# An Efficient Synthesis Strategy to the Core Structure of 6–5–6–5–6-membered Epipolythiodiketopiperazines

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## 1. Materials and Methods

**Solvents and reagents:** All commercial chemicals and solvents were purchased from ABCR, ACROS, ALFA-AESAR, COMBI-BLOCKS, FLUKA, FLUOROCHEM, MERCK,SIGMA-ALDRICH or TCI and used without further purification with the following exceptions: Deuterated solvents for NMR spectroscopy were obtained from ARMAR CHEMICALS, Döttingen, Switzerland. THF and $CH_2Cl_2$ were dried using an LC TECHNOLOGY SOLUTIONS *SP-1* solvent purification system under an atmosphere of dry $N_2$. $NEt_3$ and furan were distilled form $CaH_2$ under an atmosphere of dry $N_2$. MeOH was distilled from magnesium turnings under an atmosphere of dry $N_2$.

**Reaction handling:** All non-aqueous reactions were performed in flame-dried glassware under a positive pressure of dry $N_2$ unless otherwise stated. Reactions were magnetically stirred and monitored by thin layer chromatography (TLC). TLC was performed on MERCK silica gel 60 $F_{254}$ TLC glass plates and visualized with UV fluorescence quenching at 254 nm and 366 nm and by $KMnO_4$ or ceric ammonium nitrate (CAN) stain. Solvent evaporation under reduced pressure was performed by rotary evaporation at 40°C at the appropriate pressure. Column chromatographic purification was performed as flash column chromatography with 0.3–0.5 bar of overpressure using FLUKA silica gel (230–400 mesh, 60 Å) as stationary phase.[1] Distilled technical grade solvents were employed. The yields refer to chromatographically purified compounds, unless stated otherwise.

**NMR spectroscopy:** NMR data was recorded on BRUKER *Ascend* (400 MHz), BRUKER *AV* (400 MHz, 500 MHz, 600 MHz) or BRUKER *DRX* (400 MHz, 500 MHz, 600 MHz) spectrometers. Measurements were carried out at 25°C. Chemical shifts (δ) are reported in ppm with the residual solvent signal as internal standard (chloroform at 7.26 and 77.16, dichloromethane at 5.32 and 54.00 and methanol at 3.31 and 49.00, tetrahydrofuran at 3.58 and 67.57 ppm for $^{1}H$ and $^{13}C$ spectroscopy, respectively), unless otherwise noted. The data is reported as (s = singlet, d = doublet, t= triplet, m = multiplet or unresolved, br = broad signal, coupling constant(s) *J* in Hz, integration). $^{13}C$ NMR spectra were recorded with complete $^{1}H$-decoupling. Service measurements were performed by the NMR service team of the LABORATORIUM FÜR ORGANISCHE CHEMIE at ETH ZÜRICH by PHILIPP ZUMBRUNNEN, RAINER FRANKENSTEIN and RENÉ ARNOLD under direction of Dr. MARC-OLIVIER EBERT.

**IR spectroscopy:** Infrared spectra were recorded on a PERKIN ELMER Spectrum *TWO FT-IR (UATR)* instrument as thin films. Absorptions are given in wavenumbers ($cm^{-1}$).

[1] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923-2925.

**Mass spectrometry:** Mass spectrometric analyses were performed as high resolution ESI measurements on a BRUKER DALTONICS *maXis ESI-QTOF* instrument or as high resolution EI measurements on a WATERS MICROMASS *AutoSpec Ultima* instrument or as high resolution MALDI measurements on a BRUKER DALTONICS *solariX* instrument by the mass spectrometry service of the LABORATORIUM FÜR ORGANISCHE CHEMIE at ETH ZÜRICH by LOUIS BERTSCHI, ROLF HÄFLIGER, OSWALD GRETER under direction of Dr. XIANGYANG ZHANG.

**Elemental analysis:** Microanalyses were obtained using a LECO *TrueSpec Micro* (C, H) and a LECO *RO-478* (O) instrument. For determination of Br, the sample was first oxidized by the SCHÖNINGER method[2] and then analyzed by ion chromatography on a METROHM *761 Compact IC*. The measurements were performed by the microanalysis service of the LABORATORIUM FÜR ORGANISCHE CHEMIE at ETH ZÜRICH by MICHAEL SCHNEIDER.

**Optical rotations:** Optical rotations were measured on a JASCO *DIP-2000* polarimeter at the indicated wavelength with 100 mm path length cell. Concentrations are given in g/100 mL in the indicated solvent.

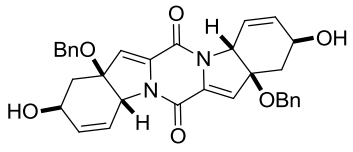
**Melting point:** Melting points were determined using a BÜCHI *SMP-20* instrument in an open capillary and are uncorrected.

**SFC:** Enantiomeric excesses were determined by chiral analytical chromatography on a JASCO *2080Plus* supercritical fluid chromatography (SFC) apparatus. Utilized columns and conditions are specified, retention times ($t_R$) are given in minutes.

**X-Ray Diffraction:** Single crystal X-ray diffraction analyses were performed on a BRUKER *ApexII Duo* or on a BRUKER *Kappa ApexII* apparatus by Dr. MICHAEL WÖRLE, Dr. NILS TRAPP and MICHAEL SOLAR of the SMALL MOLECULE CRYSTALLOGRAPHY CENTER at ETH ZÜRICH.

[2] (a) Schöninger, W. *Microchim. Acta* **1955**, *43*, 123–129; (b) Schöninger, W. *Microchim. Acta* **1956**, *44*, 869–876.

## 2. Experimental Procedures



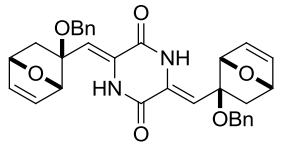

**1**
$C_{32}H_{30}N_2O_6$
538.59

**(2*S*,4a*R*,7a*S*,9*S*,11a*R*,14a*S*)-7a,14a-bis(benzyloxy)-2,9-dihydroxy-1,7a,8,9,11a,14a-hexahydropyrazino[1,2-a:4,5-a']diindole-6,13(2H,4aH)-dione (1):** A solution of *bis*(alkylidene)diketopiperazine **2** (7.50 g, 13.9 mmol, 1.00 equiv.) and 2,6-lutidine (12.4 mL, 111 mmol, 8.00 equiv.) in $CH_2Cl_2$ (150 mL) was cooled to 0 °C and $Me_3SiOTf$ (15.1 mL, 84.0 mmol, 6.00 equiv.) was added dropwise. After 30 min, the reaction was warmed to ambient temperature and stirred overnight. Methanol (5.63 mL, 139 mmol, 10.0 equiv.) was added dropwise at 0 °C and then the reaction was poured onto satd. aq. $NaHCO_3$ solution (200 mL). The organic layer was separated and the aqueous layer was extracted with $CH_2Cl_2$ (3 x 100 mL). The combined organic layers were dried over $Na_2SO_4$ and the solvent was evaporated to furnish the *bis*(silyl ether) **20**. The residue was dissolved in MeOH–THF (4:1, 200 mL) and $K_2CO_3$ (15.4 g, 111 mmol, 8.00 equiv.) was added. After 30 min of vigorous stirring, the reaction was poured onto a mixture of $H_2O$ (100 mL) satd. aq. $NaHCO_3$ solution (100 mL) and $CH_2Cl_2$ (200 mL). The organic layer was separated and the aqueous layer was extracted with $CH_2Cl_2$ (3 x 200 mL). The combined organic layers were dried over $Na_2SO_4$, filtered and the solvent was removed under reduced pressure. Flash column chromatography (3:7→7:3→0:1 $CH_2Cl_2$:AcOEt) yielded the product as a yellow powder. AcOEt (100 mL) was added and the suspension was stirred for 30 min. Filtration yielded *bis*(alkylidene)diketopiperazine **1** (5.77 g, 77%) as a slightly yellow powder. Samples of the enantiomer of **1** (*ent*-**1**)suitable for single crystal X-ray diffraction were obtained by crystallization from $CH_2Cl_2$.[3]

**TLC:** $R_f$ = 0.31 (AcOEt), $KMnO_4$, 254 nm and 366 nm; **$^1$H-NMR** (400 MHz, THF-$D_8$): δ 7.33 – 7.11 (m, 10H), 6.17 (s, 2H), 5.94 (d, *J* = 3.2 Hz, 4H), 4.89 (d, *J* = 2.6 Hz, 2H), 4.53 (d, *J* = 11.2 Hz, 2H), 4.44 (d, *J* = 11.2 Hz, 2H), 4.22 (d, *J* = 6.0 Hz, 2H), 4.10 (dt, *J* = 10.7, 5.3 Hz, 2H), 2.61 (dd, *J* = 12.2, 4.9 Hz, 2H), 1.84 (dd, *J* = 12.2, 10.8 Hz, 2H); **$^{13}$C NMR** (100 MHz, THF-$D_8$) δ 152.2, 140.1, 139.7, 138.4, 129.0, 128.4, 128.1, 122.2, 118.5, 84.4, 65.7, 65.6, 62.7, 40.7; **IR** (thin film): 3419, 2867, 1683, 1636, 1418, 1336, 1083, 1050, 896, 851, 776, 670, 746 $cm^{-1}$; **HRMS** (ESI): *m/z* calculated for $C_{32}H_{30}N_2NaO_6$

[3] The enantiomer of **1** (e*nt*-**1**) was obtained as described for the preparation of **1**, with the exception that the enantiomer of **18** was used as catalyst precursor in the initial Diels-Alder reaction between 2-bromoacrolein (**11**) and furan.

[(M + $Na^+$)] 561.1996; found 561.1997; **Optical rotation** $[\alpha]^{22}_D$ (c = 0.500, THF): +119; **Mp:** 146 °C (decomposition).




**2**

$C_{32}H_{30}N_2O_6$

538.59

**(3*Z*,6*Z*)-3,6-bis(((1*S*,2*S*,4*S*)-2-(benzyloxy)-7-oxabicyclo[2.2.1]hept-5-en-2-yl)methylene)piperazine-2,5-dione (2).**

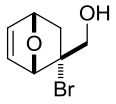
**Method A:** $(COCl)_2$ (8.48 mL, 97.0 mmol, 1.50 equiv.) was dissolved in $CH_2Cl_2$ (400 mL) and cooled to –78 °C. A solution of DMSO (9.17 mL, 129 mmol, 2.00 equiv.) in $CH_2Cl_2$ (75 mL) was added dropwise at a rate that kept the internal temperature below –70 °C. After 5 min, a solution of alcohol **15** (15.0 g, 64.6 mmol, 1.00 equiv.) in $CH_2Cl_2$ (75 mL) was added dropwise at a rate that kept the internal temperature below –70 °C. The turbid reaction mixture was stirred for 45 min and then a solution of DBU (48.7 mL, 323 mmol, 5.00 equiv.) in $CH_2Cl_2$ (50 mL) was added dropwise at a rate that kept the internal temperature below –70 °C. After complete addition, 1,4-diacetylpiperazine-2,5-dione[4] (**4**, 4.86 g, 24.5 mmol, 0.380 equiv.) was added in one portion, followed by a solution of DBU (146 mL, 969 mmol, 15.0 equiv.) in $CH_2Cl_2$ (100 mL). It was warmed to 0 °C and stirred for 48 h. The reaction was poured onto satd. aq. $NH_4Cl$ solution (600 mL) and the organic layer was separated. The aqueous layer was extracted with $CH_2Cl_2$ (4 x 300 mL) and the combined organic layers were dried over $Na_2SO_4$. The solvent was evaporated and the residue was purified by flash column chromatography (4:1 $CH_2Cl_2$:AcOEt) to give the product as a yellow solid. $Et_2O$ (100 mL) was added to the residue and the solid was crushed to a fine powder. Filtration yielded *bis*(alkylidene)diketopiperazine **2**(7.52 g, 57 % (referred to **4**)) as a white powder.

**Method B:** $(COCl)_2$ (67.8 μL, 0.775 mmol, 1.80 equiv.) was dissolved in $CH_2Cl_2$ (7 mL) and cooled to –78 °C. A solution of DMSO (76.4 μL, 1.08 mmol, 2.50 equiv.) in $CH_2Cl_2$ (1 mL) was added dropwise at a rate that kept the internal temperature below –70 °C. After 5 min, a solution of *N*-acetyl diketopiperazine **15** (100 mg, 0.431 mmol, 1.00 equiv.) in $CH_2Cl_2$ (1 mL) was added dropwise at a rate that kept the internal temperature below –70 °C. The turbid reaction mixture was stirred for 45 min and then a solution of DBU (973 μL, 6.46 mmol, 15.0 equiv.) in $CH_2Cl_2$ (1 mL) was added dropwise at a rate

[4] 1,4-diacetylpiperazine-2,5-dione was purchased from TCI or prepared according to Balducci, D.; Conway, P.A.; Sapuppo, G.; Müller-Bunz, H.; Paradisi, F. *Tetrahedron* **2012**, *68*, 7374–7379.

that kept the internal temperature below –70 °C. After complete addition, **16** (127 mg, 0.344 mmol, 0.800 equiv.) was added in one portion and it was warmed to 0 °C and stirred for 48 h. The reaction was poured onto satd. aq. $NH_4Cl$ solution (20 mL) and the organic layer was separated. The aqueous layer was extracted with $CH_2Cl_2$ (4 x 20 mL) and the combined organic layers were dried over $Na_2SO_4$. The solvent was evaporated and the residue was purified by flash column chromatography (4:1 $CH_2Cl_2$:AcOEt) to give the product as a yellow solid. $Et_2O$ (2 mL) was added to the residue and the solid was crushed to a fine powder. Filtration yielded *bis*(alkylidene)diketopiperazine **2** (112 mg, 60 % (referred to **16**)) as a white powder.

**TLC:** $R_f$ = 0.24 (1:1 Hexanes:AcOEt), $KMnO_4$, 254 nm and 366 nm; **$^1$H-NMR** (400 MHz, $CDCl_3$): δ 9.10 (s, 2H), 7.46 – 7.27 (m, 10H), 6.54 (dd, *J* = 5.8, 1.6 Hz, 2H), 6.39 (dd, *J* = 5.8, 1.8 Hz, 2H), 5.73 (s, 2H), 5.15 (dt, *J* = 4.6, 1.1 Hz, 2H), 5.08 (dd, *J* = 1.7, 0.8 Hz, 2H), 4.58 (d, *J* = 11.4 Hz, 2H), 4.53 (d, *J* = 11.4 Hz, 2H), 2.41 (dd, *J* = 11.9, 4.7 Hz, 2H), 1.68 (d, *J* = 11.9 Hz, 2H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 155.3, 139.9, 137.3, 133.2, 128.8, 128.5, 128.2, 127.9, 118.2, 85.7, 83.6, 78.8, 67.7, 41.4; **IR** (thin film): 3316, 2953, 1694, 1654, 1417, 1338, 1313, 1221, 1065, 1022, 918, 746, 699, 466 $cm^{-1}$; **HRMS** (ESI): *m/z* calculated for $C_{32}H_{30}N_2NaO_6$ [(M + $Na^+$)] 561.1996; found 561.1991; **Optical rotation** $[\alpha]^{23}_D$ (c = 0.500, THF): –109; **Mp:** 112 °C (decomposition).




**13**
$C_7H_9BrO_2$
205.05

**((1*S*,2*R*,4*S*)-2-bromo-7-oxabicyclo[2.2.1]hept-5-en-2-yl)methanol (13):**[5] Ligand precursor **18** (9.66 g, 25.9 mmol, 7.00 mol%) was suspended in $CH_2Cl_2$ (120 mL) and *n*-$BuBCl_2$[6] (3.34 g, 24.1 mmol, 6.50 mol%) was added dropwise at 0 °C. After complete addition, the reaction mixture was stirred at ambient temperature for 1 h. The solvent was completely removed under high vacuum and the off-white catalyst **16**[7] was dissolved in $CH_2Cl_2$ (300 mL). The reaction mixture was cooled to –78 °C and furan

[5] Compound was prepared according to a modified procedure of Corey, E.J.; Loh, T.-P. *Tetrahedron Lett.* **1993**, *34*, 3979–3982.

[6] *n*-$BuBCl_2$ was prepared according to Brown, H.C.; Levy, A.B. *J. Organomet. Chem.* **1972**, *44*, 233–236. *n*-$BuBCl_2$ (**$^1$H NMR** (500 MHz, $CD_2Cl_2$): δ 1.61 – 1.54 (m, 4H), 1.40 – 1.30 (m, 2H), 0.92 (t, J = 7.4 Hz, 3H); **$^{13}$C NMR** (125 MHz, $CD_2Cl_2$): δ 30.3 (br), 27.7, 25.3, 14.1; **$^{11}$B NMR** (160 MHz, $CD_2Cl_2$): δ 63.3 (br s)) was obtained as a clear liquid that was extremely pyrophoric. Care should be taken while handling this compound.

[7] **$^1$H NMR** (400 MHz, $CD_2Cl_2$): δ 8.29 (br s, 1H), 7.85 (d, *J* = 7.9 Hz, 1H), 7.77 (d, *J* = 8.3 Hz, 2H), 7.40 – 7.30 (m, 3H), 7.22 – 7.08 (m, 2H), 7.05 (d, J = 2.5 Hz, 1H), 4.26 (qd, J = 7.5, 3.3 Hz, 1H), 4.18 (d, J = 3.1 Hz, 1H), 2.43 (s, 3H), 1.68 (d, J = 7.5 Hz, 3H), 1.10 – 0.93 (m, 2H), 0.87 – 0.72 (m, 4H), 0.65 – 0.58 (m, 3H); **$^{13}$C NMR** (100 MHz,

(156 mL, 2.15 mol, 5.00 equiv.) was added dropwise. After 10 min., 2-bromoacrolein[8] (**11**, 50.0 g, 370 mmol, 1.00 equiv.) was added dropwise and the reaction was stirred at –78 °C for 5 h.

$NaBH_4$ (28.0 g, 741 mmol) was added portion wise to THF–Water (5:1, 600 mL) at 0 °C. After the hydrogen evolution settled, the –78 °C cold reaction mixture was transferred to this solution by cannula within 5 min under vigorous stirring. After another 10 minutes, satd. aq. $NH_4Cl$ solution (500 mL) was added dropwise at 0 °C and the reaction mixture was stirred until gas evolution ceased. 2 N HCl (500 mL) was added carefully at 0 °C followed by AcOEt (500 mL). The layers were separated and the aqueous layer was extracted with AcOEt (3 x 250 mL). The combined organic layers were washed with 2 N HCl (250 mL) and brine (250 mL), dried over $Na_2SO_4$, filtered and evaporated. The residue was purified by flash column chromatography (3:1 Hexanes:AcOEt) to yield **13** 85% *ee* (determined by its benzoate **13b**). The product was dissolved in a minimum of refluxing $Et_2O$–pentane (1:1) and the mixture was then cooled to ambient temperature. Pentane was added dropwise until the solution turned cloudy and the mixture was then kept at –20 °C over night. Filtration yielded a first crop of crystals and from the mother liquor another two crops of crystals could be obtained in the same way to yield alcohol **13** (45.5 g, 60%, 98% *ee* as determined by its benzoate **13b**). Samples of this compound suitable for single crystal X-ray diffraction were obtained by crystallization from $Et_2O$-pentane.

**TLC:** $R_f$ = 0.33 (2:1 Hexanes:AcOEt), $KMnO_4$, not UV active; **$^1$H-NMR** (400 MHz, $CDCl_3$): δ 6.50 (dd, *J* = 5.9, 1.7 Hz, 1H), 6.45 (dd, *J* = 6.0, 1.7 Hz, 1H), 5.03 – 5.00 (m, 2H), 3.85 (dd, *J* = 12.1, 5.2 Hz, 1H), 3.78 (dd, *J* = 12.1, 8.7 Hz, 1H), 2.31 (dd, *J* = 8.7, 5.2 Hz, 1H), 2.09 (dd, *J* = 12.7, 4.7 Hz, 1H), 1.73 (d, *J* = 12.8 Hz, 1H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 136.2, 135.4, 81.8, 79.4, 70.7, 67.6, 39.0; **IR** (thin film): 3273, 3007, 2937, 1450, 1441, 1362, 1262, 1181, 1089, 1045, 1002, 930, 863, 782, 719, 704, 613, 538 $cm^{-1}$; **Elemental Analysis**: calculated for $C_7H_9BrO_2$ 41.00% C, 4.42% H, 15.61% O, 38.97% Br; found 41.07% C, 4.33% H, 15.54% O, 38.81% Br; **Optical Rotation** $[\alpha]^{23}_D$ (c = 1.00, $CHCl_3$): –25.1; **Mp:** 63 °C.

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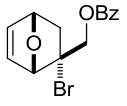
$CD_2Cl_2$): δ 172.5, 145.7, 137.3, 136.5, 130.8, 127.7, 127.4, 123.2, 122.7, 120.7, 120.2, 114.0, 111.6, 66.9, 34.6, 25.5, 25.2, 21.9, 17.5, 14.0, 12.8 (br s). NMR data is in agreement with those reported in the literature[5].

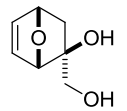
[8] Compound was prepared according to Nicolaou, K.C.; Brenzovich, W.E.; Bulgera, P.G.; Francisa, T.M. *Org. Biomol. Chem.* **2006**, *4*, 2119–2157. 2-Bromoacrolein (**11**) can be stored at –78 °C, but it is best used directly after its preparation.



**13b**
$C_{14}H_{13}BrO_3$
309.16

**((1*S*,2*R*,4*S*)-2-bromo-7-oxabicyclo[2.2.1]hept-5-en-2-yl)methyl benzoate (13b):** To a solution of alcohol **13** (320 mg, 1.56 mmol, 1.00 equiv.) in $CH_2Cl_2$ (5 mL) was added $NEt_3$ (653 μL, 4.68 mmol, 3.00 equiv.) followed by BzCl (362 μL, 3.12 mmol, 2.00 equiv.) and DMAP (38.1 mg, 0.312 mmol, 20.0 mol%). After 12 h at ambient temperature, 2 N HCl (5 mL) was added, the layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (1 x 5 mL). The combined organic layers were dried over $Na_2SO_4$, filtered and the solvent was evaporated. The residue was purified by flash column chromatography (9:1→4:1 Pentane:$Et_2O$) to yield benzoate **13b** (423 mg, 88%) as a colorless oil that solidified slowly in the freezer.

**TLC:** $R_f$ = 0.36 (4:1 Hexanes:$Et_2O$), $KMnO_4$, 254 nm, **$^1$H-NMR** (400 MHz, $CDCl_3$): δ 8.16 – 8.09 (m, 2H), 7.63 – 7.56 (m, 1H), 7.52 – 7.43 (m, 2H), 6.53 (dd, *J* = 5.8, 1.6 Hz, 1H), 6.50 (dd, *J* = 5.8, 1.6 Hz, 1H), 5.10 (d, *J* = 1.5 Hz, 1H), 5.08 – 5.05 (m, 1H), 4.72 (d, *J* = 11.9 Hz, 1H), 4.53 (d, *J* = 2.0 Hz, 1H), 2.21 (dd, *J* = 12.7, 4.7 Hz, 1H), 1.83 (d, *J* = 12.7 Hz, 1H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 166.0, 136.2, 135.3, 133.4, 129.9, 128.6, 82.1, 79.5, 71.5, 60.4, 39.9; **IR** (thin film): 3010, 1723, 1602, 1451, 1372, 1316, 1272, 1178, 1112, 1071, 1013, 1028, 709 $cm^{-1}$; **HRMS** (ESI): *m/z* calculated for $C_{14}H_{14}{}^{79}BrO_3$ [(M + $H^+$)] 309.0121; found 309.0125; **Optical rotation** $[\alpha]^{23}_D$ (c = 1.00, $CHCl_3$): –33.3; **Mp:** 45 °C; **SFC** (DAICEL *Chiralpak IB*; 1% *i*-PrOH in $CO_2$; 100 bar; 2.0 mL/min; 25 °C): major enantiomer $t_R$ = 13.5 min, minor enantiomer $t_R$ = 15.3 min, 98% *ee*.

