2.46 (pdt, 1H, *J* = 14.1, 2.8 Hz),

2.70 (ddd, 1H, J = 14.0, 3.4, 1.2 Hz), 3.72 (d, 1H, J = 11.0 Hz), 3.78 (d, 1H, J = 3.4 Hz), 3.97 (brs, 1H), 4.38 (brs, 1H); **^{13}C-NMR** (125 MHz, Acetone-D6): δ 19.0, 37.0, 39.5, 47.2, 68.6, 81.0, 210.3; **CHN** calcd. C: 58.32, H: 8.39 found C: 57.95, H: 8.32; $[\alpha]_D^{20}$: +23.2° (c = 0.50, $CHCl_3$, *ee* >99%).



(2*S*,3*R*,5*R*) 2,5-dihydroxy-3-methyl-cyclohexanone (–)-4

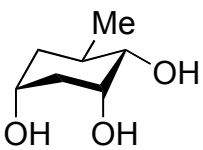


$C_7H_{12}O_3$
Mol.Wt.: 144.17

Following the same protocol, (–)-**6** (35 mg, 0.24 mmol) dissolved in abs. CH_2Cl_2 (2 mL) and abs. MeOH (1 mL) was ozonolyzed to furnish after reductive work-up with Me_2S (0.17 mL, 2.42 mmol, 10 eq.) and flash chromatography (FLORISIL®, Et_2O/EE 9:1 to 1:1) the title compound (–)-**4** (29 mg, 0.20 mmol, 82%) as a white powder. Spectroscopic data are identical to (+)-**4**. **CHN** calcd. C: 58.32, H: 8.39 found C: 58.65, H: 8.65; $[\alpha]_D^{20}$: –25.0° (c = 0.50, $CHCl_3$, *ee* >99%).

5 Synthesis of the carbasugars (–)-7, (–)-9, (+)-10 and (+)-11

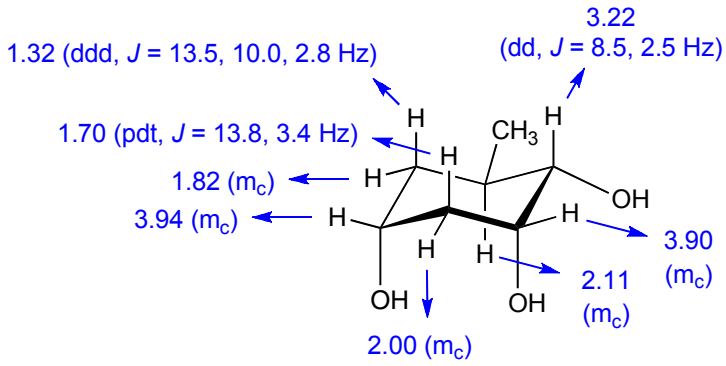
(1*S*,2*R*,4*R*,6*R*) 6-Methylcyclohexane-1,2,4-triol (–)-7



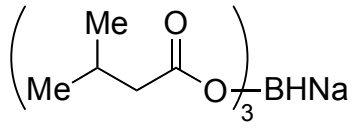
$C_7H_{14}O_3$
Mol.Wt.: 146.18

(–)-**4** (25 mg, 0.173 mmol) was dissolved in dry THF (1.7 mL) and L-selectride® (0.87 mL, 0.87 mmol, 3 eq., 1 M in THF) was added at -78°C. After 1 h, the acetone bath was removed and the reaction was further stirred for 2 h at 0°C. Then EtOH (0.5 mL), an aqueous solution of H_2O_2 (1 mL, 35% wt) and NaOH (1.5 mL, 10% wt) were subsequently added at 0°C and the whole was allowed to warm to 25°C and further stirred for 2 h. Silica

(pre-treated with MeOH/Et_3N (100:1), 30 mg) was poured into the mixture and all volatile materials were subsequently removed in *vacuo*. Flash chromatography (silica gel pre-treated with MeOH/Et_3N (100:1), AcOEt:MeOH 9:1 to 7:3) afforded the title compound (–)-**7** (25 mg, 0.171 mmol, 98%) as a highly viscous colorless oil. The diastereoselectivity was estimated by ^{1}H-NMR (*dr* >99:1). Analytical data for the title compound: **R_f** (AcOEt/MeOH 9:1) 0.32; **^{1}H-NMR** (500 MHz, CD_3OD): δ 1.02 (d, 3H, *J* = 6.9 Hz), 1.32 (ddd, 1H, *J* = 13.5, 10.0, 2.8 Hz), 1.70 (pdt, 1H = 13.8, 3.4 Hz), 1.82 (m_c, 1H), 2.00 (m_c, 1H), 2.11 (m_c, 1H), 3.22 (dd, 1H, *J* = 8.5, 2.5 Hz), 3.90 (m_c, 1H), 3.94 (m_c, 1H); **^{13}C-NMR** (125 MHz, CD_3OD): δ 18.2, 30.1, 37.3, 39.7, 67.6, 71.4, 77.1; **HRMS** (CI/NH_3, 110 eV, $[M+NH_4]^+$): *m/z* calcd. for $C_7H_{18}NO_3$: 164.1286, found: 164.1284; $[\alpha]_D^{20}$: –33.5° (c = 1, MeOH, *dr* >99:1, *ee* >99%).



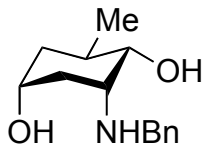
Sodium tris[(3-methylbutanoyl)oxy]borohydride



$C_{15}H_{28}BNaO_6$
Mol.Wt.: 338.18

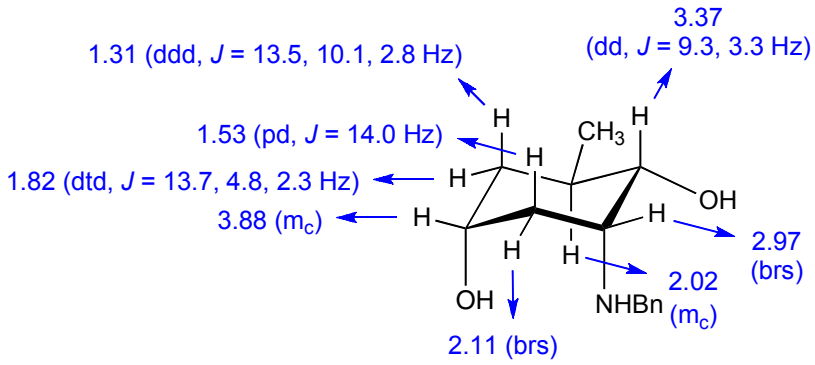
To a suspension of $NaBH_4$ (1.5 g, 39.6 mmol) in dry CH_2Cl_2 (80 mL) was added dropwise isovaleric acid (15 mL, 138.7 mmol, 3.5 eq.) at 0°C. The reaction was then allowed to warm to 25°C and was further stirred for 6 h. The solvent was removed in *vacuo* and the slurry residue was digested in chilled pentane, the resulting precipitate filtered and washed with chilled pentane (2×20 mL) to afford after drying on high *vacuum* overnight the title compound (7.14 g, 21.1 mmol, 54%) as a white powder. Analytical data for the title compound: **mp** 102°C; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 0.88 (d, 18H, *J* = 6.6 Hz), 2.04 (m_c, 3H), 2.13 (d, 6H, *J* = 7.1 Hz), 3.87 (brs, 1H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 22.4 (6C), 25.7 (3C), 45.5 (3C), 178.5 (3C); **^{11}B-NMR** (160 MHz, $CDCl_3$): δ –1.48; **CHN** calcd. C: 53.27, H: 8.35 found C: 52.95, H: 8.20.

(1*S*,2*R*,4*R*,6*R*)-2-(benzylamino)-6-methylcyclohexane-1,4-diol (–)-8

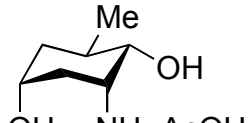


$C_{14}H_{21}NO_2$
Mol.Wt.: 235.32

(–)-**4** (13 mg, 0.090 mmol) was suspended in dry DCE (1 mL) at 0°C, AcOH (5.1 µL, 0.090 mmol, 1 eq.) and benzylamine (11.8 µL, 0.108 mmol, 1.2 eq.) were added, then the reducing agent $NaBH(Oi\text{-}Val)_3$ (46 mg, 0.135 mmol, 1.5 eq.) was poured and the mixture was stirred at 0°C for 3 h. Then few drops of a solution of saturated Na, K-tartrate were added and the whole was stirred 1 h. Silica (pre-treated with MeOH/Et_3N (100:1), 20 mg) was poured into the mixture and all volatile materials were subsequently removed in *vacuo*. Filtration on a small pad of pre-treated silica gel with AcOEt/MeOH 9:1 furnished the crude mixture of epimers (21 mg, 0.089 mmol, 98%), the diastereoselectivity was estimated by ^{1}H-NMR (*dr syn*/*anti* 5:1). Separation of the isomers by flash chromatography (silica gel pre-treated with MeOH/Et_3N (100:1), AcOEt pure to AcOEt:MeOH 9:1 to 7:3) afforded the title compound (–)-**8** (13 mg, 0.055 mmol, 61%, *dr* >99:1) as a viscous light yellow oil. Analytical data for the title compound: $\mathbf{R_f}$ (AcOEt/MeOH 9:1) 0.37; **^{1}H-NMR** (500 MHz, CD_3OD): δ 0.98 (d, 3H, *J* = 6.9 Hz), 1.31 (ddd, 1H, *J* = 13.5, 10.1, 2.8 Hz), 1.53 (pd, 1H = 14.0 Hz), 1.82 (dtd, 1H, *J* = 13.7, 4.8, 2.3 Hz), 2.02 (m_c, 1H), 2.11 (brs, 1H), 2.97 (brs, 1H), 3.37 (dd, 1H, *J* = 9.3, 3.3 Hz), 3.65 (d, 1H, *J* = 12.7 Hz), 3.88 (m_c, 1H), 3.93 (d, 1H, *J* = 12.7 Hz), 7.21-7.26 (m, 1H), 7.28-7.32 (m, 4H,); **^{13}C-NMR** (100 MHz, CD_3OD): δ 18.5, 30.7, 33.1, 40.4, 52.3, 58.6, 68.5, 75.8, 128.2, 129.3 (2C), 129.5 (2C), 140.8; **MS** (CI/NH_3, M = 235.32 g/mol, 110 eV): *m*/*z* (%) = 236 $[M+H]^+$, 100), 162 (16), 91 (10); **HRMS** (CI/NH_3, 110 eV, $[M+H]^+$): *m*/*z* calcd. for $C_{14}H_{22}NO_2$: 236.1650, found: 236.1654; $[\alpha]_D^{20}$: –16.0° (c = 0.9, MeOH, *dr* >99:1, *ee* >99%).



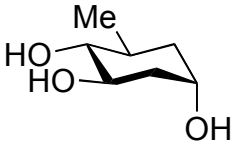
(1*S*,2*R*,4*R*,6*R*)-2-amino-6-methylcyclohexane-1,4-diol acetate (–)-9



$C_9H_{19}NO_4$
Mol.Wt.: 205.25

(–)-**8** (13 mg, 0.055 mmol) was dissolved in MeOH (2 mL), then AcOH (5 µL, 0.082 mmol, 1.5 eq.) and $Pd(OH)_2$ (7.7 mg, 0.011 mmol, 0.2 eq, 20% wt) were added and the mixture was stirred at 25°C overnight under 1 atm of H_2. The crude was filtered on celite, the solvent was removed in *vacuo* to afford the title compound (–)-**9** (11.3 mg, 0.055 mmol, 99%) as a colorless hygroscopic solid. Analytical data for the title compound: **^{1}H-NMR** (400 MHz, CD_3OD): δ 1.04 (d, 3H, *J* = 6.8 Hz), 1.37 (ddd, 1H, *J* = 13.5, 10.0, 2.8 Hz), 1.78-1.89 (m, 2H), 1.89 (s, 3H), 1.95-2.05 (m, 2H), 3.38 (pq, 1H, *J* = 3.9 Hz), 3.43 (dd, 1H, *J* = 8.6, 3.7 Hz), 4.00 (psept, 1H, *J* = 2.4 Hz); **^{13}C-NMR** (100 MHz, CD_3OD): δ 18.1, 23.9, 30.5, 34.0, 39.2, 52.9, 66.2, 73.1, 179.9; **MS** (CI/NH_3, M = 146.21 g/mol, 110 eV): *m*/*z* (%) = 146 $[M+H]^+$, 100), 72 (11); **HRMS** (CI/NH_3, 110 eV, $[M+H]^+$): *m*/*z* calcd. for $C_7H_{16}NO_2$: 146.1181, found: 146.1178; $[\alpha]_D^{20}$: −13.8° (c = 0.5, MeOH, *ee* >99%).