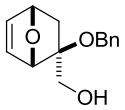


**14**
$C_7H_{10}O_3$
142.15

**(1*S*,2*S*,4*S*)-2-(hydroxymethyl)-7-oxabicyclo[2.2.1]hept-5-en-2-ol (14):**[5] $K_2CO_3$ (53.9 g, 390 mmol, 2.00 equiv.), alcohol **13** (40.0 g, 195 mmol, 1.00 equiv.) and 18-Crown-6 (1.03 g, 3.90 mmol, 2.00 mol%) were dissolved in dioxane–water (1:1, 520 mL) and heated to reflux for 20 h. The reaction was cooled to ambient temperature and most of the solvent was removed under reduced pressure. The residue was lyophilized to complete dryness and the solid residue was washed with AcOEt until no product was detected by TLC in the washing any more. The filtrate was dried over $Na_2SO_4$, evaporated and the residue

was purified by flash column chromatography (9:1→5:1 $CH_2Cl_2$:MeOH). To the yellow crystalline product was added $Et_2O$ (100 mL) and the solid was crushed to a fine powder. It was filtered and the filter cake was washed with $Et_2O$ (50 mL). The white solid was dried under vacuum to yield the diol **14** (22.9 g, 83%).

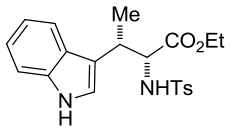
**TLC:** $R_f$ = 0.45 (9:1 $CH_2Cl_2$:MeOH), $KMnO_4$, not UV active; **$^1$H-NMR** (400 MHz, $CDCl_3$): δ 6.42 – 6.37 (m, 2H), 5.02 (dd, *J* = 4.6, 1.3 Hz, 1H), 4.71 (d, *J* = 1.3 Hz, 1H), 3.66 (dd, *J* = 11.5, 4.2 Hz, 1H), 3.49 (s, 1H), 3.32 (dd, *J* = 11.5, 7.6 Hz, 1H), 3.16 (dd, *J* = 7.8, 4.4 Hz, 1H), 1.77 (dd, *J* = 12.3, 4.8 Hz, 1H), 1.36 (d, *J* = 12.3 Hz, 1H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 138.1, 133.2, 85.7, 81.5, 78.3, 67.6, 38.9; **IR** (thin film): 3380, 3312, 3002, 2962, 1402, 1371, 1314, 1175, 1091, 1024, 1007, 912, 720, 670 $cm^{-1}$; **HRMS** (ESI): *m/z* calculated for $C_7H_{10}NaO_3$ [(M + $Na^+$)] 165.0522; found 165.0530; Optical rotation $[\alpha]^{22}_D$ (c = 1.00, $CHCl_3$): –22.7; **Mp:** 84 °C.




**15**
$C_{14}H_{16}O_3$
232.28

**((1*S*,2*S*,4*S*)-2-(benzyloxy)-7-oxabicyclo[2.2.1]hept-5-en-2-yl)methanol (15):** Diol **14** (18.0 g, 127 mmol, 1.00 equiv.) was dissolved in $CH_2Cl_2$ (150 mL) and benzaldehyde dimethyl acetal (19.0 mL, 127 mmol, 1.00 equiv.), followed by CSA (735 mg, 3.17 mmol, 2.50 mol%) were added. After 1 h at ambient temperature, the reaction was evaporated. The residue was dissolved in $CH_2Cl_2$ (150 mL), benzaldehyde dimethyl acetal (9.50 mL, 63.3 mmol, 0.50 equiv.) was added and the reaction was stirred at ambient temperature for 30 min. $NEt_3$ (529 μL, 3.80 mmol, 3.00 mol%) was added and the reaction mixture was evaporated. The residue was dried under high vacuum for 30 min, dissolved in $CH_2Cl_2$ (300 mL) and the solution was cooled to 0 °C. DIBAL-H (1.0 M in $CH_2Cl_2$, 317 mL, 317 mmol, 2.50 equiv.) was added dropwise and the reaction was stirred for 4 h at 0 °C. MeOH (103 mL, 2.54 mol, 20.0 equiv.) was added dropwise at 0 °C and after the gas evolution ceased, the reaction was carefully poured onto a mixture of satd. aq. Rochelle's salt solution (500 mL), ice (500 g) and AcOEt (500 mL) and stirred overnight. The organic layer was separated and the aqueous layer was extracted with AcOEt (3 x 300 mL). The combined organic layers were dried over $Na_2SO_4$ and the solvent was evaporated. The residue was purified by flash column chromatography (2:1→4:1 $Et_2O$:Pentane) to yield the product as a yellow solid. Hexanes (150 mL) were added to the residue and the solid was carefully crushed to a fine powder. The slurry was filtered and the filter cake was washed with Hexanes (150 mL) to yield the alcohol **15** (22.5 g, 76%) as a white powder.

**TLC:** $R_f$ = 0.32 (4:1 $Et_2O$:Pentane), $KMnO_4$, 254 nm; **$^1$H-NMR** (400 MHz, $CDCl_3$): δ 7.42 – 7.24 (m, 5H), 6.49 (dd, *J* = 5.9, 1.8 Hz, 1H), 6.46 (dd, *J* = 5.8, 1.6 Hz, 1H), 5.09 (dt, *J* = 4.8, 1.3 Hz, 1H), 4.95 (t, *J* = 1.4 Hz, 1H), 4.64 (s, 2H), 3.80 (dd, *J* = 11.9, 3.7 Hz, 1H), 3.34 (dd, *J* = 11.9, 8.9 Hz, 1H), 2.17 (dd, *J* = 9.0, 3.7 Hz, 1H), 2.08 (dd, *J* = 12.3, 4.8 Hz, 1H), 1.22 (d, *J* = 12.3 Hz, 1H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 139.0, 138.6, 134.2, 128.6, 127.7, 127.5, 87.5, 83.7, 78.4, 66.8, 66.4, 33.3; **IR** (thin film): 3290, 3076, 3009, 2944, 1497, 1453, 1372, 1318, 1192, 1133, 1099, 1048, 1007, 916, 892, 732, 697 $cm^{-1}$; **HRMS** (ESI): *m/z* calculated for $C_{14}H_{16}NaO_3$ [(M + $Na^+$)] 255.0992; found 255.0996; **Optical rotation** $[\alpha]^{22}_D$ (c = 1.00, $CHCl_3$): –14.1; **Mp:** 64 °C.



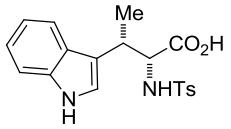

**18-Ethyl ester**
$C_{21}H_{24}N_2O_4S$
400.49

**(2*R*,3*S*)-ethyl 3-(1H-indol-3-yl)-2-(4-methylphenylsulfonamido)butanoate (18-Ethyl ester):** A solution of $NEt_3$ (72.0 mL, 517 mmol, 3.00 equiv.) in $CH_2Cl_2$ (400 mL) was cooled to 0 °C, then ethyl (2*R*,3*S*)-2-amino-3-(1H-indol-3-yl)butanoate methanesulfonate salt[9] (**17**, 59.0 g, 172 mmol, 1.00 equiv.) was added in portions over 10 min. DMAP (0.421 g, 3.45 mmol, 2.00 mol%) was added, followed by dropwise addition of a solution of *p*-TsCl (33.5 g, 172 mmol, 1.00 equiv.) in $CH_2Cl_2$ (150 mL). After complete addition, the reaction mixture was warmed to ambient temperature and stirred for 3 h. 2 N HCl (300 mL) was added and the layers were separated. The aqueous layer was extracted with $Et_2O$ (2 x 250 mL). The combined organic layers were washed with 1 N HCl (300 mL), water (300 mL) and brine (300 mL) and dried over $Na_2SO_4$. The solvent was evaporated and the residue was recrystallized from hot EtOH (180 mL) to yield ester **18-**ethyl ester (60.9 g, 88%) as a white powder. Samples of this compound suitable for single crystal X-ray diffraction were obtained by crystallization from $CDCl_3$.

**TLC:** $R_f$ = 0.55 (1:1 Hexanes:AcOEt), $KMnO_4$, 254 nm and 366 nm; **$^1$H-NMR** (400 MHz, $CDCl_3$): δ 8.10 (s, 1H), 7.55 – 7.49 (m, 3H), 7.31 – 7.26 (m, 1H), 7.18 – 7.13 (m, 1H), 7.11 – 7.00 (m, 4H), 5.23 (d, *J* = 10.0 Hz, 1H), 4.13 (dd, *J* = 9.9, 5.7 Hz, 1H), 3.75 (qd, *J* = 7.2, 1.7 Hz, 2H), 3.50 (dt, *J* = 12.9, 7.0 Hz, 1H), 2.32 (s, 3H), 1.41 (d, *J* = 7.1 Hz, 3H), 0.90 (t, *J* = 7.1 Hz, 3H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 171.3, 143.4, 136.4, 136.2, 129.4, 127.2, 126.5, 122.1, 119.5, 118.8, 115.8, 111.3, 61.5, 60.8, 34.5, 21.6, 16.3, 13.8; **IR** (thin film): 3403, 3277, 2936, 1730, 1598, 1458, 1337, 1194, 1159, 1122, 1091,

[9] Ethyl (2R,3S)-2-amino-3-(1H-indol-3-yl)butanoate methanesulfonate salt (**17**) was prepared according to Sawai, Y.; Mizuno, M.; Ito T.; Kawakami, J.-I.; Yamano, M. *Tetrahedron* **2009**, *65*, 7122–7128.

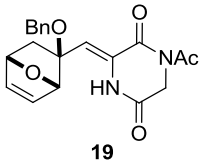
1022, 921, 813, 742, 665, 554 $cm^{-1}$; **HRMS** (ESI): *m/z* calculated for $C_{21}H_{25}N_2O_4S$ [(M + $H^+$)] 401.1530; found 401.1532; **Optical rotation** $[\alpha]^{25}_D$ (c = 1.0, $CHCl_3$): –7.2; **Mp:** 141 °C. **SFC** (DAICEL *Chiralcel OJ-H*; 15% *i*-PrOH in $CO_2$; 100 bar; 2.0 mL/min; 25 °C): major enantiomer: $t_R$ = 13.5 min, minor enantiomer $t_R$ = 16.9 min, >99.5% *ee*.




**18**
$C_{19}H_{20}N_2O_4S$
372.44

**(2*R*,3*S*)-3-(1H-indol-3-yl)-2-(4-methylphenylsulfonamido)butanoic acid (18):** To a solution of **18-Ethyl ester** (59.0 g, 147 mmol, 1.00 equiv.) in THF–EtOH (1:1, 400 mL) was added LiOH•$H_2O$ (18.7 g, 442 mmol, 3.00 equiv.) and the resulting reaction mixture was heated to reflux for 14 h. It was cooled to 0 °C and 2 N HCl (300 mL) was added dropwise. AcOEt (300 mL) was added, the organic layer was separated and the aqueous layer was extracted with AcOEt (2 x 300 mL). The combined organic layers were washed with brine (300 mL), dried over $Na_2SO_4$, filtered and the solvent was removed under reduced pressure. Benzene (300 mL) was added to the residue and the slurry was evaporated. This was repeated twice. The residue was then suspended in benzene (200 mL) and warmed to 40 °C. The warm suspension was filtered and the filter cake was washed with benzene (2 x 150 mL). The filter cake was dried under reduced pressure to yield **18** as a benzene solvate. The white solid was suspended in cyclohexane (500 mL) and the solvent was evaporated. This was repeated twice. $CH_2Cl_2$ (500 mL) was added and the solvent was evaporated. This was repeated twice. The residue was dried under high vacuum for 2 days to yield the carboxylic acid **18** (51.7 g, 94%) as a white solid.

**TLC:** $R_f$ = 0.50 (4:1 $CH_2Cl_2$:MeOH), $KMnO_4$, 254 nm; **$^1$H-NMR** (400 MHz, $CD_3OD$): δ 7.47 – 7.39 (m, 1H), 7.38 – 7.30 (m, 2H), 7.29 – 7.21 (m, 1H), 7.08 – 7.01 (m, 1H), 7.00 – 6.96 (m, 3H), 6.96 – 6.90 (m, 1H), 4.12 (d, *J* = 5.5 Hz, 1H), 3.59 – 3.50 (m, 1H), 2.28 (s, 3H), 1.35 (d, *J* = 7.2 Hz, 3H); **$^{13}$C NMR** (100 MHz, $CD_3OD$): δ 174.9, 144.0, 138.5, 138.0, 130.0, 127.6, 127.6, 123.3, 122.1, 119.6, 119.2, 116.5, 112.3, 61.9, 34.8, 21.5, 15.9; **IR** (thin film): 3476, 3390, 1720, 1691, 1459, 1424, 1333, 1170, 1161, 1095, 910, 823, 752, 736, 534 $cm^{-1}$; **HRMS** (ESI): *m/z* calculated for $C_{19}H_{21}N_2O_4S$ [(M + $H^+$)] 373.1217; found 373.1217; **Optical rotation** $[\alpha]^{23}_D$ (c = 1.00, MeOH): +42.7; **Mp** 192 °C.



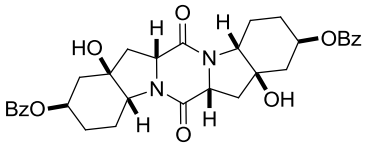

**19**

$C_{20}H_{20}N_2O_5$

368.38

**(*Z*)-1-acetyl-3-(((1*S*,2*S*,4*S*)-2-(benzyloxy)-7-oxabicyclo[2.2.1]hept-5-en-2-yl)methylene)piperazine-2,5-dione (19):** A solution of $(COCl)_2$ (339 µL, 3.87 mmol, 1.50 equiv.) in $CH_2Cl_2$ (15 mL) was cooled to –78 °C and a solution of DMSO (367 µL, 5.17 mmol, 2.00 equiv.) in $CH_2Cl_2$ (1 mL) was added dropwise. After 10 min, a solution of alcohol **15** (600 mg, 2.58 mmol, 1.00 equiv.) in $CH_2Cl_2$ (3 mL) was added dropwise and the solution was stirred for 45 min at –78 °C. A solution of DBU (2.34 mL, 15.5 mmol, 6.00 equiv.) in $CH_2Cl_2$ (2 mL) was added dropwise so that the internal temperature did not rise above –70 °C. After complete addition, solid 1,4-diacetylpiperazine-2,5-dione[4] (**4**, 665 mg, 3.36 mmol, 1.30 equiv.) was added in one portion and the reaction was warmed to 0 °C. After 2 h, the reaction was quenched by addition of satd. aq. $NH_4Cl$ solution (20 mL), the organic layer was separated and the aqueous layer was extracted with $CH_2Cl_2$ (3 x 20 mL). The combined organic layers were dried over $Na_2SO_4$ and the solvent was evaporated. Flash column chromatography (2:1→1:1→1:2 Hexanes:AcOEt) yielded *N*-acetyl diketopiperazine **19** (753 mg, 79%) as a white solid.

**TLC:** $R_f$ = 0.62 (1:2 Hexanes:AcOEt), $KMnO_4$, 254 nm; **$^1$H-NMR** (400 MHz, $CD_2Cl_2$): δ 8.91 (s, 1H), 7.42 – 7.28 (m, 5H), 6.58 (dd, *J* = 5.9, 1.7 Hz, 1H), 6.39 (dd, *J* = 5.9, 1.8 Hz, 1H), 5.91 (s, 1H), 5.13 (dt, *J* = 4.5, 1.2 Hz, 1H), 5.10 – 5.08 (m, 1H), 4.55 (d, *J* = 11.2 Hz, 1H), 4.49 (d, *J* = 11.3 Hz, 1H), 4.42 – 4.30 (m, 2H), 2.56 (s, 3H), 2.40 (dd, *J* = 11.9, 4.7 Hz, 1H), 1.72 (d, *J* = 11.8 Hz, 1H); **$^{13}$C NMR** (100 MHz, $CD_2Cl_2$): δ 173.0, 162.0, 159.5, 140.6, 137.9, 133.4, 129.6, 129.1, 128.6, 128.4, 120.6, 86.0, 83.8, 79.3, 68.0, 46.7, 42.1, 27.6; **IR** (thin film): 3315, 3008, 1700, 1640, 1430, 1368, 1228, 1108, 1065, 1022, 920, 800, 742, 701, 618, 566 cm$^{-1}$; **HRMS** (ESI): *m/z* calculated for $C_{20}H_{20}N_2NaO_5$ [(M + Na$^+$)] 391.1264; found 391.1267; **Optical rotation** $[\alpha]^{23}_D$ (c = 0.500, $CHCl_3$): –52.5; **Mp:** 106 °C (decomposition).



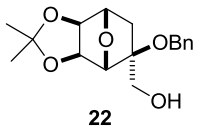
**21**

$C_{32}H_{34}N_2O_8$

574.62

**(2*R*,4a*R*,6a*R*,7a*R*,9*R*,11a*R*,13a*R*,14a*R*)-7a,14a-dihydroxy-6,13-dioxooctadecahydropyrazino[1,2-a:4,5-a']diindole-2,9-diyl dibenzoate (21):** To a solution of diketopiperazine **1** (500 mg, 0.928 mmol, 1.00 equiv.), $NEt_3$ (1.23 mL, 9.28 mmol, 10.0 equiv.) and DMAP (113 mg, 0.928 mmol, 1.00 equiv.) in $CH_2Cl_2$ (10 mL) was added benzoyl chloride (783 mg, 647 μL, 5.57 mmol, 5.00 equiv.) dropwise at 0 °C. After 30 min it was warmed to ambient temperature and stirred for 30 min. Methanol (376 μL, 9.28 mmol, 10.0 equiv.) was added dropwise and the reaction was stirred for 30 min, then it was poured onto satd. aq. $NaHCO_3$ solution (10 mL). The organic layer was separated and the aqueous layer was extracted with $CH_2Cl_2$ (3 x 10 mL). The combined organic layers were dried over $Na_2SO_4$, filtered and the solvent was evaporated. The residue was purified by flash column chromatography (5:1→2:1→1:2 Hexanes:AcOEt) to yield the allylic benzoate as an oil. The crude product was dissolved in AcOEt–MeOH (4:1, 25 mL) and Pd–C (10%, 988 mg, 0.928 mmol, 1.00 equiv.) was added carefully under $N_2$. Hydrogen was purged through the solution for 6 h and then the reaction was stirred under an atmosphere of hydrogen overnight. The reaction mixture was filtered under $N_2$ and the filter cake was rinsed with AcOEt–MeOH (1:1, 25 mL). The filtrate was evaporated and the residue was purified by flash column chromatography (97:3→95:5→90:10 $CH_2Cl_2$:MeOH) to yield the benzoate **21** (227 mg, 43%) as a white powder.

**TLC:** $R_f$ = 0.49 (10:1 $CH_2Cl_2$:MeOH), CAM, 254 nm; **$^1$H-NMR** (400 MHz, $CD_3OD$): δ 8.05 – 7.96 (m, 4H), 7.64 – 7.57 (m, 2H), 7.52 – 7.42 (m, 4H), 5.02 (tt, *J* = 11.4, 4.2 Hz, 2H), 4.70 (dd, *J* = 10.3, 7.1 Hz, 2H), 3.88 – 3.76 (m, 2H), 2.63 – 2.52 (m, 4H), 2.48 (dd, *J* = 13.4, 10.6 Hz, 2H), 2.13 (ddd, *J* = 13.5, 7.3, 1.4 Hz, 2H), 2.10 – 2.03 (m, 2H), 1.91 (dd, *J* = 12.9, 11.6 Hz, 2H), 1.61 (tdd, *J* = 14.5, 12.7, 11.3, 3.4 Hz, 2H), 1.03 (tddd, *J* = 14.2, 11.1, 3.4 Hz, 2H); **$^{13}$C NMR** (100 MHz, $CD_3OD$): δ 170.2, 167.2, 134.3, 131.5, 130.5, 129.6, 78.8, 71.8, 63.9, 60.7, 41.3, 37.2, 29.9, 28.0; **IR** (thin film): 3285, 2947, 2868, 1711, 1651, 1450, 1431, 1314, 1280, 1108, 1070, 1026, 773, 713 cm$^{-1}$; **HRMS** (ESI): *m/z* calculated for $C_{32}H_{35}N_2O_8$ [(M + H$^+$)] 575.2388; found 575.2386; **Optical rotation** $[\alpha]^{23}_D$ (c = 0.476, MeOH): –20.2; **Mp** >240 °C.



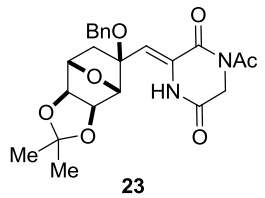
**22**

$C_{17}H_{22}O_5$

306.35

**((3a*S*,4*S*,5*S*,7*S*,7a*S*)-5-(benzyloxy)-2,2-dimethylhexahydro-4,7-epoxybenzo[d][1,3]dioxol-5-yl)methanol (22):** A solution of olefin **15** (1.00 g, 4.31 mmol, 1.00 equiv.), *N*-Methylmorpholine *N*-oxide hydrate (1.01 g, 8.61 mmol, 2.00 equiv.) and $K_2OsO_4$•2 $H_2O$ (79.0 mg, 0.215 mmol, 5.00 mol%) in Acetone–MeCN–$H_2O$ (1:1:1, 30 mL) was heated to 60 °C for 18 h. The reaction was cooled to ambient temperature and diluted with $H_2O$ (10 mL), 2 N HCl (10 mL) and $CHCl_3$–*i*-PrOH (2:1, 20 mL). The organic layer was separated and the aqueous layer was extracted with $CHCl_3$–*i*-PrOH (2:1, 5 x 20 mL). The combined organic layers were dried over $Na_2SO_4$, filtered and the solvent was removed under reduced pressure. Toluene (20 mL) was added to the mixture and the solvent was evaporated. The residue was suspended in acetone (10 mL) and 2,2-dimethoxypropane (580 μL, 4.74 mmol, 1.10 equiv.) was added, followed by CSA (100 mg, 0.431 mmol, 10.0 mol%) and the reaction mixture was stirred for 10 min. sater (100 μL) was added and the reaction was stirred for another 5 min, before it was quenched by addition of $NEt_3$ (500 μL). The solvent was evaporated and the residue was purified by flash column chromatography (2:1→1:1→1:2 Hexanes:AcOEt) to yield acetonide **22** (738 mg, 56%) as a white powder.

**TLC:** $R_f$ = 0.42 (1:2 Hexanes:AcOEt), CAM, 254 nm; **$^1$H-NMR** (400 MHz, $CDCl_3$): δ 7.37 – 7.27 (m, 5H), 4.62 – 4.59 (m, 2H), 4.55 (d, *J* = 5.4 Hz, 1H), 4.54 – 4.52 (m, 1H), 4.50 (dd, *J* = 6.3, 1.3 Hz, 1H), 4.22 (d, *J* = 5.5 Hz, 1H), 3.82 (dd, *J* = 12.2, 4.6 Hz, 1H), 3.49 (dd, *J* = 12.1, 7.9 Hz, 1H), 2.19 (dd, *J* = 7.9, 4.6 Hz, 1H), 2.00 (dd, *J* = 13.7, 6.3 Hz, 1H), 1.50 (s, 3H), 1.30 (s, 3H), 1.27 (d, *J* = 13.7 Hz, 1H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 138.7, 128.6, 127.7, 127.4, 112.1, 85.1, 83.7, 82.1, 79.6, 78.7, 65.9, 64.8, 34.4, 26.0, 25.2; **IR** (thin film):3478, 2986, 1456, 1376, 1275, 1200, 1100, 1048, 988, 938, 872, 824, 722, 697, 582 $cm^{-1}$; **HRMS** (ESI): *m/z* calculated for $C_{17}H_{22}NaO_5$ [(M + $Na^+$)] 329.1359; found 329.1362; **Optical rotation** $[\alpha]^{22}_D$ (c = 0.500, $CHCl_3$): +13.0; **Mp** 139 °C.



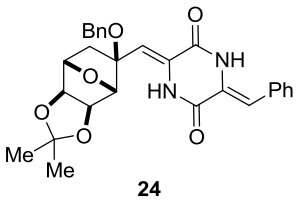

**23**

$C_{23}H_{26}N_2O_7$

442.46

**(*Z*)-1-acetyl-3-(((3a*S*,4*S*,5*S*,7*S*,7a*S*)-5-(benzyloxy)-2,2-dimethylhexahydro-4,7-epoxybenzo[d][1,3]dioxol-5-yl)methylene)piperazine-2,5-dione (23):** A solution of $(COCl)_2$ (223 μL, 2.55 mmol, 1.50 equiv.) in $CH_2Cl_2$ (20 mL) was cooled to –78 °C and a solution of DMSO (241 μL, 3.39 mmol, 2.00 equiv.) in $CH_2Cl_2$ (1 mL) was added dropwise. After 10 min, a solution of alcohol **22** (520 mg, 1.70 mmol, 1.0 equiv.) in $CH_2Cl_2$ (5 mL) was added dropwise and the solution was stirred for 45 min at –78 °C. A solution of DBU (1.54 mL, 10.2 mmol, 6.00 equiv.) in $CH_2Cl_2$ (3 mL) was added dropwise. After complete addition, solid 1,4-diacetylpiperazine-2,5-dione (**4**, 437 mg, 2.21 mmol, 1.30 equiv.) was added and the reaction was warmed to 0 °C. After 2 h the reaction was warmed to ambient temperature and stirred for 1 h. It was quenched by addition of satd. aq. $NH_4Cl$ solution (50 mL), the organic layer was separated and the aqueous layer was extracted with $CH_2Cl_2$ (3 x 30 mL). The combined organic layers were dried over $Na_2SO_4$ and the solvent was evaporated. Flash column chromatography (2:1→1:1→1:2 Hexanes:AcOEt) yielded the product as wax. Trituration with $Et_2O$ (5 mL) and filtration yielded *N*-acetyl diketopiperazine **23** (565 mg, 75%) as a white solid.

**TLC:** $R_f$ = 0.37 (1:1 Hexanes:AcOEt), $KMnO_4$, 254 nm; **$^1$H-NMR** (400 MHz, $CDCl_3$): δ 8.93 (s, 1H), 7.38 – 7.27 (m, 5H), 6.05 (d, *J* = 0.8 Hz, 1H), 4.64 – 4.57 (m, 2H), 4.52 – 4.33 (m, 5H), 4.30 (d, *J* = 5.5 Hz, 1H), 2.63 (s, 3H), 2.36 (ddd, *J* = 13.7, 6.2, 1.4 Hz, 1H), 1.54 (d, *J* = 13.6 Hz, 1H), 1.48 (s, 3H), 1.28 (s, 3H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 172.5, 161.4, 158.7, 136.8, 130.6, 128.8, 128.3, 127.7, 116.8, 112.7, 85.7, 84.0 82.0, 79.7, 79.0, 66.7, 46.3, 39.3, 27.5, 26.0, 25.3; **IR** (thin film): 3313, 2941, 1702, 1640, 1431, 1370, 1221, 1096, 1050, 868, 742, 700 $cm^{-1}$; **HRMS** (MALDI): *m/z* calculated for $C_{23}H_{26}N_2NaO_7$ [$(M + Na^+)$] 465.1632; found 465.1634; **Optical rotation** $[\alpha]^{22}_D$ (c = 0.500, $CHCl_3$): +39.6; **Mp:** 175 °C.



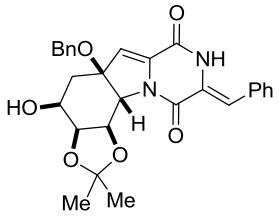
**24**

$C_{28}H_{28}N_2O_6$

488.53

**(3*Z*,6*Z*)-3-benzylidene-6-(((3a*S*,4*S*,5*S*,7*S*,7a*S*)-5-(benzyloxy)-2,2-dimethylhexahydro-4,7-epoxybenzo[d][1,3]dioxol-5-yl)methylene)piperazine-2,5-dione (24):** To a solution of *N*-acetyl diketopiperazine **23** (350 mg, 0.791 mmol, 1.00 equiv.) and benzaldehyde (241 μL, 2.37 mmol, 3.00 equiv.) in $CH_2Cl_2$ (10 mL) was added DBU (477 μL, 3.16 mmol, 4.00 equiv.) and the reaction mixture was stirred for 6 h. Satd. aq. $NH_4Cl$ solution (20 mL) was added and the organic layer was separated. The aqueous layer was extracted with $CH_2Cl_2$ (3 x 20 mL) and the combined organic layers were dried over $Na_2SO_4$. Evaporation yielded an oil that was purified by flash column chromatography (4:1 $CH_2Cl_2$:AcOEt) to yield the *bis*(alkylidene)diketopiperazine **24** as a wax. The wax was triturated with $Et_2O$ (10 mL) and sonicated for 10 min. The slurry was filtered and washed with $Et_2O$ (2 x 10 mL) to yield the *bis*(alkylidene)diketopiperazine **24** (320 mg, 83%) as a white powder.

**TLC:** $R_f$ = 0.56 (7:3 $CH_2Cl_2$:AcOEt), $KMnO_4$, 254 nm and 366 nm; **$^1$H-NMR** (400 MHz, $CDCl_3$): δ 9.06 (s, 1H), 8.11 (s, 1H), 7.51 – 7.44 (m, 2H), 7.43 – 7.28 (m, 8H), 7.05 (s, 1H), 5.89 (s, 1H), 4.65 – 4.62 (m, 1H), 4.59 (dd, *J* = 6.2, 1.3 Hz, 1H), 4.52 – 4.43 (m, 2H), 4.30 (d, *J* = 5.5 Hz, 1H), 2.36 (ddd, *J* = 13.7, 6.4, 1.3 Hz, 1H), 1.57 – 1.51 (m, 2H), 1.48 (s, 3H), 1.28 (s, 3H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 156.0, 156.0 137.0, 132.7, 130.3, 129.8, 129.3, 128.8, 128.5, 128.3, 127.8, 125.4, 117.8, 114.0, 112.6, 86.0, 84.1, 82.0, 79.7, 79.0, 66.6, 39.2, 26.0, 25.4; **IR** (thin film): 3205, 2943, 1687, 1638, 1395, 1346, 1207, 1164, 1095, 1051, 929, 876, 768, 750, 695 $cm^{-1}$; **HRMS** (ESI): *m/z* calculated for $C_{28}H_{29}N_2O_6$ $[(M + H^+)]$ 489.2020; found 489.2020; **Optical rotation** $[\alpha]^{23}_D$ (c = 0.500, THF): +25.0; **Mp:** 238 °C (decomposition).



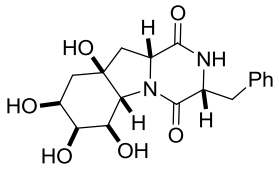

**25**

$C_{28}H_{28}N_2O_6$

488.53

**(3a*S*,4*S*,5a*S*,11a*R*,11b*R*,*Z*)-9-benzylidene-5a-(benzyloxy)-4-hydroxy-2,2-dimethyl-3a,4,5,5a,8,9-hexahydro-[1,3]dioxolo[4,5-g]pyrazino[1,2-a]indole-7,10(11aH,11bH)-dione (25):** To a solution of *bis*(alkylidene)diketopiperazine **24** (200 mg, 0.409 mmol, 1.00 equiv.) and 2,6-lutidine (334 μL, 2.87 mmol, 7.00 equiv.) in $CH_2Cl_2$ (10 mL) was added $Me_3SiOTf$ (370 μL, 2.05 mmol, 5.00 equiv.) dropwise. After 6 h, MeOH (166 μL, 4.09 mmol, 10.0 equiv.) was added and the solvent was evaporated to furnish the crude silyl ether. The residue was dissolved in MeOH (10 mL) and $K_2CO_3$ (566 mg, 4.09 mmol, 10.0 equiv.) was added. After 2 h of vigorous stirring, the reaction was poured onto a mixture of satd. aq. $NH_4Cl$ solution (50 mL) and AcOEt (50 mL). The organic layer was separated and the aqueous layer was extracted with AcOEt (3 x 50 mL). The combined organic layers were dried over $Na_2SO_4$, filtered and the solvent was removed under reduced pressure. Flash column chromatography (2:1→1:1→1:2 Hexanes:AcOEt) yielded the product as a foam. Trituration with diisopropyl ether (4 mL) and sonication for 30 min induced crystallization. Evaporation yielded the *bis*(alkylidene)diketopiperazine **25** (162 mg, 81%) as a white powder.

**TLC:** Rf = 0.13 (1:1 Hexanes:AcOEt), $KMnO_4$, 254 nm and 366 nm; **$^1$H NMR** (400 MHz, $CDCl_3$): δ 8.12 (s, 1H), 7.52 – 7.42 (m, 2H), 7.43 – 7.24 (m, 8H), 7.07 (s, 1H), 6.15 (s, 1H), 5.24 (dd, *J* = 7.2, 2.1 Hz, 1H), 4.81 (d, *J* = 2.1 Hz, 1H), 4.55 (s, 2H), 4.36 (ddd, *J* = 7.2, 4.3, 1.5 Hz, 1H), 3.53 – 3.39 (m, 1H), 2.45 – 2.30 (m, 2H), 2.01 (ddd, *J* = 12.5, 3.0, 1.6 Hz, 1H), 1.59 (s, 3H), 1.43 (s, 3H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): 155.9, 153.8, 137.9, 134.9, 132.7, 129.8, 129.3, 128.6, 128.5, 127.9, 127.7, 126.5, 120.7, 117.6, 109.1, 85.7, 73.3, 72.8, 66.2, 65.7, 62.3, 34.2, 26.3, 24.2; **IR** (thin film): 3376, 5989, 2937, 1686, 1650, 1629, 1497, 1453, 1402, 1369, 1340, 1263, 1212, 1114, 1053, 889, 749, 696 $cm^{-1}$; **HRMS** (MALDI): *m/z* calculated for $C_{28}H_{28}N_2NaO_6$ [$(M + Na^+)$] 511.1840; found 511.1844; **Optical Rotation** $[\alpha]^{23}_{436nm}$ (c = 0.500, $CHCl_3$): –27.0; **Mp**: 106 °C (decomposition).



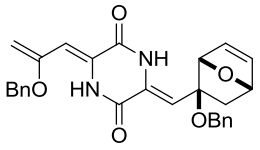
**26**

$C_{18}H_{22}N_2O_6$

362.38

**(3*R*,5a*R*,6*R*,7*S*,8*S*,9a*R*,10a*R*)-3-benzyl-6,7,8,9a-tetrahydroxydecahydropyrazino[1,2-a]indole-1,4-dione (26):** *Bis*(alkylidene)diketopiperazine **25** (75.0 mg, 0.154 mmol, 1.00 equiv.) and Pd–C (10%, 327 mg, 0.307 mmol, 2.00 equiv.) were suspended in AcOEt–MeOH (1:1, 10 mL) and hydrogen was purged through the solution for 4 h. The reaction mixture was purged with $N_2$ for 15 minutes and then filtered over celite under an atmosphere of $N_2$. The filter cake was washed with AcOEt–MeOH (1:1, 3 x 30 mL) and the combined filtrates were evaporated. The residue was purified by flash column chromatography (4%→6%→8%→10%→15% MeOH in $CH_2Cl_2$) to yield the tetraol 26 (24.3 mg, 44%) as a white powder.

**TLC:** Rf = 0.20 (4:1 $CH_2Cl_2$:MeOH), CAM, not UV active; **$^1$H NMR** (600 MHz, $CD_3OD$): δ 7.37 – 7.27 (m, 4H), 7.25 – 7.20 (m, 1H), 4.64 (ddd, *J* = 9.5, 7.8, 1.4 Hz, 1H), 4.49 (ddd, *J* = 7.6, 4.9, 1.4 Hz, 1H), 4.06 (d, *J* = 8.6 Hz, 1H), 3.83 (t, *J* = 2.4 Hz, 1H), 3.62 (ddd, *J* = 12.4, 4.9, 2.2 Hz, 1H), 3.40 (dd, *J* = 15.0, 4.9 Hz, 1H), 3.28 (dd, *J* = 8.7, 2.6 Hz, 1H), 3.01 (dd, *J* = 14.9, 7.5 Hz, 1H), 2.22 (t, *J* = 12.6 Hz, 1H), 2.05 – 1.99 (m, 3H); **$^{13}$C NMR** (150 MHz, $CD_3OD$): δ 173.0, 171.9, 138.0, 130.4, 129.6, 127.9, 77.6, 77.5, 73.9, 69.6, 67.7, 59.9, 57.2, 38.8, 37.7, 35.7; **IR** (thin film): 3376, 2927, 1680, 1646, 1497, 1419, 1300, 1143, 1075, 1020, 745, 700; **HRMS** (MALDI): *m/z* calculated for $C_{18}H_{22}N_2NaO_6$ [(M + $Na^+$)] 385.1370; found 385.1369; **Optical Rotation** $[\alpha]^{23}_D$ (c = 0.500, MeOH): +47.8; **Mp**: 185 °C (decomposition).



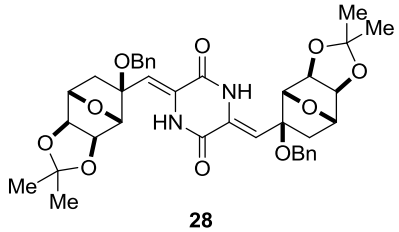
**27**

$C_{28}H_{26}N_2O_5$

470.52

**(3*Z*,6*Z*)-3-(((1S,2*S*,4*S*)-2-(benzyloxy)-7-oxabicyclo[2.2.1]hept-5-en-2-yl)methylene)-6-(2-(benzyloxy)allylidene)piperazine-2,5-dione (27):** Analytical data for compound (±)-**27**:

**Appearance:** slightly yellow solid; **TLC:** $R_f = 0.80$ (3:7 Hexanes:AcOEt), $KMnO_4$, 254 nm and 366 nm; **$^1$H NMR** (400 MHz, $CDCl_3$): δ 9.52 (s, 1H), 9.05 (s, 1H), 7.48 – 7.26 (m, 10H), 6.52 (dd, *J* = 5.8, 1.7 Hz, 1H), 6.35 (dd, *J* = 5.8, 1.9 Hz, 1H), 6.30 (s, 1H), 5.70 (s, 1H), 5.14 (dt, *J* = 4.6, 1.2 Hz, 1H), 5.10 – 5.05 (m, 1H), 4.96 (s, 2H), 4.58 – 4.47 (m, 4H), 2.41 (dd, *J* = 11.8, 4.7 Hz, 1H), 1.67 (d, *J* = 11.8 Hz, 1H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 157.3, 155.9, 155.4, 139.8, 137.2, 135.5, 133.2, 129.1, 128.8, 128.2, 128.0, 127.6, 126.0, 117.5, 111.1, 94.9, 85.6, 83.5, 78.8, 70.7, 67.7, 41.6; **IR** (thin film): 3347, 2248, 1688, 1645, 1589, 1454, 1397, 1369, 1335, 1310, 1219, 1059, 1026, 916, 801, 729, 698, 473; **HRMS** (MALDI): *m/z* calculated for $C_{28}H_{27}N_2O_5$ [$(M + H^+)$] 471.1914; found 471.1916;



**28**

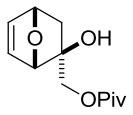
$C_{38}H_{42}N_2O_{10}$

686.75

**(3Z,6Z)-3,6-bis(((3aS,4S,5S,7S,7aS)-5-(benzyloxy)-2,2-dimethylhexahydro-4,7-epoxybenzo[d][1,3]dioxol-5-yl)methylene)piperazine-2,5-dione (28):** A solution of $(COCl)_2$ (118 μL, 1.35 mmol, 1.80 equiv.) in $CH_2Cl_2$ (10 mL) was cooled to –78 °C and a solution of DMSO (133 μL, 1.88 mmol, 2.50 equiv.) in $CH_2Cl_2$ (1 mL) was added dropwise. After 10 min, a solution of acetonide **22** (230 mg, 0.751 mmol, 1.00 equiv.) in $CH_2Cl_2$ (3 mL) was added dropwise and the reaction stirred for 45 min. A solution of DBU (1.67 mL, 11.3 mmol, 15.0 equiv.) in $CH_2Cl_2$ (1 mL) was added dropwise at a rate so that the internal temperature did not rise above –70 °C. After complete addition, *N*,*N*'-diacetylpiperazine-2,5-dione (**4**, 59.5 mg, 0.300 mmol, 0.400 equiv.) was added in one portion. After 10 min, the reaction was warmed to 0 °C and stirred for 3 h; then it was warmed to ambient temperature and stirred overnight. The reaction was quenched by addition of satd. aq. $NH_4Cl$ solution (20 mL), the

organic layer was separated and the aqueous layer was extracted with $CH_2Cl_2$ (3 x 20 mL). The combined organic layers were dried over $Na_2SO_4$, filtered and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (2:1→1:1→1:2 Hexanes:AcOEt) to yield **28** as a slightly yellow solid. $Et_2O$ (5 mL) was added and the solid was crushed to a fine powder. The suspension was filtered and the filter cake was dried to yield *bis*(acetonide) **28** (164 mg, 80% (referred to **4**)) as a white powder.

**TLC:** $R_f$ = 0.27 (1:1 Hexanes:AcOEt), $KMnO_4$, 254 nm and 366 nm; **$^1$H-NMR (400 MHz, $CD_2Cl_2$)** δ 9.00 (s, 2H), 7.41 – 7.28 (m, 10H), 5.91 (s, 2H), 4.58 (s, 2H), 4.54 (dd, *J* = 6.2, 1.2 Hz, 2H), 4.48 (d, *J* = 5.4 Hz, 2H), 4.46 (d, *J* = 10.8 Hz, 2H), 4.40 (d, *J* = 11.3 Hz, 2H), 4.30 (d, *J* = 5.5 Hz, 2H), 2.33 (dd, *J* = 13.5, 6.3 Hz, 2H), 1.57 (d, *J* = 13.6 Hz, 2H), 1.43 (s, 6H), 1.26 (s, 6H); **$^{13}$C NMR (100 MHz, $CD_2Cl_2$)** δ 155.2, 137.8, 130.8, 129.1, 128.6, 128.4, 114.9, 112.6, 86.5, 84.5, 82.3, 80.2, 79.5, 66.6, 39.5, 26.1, 25.4; **IR** (thin film) ν 3318, 2990, 2940, 1695, 1638, 1418, 1381, 1338, 1209, 1168, 1095, 1053, 1016, 928, 876, 736, 679, 469 $cm^{-1}$; **HRMS** (ESI): *m/z* calculated for $C_{38}H_{42}N_2NaO_{10}$ [(M + $Na^+$)] 709.2732; found 709.2725; **Optical Rotation** $[\alpha]^{22}_D$ (c = 0.500, $CHCl_3$): +93.6; **Mp:** 224 °C (decomposition).

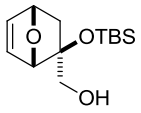



**29**
$C_{12}H_{18}O_4$
226.27

**((1*S*,2*S*,4*S*)-2-hydroxy-7-oxabicyclo[2.2.1]hept-5-en-2-yl)methyl pivalate (29):** To a solution of diol **14** (1.00 g, 7.03 mmol, 1.00 equiv.), $NEt_3$ (1.96 mL, 14.1 mmol, 2.00 equiv.) and DMAP (129 mg, 1.06 mmol, 15.0 mol%) in $CH_2Cl_2$ (30 mL) was added pivaloyl chloride (909 μL, 7.39 mmol, 1.05 equiv.) dropwise. After complete addition, the reaction was stirred for 30 min and then quenched by addition of satd. aq. $NH_4Cl$ solution (20 mL) and water (10 mL). The organic layer was separated and the aqueous layer was extracted with AcOEt (3 x 20 mL). The combined organic layers were dried over $Na_2SO_4$, filtered and the solvent was evaporated. Flash column chromatography (1:2→0:1 Hexanes:AcOEt) yielded the crude pivalate that was dissolved in a AcOEt (10 mL) and hexanes were added until precipitation started. The mixture was evaporated to yield pivalate **29** (1.48 g, 93%) as a white solid.

**TLC:** $R_f$ = 0.63 (AcOEt), $KMnO_4$, not UV active; **$^1$H-NMR** (400 MHz, $CDCl_3$): δ 6.45 (dd, *J* = 5.9, 1.7 Hz, 1H), 6.33 (dd, *J* = 5.9, 1.8 Hz, 1H), 5.06 (dt, *J* = 4.8, 1.2 Hz, 1H), 4.66 (t, *J* = 1.3 Hz, 1H), 4.23 (d, *J* = 11.7 Hz, 1H), 3.88 (dd, *J* = 11.8, 0.8 Hz, 1H), 2.43 (d, *J* = 0.9 Hz, 1H), 1.85 (dd, *J* = 12.3, 4.7 Hz, 1H), 1.49 (d, *J* = 12.3 Hz, 1H), 1.24 (s, 9H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 178.5, 138.6, 133.1, 85.9,

79.6, 78.3, 69.2, 39.6, 39.1, 27.3; **IR** (thin film): 3490, 3438, 2960, 1725, 1706, 1294, 1183, 1093, 917 $cm^{-1}$; **HRMS** (ESI): *m/z* calculated for $C_{12}H_{19}O_4$ [(M + $H^+$)] 227.1278; found 227.1283; **Optical rotation** $[\alpha]^{23}_D$ (c = 0.500, $CHCl_3$): –27.0; **Mp:** 66 °C.