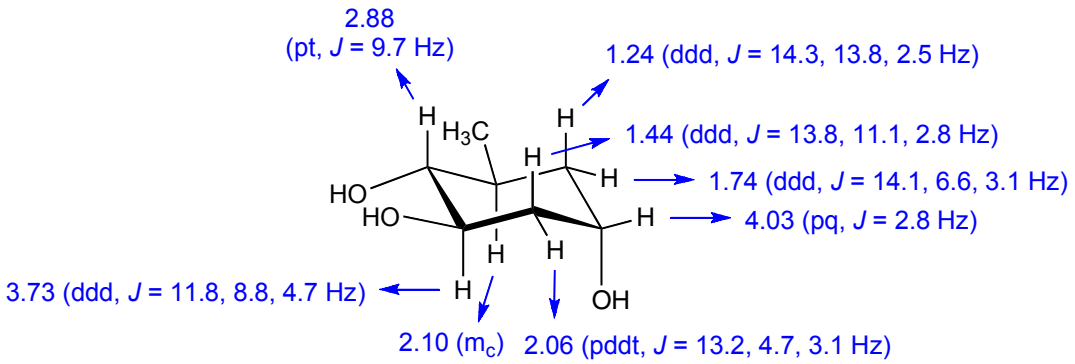
(1*R*,2*R*,4*S*,6*S*)-6-methylcyclohexane-1,2,4-triol (+)-10



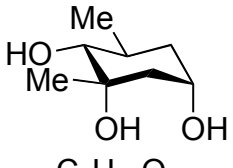
$C_7H_{14}O_3$
Mol.Wt.: 146.18

$NaBH(O\textit{i}\text{-Val})_3$ (363 mg, 0.20 mmol, 5 eq.) was dissolved in abs. MeCN (0.6 mL) and abs. AcOH (0.6 mL) and the whole was cooled to -35°C. To this mixture, a solution of the ketone (+)-**4** (30 mg, 0.20 mmol, 1 eq.) in abs. MeCN (0.4 mL) and abs. AcOH (0.4 mL) was slowly added and the reaction was further stirred for 1h. The mixture was diluted with MeOH (0.5 mL) and water (0.5 mL) and a spatula of Na, K-tartrate was poured and the whole was stirred vigorously overnight. After filtration of the salts, which were washed with AcOEt, silica (pre-treated with MeOH/Et_3N (100:1), 50 mg) was poured into the filtrate and all volatile materials were removed in *vacuo*. Flash chromatography (silica gel pre-treated with MeOH/Et_3N (100:1), AcOEt:MeOH 9:1 to 7:3) afforded the title compound (+)-**10** and its epimer (26 mg, 0.17 mmol, 85%) as a highly viscous colourless oil. The diastereoselectivity was estimated by ^{1}H-NMR (*dr anti*/*syn* 91:9). **R_f** (AcOEt/MeOH 9:1) 0.18; **^{1}H-NMR** (500 MHz, CD_3OD): δ 1.00 (d, 3H, *J* = 6.6 Hz), 1.24 (ddd, 1H, *J* = 14.3, 13.8, 2.5 Hz), 1.44 (ddd, 1H, *J* = 13.8, 11.1, 2.8 Hz), 1.74 (ddd, 1H, *J* = 14.1, 6.6, 3.1 Hz), 1.84 (m_c, 1H), 2.06 (pddt, 1H, *J* = 13.2, 4.7, 3.1 Hz), 2.88 (pt, 1H, *J* = 9.7 Hz), 3.73 (ddd, 1H, *J* = 11.8, 8.8, 4.7

Hz), 4.03 (pq, 1H, , J = 2.8 Hz); **^{13}C-NMR** (125 MHz, CD_3OD): δ 18.4, 32.9, 40.5, 40.8, 67.1, 71.5, 82.0; **HRMS** (EI, 70 eV, [M-H_2O]): *m/z* calcd. for $C_7H_{12}O_2$: 128.0837, found: 128.0838; $[\alpha]_D^{20}$: +10.4° (c = 1, MeOH, *dr* 91:9, *ee* >99%).

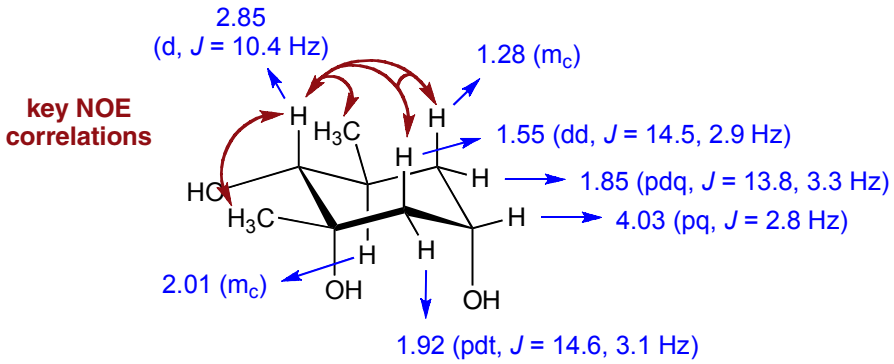


(1*R*,2*S*,4*S*,6*S*)-2,6-dimethylcyclohexane-1,2,4-triol (+)-11



$C_8H_{16}O_3$
Mol.Wt.: 160.21

To a solution of (+)-**4** (15 mg, 0.104 mmol) in freshly distilled THF (1 mL) was slowly added MeMgCl (0.22 mL, 0.624 mmol, 6 eq., 2.8 M in THF) at -78°C and the mixture was stirred at this temperature for 1 h and at 0°C for 2 h. The mixture was diluted with THF (1 mL) and sat. NH_4Cl was carefully added until the gas evolution stopped. Then silica (pre-treated with MeOH/Et_3N (100:1), 20 mg) was poured and all volatile materials were removed in *vacuo*. Flash chromatography (silica gel pre-treated with MeOH/Et_3N (100:1), AcOEt:MeOH 95:5) afforded the title compound (+)-**11** and its isomer (15 mg, 0.093 mmol, 90%) as a highly viscous colorless oil. The diastereoselectivity was estimated by ^{1}H-NMR (*dr anti*/*syn* 94:6). **R_f** (AcOEt) 0.38; **^{1}H-NMR** (500 MHz, CD_3OD): δ 1.03 (d, 3H, J = 6.4 Hz), 1.18 (s, 3H), 1.28 (m_c, 1H), 1.55 (dd, 1H, J = 14.5, 2.9 Hz), 1.85 (pdq, 1H, J = 13.8, 3.3 Hz), 1.92 (pdt, 1H, J = 14.6, 3.1 Hz), 2.01 (m_c, 1H), 2.85 (d, 1H, J = 10.4 Hz), 3.97 (pquint, 1H, J = 2.9 Hz); **^{13}C-NMR** (125 MHz, CD_3OD): δ 18.9, 26.9, 30.0, 41.6, 43.1, 68.3, 74.7, 81.6 (C1); **MS** (CI/NH_3, M = 160.21 g/mol, 110 eV): *m/z* (%) = 178 ($[M+NH_4]^+$, 100), 161 (81), 143 (20), 125 (14); **HRMS** (CI/NH_3, 110 eV, $[M+NH_4]^+$): *m/z* calcd. for $C_8H_{20}NO_3$: 178.1443, found: 178.1446; $[\alpha]_D^{20}$: +25.6° (c = 0.5, MeOH, *dr* 94:6, *ee* >99%).



III Literature

[1] Still, W.C.; Kahn, M.; Mitra, A. *J. Org. Chem.* 1978, **43**, 2923.

[2] Breit, B.; Breuninger, D. *Eur. J. Org. Chem.* 2005, **18**, 3916.

[3] Tullis, J. S; Vares, L.; Kann, N.; Norrby, P.-O.; Rein, T.; *J. Org. Chem.* 1998, **63**, 8284.

[4] Breit, B.; Breuninger, D. *Synthesis* 2005, 2782.

[5] NaH (60% suspension in mineral oil, Fluka) was washed twice with PE (0.5 mL/mmol) and dissolved in freshly distilled THF (0.5 mL/mmol) before use.

[6] $SnCl_4(THF)_2$ was prepared by the slow addition of an excess THF to a solution of $SnCl_4$ in CH_2Cl_2 at 0°C. The white precipitate is filtered, washed twice with cold CH_2Cl_2 and dried overnight in *vacuo*.

IV HPLC chromatograms and copies of ^{1}H and ^{13}C spectra

Chromatogram of (±)-**1**

D-7000 HSM: bigot Series: 0045 Report: original System: Sys 2

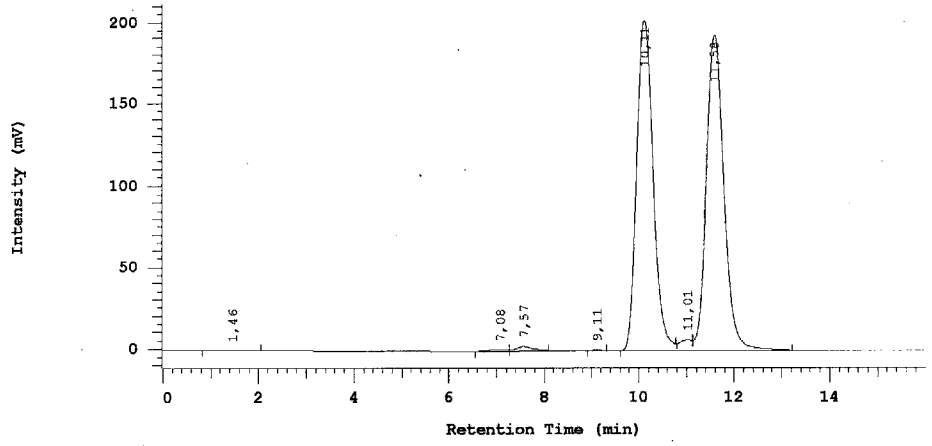
Universität Freiburg
Inst. für Organische Chemie und Biochemie

Analyzed: 21.01.08 12:50 Reported: 21.01.08 13:07
Processed: 21.01.08 13:07

Data Path: D:\HSM\bigot\DATA\0045\
Processing Method: OD-H Heptan/IPA 100/1 238nm

System(acquisition): Sys 2 Series:0045
Application: bigot Vial Number: 1
Sample Name: ABx-743 rac Vial Type: UNK
Injection from this vial: 1 of 1 Volume: 1,0 ul
Sample Description:

Chrom Type: HPLC Channel : 1



Acquisition Method: OD-H Heptan/IPA 100/1 238nm
Column Type: Chiralcel OD-H Developed by: fehrenbach
Pump A Type: L-7100
Solvent A: Heptan Solvent B: i-Propanol
Solvent C: nHept/IPA 100/1 Solvent D: Äthanol
Method Description: n-Heptan /IPA 100/1 , 238nm, 0,5ml/min

Chrom Type: HPLC Channel : 1

Peak Quantitation: AREA
Calculation Method: AREA%

No.	RT	Area %	Area	BC
1	1,46	0,015	1479	BB
2	7,08	0,221	21367	BV
3	7,57	0,593	57378	VB
4	9,11	0,065	6284	BB
5	10,11	48,696	4710070	BV
6	11,01	1,150	111183	VV
7	11,58	49,260	4764536	VB
		100,000	9672297	