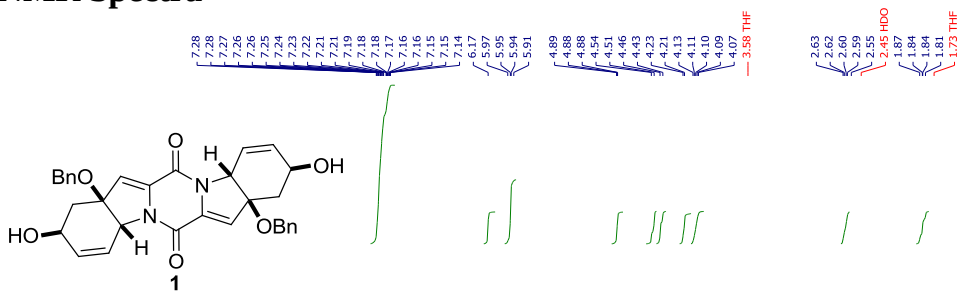


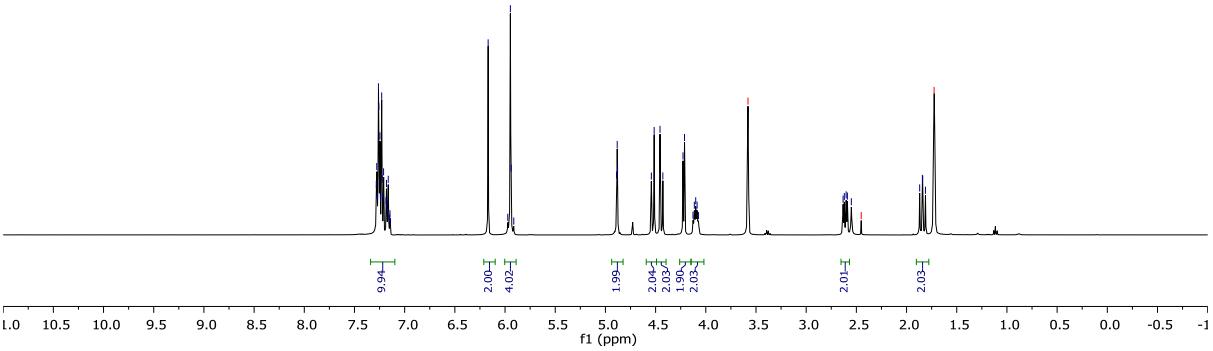

**30**
$C_{13}H_{24}O_3Si$
256.41

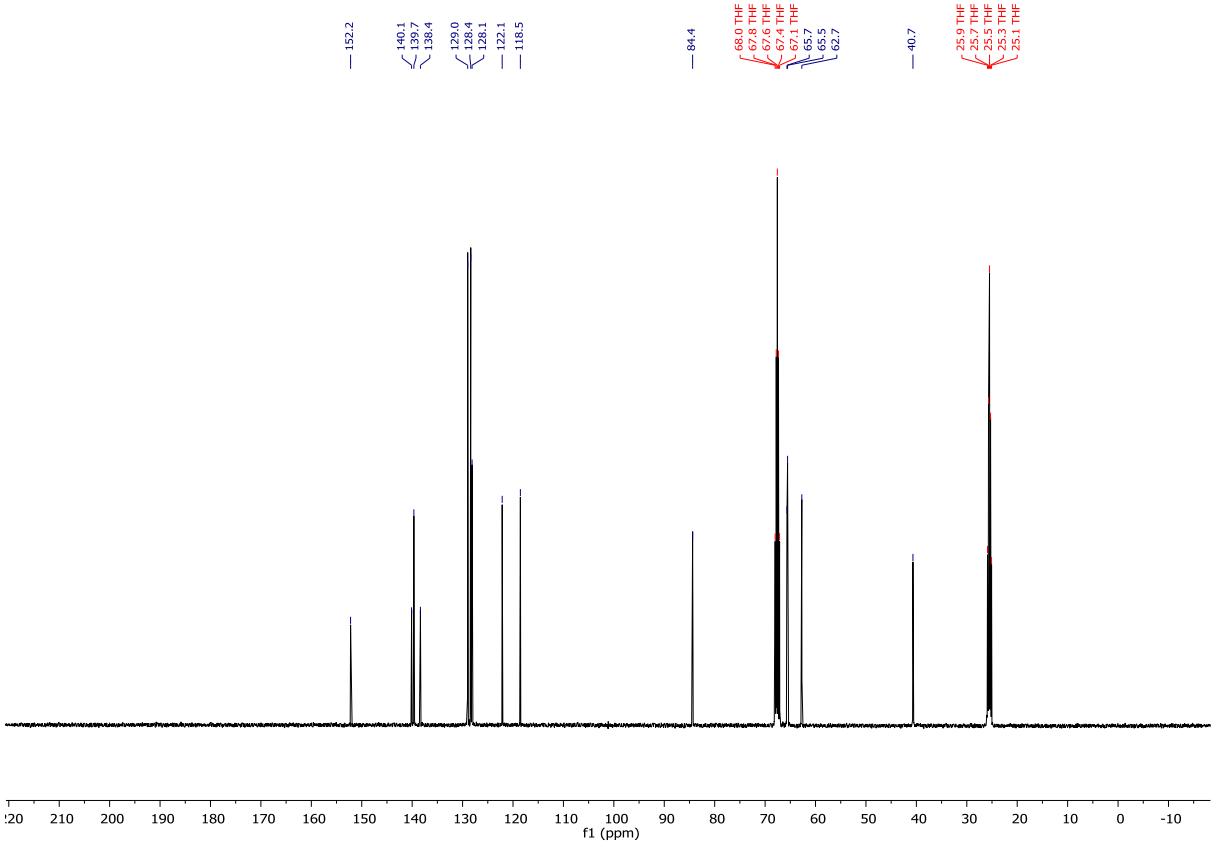
**((1*S*,2*S*,4*S*)-2-((tert-butyldimethylsilyl)oxy)-7-oxabicyclo[2.2.1]hept-5-en-2-yl)methanol (30):** A solution of pivalate **29** (1.35 g, 5.97 mmol, 1.00 equiv.) and 2,6-lutidine (1.39 mL, 11.9 mmol, 2.00 equiv.) was cooled to 0 °C and TBSOTf (1.64 mL, 7.16 mmol, 1.20 equiv.) was added dropwise. After 30 min the reaction was warmed to ambient temperature and stirred for 3 h. The reaction was quenched by addition of satd. aq. $NH_4Cl$ solution (30 mL), the organic layer was separated and the aqueous layer was extracted with $CH_2Cl_2$ (2 x 30 mL). The combined organic layers were dried over $Na_2SO_4$, filtered and the solvent was evaporated. To the crude product was added Toluene (100 mL) and the mixture was evaporated. The residue was dissolved in $CH_2Cl_2$ (50 mL) and cooled to –78 °C, then DIBAL-H (1.2 M in PhMe, 14.9 mL, 17.9 mmol, 3.00 equiv.) was added dropwise and the reaction was stirred for 30 min at –78 °C. MeOH (6 mL) was added dropwise and after complete addition the reaction was warmed to 0 °C. Satd. aq. Rochelle's salt solution (25 mL) and water (25 mL) were carefully added and the mixture was stirred at ambient temperature for 2 h. The organic layer was separated and the aqueous layer was extracted with AcOEt (3 x 50 mL). The combined organic layers were washed with brine (1 x 50 mL), dried over $Na_2SO_4$, filtered and the solvent was evaporated. Flash column chromatography (6:1 Hexanes:AcOEt) yielded the silyl ether **30** (1.13 g, 74%) as an oil.

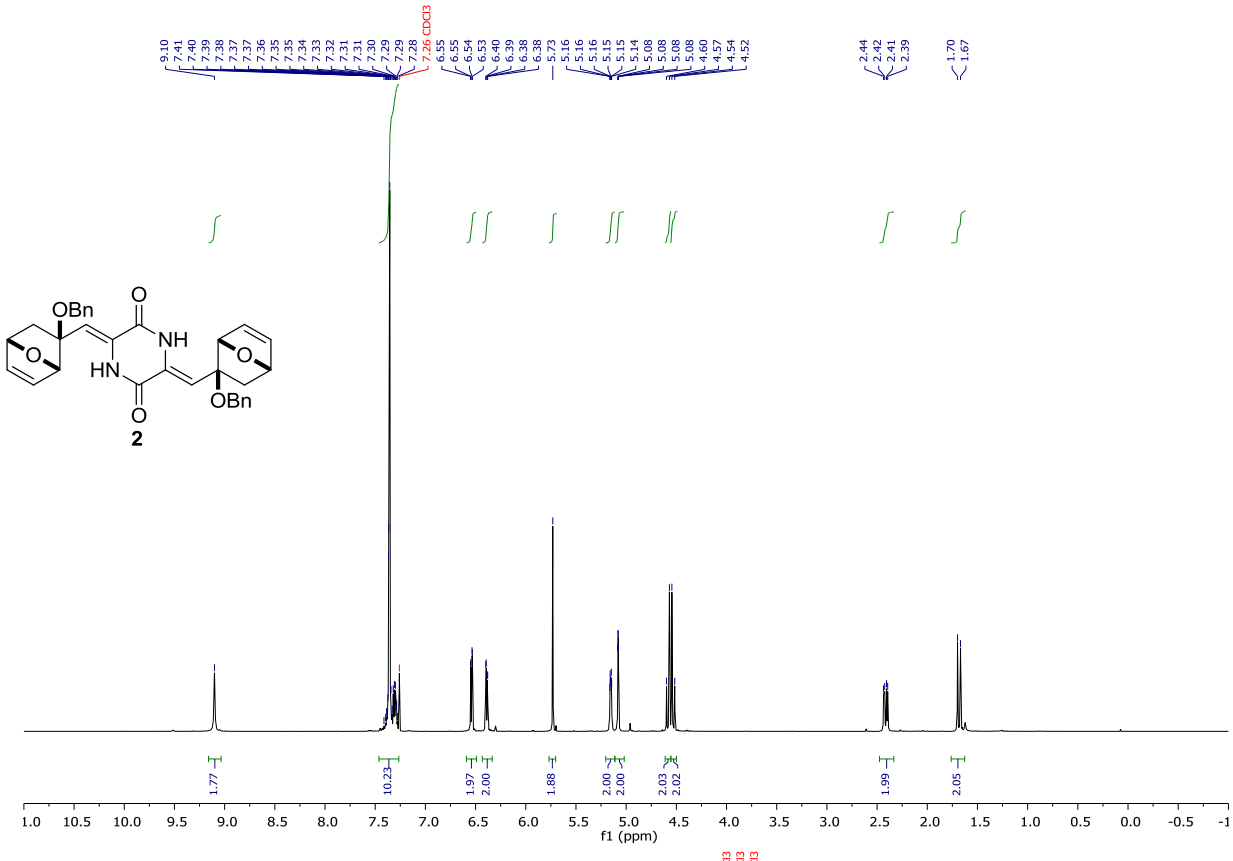
**TLC:** $R_f$ = 0.53 (2:1 Hexanes:AcOEt), $KMnO_4$, not UV active; **$^1$H-NMR** (400 MHz, $CDCl_3$): δ 6.43 – 6.36 (m, 2H), 5.04 – 4.99 (m, 1H), 4.68 (d, *J* = 1.3 Hz, 1H), 3.56 (dd, *J* = 11.1, 3.9 Hz, 1H), 3.25 (dd, *J* = 11.1, 9.1 Hz, 1H), 2.17 (dd, *J* = 9.1, 3.8 Hz, 1H), 1.87 (dd, *J* = 12.3, 4.8 Hz, 1H), 1.26 (d, *J* = 12.3 Hz, 1H), 0.89 (s, 9H), 0.17 (s, 6H); **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 138.7, 133.6, 85.1, 84.4, 78.2, 69.6, 37.7, 26.1, 18.4, –2.6, –3.2; **IR** (thin film): 3476, 2953, 2929, 2856, 1249, 1313, 1097, 1059, 1004, 915, 834, 804, 776 $cm^{-1}$; **HRMS** (ESI): *m/z* calculated for $C_{13}H_{24}NaO_3Si$ [(M + $Na^+$)] 279.1387; found 279.1394; **Optical rotation** $[\alpha]^{22}_D$ (c = 0.735, $CHCl_3$): +12.8.

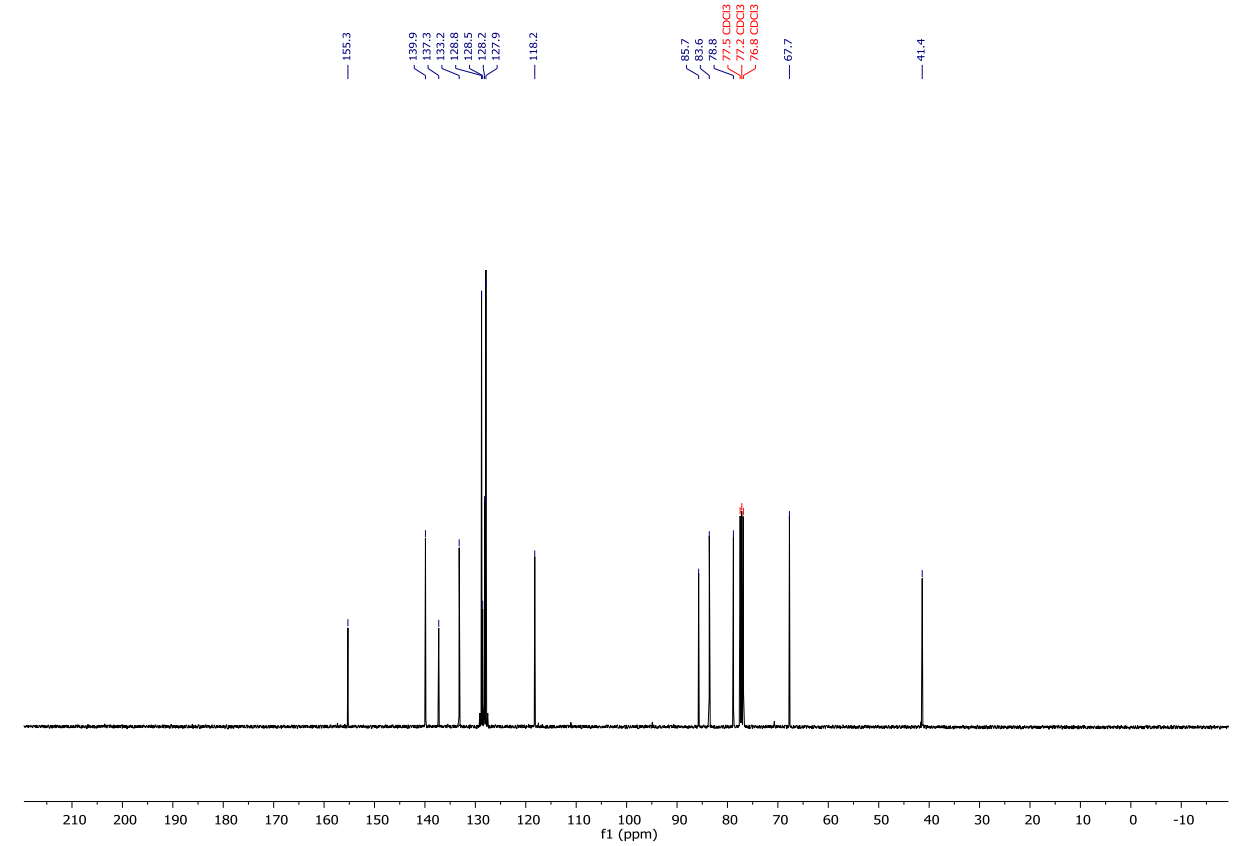
## 3. NMR Spectra

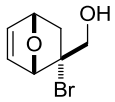


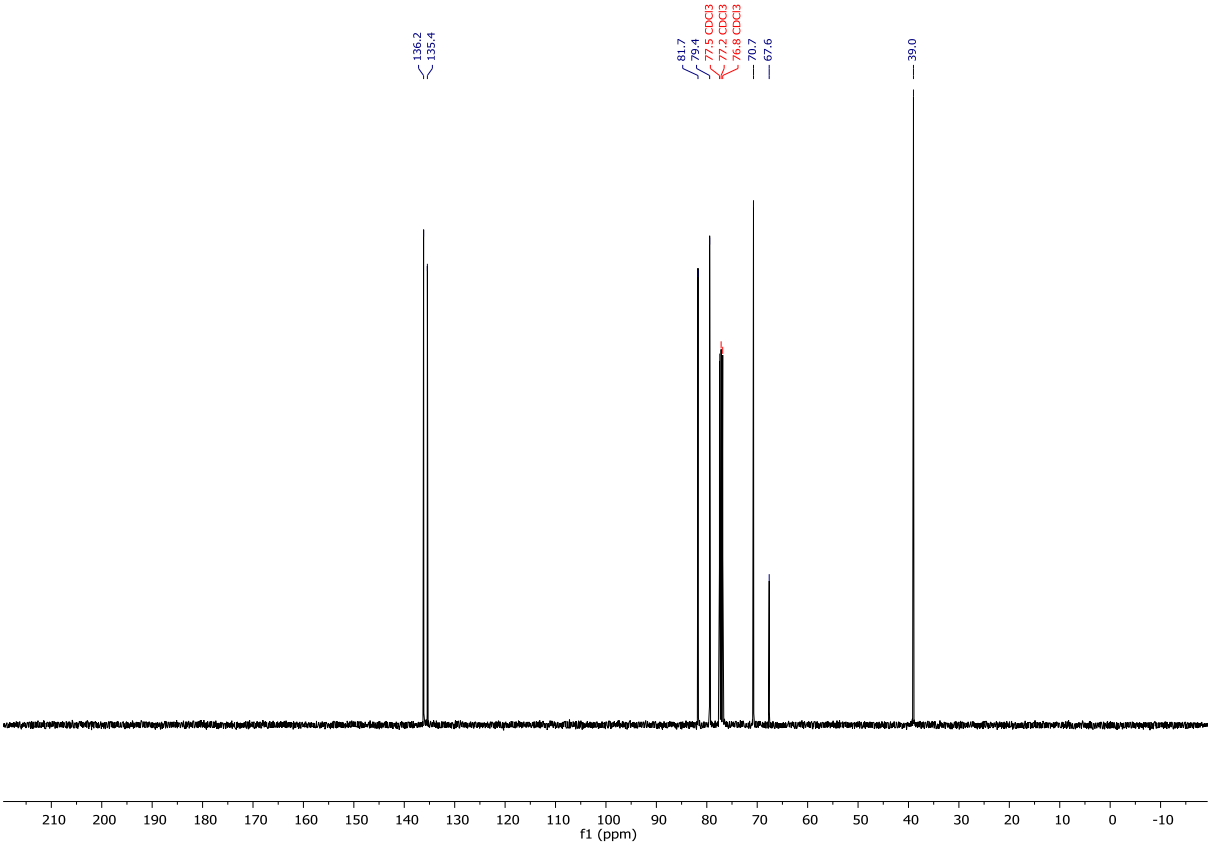

OBn
O
NH
HN
O
O
OBn
O
2
f1 (ppm)

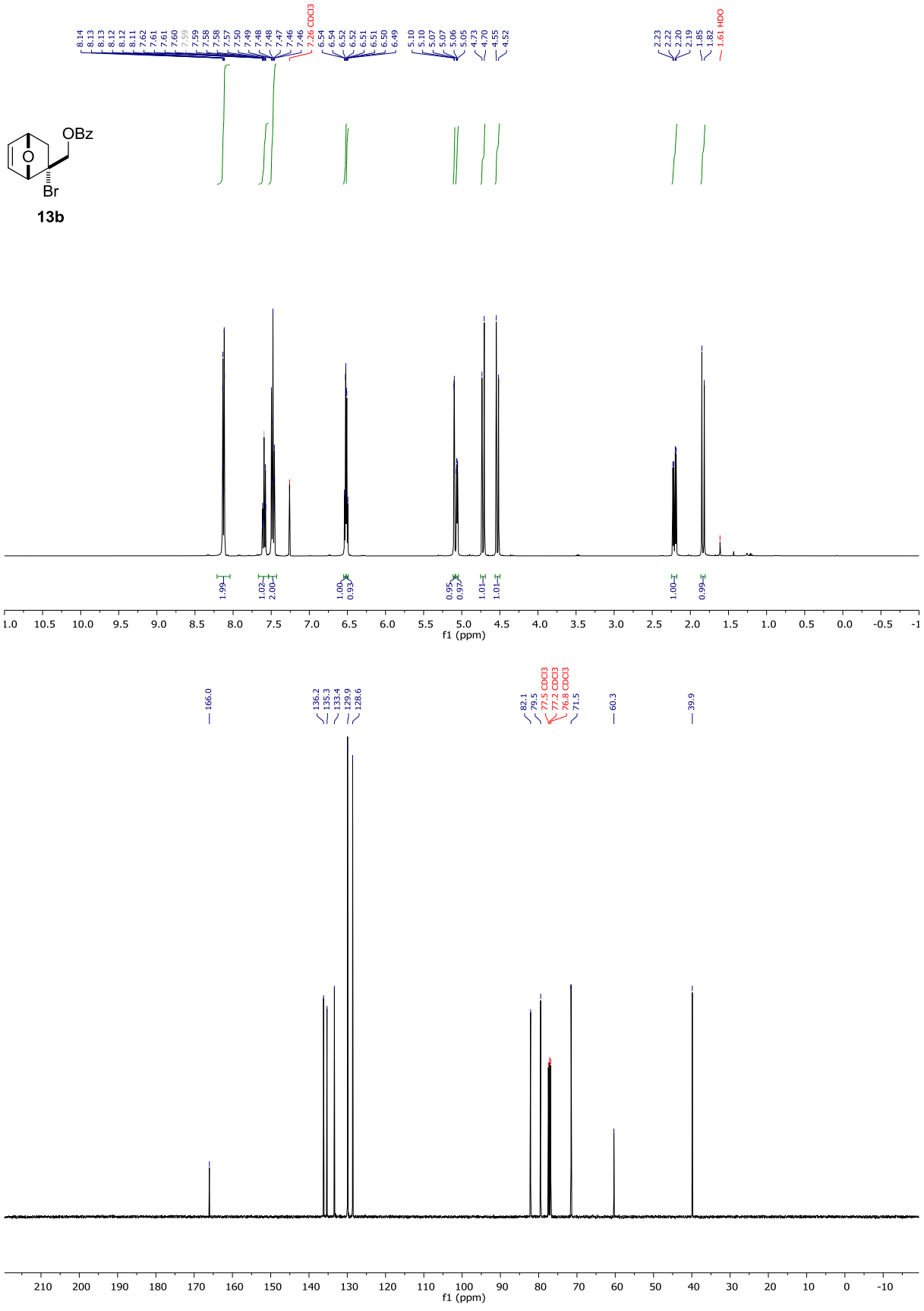

f1 (ppm)

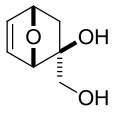

OH
O
Br

**13**


7.26 CDCl3
6.51
6.50
6.49
6.49
6.46
6.45
6.44
6.44
5.02
5.02
5.02
5.01
5.00
3.87
3.86
3.84
3.83
3.81
3.78
3.78
3.75
2.33
2.32
2.31
2.30
2.11
2.10
2.08
2.07
1.75
1.71
1.65 HDO
1.99
1.96
1.05
1.04
1.00
1.05
1.04
f1 (ppm)

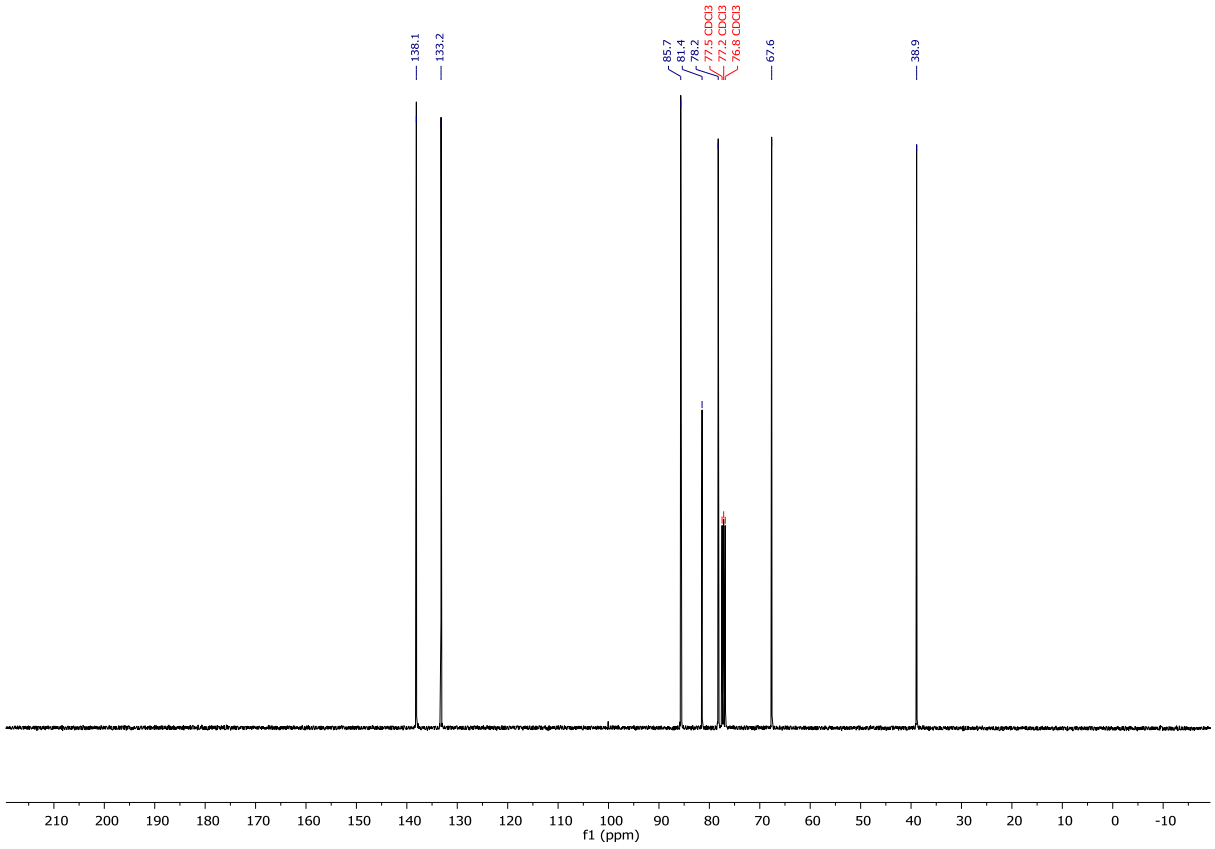

136.2
135.4
81.7
79.4
77.5 CDCl3
77.2 CDCl3
76.8 CDCl3
70.7
67.6
39.0
f1 (ppm)

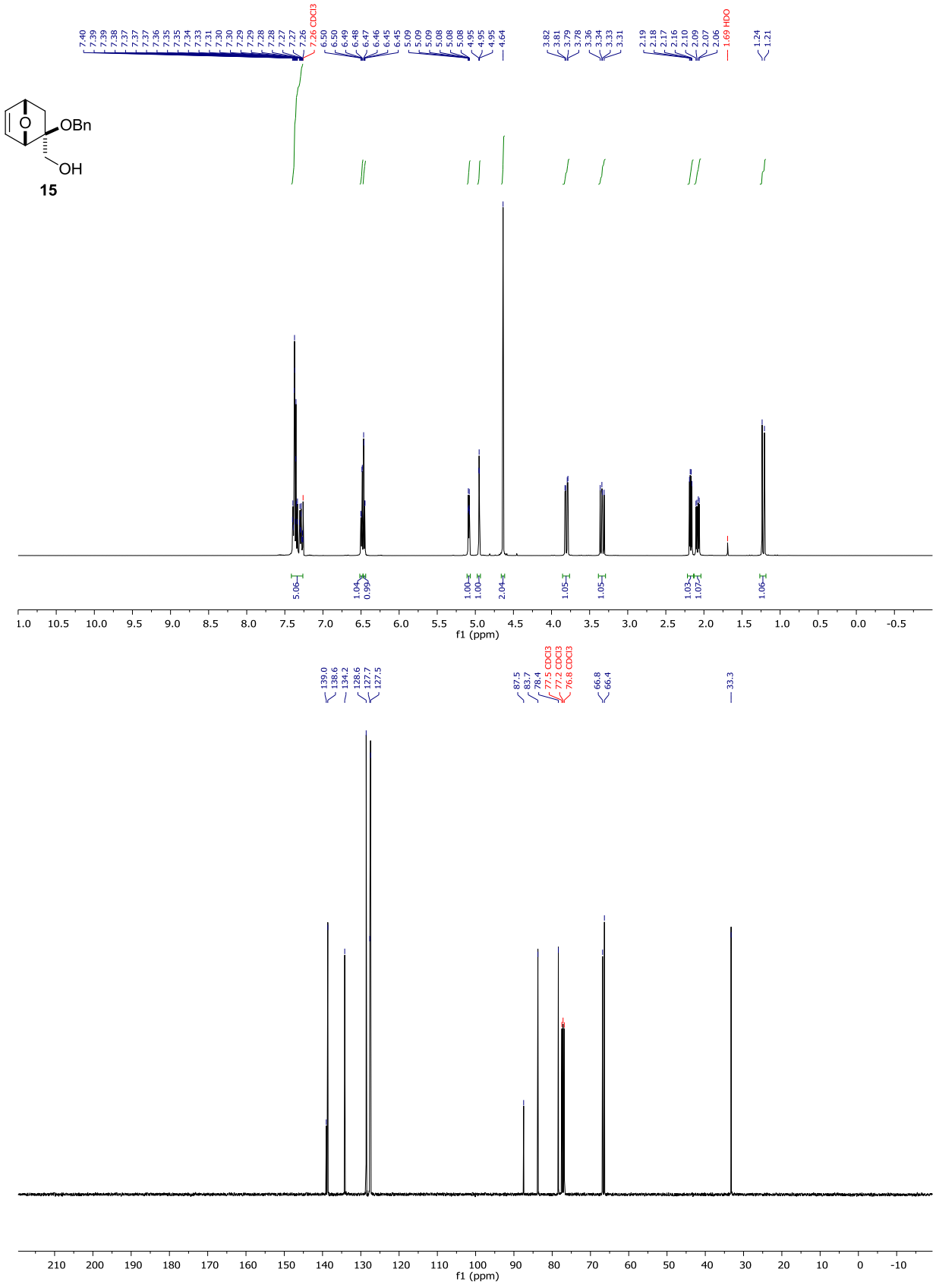

OBz
O
Br
13b
f1 (ppm)
f1 (ppm)

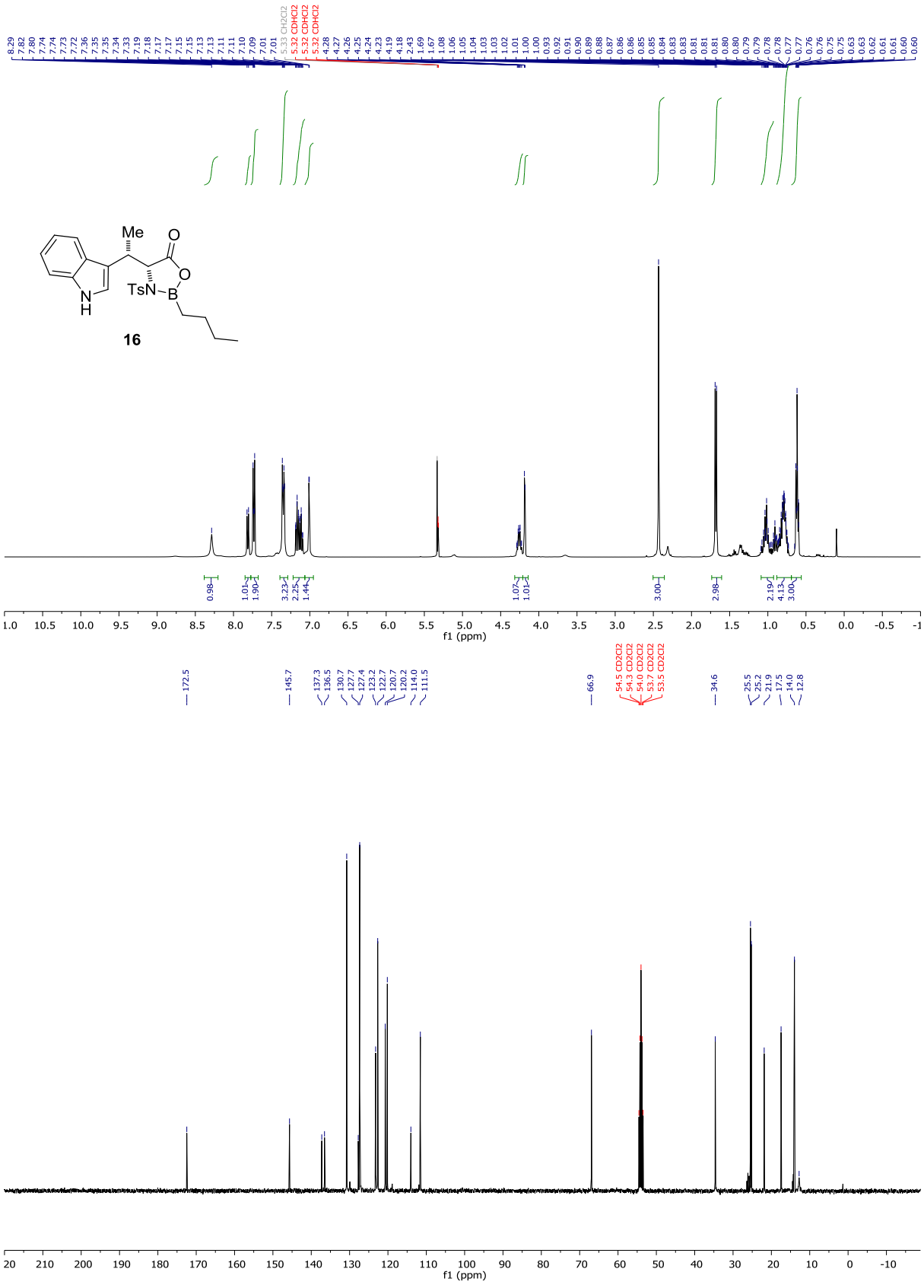

O
OH
OH

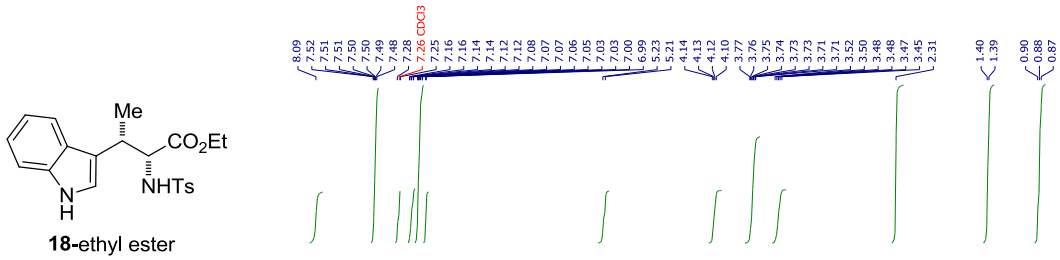
**14**


7.26 CDCl3
6.41
6.41
6.40
6.39
6.39
6.38
6.38
5.03
5.03
5.02
5.01
4.71
4.71
3.68
3.67
3.65
3.64
3.49
3.34
3.32
3.31
3.29
3.18
3.17
3.16
3.15
1.79
1.78
1.76
1.75
1.37
1.34
2.01
1.00
1.02
1.04
1.05
1.06
1.06
1.04
1.05
f1 (ppm)

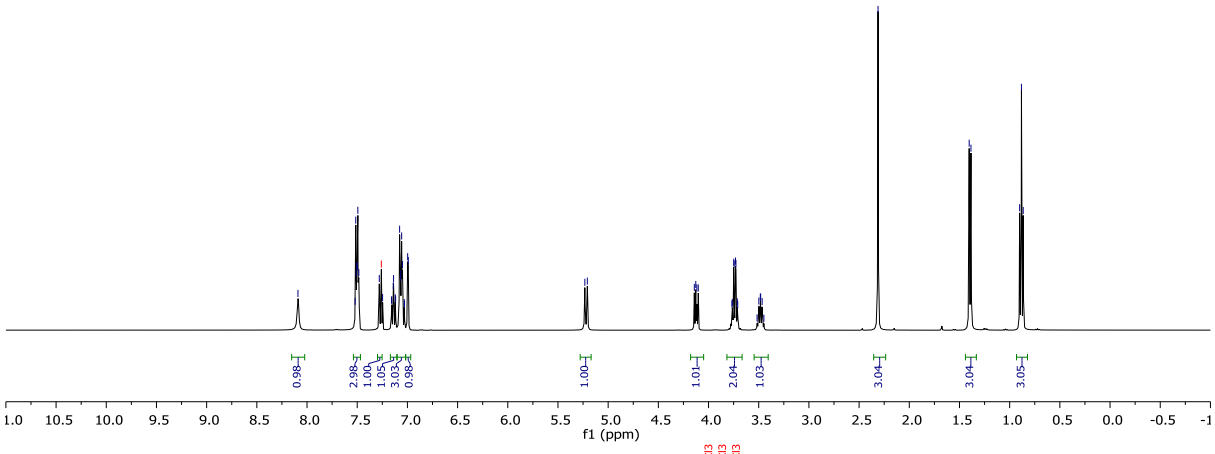

138.1
133.2
85.7
81.4
78.2
77.5 CDCl3
77.2 CDCl3
76.8 CDCl3
67.6
38.9
f1 (ppm)

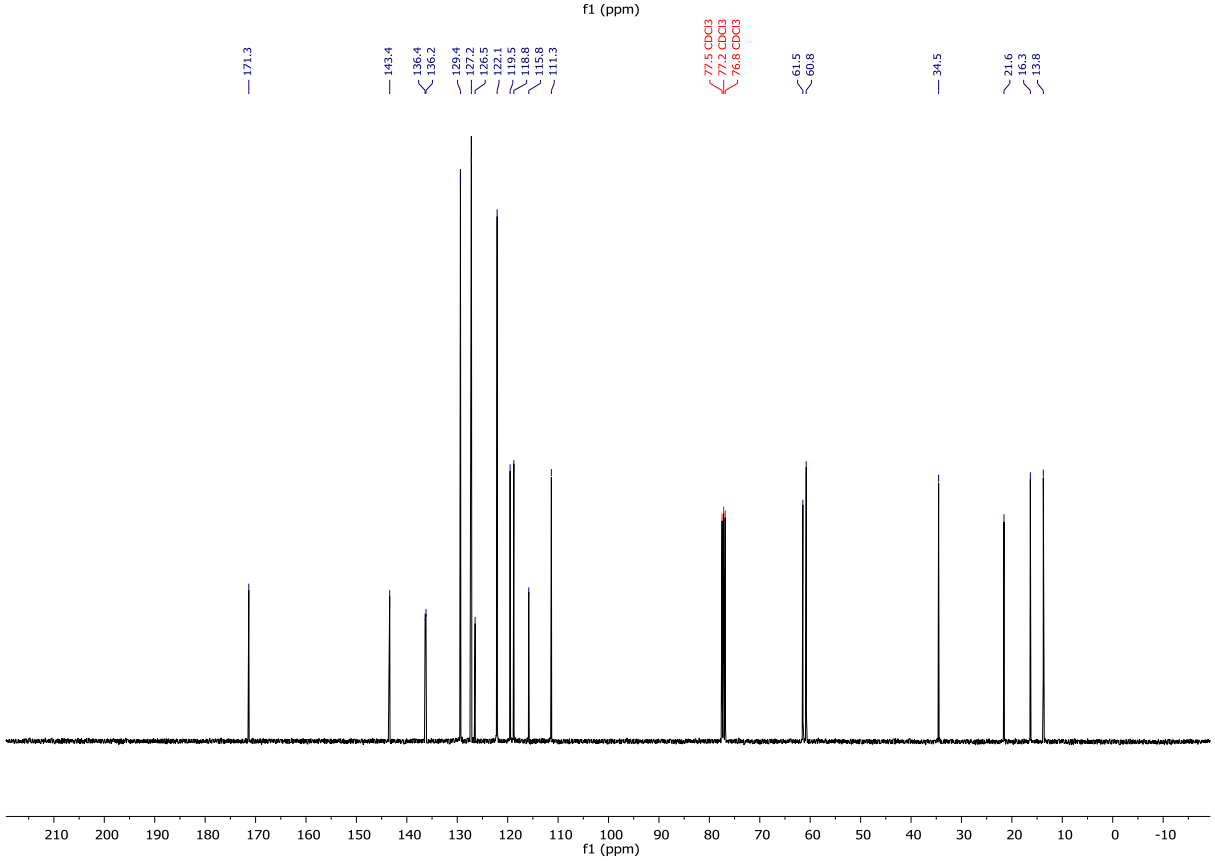

OBn
OH
15
f1 (ppm)
f1 (ppm)

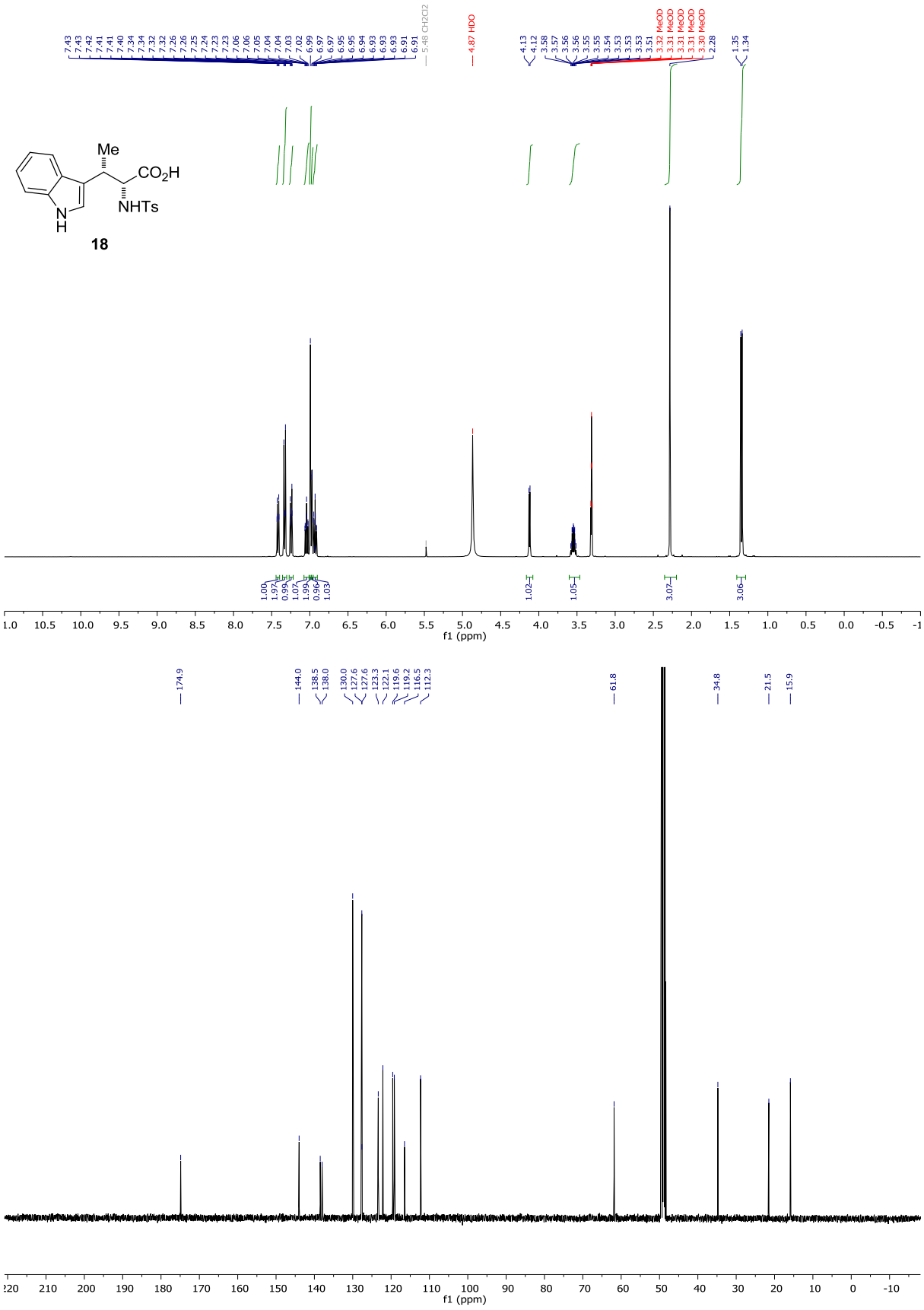

Me
O
O
TsN
B
N
H
16
f1 (ppm)
f1 (ppm)