Peak rejection level: 0

Page Indicatòr 1

Chromatogram of (–)-**1**

D-7000 HSM: bigot Series: 0036 Report: original System: Sys 1

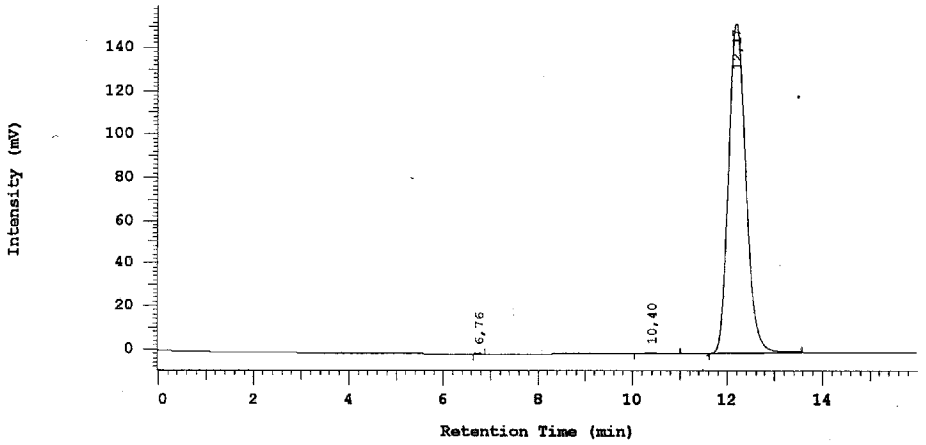
Universität Freiburg
Inst. für Organische Chemie und Biochemie

Analyzed: 23.07.07 10:23 Reported: 23.07.07 10:40
Processed: 23.07.07 10:40

Data Path: D:\HSM\bigot\DATA\0036\
Processing Method: OD-H Heptan/IPA 100/1 238nm

System(acquisition): Sys 1 Series:0036
Application: bigot Vial Number: 1
Sample Name: ABVIII-629-Sp Vial Type: UNK
Injection from this vial: 1 of 1 Volume: 1,0 ul
Sample Description:

Chrom Type: HPLC Channel : 1



Acquisition Method: OD-H Heptan/IPA 100/1 238nm
Column Type: Chiralcel OD-H Developed by: fehrenbach
Pump A Type: L-7100
Solvent A: Heptan Solvent B: i-Propanol
Solvent C: nHept/IPA 100/1 Solvent D: Äthanol
Method Description: n-Heptan /IPA 100/1 , 238nm, 0,5ml/min

Chrom Type: HPLC Channel : 1

Peak Quantitation: AREA
Calculation Method: AREA%

No.	RT	Area %	Area	BC
1	6,76	0,013	493	BB
2	10,40	0,202	7583	BB
3	12,17	99,785	3742293	BB
		100,000	3750369	

Peak rejection level: 0

Page Indicator 1

Chromatogram of (+)-**1**

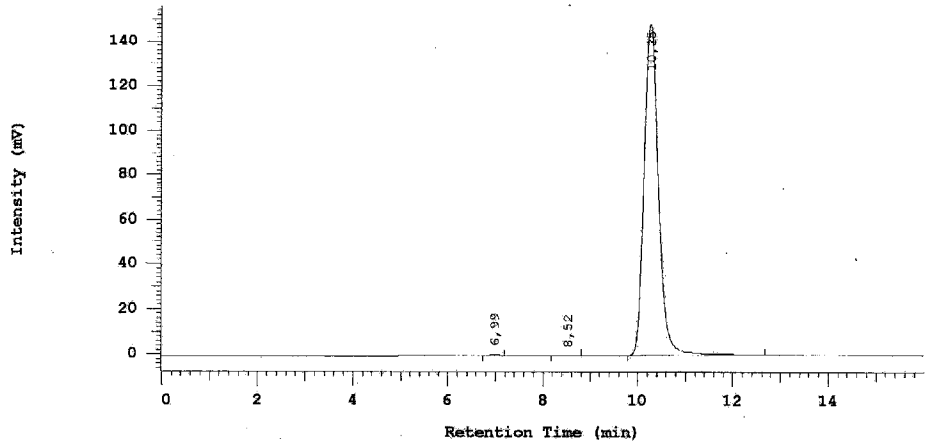
D-7000 HSM: bigot Series: 0044 Report: original System: Sys 2

Universität Freiburg
Inst. für Organische Chemie und Biochemie

Analyzed: 21.01.08 11:15 Reported: 21.01.08 11:32
Processed: 21.01.08 11:32

Data Path: D:\HSM\bigot\DATA\0044\
Processing Method: OD-H Heptan/IPA 100/1 238nm
System(acquisition): Sys 2 Series:0044
Application: bigot Vial Number: 1
Sample Name: ABx-743 Rp Vial Type: UNK
Injection from this vial: 1 of 1 Volume: 1,0 ul
Sample Description:

Chrom Type: HPLC Channel : 1



Acquisition Method: OD-H Heptan/IPA 100/1 238nm
Column Type: Chiralcel OD-H Developed by: fehrenbach
Pump A Type: L-7100
Solvent A: Heptan Solvent B: i-Propanol
Solvent C: nHept/IPA 100/1 Solvent D: Äthanol
Method Description: n-Heptan /IPA 100/1 , 238nm, 0,5ml/min

Chrom Type: HPLC Channel : 1

Peak Quantitation: AREA
Calculation Method: AREA%

No.	RT	Area %	Area	BC
1	6,99	0,211	6358	BB
2	8,52	0,101	3030	BB
3	10,25	99,688	3004580	BB
		100,000	3013968	

Peak rejection level: 0

Page Indicator 1

Chromatogram of (±)-**12**

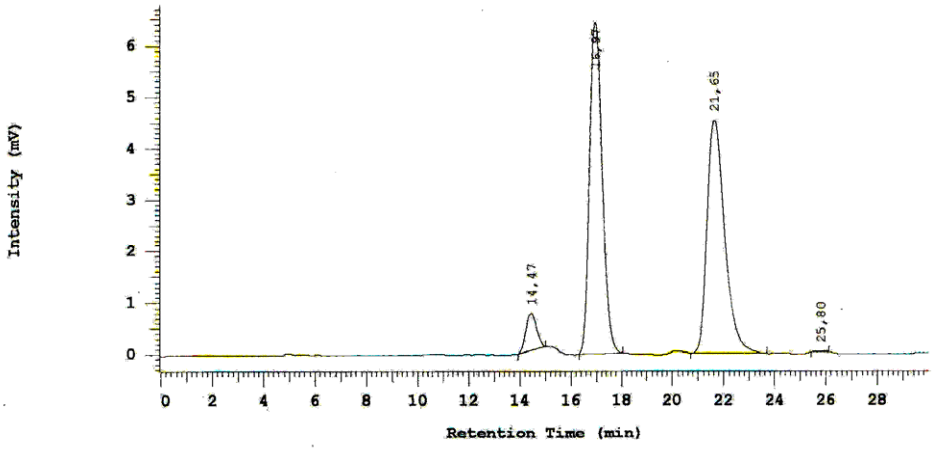
D-7000 HSM: bigot Series: 0046 Report: modified System: Sys 1

Universität Freiburg
Inst. für Organische Chemie und Biochemie

Analyzed: 28.01.08 10:26 Reported: 28.01.08 10:58
Processed: 28.01.08 10:58

Data Path: D:\HSM\bigot\DATA\0046\
Processing Method: OD-H Heptan/IPA 200/1 273nm
System(acquisition): Sys 1 Series:0046
Application: bigot Vial Number: 1
Sample Name: ABx-748 Vial Type: UNK
Injection from this vial: 1 of 1 Volume: 1,0 ul
Sample Description:

Chrom Type: HPLC Channel : 1



Acquisition Method: OD-H Heptan/IPA 200/1 273nm
Column Type: Chiralcel OD-H Developed by: fehrenbach
Pump A Type: L-7100
Solvent A: Heptan Solvent B: i-Propanol
Solvent C: nHept/IPA 200:1 Solvent D: Äthanol
Method Description: n-Heptan/IPA 200/1 , 273nm, 0,8ml/min, 30°C.

Chrom Type: HPLC Channel : 1

Peak Quantitation: AREA
Calculation Method: AREA%

No.	RT	Area %	Area	BC
1	14,47	4,528	19908	BB
2	16,97	47,880	210496	BB
3	21,65	47,387	208330	MC
4	25,80	0,204	899	BB
		100,000	439633	

Peak rejection level: 0

Page Indicator 1 / 3

Chromatogram of (+)-**12**

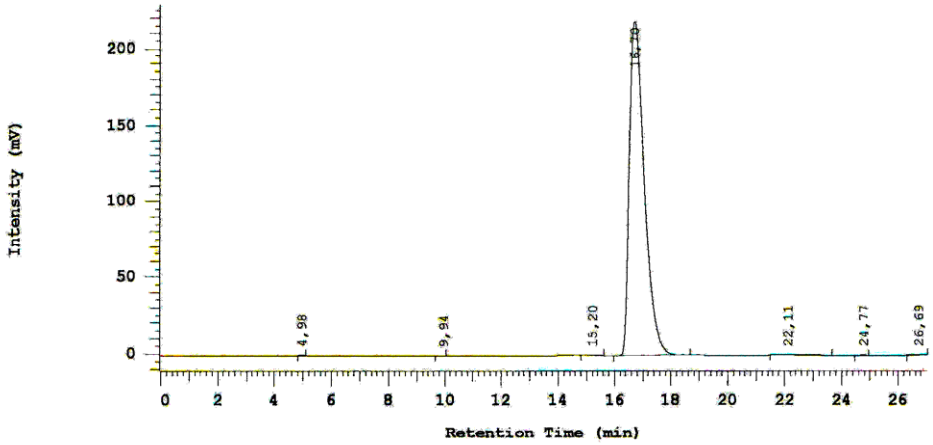
D-7000 HSM: bigot Series: 0039 Report: original System: Sys 1

Universität Freiburg
Inst. für Organische Chemie und Biochemie

Analyzed: 06.09.07 14:33 Reported: 06.09.07 15:00
Processed: 06.09.07 15:00

Data Path: D:\HSM\bigot\DATA\0039\
Processing Method: OD-H Heptan/IPA 200/1 273nm
System(acquisition): Sys 1 Series:0039
Application: bigot Vial Number: 1
Sample Name: AB-612-3 Vial Type: UNK
Injection from this vial: 1 of 1 Volume: 1,0 ul
Sample Description:

Chrom Type: HPLC Channel : 1



Acquisition Method: OD-H Heptan/IPA 200/1 273nm
Column Type: Chiralcel OD-H (8mt) Developed by: fehrenbach
Pump A Type: L-7100
Solvent A: Heptan Solvent B: i-Propanol
Solvent C: nHept/IPA 200:1 Solvent D: Äthanol
Method Description: n-Heptan/IPA 200/1 , 273nm, 0,8ml/min, 30°C.