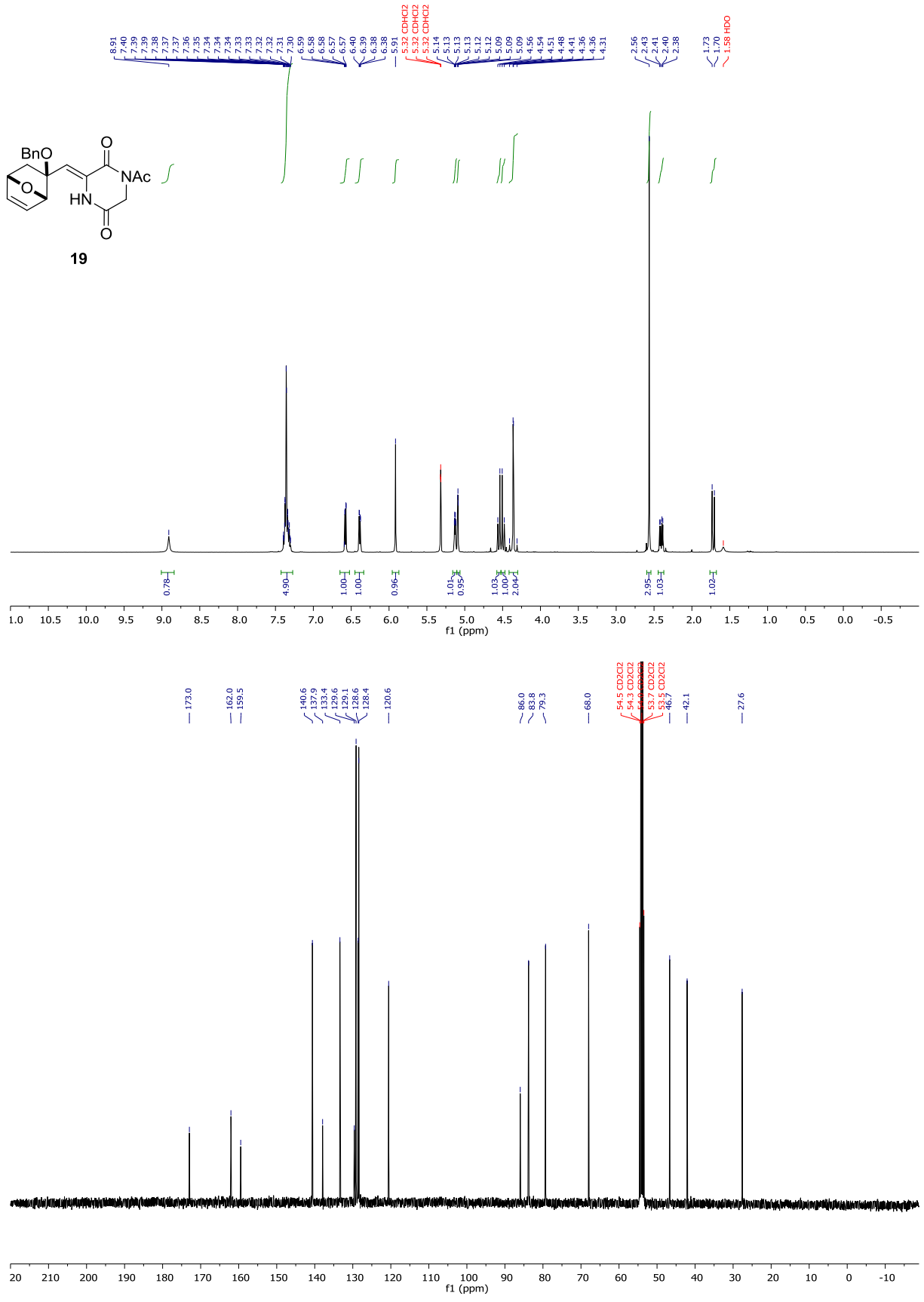


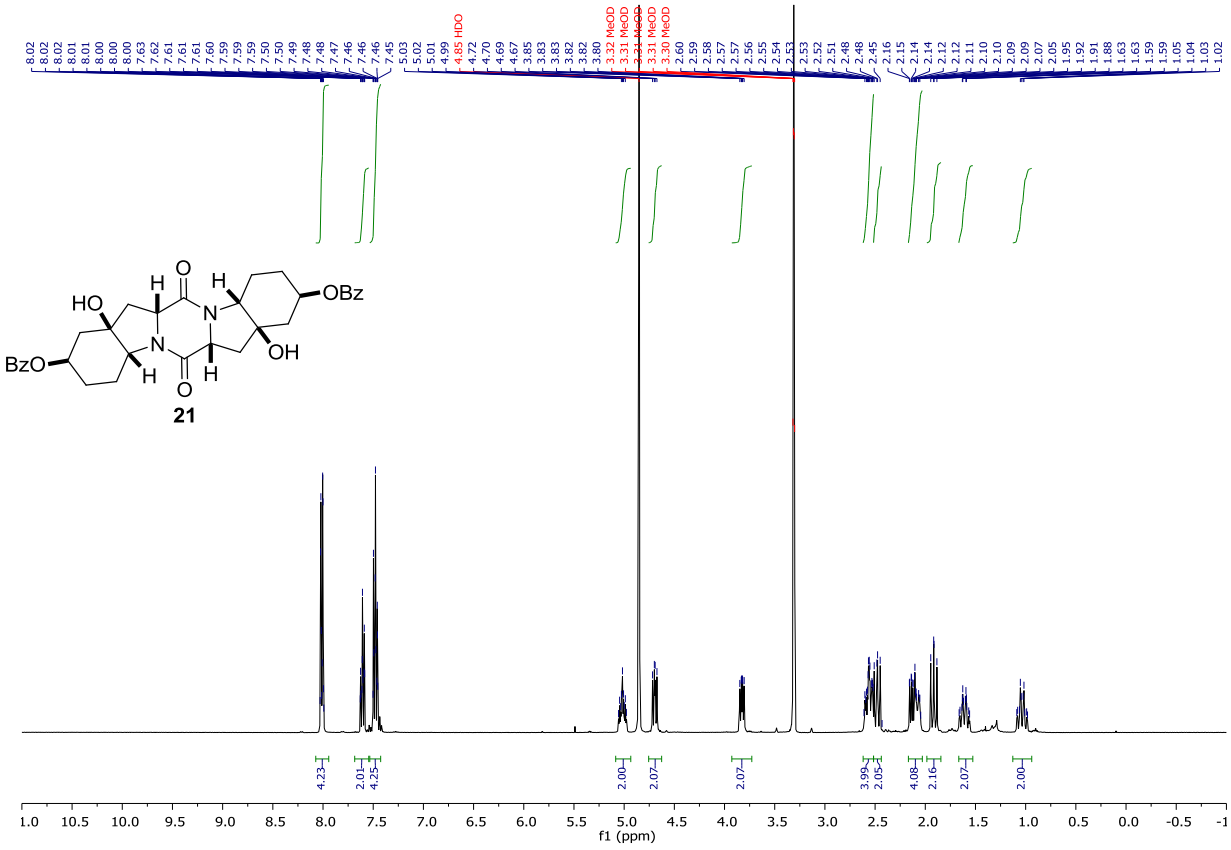

**18-**ethyl ester

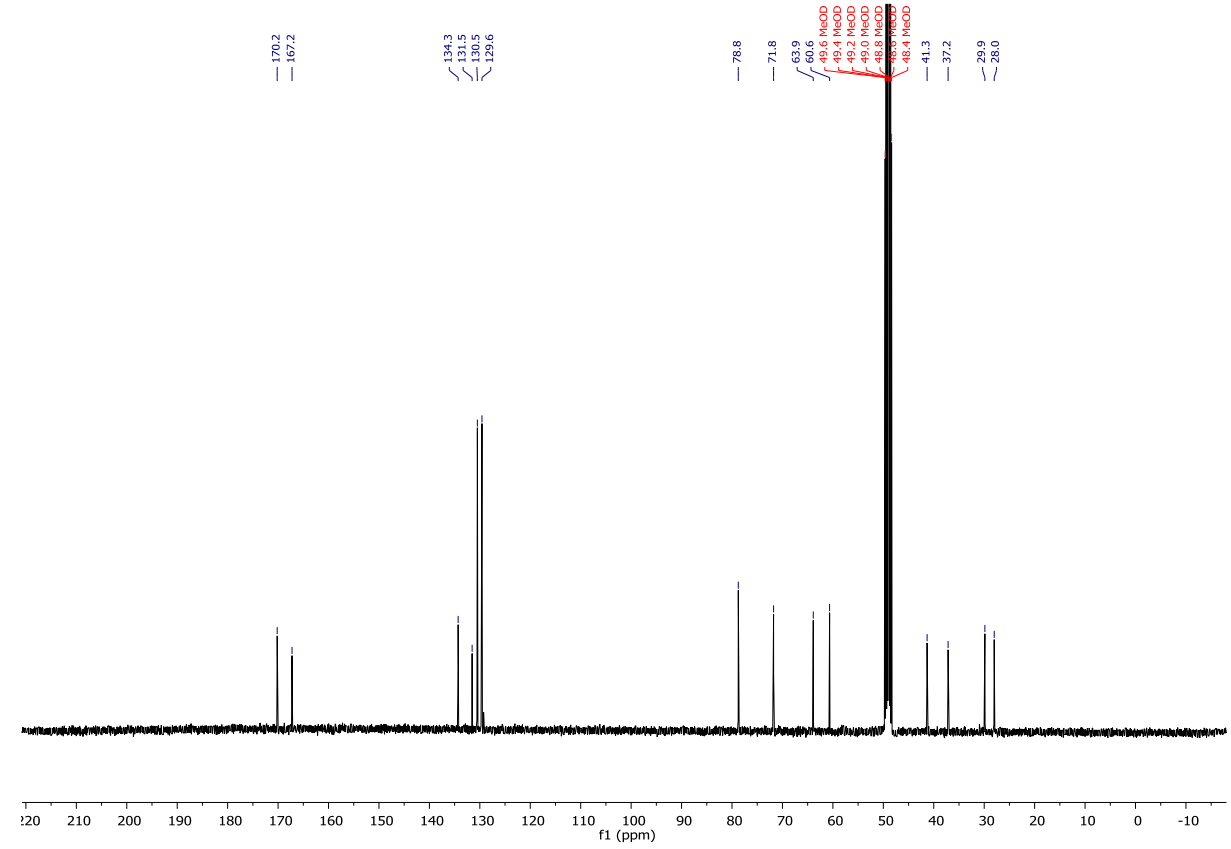


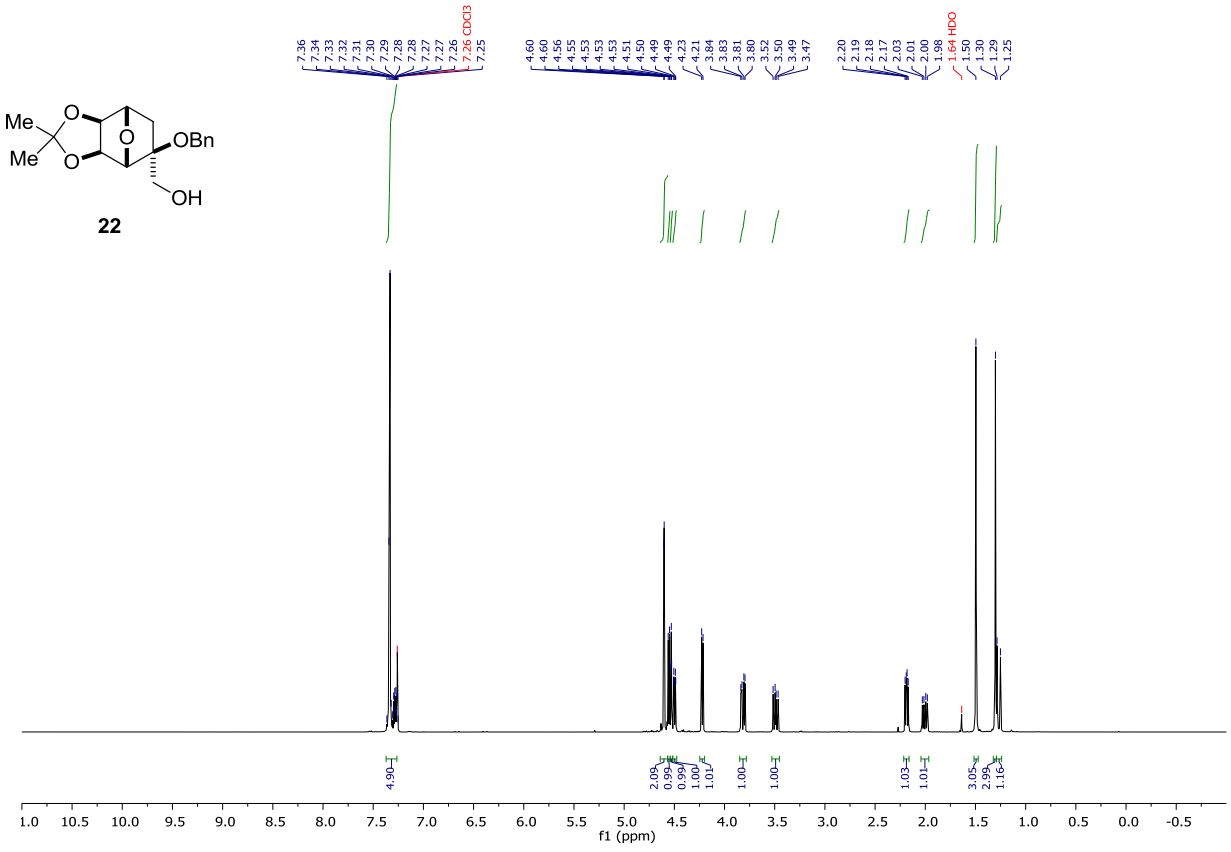



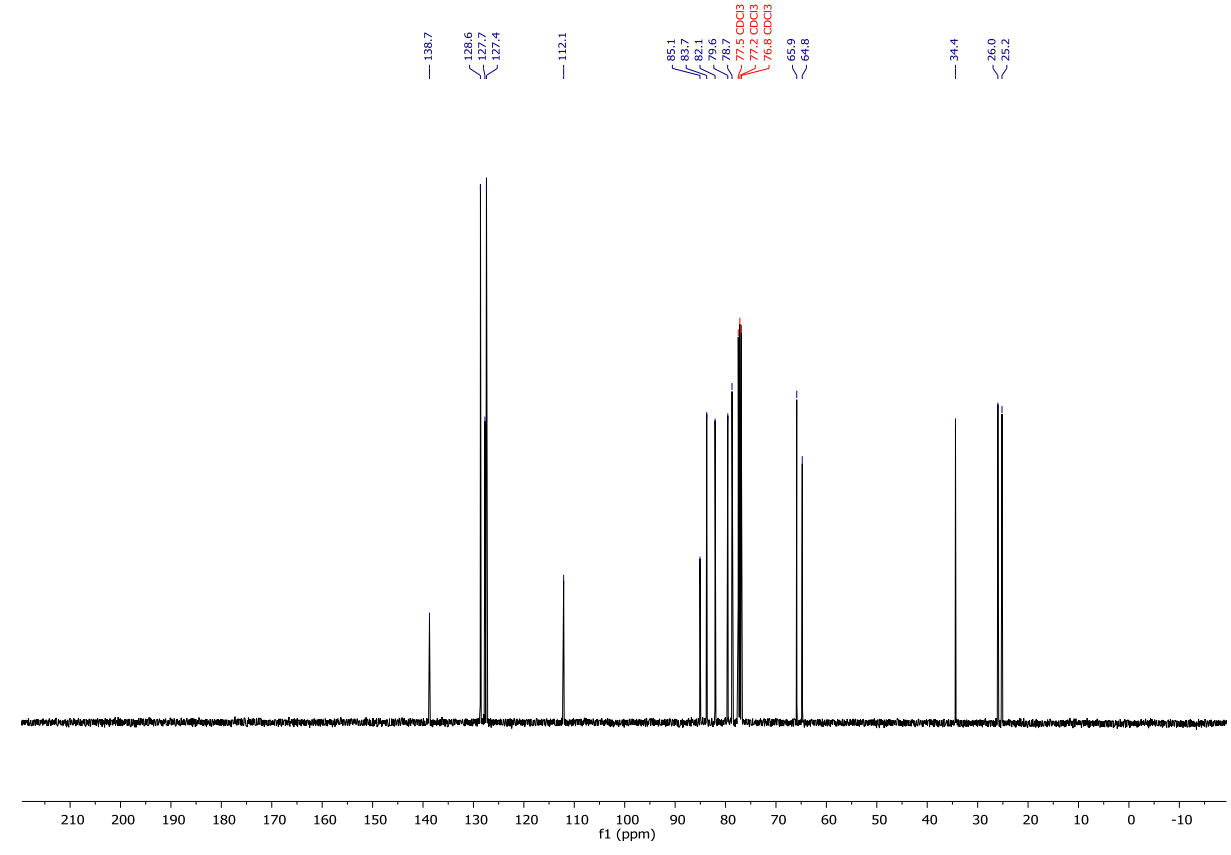

Me
CO2H
NHTs
N
H
18
f1 (ppm)
f1 (ppm)

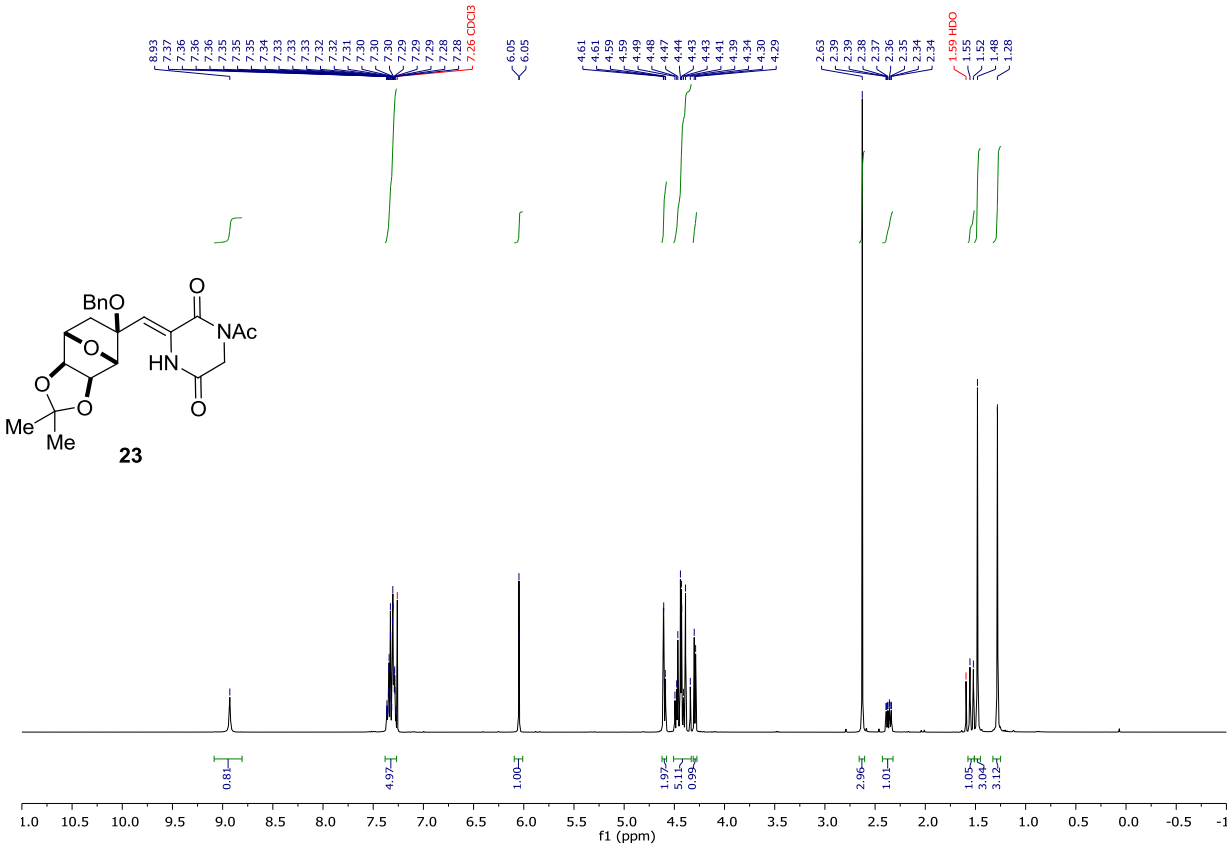

BnO
O
NAc
HN
O
O
19
f1 (ppm)
f1 (ppm)

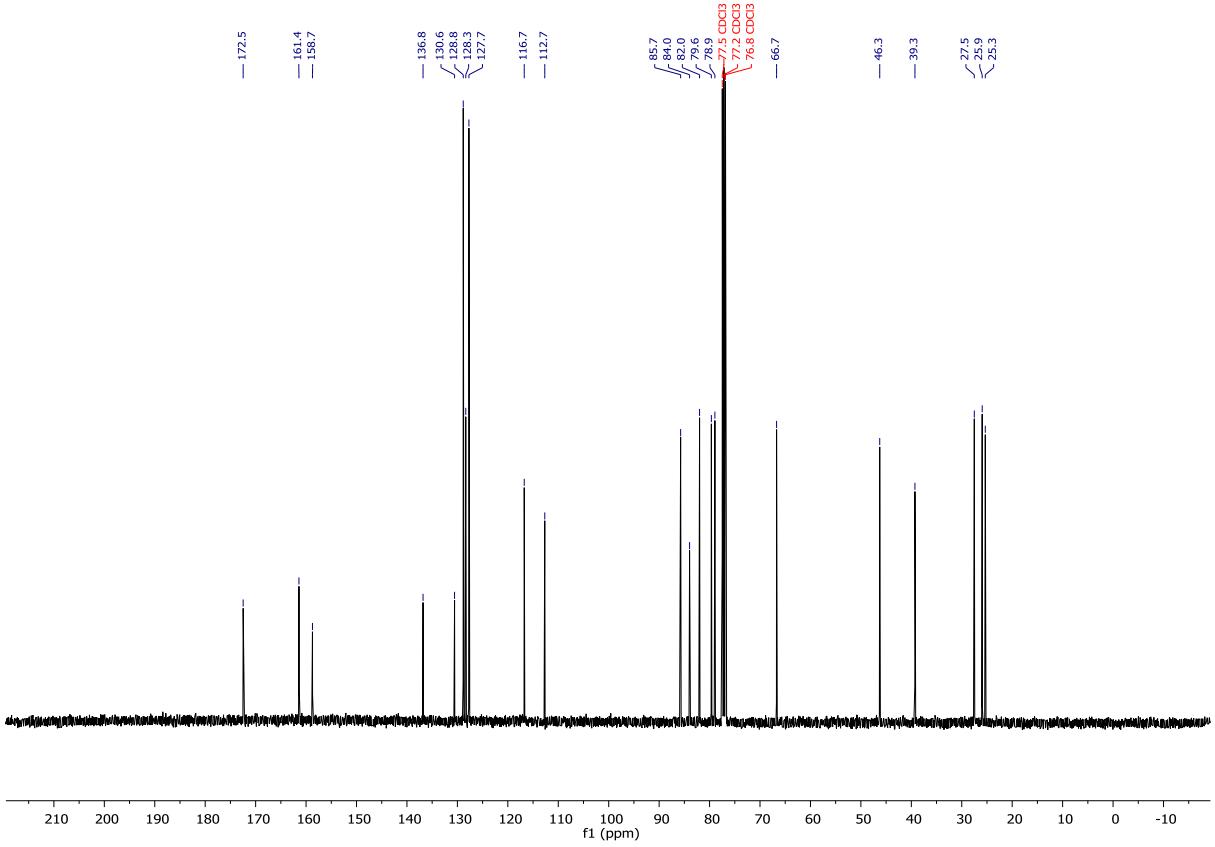

HO
H
O
H
OBz
N
N
OH
BzO
H
H
O
21
f1 (ppm)

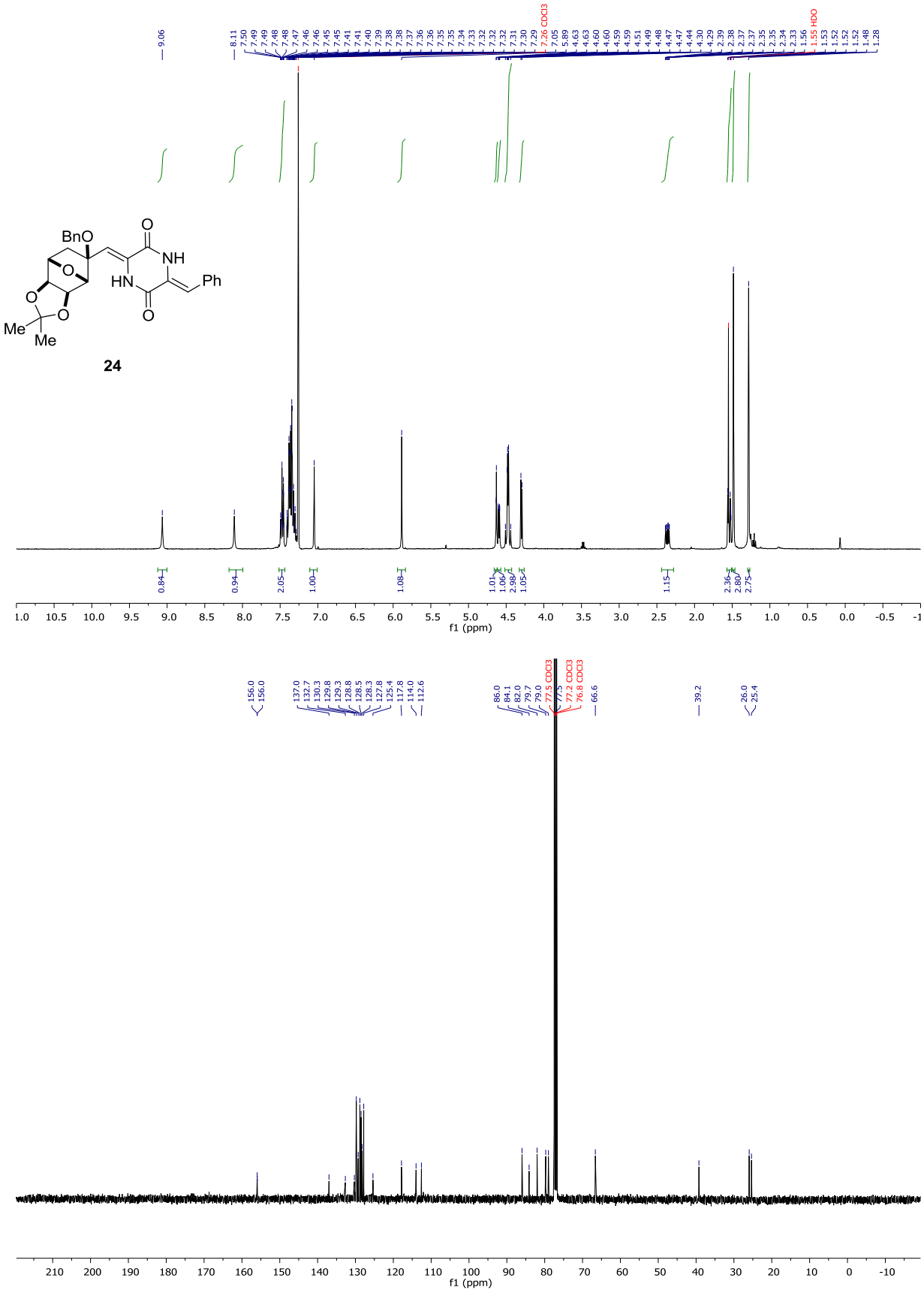

170.2
167.2
134.3
131.5
130.5
129.6
78.8
71.8
63.9
60.6
49.6 MeOD
49.4 MeOD
49.2 MeOD
49.0 MeOD
48.8 MeOD
48.4 MeOD
41.3
37.2
29.9
28.0
f1 (ppm)

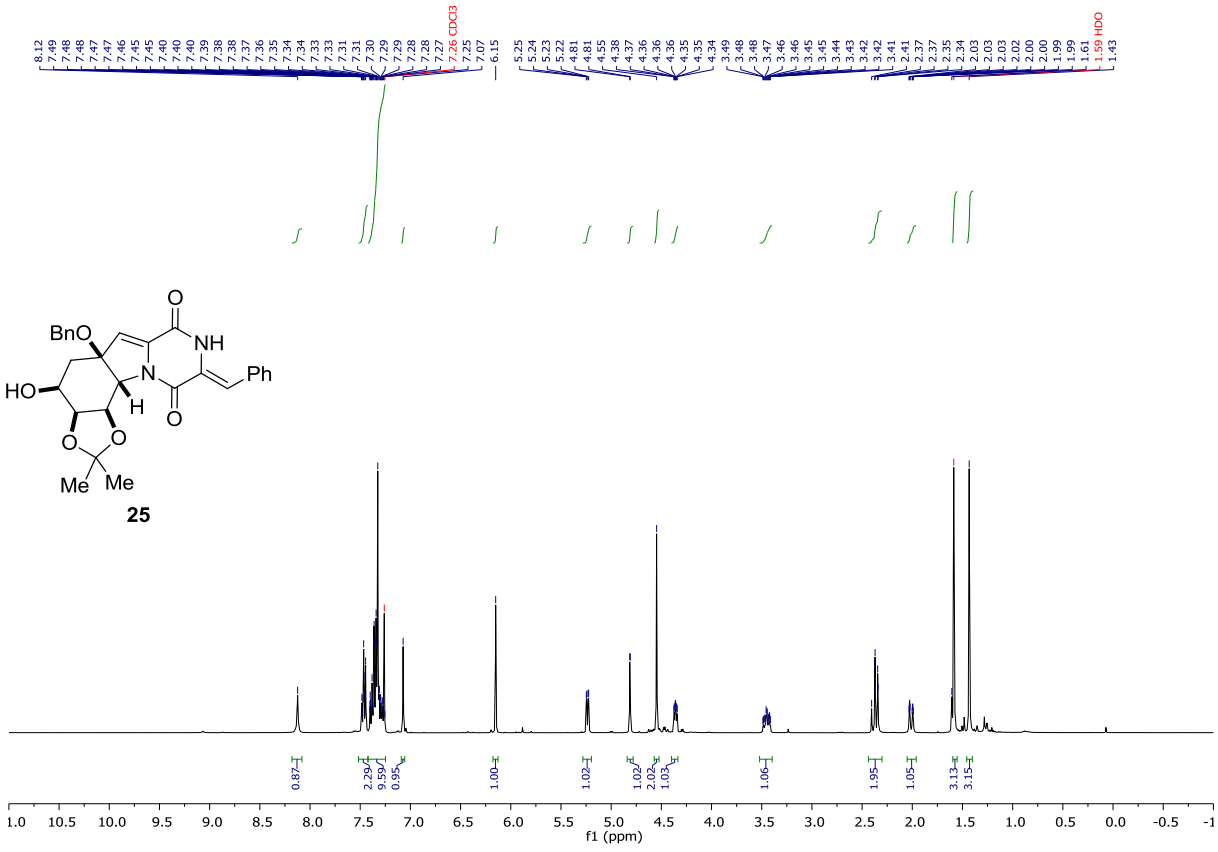

Me
Me
O
O
O
OBn
OH
22
7.36
7.34
7.33
7.32
7.31
7.30
7.29
7.28
7.28
7.27
7.27
7.26
7.26 CDCl3
7.25
4.60
4.60
4.56
4.55
4.53
4.53
4.53
4.51
4.50
4.49
4.49
4.23
4.21
3.84
3.83
3.81
3.80
3.52
3.50
3.49
3.47
2.20
2.19
2.18
2.17
2.03
2.01
2.00
1.98
1.64 HDO
1.50
1.30
1.29
1.25
4.90
2.09
0.99
0.99
1.00
1.01
1.00
1.00
1.03
1.01
3.05
2.99
1.16
f1 (ppm)

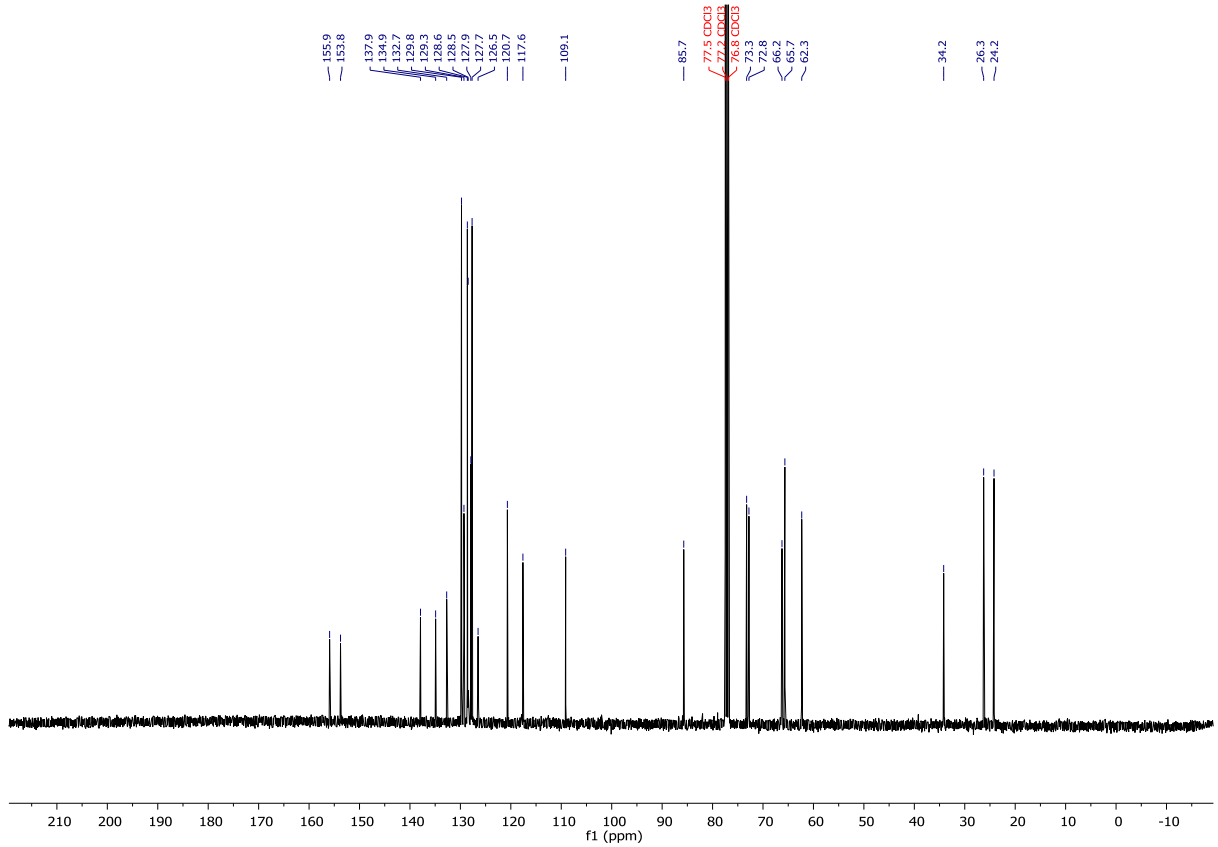

138.7
128.6
127.7
127.4
112.1
85.1
83.7
82.1
79.6
78.7
77.5 CDCl3
77.2 CDCl3
76.8 CDCl3
65.9
64.8
34.4
26.0
25.2
f1 (ppm)

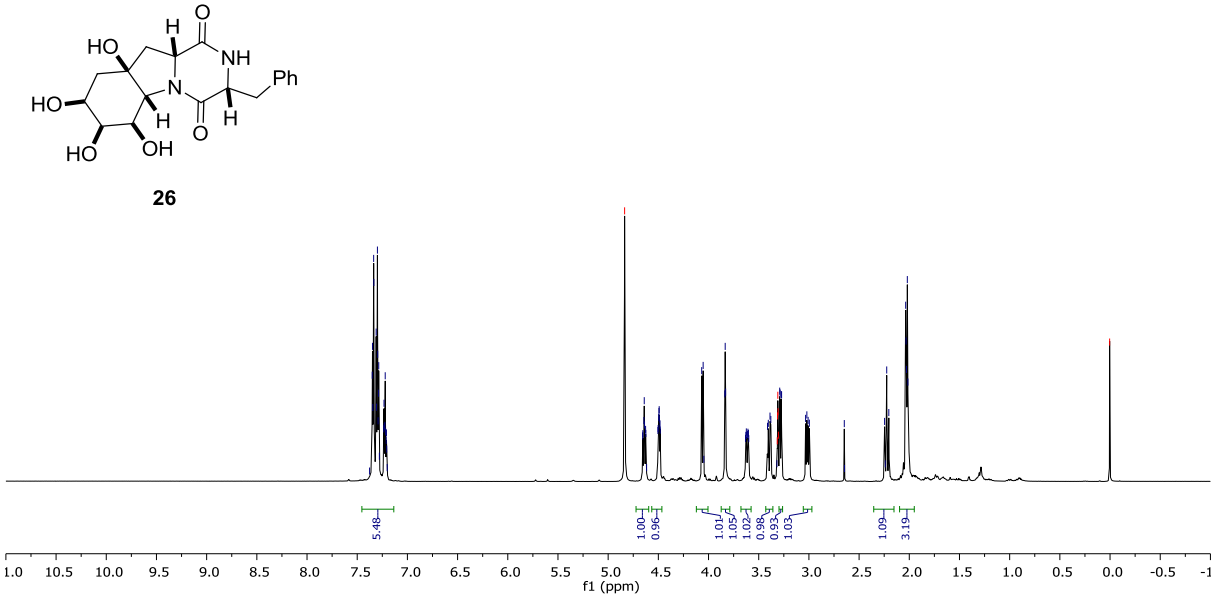

BnO
O
NAc
HN
O
O
O
Me
Me
O
23
f1 (ppm)


f1 (ppm)


BnO
O
NH
HN
Ph
O
O
O
O
Me
Me
24
f1 (ppm)
f1 (ppm)

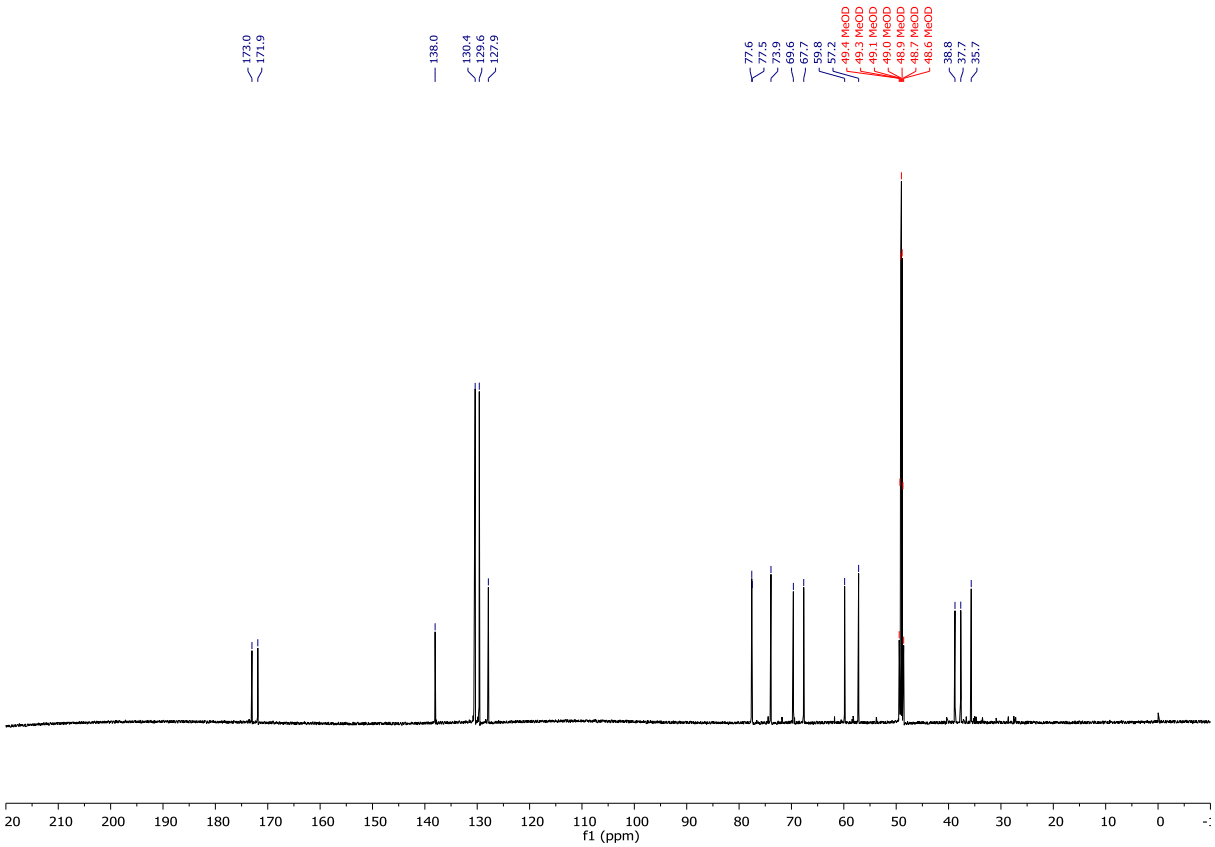

BnO
NH
Ph
HO
N
H
O
O
O
O
Me
Me
25
f1 (ppm)

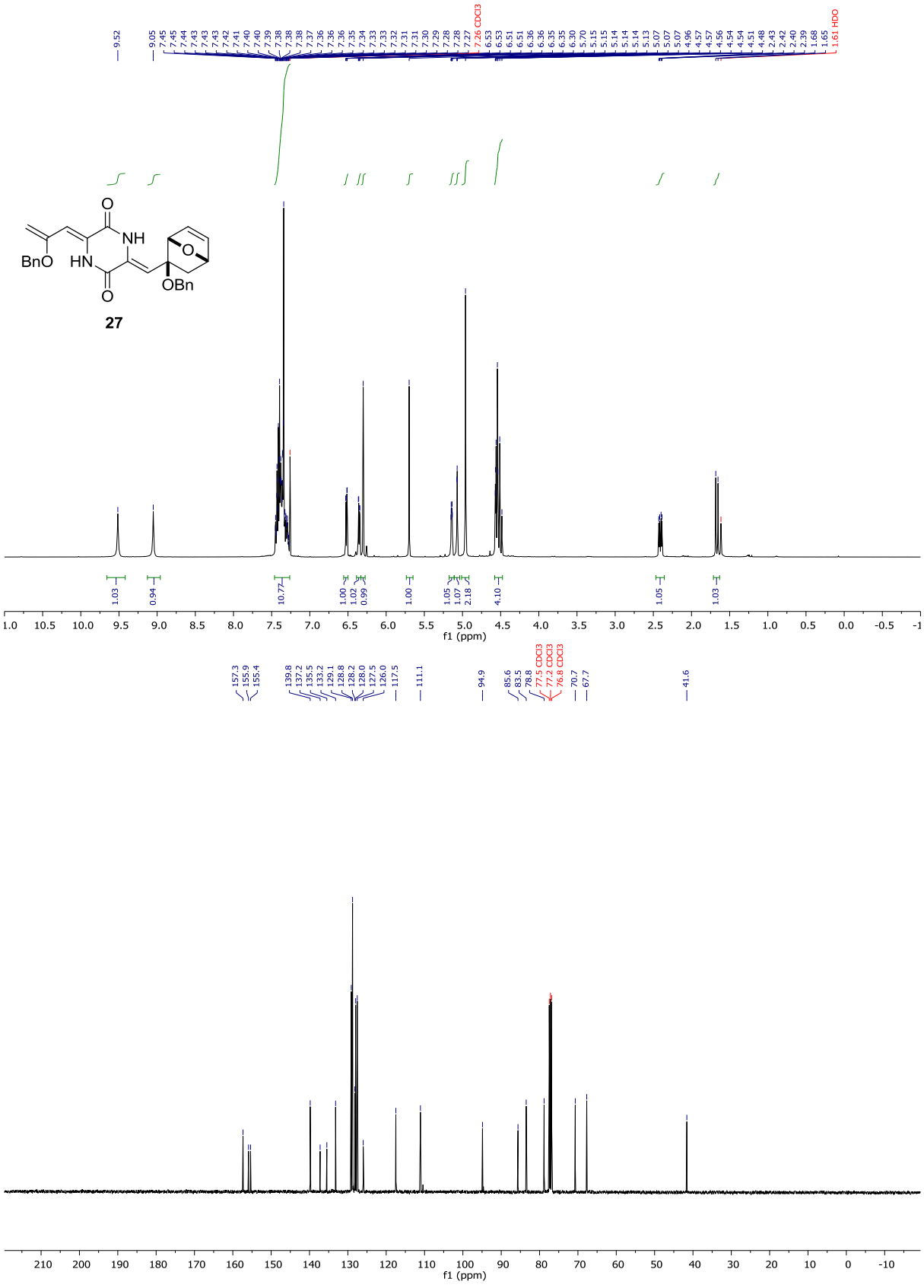

f1 (ppm)

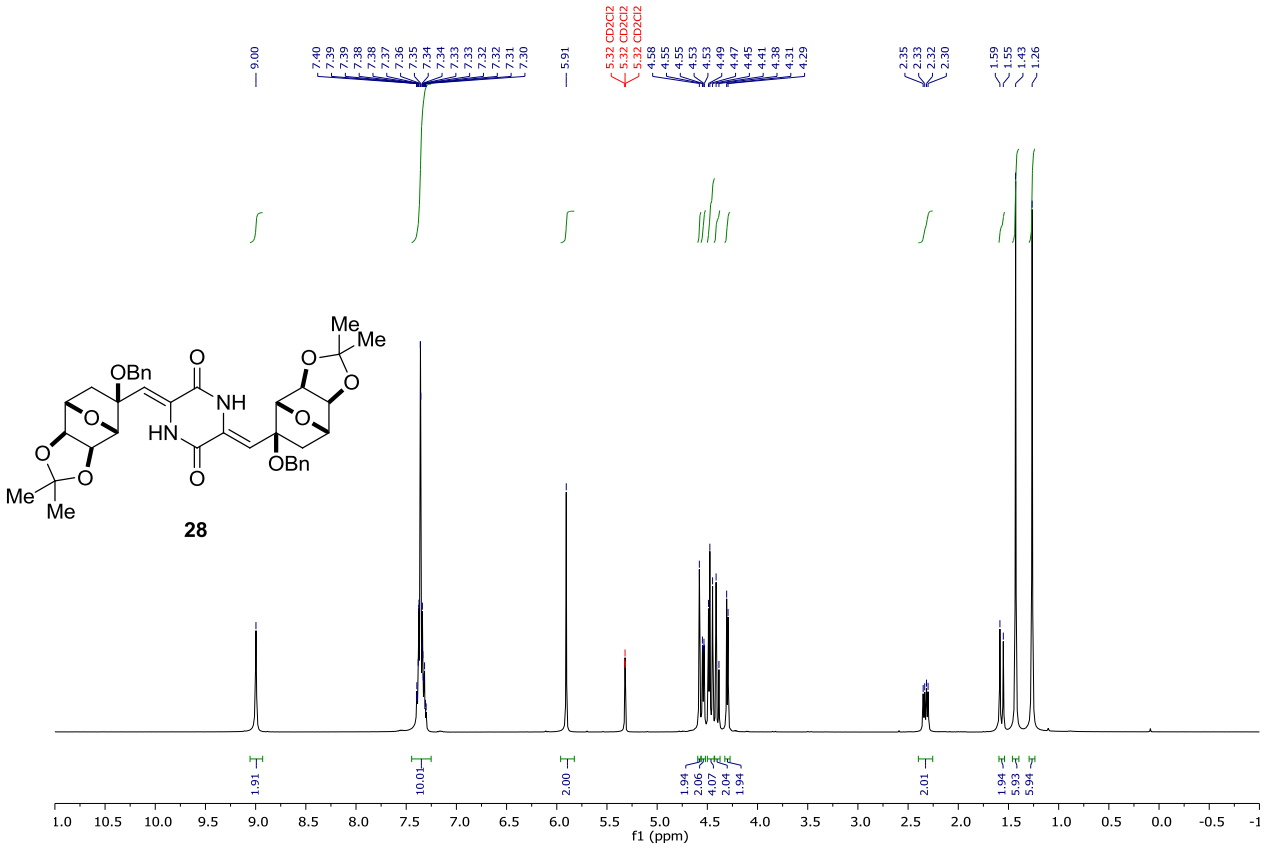


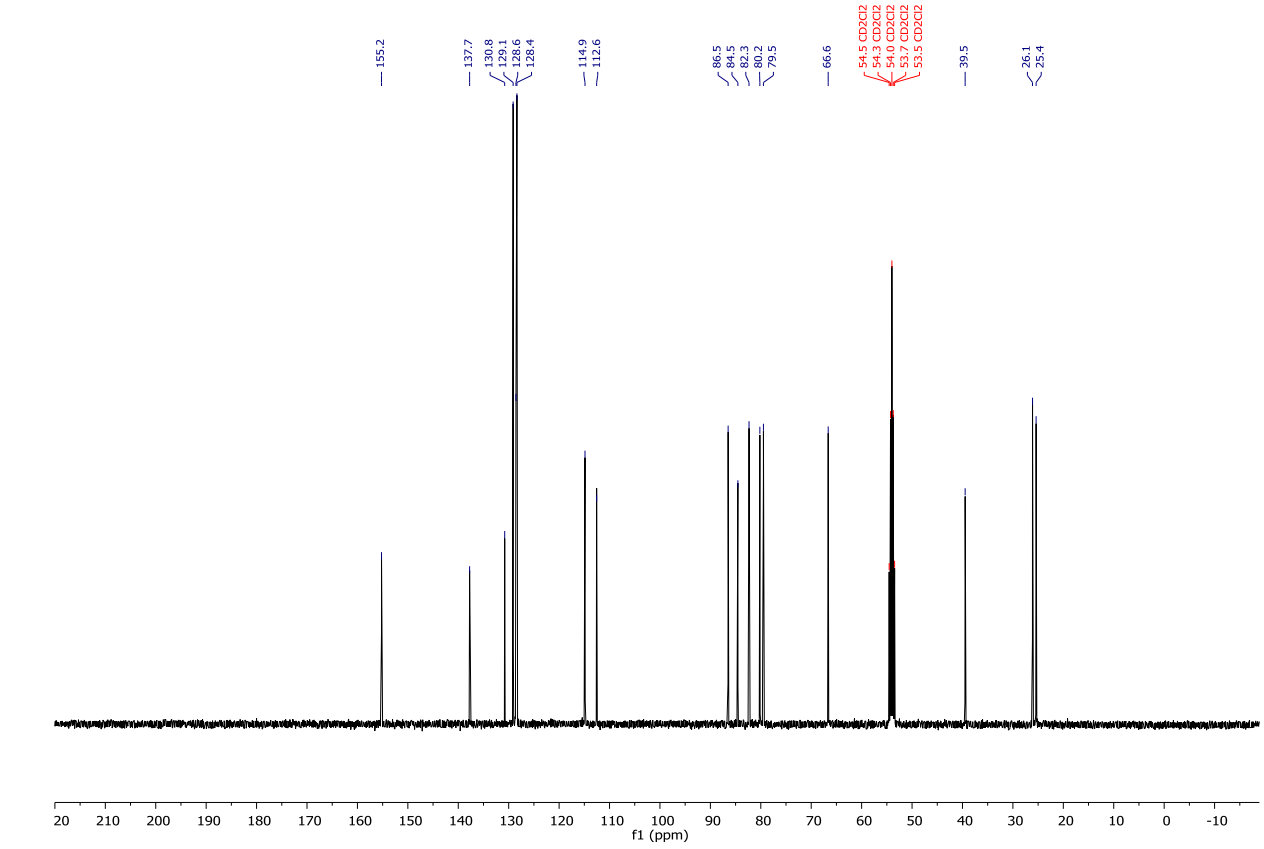

**26**

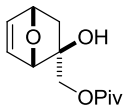



9.52
9.05
7.45
7.45
7.44
7.43
7.43
7.43
7.42
7.41
7.40
7.40
7.40
7.39
7.38
7.38
7.38
7.37
7.36
7.36
7.36
7.35
7.34
7.33
7.33
7.32
7.31
7.31
7.30
7.29
7.28
7.28
7.27
7.26 CDCl3
6.53
6.53
6.51
6.51
6.36
6.36
6.35
6.35
6.30
5.70
5.15
5.15
5.14
5.14
5.13
5.07
5.07
5.07
4.96
4.57
4.57
4.56
4.54
4.54
4.51
4.48
2.43
2.42
2.40
2.39
1.68
1.65
1.61 HDO
O
NH
BnO
HN
O
O
OBn
27
1.03
0.94
10.77
1.00
1.02
0.99
1.00
1.05
1.07
2.18
4.10
1.05
1.03
f1 (ppm)
157.3
155.9
155.4
139.8
137.2
135.5
133.2
129.1
128.8
128.2
128.0
127.5
126.0
117.5
111.1
94.9
85.6
83.5
78.8
77.5 CDCl3
77.2 CDCl3
76.8 CDCl3
70.7
67.7
41.6
f1 (ppm)