Chrom Type: HPLC Channel : 1

Peak Quantitation: AREA
Calculation Method: AREA%

No.	RT	Area %	Area	BC
1	4,98	0,019	1479	BB
2	9,94	0,005	350	BB
3	15,20	0,097	7440	BB
4	16,70	99,552	7662084	BB
5	22,11	0,279	21457	BB
6	24,77	0,008	612	BB
7	26,69	0,040	3112	BB
		100,000	7696534	

Peak rejection level: 0

Page Indicator 1

Chromatogram of (–)-**12**

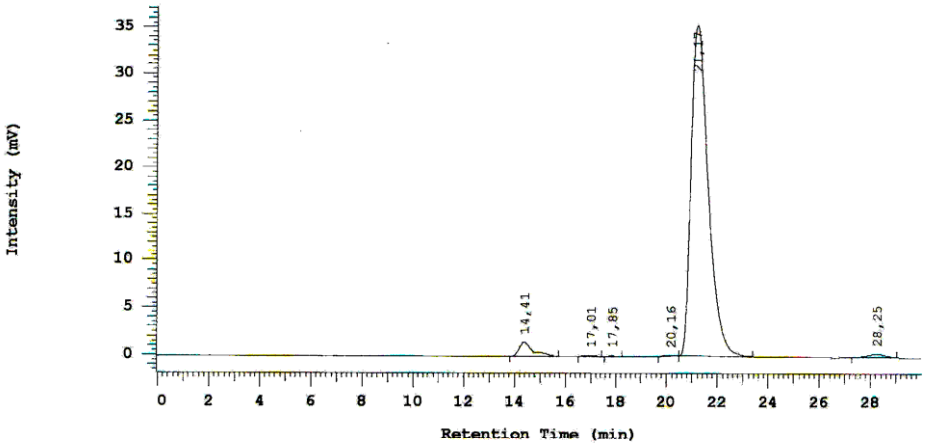
D-7000 HSM: bigot Series: 0049 Report: modified System: Sys 1

Universität Freiburg
Inst. für Organische Chemie und Biochemie

Analyzed: 28.01.08 12:23 Reported: 28.01.08 13:20
Processed: 28.01.08 13:19

Data Path: D:\HSM\bigot\DATA\0049\
Processing Method: OD-H Heptan/IPA 200/1 273nm
System(acquisition): Sys 1 Series:0049
Application: bigot Vial Number: 1
Sample Name: ABx-748-2 Vial Type: UNK
Injection from this vial: 1 of 1 Volume: 1,0 ul
Sample Description:

Chrom Type: HPLC Channel : 1



Acquisition Method: OD-H Heptan/IPA 200/1 273nm
Column Type: Chiralcel OD-H Developed by: fehrenbach
Pump A Type: L-7100
Solvent A: Heptan Solvent B: i-Propanol
Solvent C: nHept/IPA 200:1 Solvent D: Äthanol
Method Description: n-Heptan/IPA 200/1 , 273nm, 0,8ml/min, 30°C.

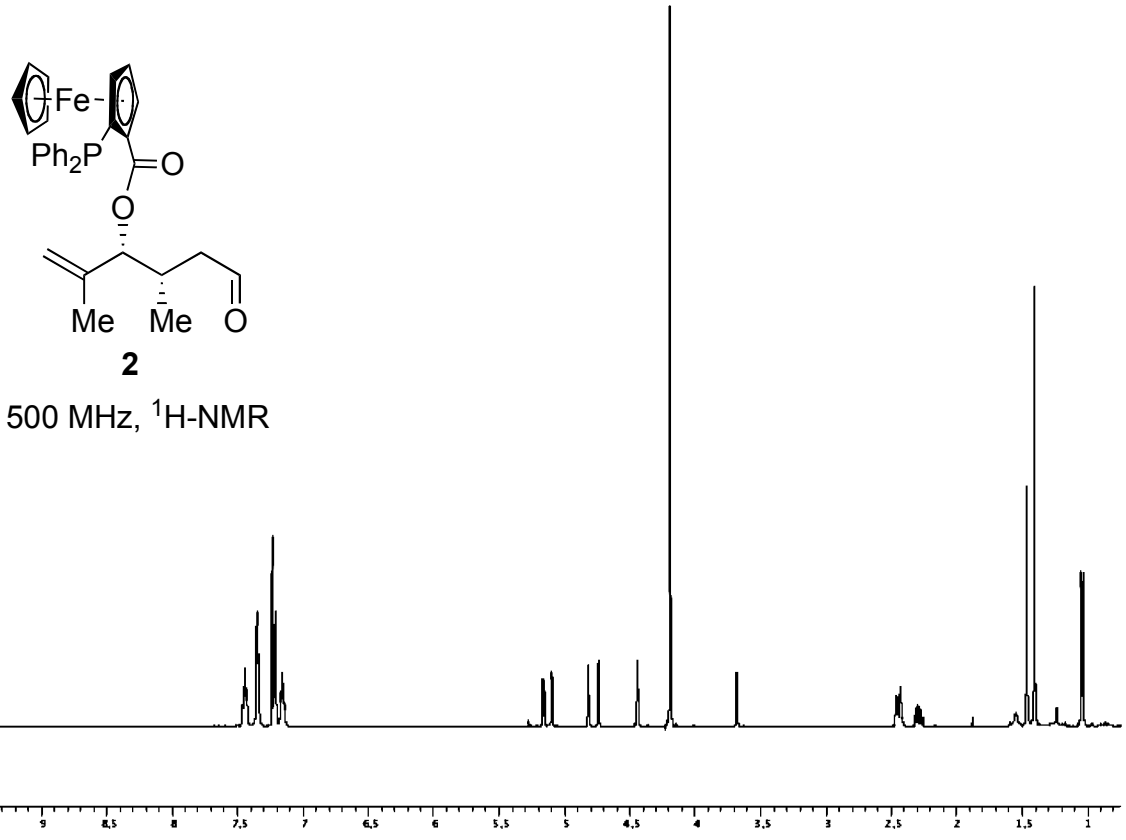
Chrom Type: HPLC Channel : 1

Peak Quantitation: AREA
Calculation Method: AREA%

No.	RT	Area %	Area	BC
1	14,41	3,311	55220	MC
2	17,01	0,239	3980	MC
3	17,85	0,097	1624	MC
4	20,16	0,151	2512	MC
5	21,17	95,240	1588606	MC
6	28,25	0,963	16057	MC
		100,000	1667999	

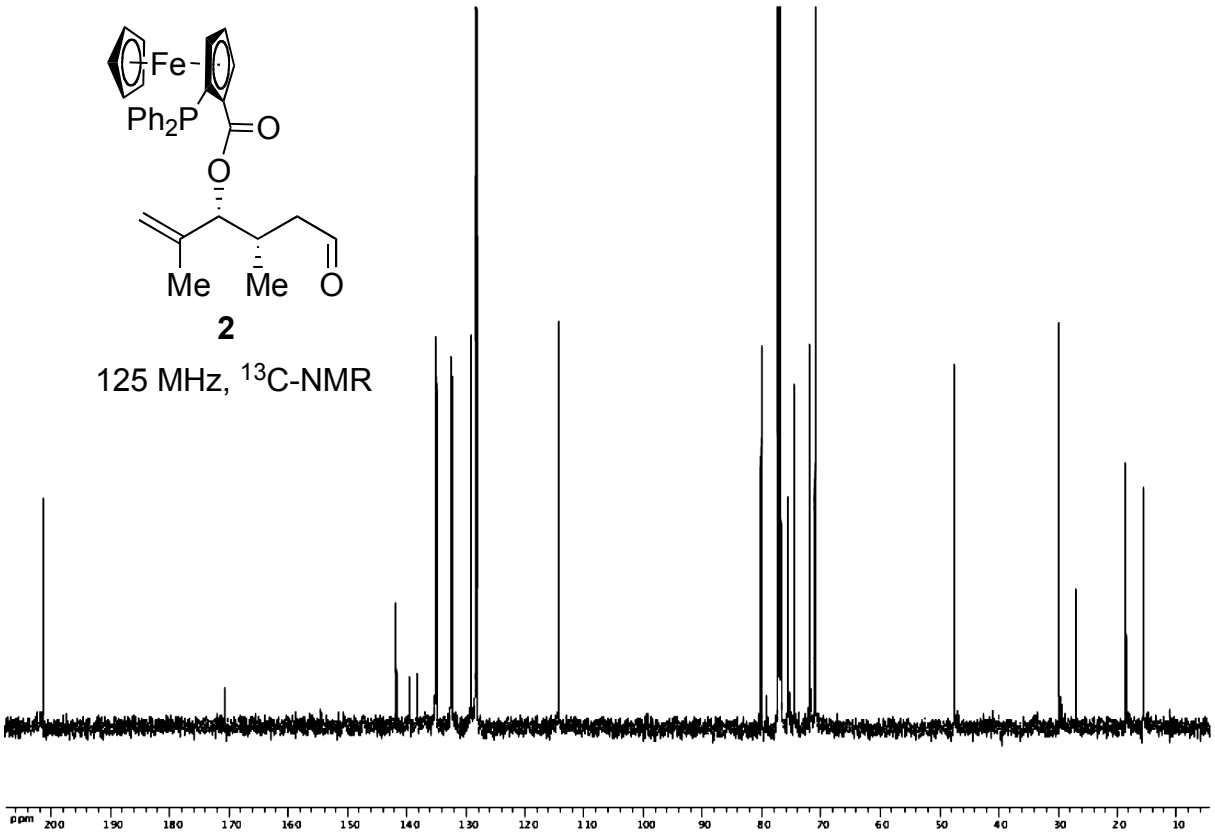
Peak rejection level: 0

Page Indicator 1 / 3



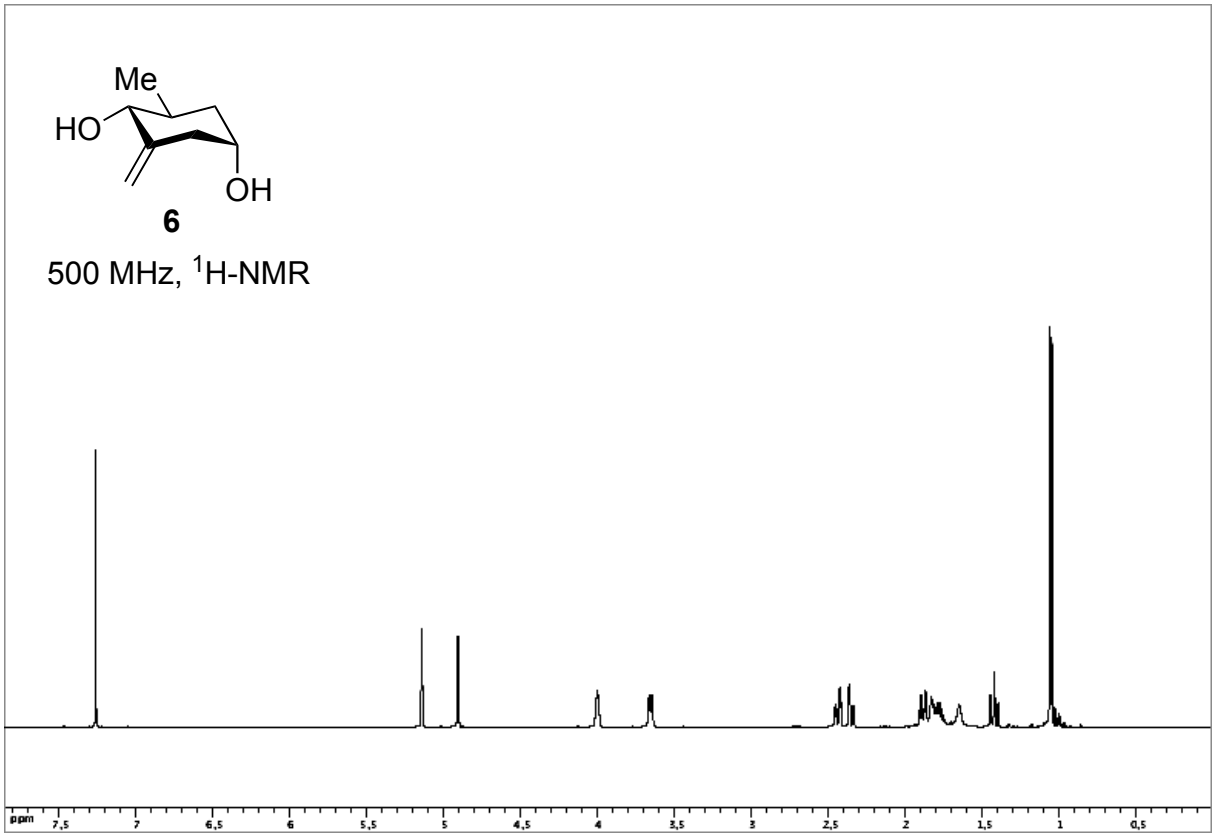
2

500 MHz, ^{1}H-NMR



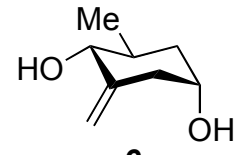
2

125 MHz, ^{13}C-NMR



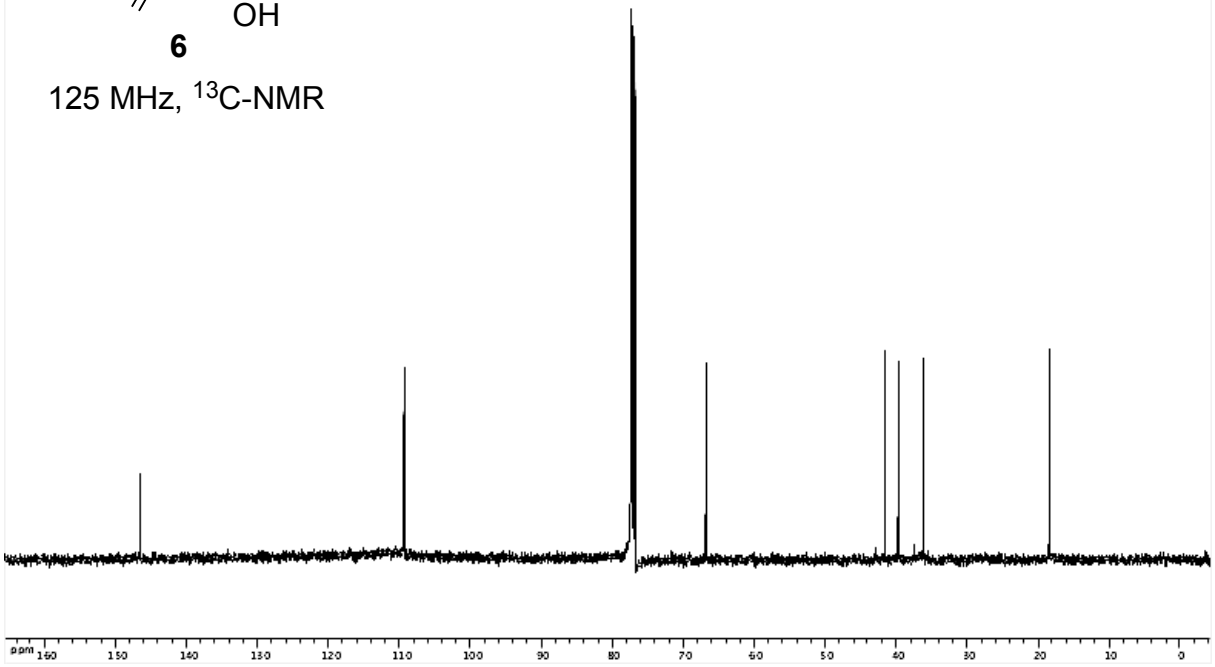
6

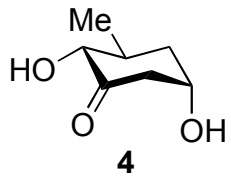
500 MHz, ^{1}H-NMR



6

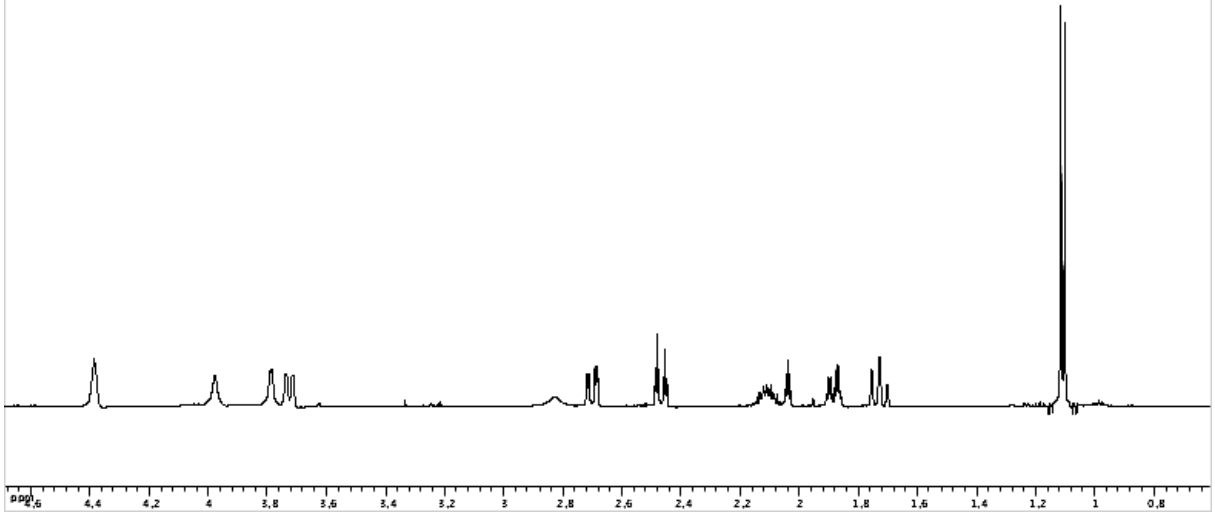
125 MHz, ^{13}C-NMR

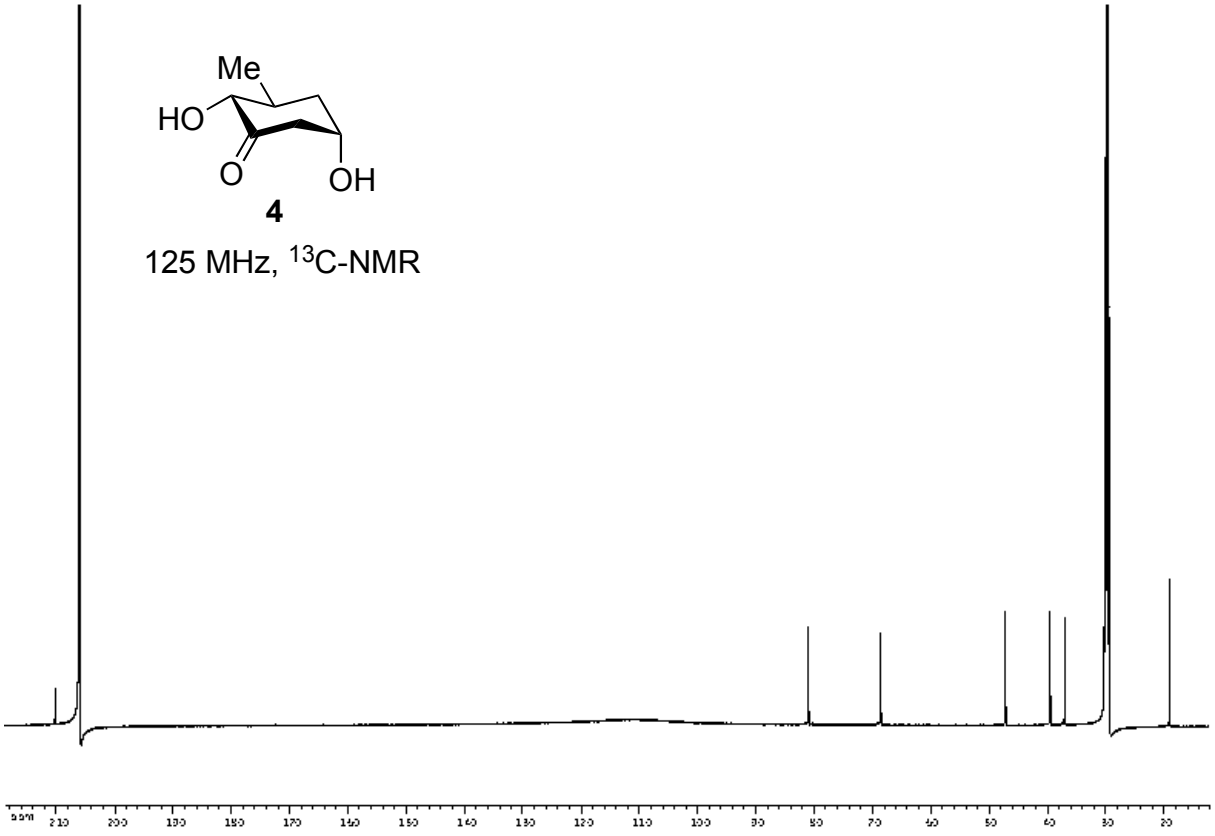




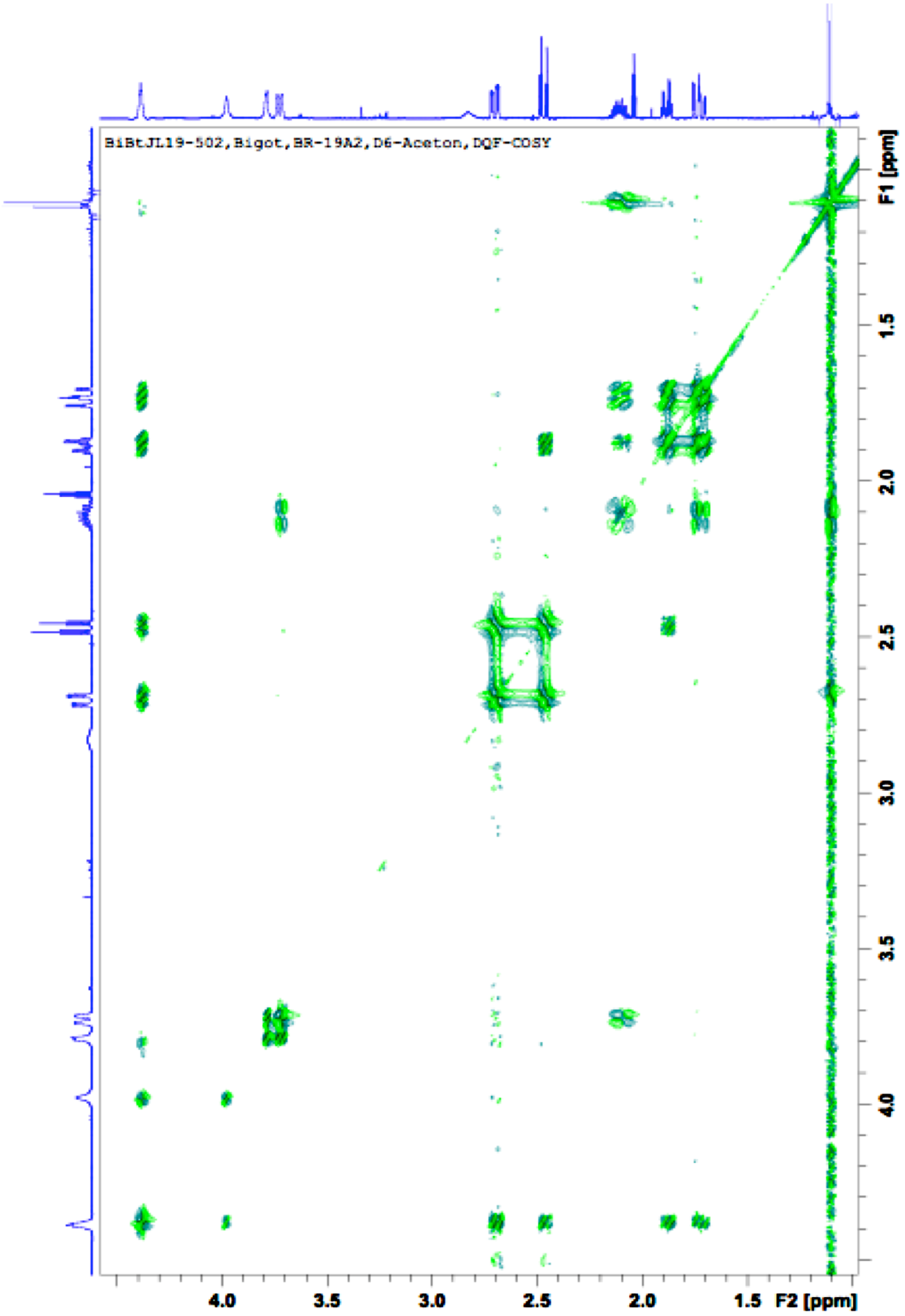
4

500 MHz, ^{1}H-NMR

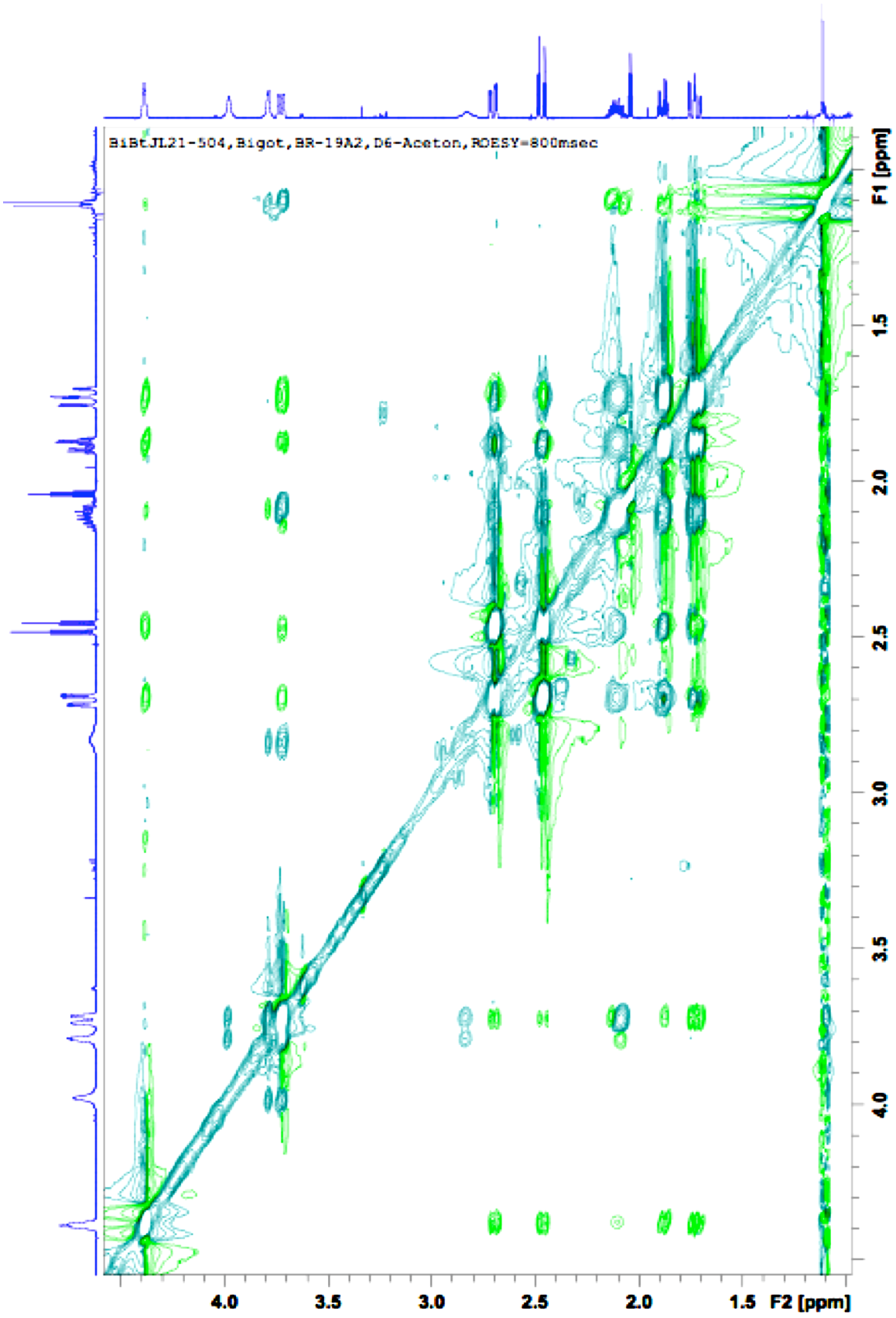


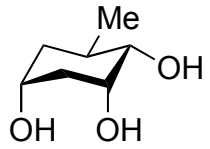


Cosy spectrum of **4**



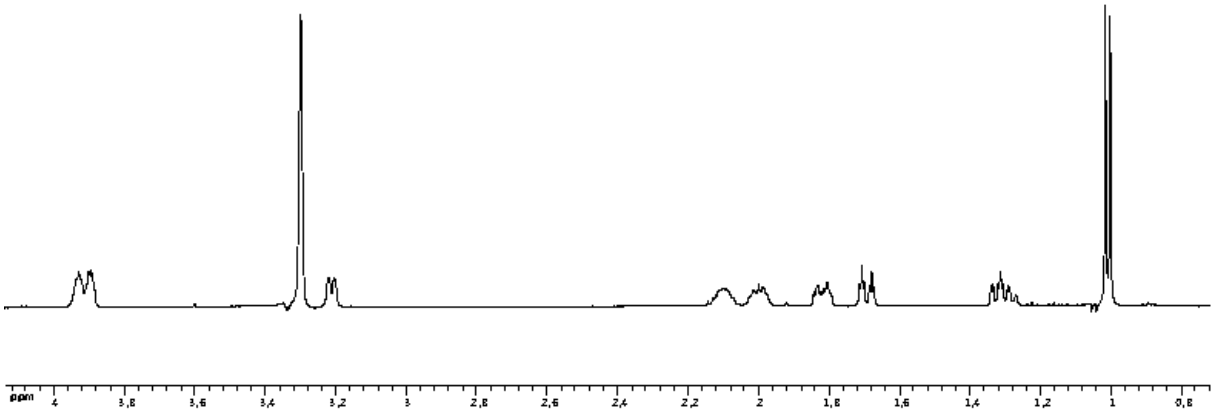
Roesy spectrum of **4**

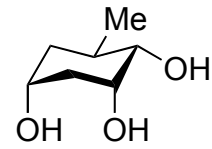

BiBtJL21-504,Bigot,BR-19A2,D6-Aceton,ROESY=800msec
F1 [ppm]
1.5
2.0
2.5
3.0
3.5
4.0
4.0
3.5
3.0
2.5
2.0
1.5 F2 [ppm]



7

500 MHz, ^{1}H-NMR

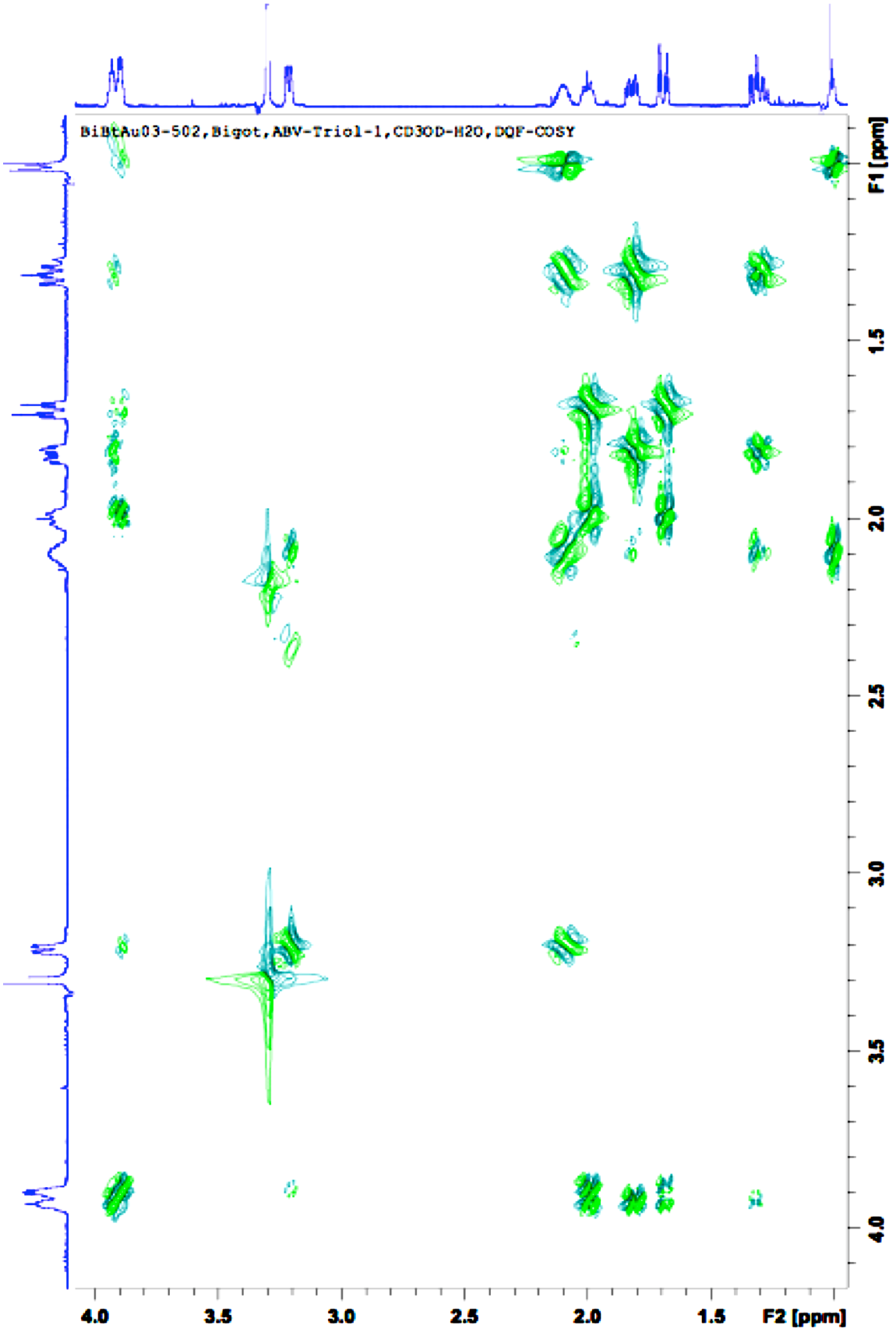


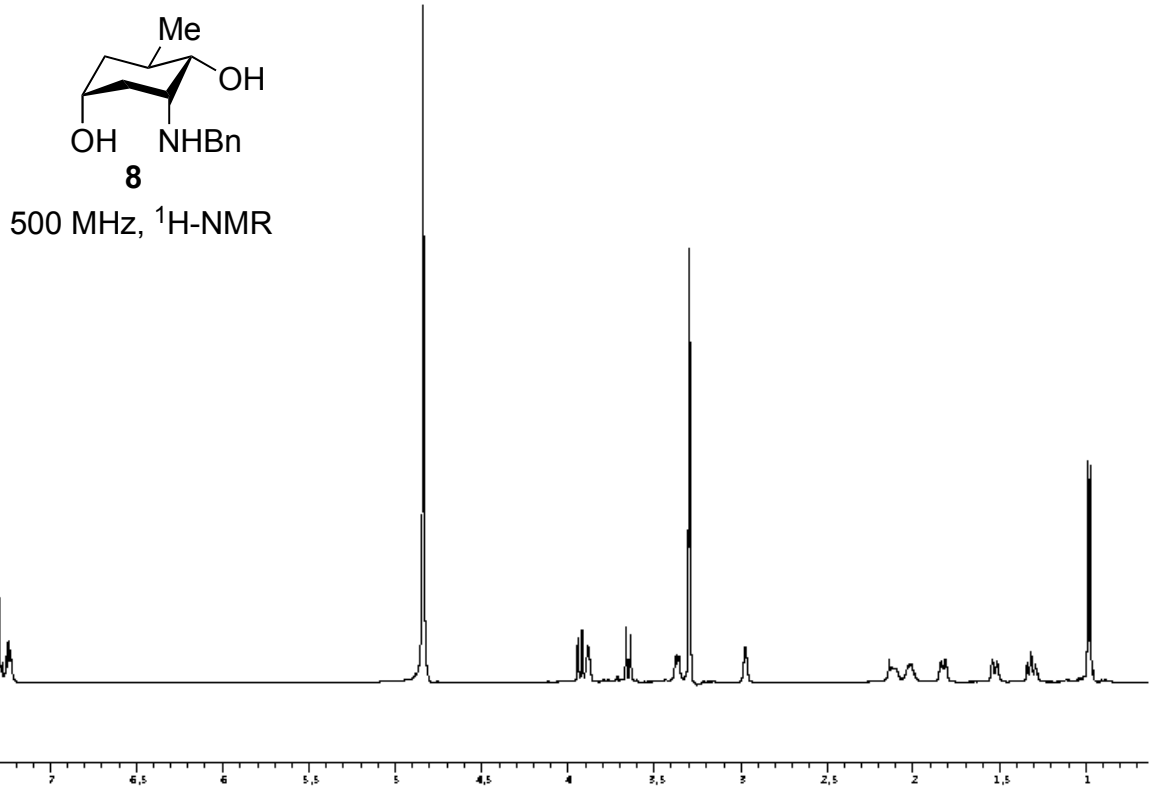


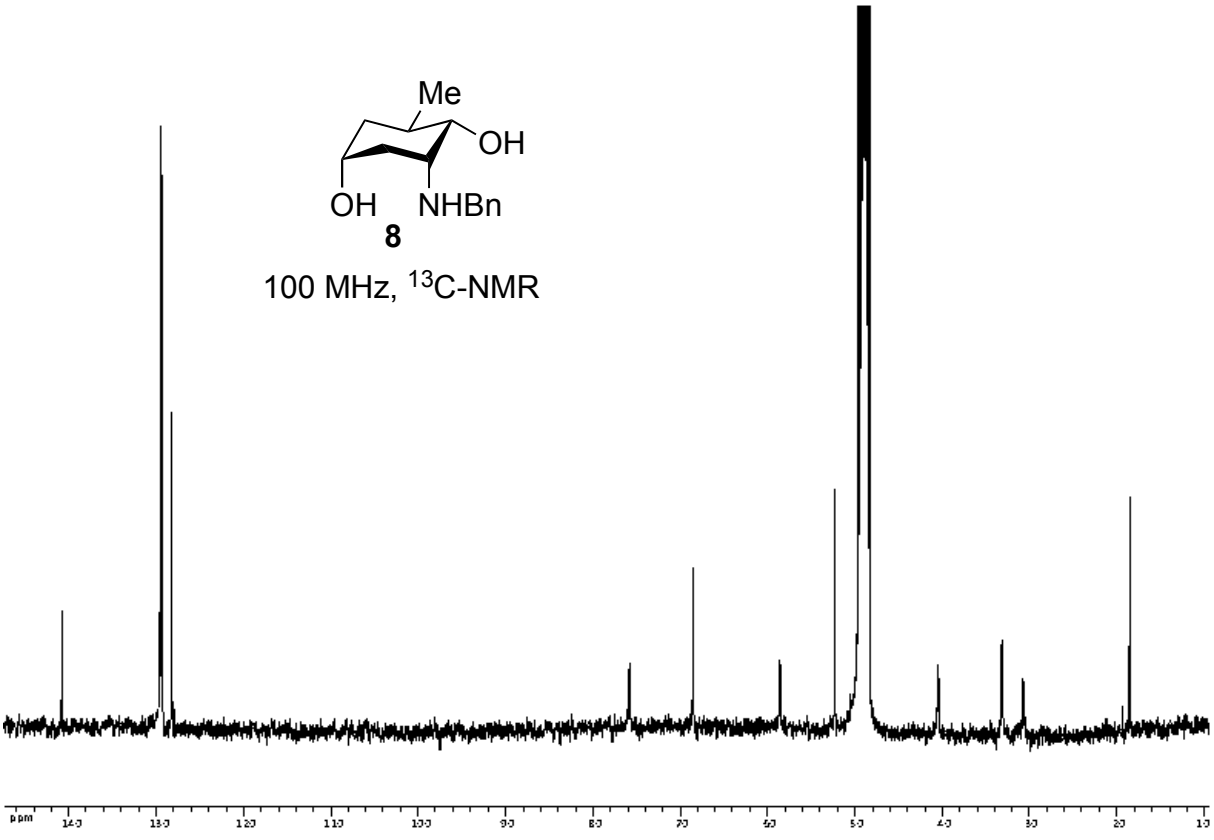
7

125 MHz, ^{13}C-NMR

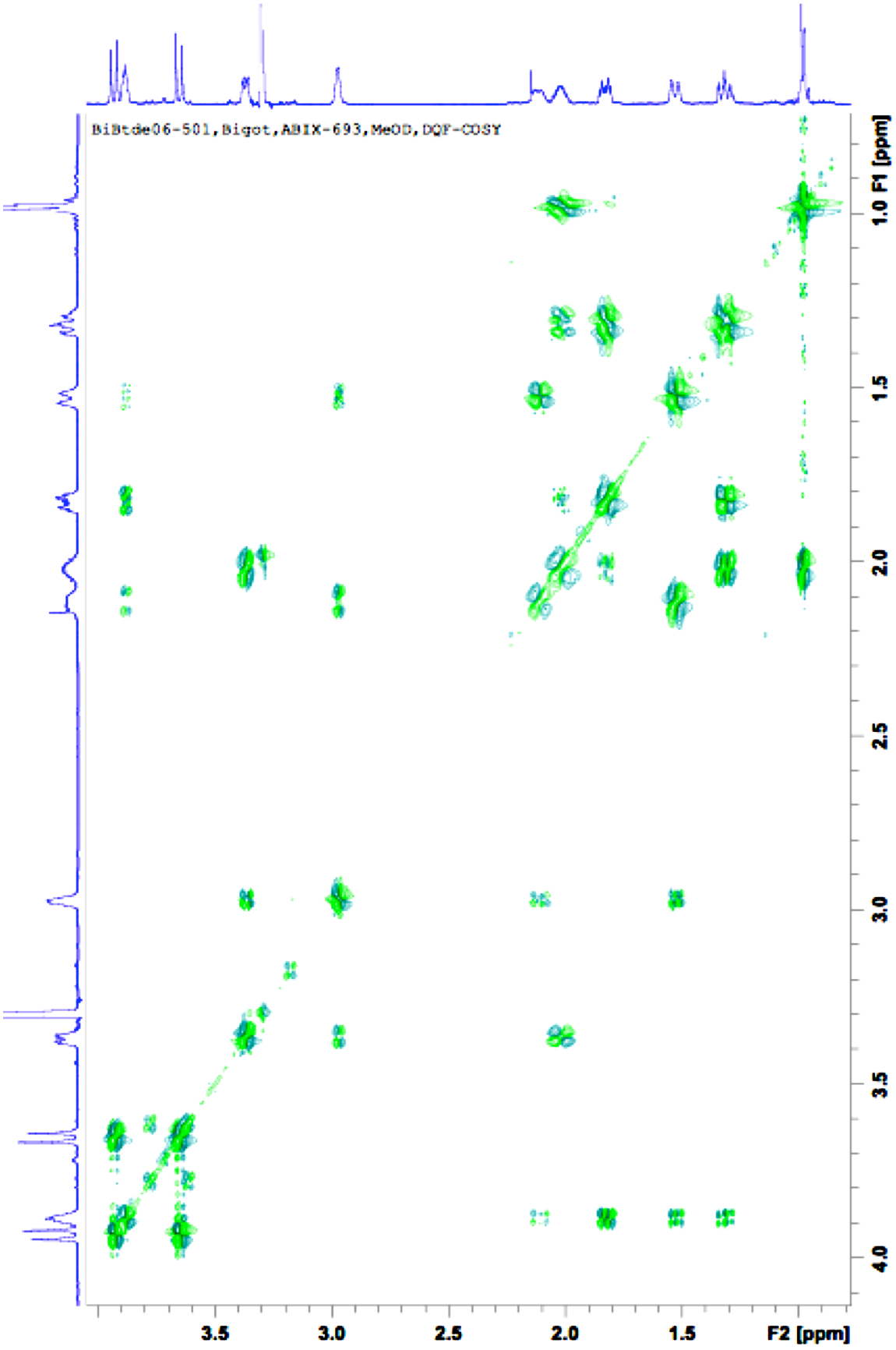
Cosy spectrum of **7**




Me
OH
OH
NHBn
8
500 MHz, 1H-NMR
ppm
7
6,5
6
5,5
5
4,5
4
3,5
3
2,5
2
1,5
1

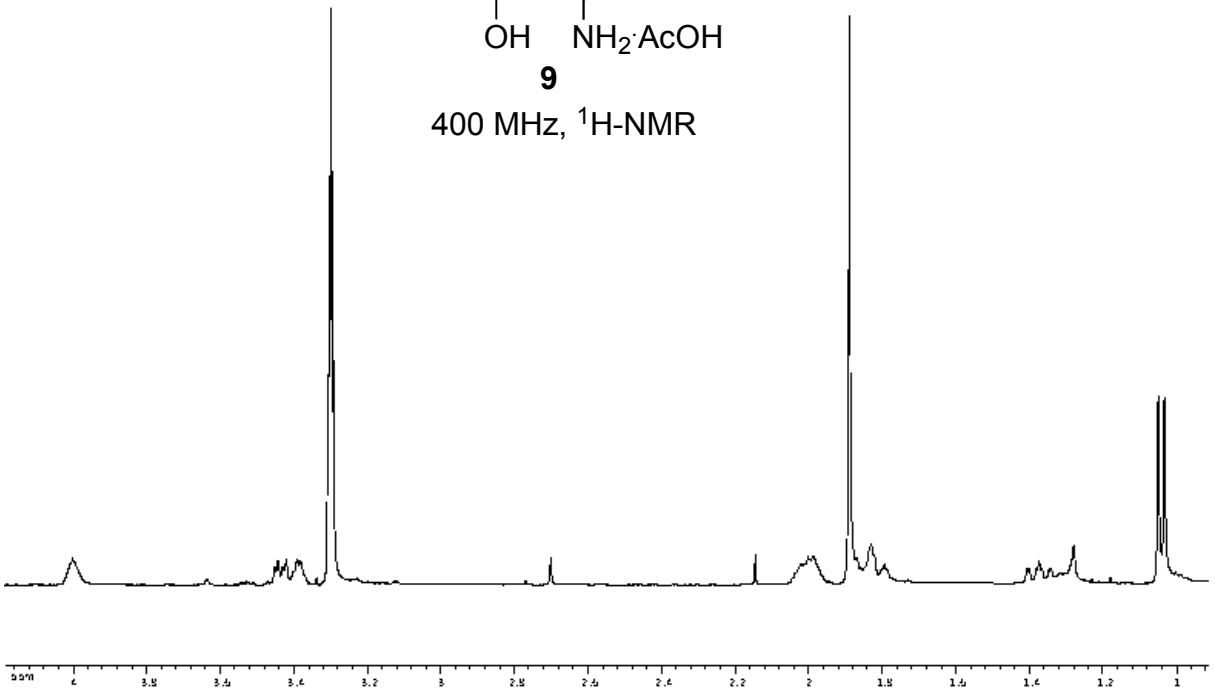

Me
OH
OH
NHBn
8
100 MHz, 13C-NMR
ppm
140
130
120
110
100
90
80
70
60
50
40
30
20
10

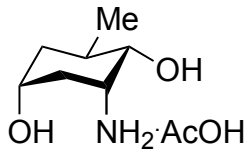
Cosy spectrum of **8**



9

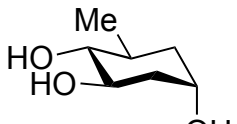
400 MHz, ^{1}H-NMR





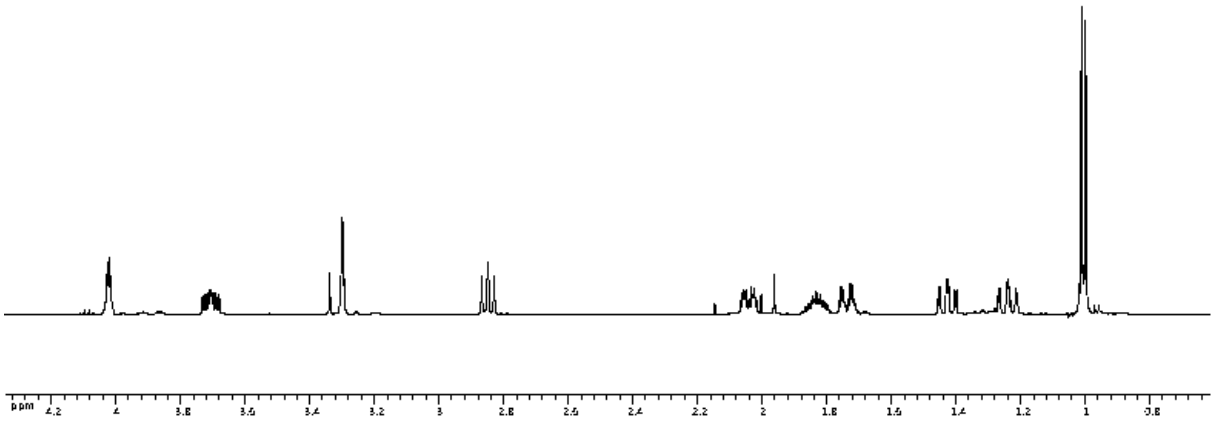
9

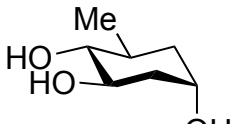
100 MHz, ^{13}C-NMR



10

500 MHz, ^{1}H-NMR

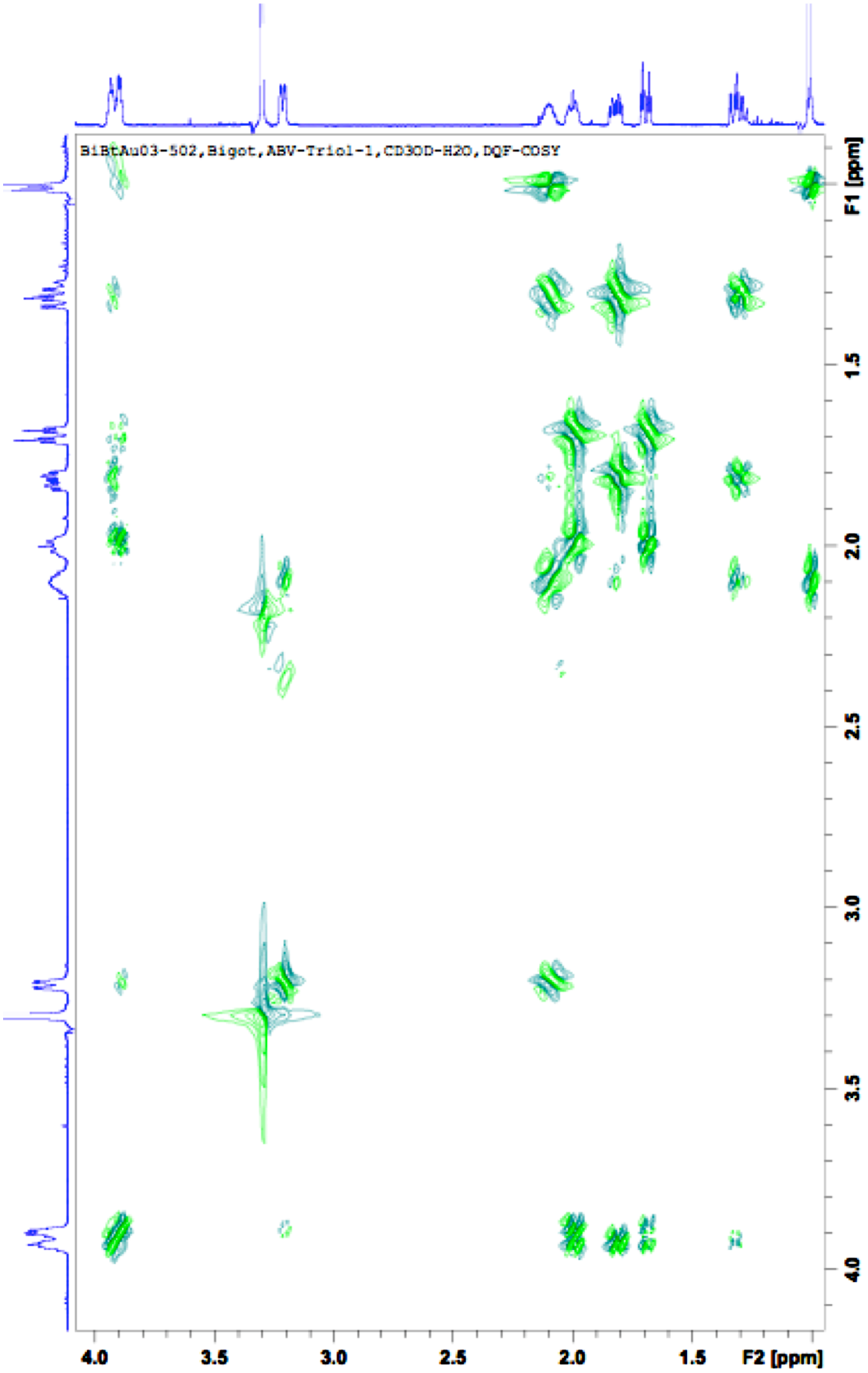


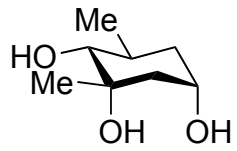


10

125 MHz, ^{13}C-NMR

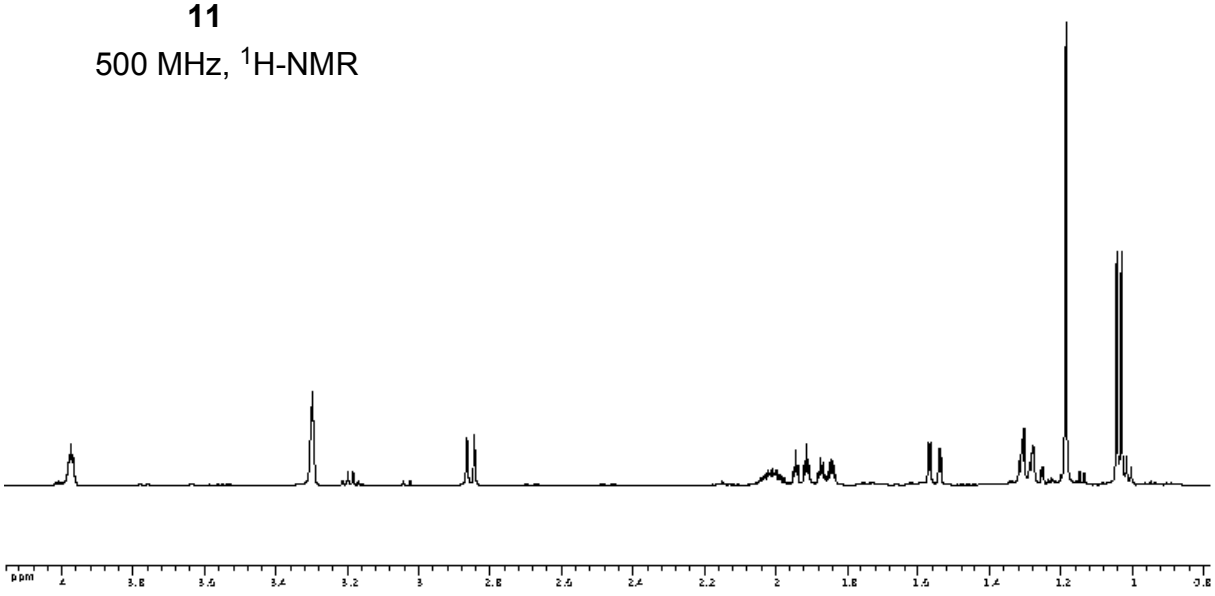
Cosy spectrum of **10**

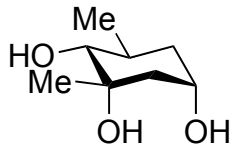




11

500 MHz, ^{1}H-NMR

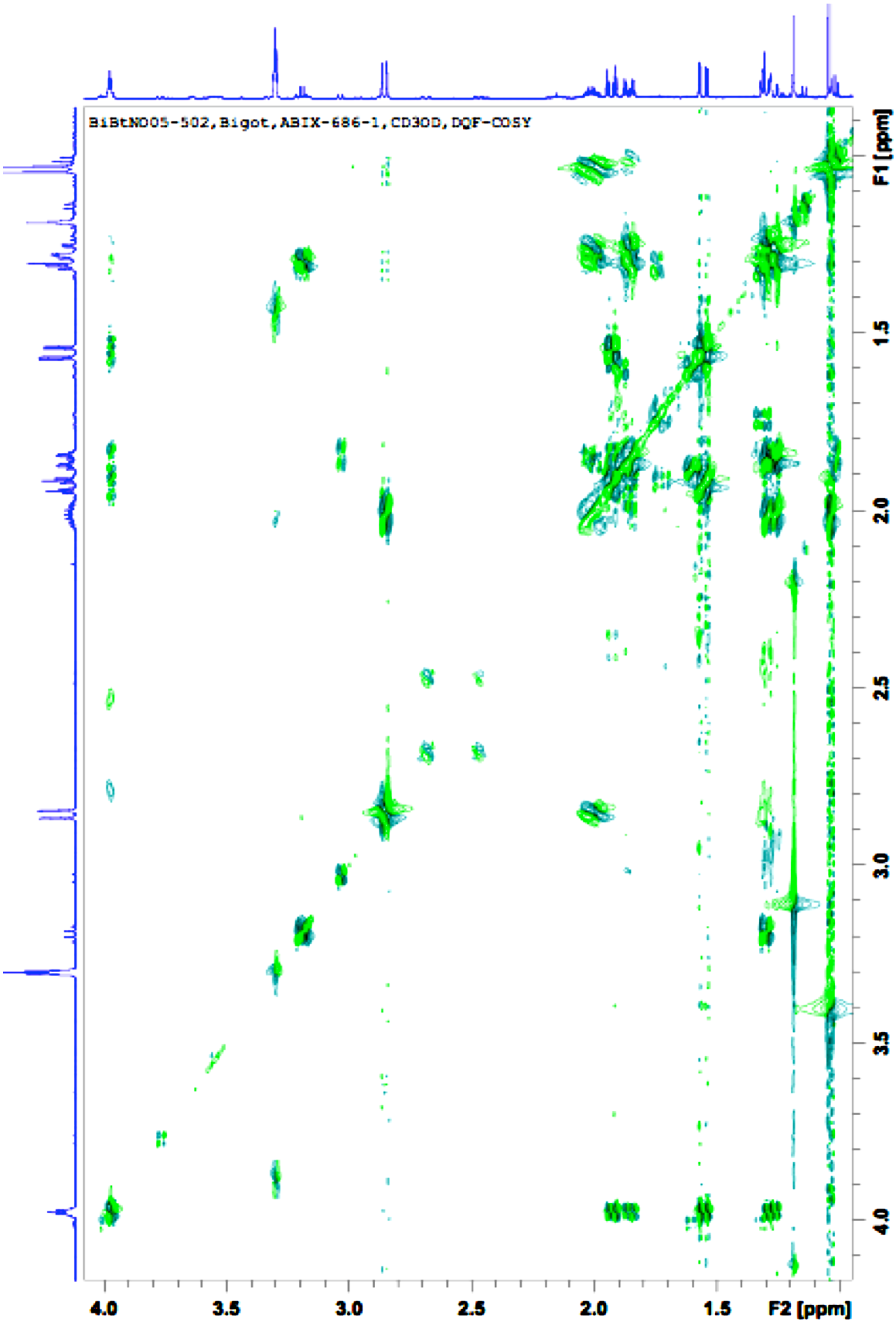




11

125 MHz, ^{13}C-NMR

Cosy spectrum of **11**



Roesy spectrum of **11**