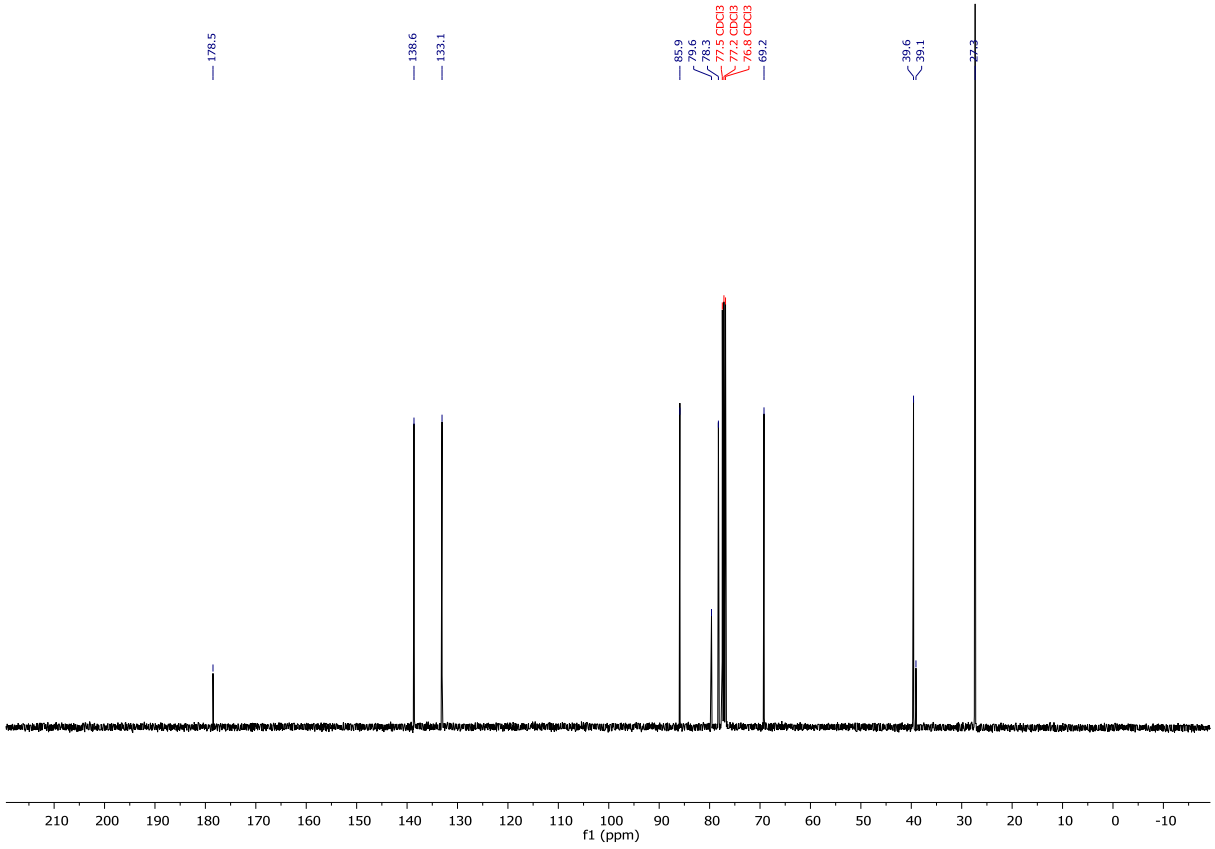

9.00
7.40
7.39
7.39
7.38
7.38
7.37
7.36
7.35
7.34
7.34
7.33
7.33
7.32
7.32
7.31
7.30
5.91
5.32 CD2Cl2
5.32 CD2Cl2
5.32 CD2Cl2
4.58
4.55
4.55
4.53
4.53
4.49
4.47
4.45
4.41
4.38
4.31
4.29
2.35
2.33
2.32
2.30
1.59
1.55
1.43
1.26
OBn
O
NH
HN
O
OBn
Me
Me
Me
Me
O
O
O
O
O
O
28
1.91
10.01
2.00
1.94
2.06
4.07
2.04
1.94
2.01
1.94
5.93
5.94
f1 (ppm)

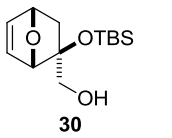

155.2
137.7
130.8
129.1
128.6
128.4
114.9
112.6
86.5
84.5
82.3
80.2
79.5
66.6
54.5 CD2Cl2
54.3 CD2Cl2
54.0 CD2Cl2
53.7 CD2Cl2
53.5 CD2Cl2
39.5
26.1
25.4
f1 (ppm)


O
OH
OPiv

**29**

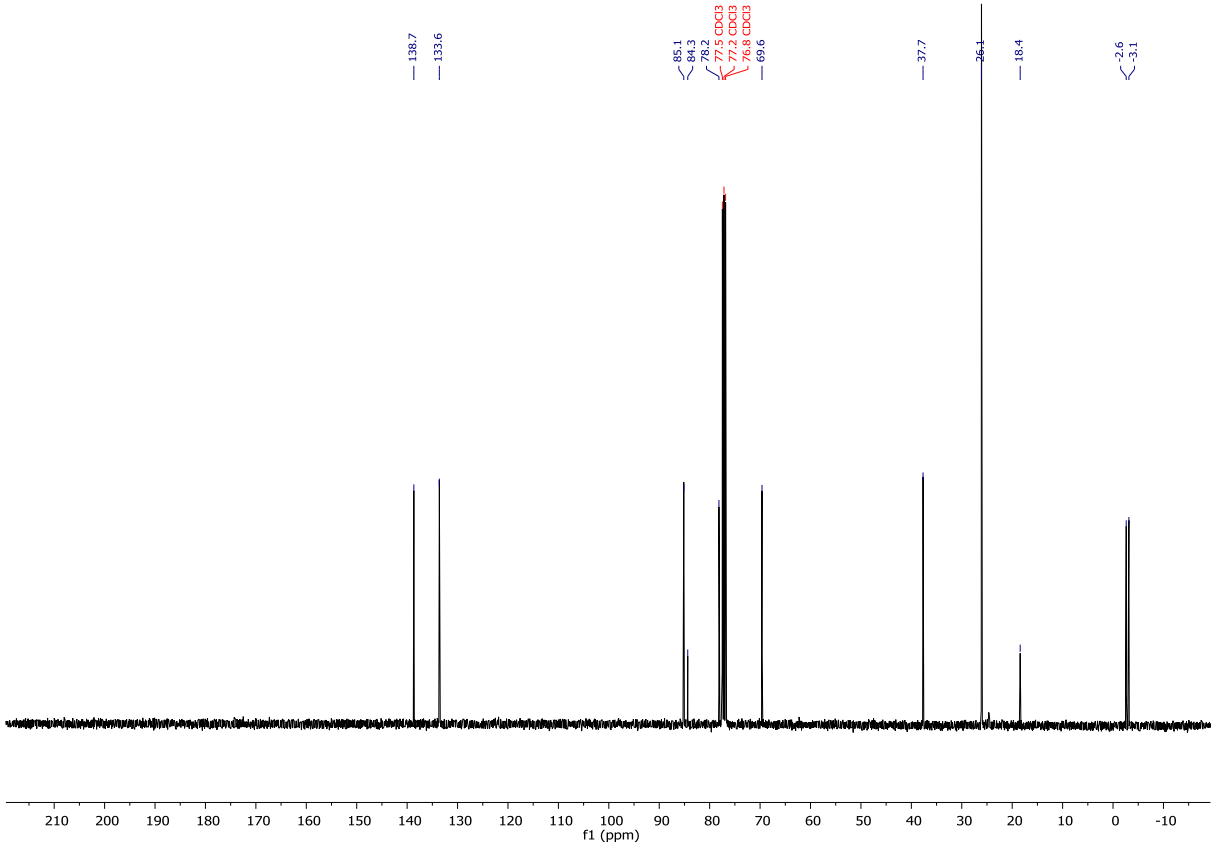

7.26 CDCl3
6.46
6.45
6.44
6.44
6.34
6.34
6.33
6.32
5.07
5.06
5.06
5.05
5.05
5.05
4.66
4.66
4.66
4.24
4.22
3.89
3.89
3.87
3.86
2.43
2.43
1.87
1.86
1.84
1.83
1.63 HDO
1.51
1.48
1.24
1.00
0.99
1.00
0.98
1.03
1.03
0.99
1.04
1.04
9.32
f1 (ppm)

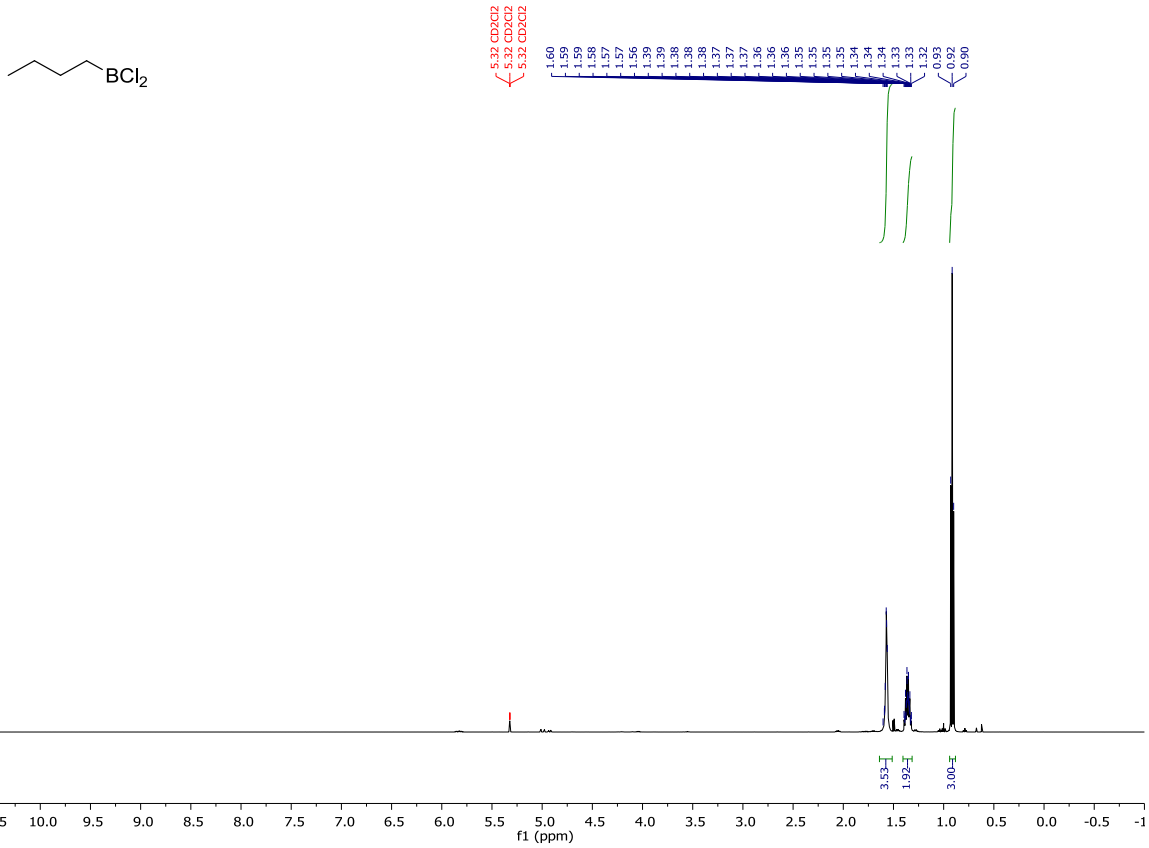

178.5
138.6
133.1
85.9
79.6
78.3
77.5 CDCl3
77.2 CDCl3
76.8 CDCl3
69.2
39.6
39.1
27.2
f1 (ppm)

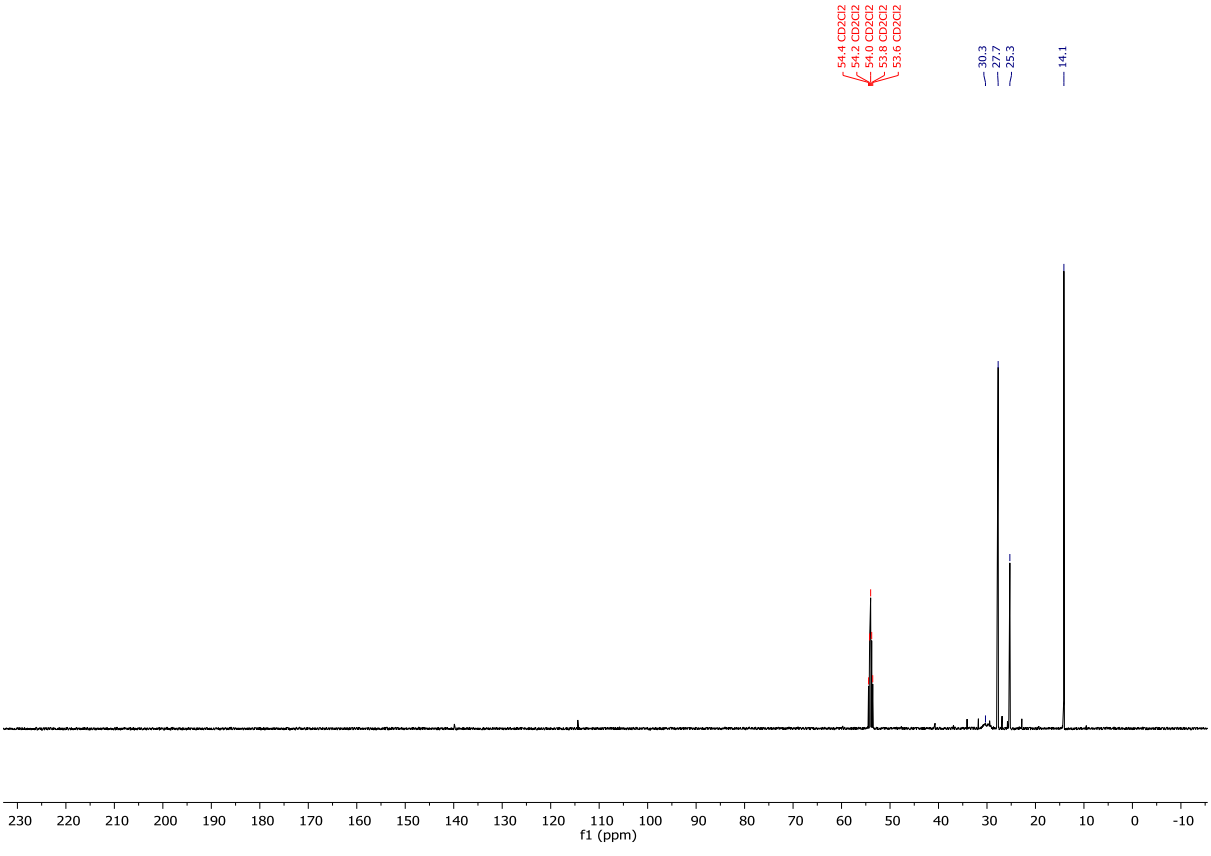

O
OTBS
OH

**30**

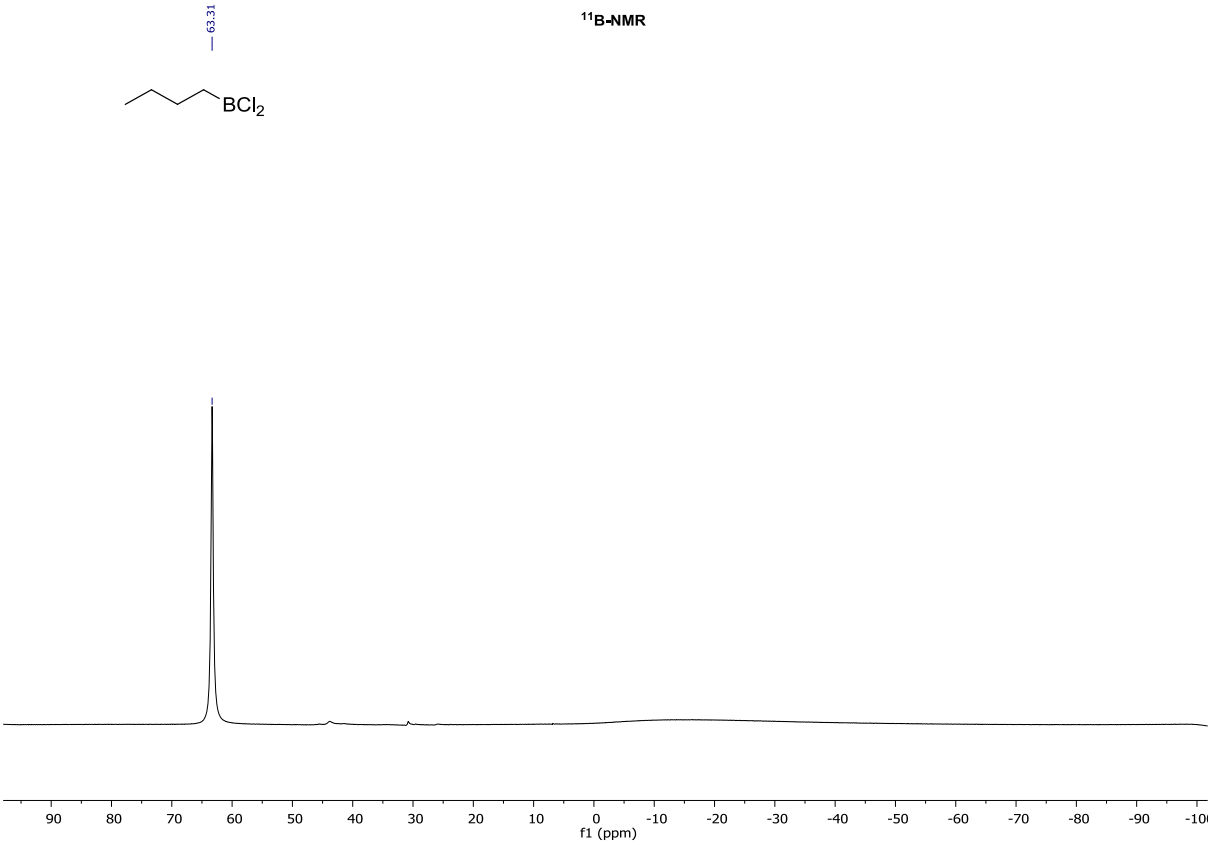

7.26 CDCl3
6.42
6.41
6.40
6.40
6.39
6.38
6.38
5.02
5.02
5.02
5.01
5.01
5.01
4.68
4.68
4.67
3.57
3.56
3.55
3.54
3.27
3.25
3.25
3.22
2.19
2.18
2.16
2.15
1.89
1.88
1.86
1.85
1.57 HDO
1.27
1.24
0.89
0.17
2.00
1.00
1.00
1.05
1.06
1.02
1.06
1.11
9.73
6.30
f1 (ppm)


138.7
133.6
85.1
84.3
78.2
77.5 CDCl3
77.2 CDCl3
76.8 CDCl3
69.6
37.7
26.1
18.4
-2.6
-3.1
f1 (ppm)

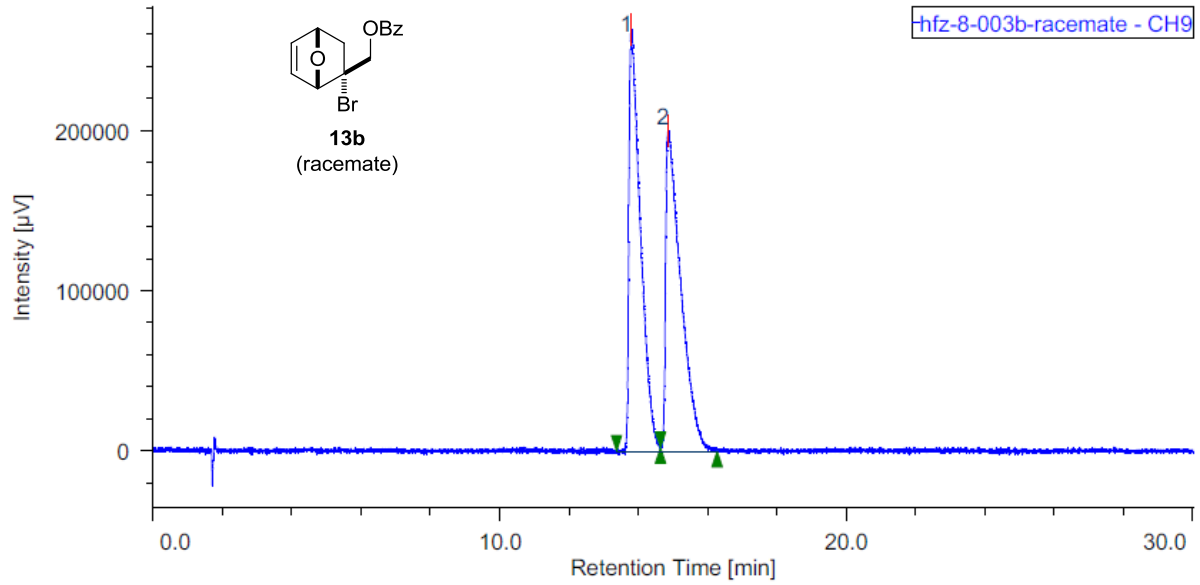

BCl2
5.32 CD2Cl2
5.32 CD2Cl2
5.32 CD2Cl2
1.60
1.59
1.59
1.58
1.57
1.57
1.56
1.39
1.39
1.38
1.38
1.38
1.37
1.37
1.37
1.36
1.36
1.36
1.35
1.35
1.35
1.35
1.34
1.34
1.34
1.33
1.33
1.32
0.93
0.92
0.90
3.53
1.92
3.00
1.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)


54.4 CD2Cl2
54.2 CD2Cl2
54.0 CD2Cl2
53.8 CD2Cl2
53.6 CD2Cl2
30.3
27.7
25.3
14.1
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

**$^{11}$B-NMR**


63.31
BCl2
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
f1 (ppm)

## 4. SFC Data

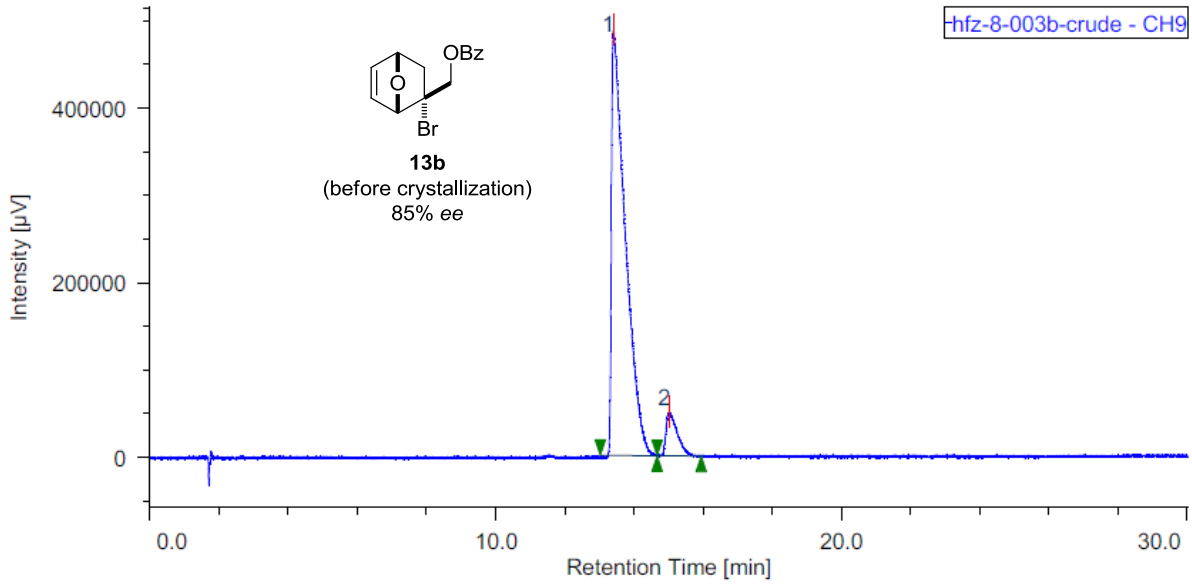



| | |
|---|---|
| Chromatogram Information | |
| User Name | sfc |
| Date Modified | 31.10.2013 22:52:26 |
| Description | |
| HPLC System Name | Jasco SFC |
| Injection Date | 31.10.2013 22:10:23 |
| Volume | 10.00 [µL] |
| Sample Number | 111 |
| Project Name | EMC-SFC |
| Acquisition Time | 30.0 [min] |
| Acquisition Sequence | hfz-8-003b |
| Control Method | column5-99CO2-25C-flow2-30min |
| Peak ID Table | |
| Calibration Method | |
| Additional Information | |

**Channel & Peak Information Table**

| | |
|---|---|
| Chromatogram Name | hfz-8-003b-racemate-CH9 |
| Sample Name | |
| Channel Name | 225.0nm |
| Sampling Interval | 400 [msec] |
| Peak Method | (Manual) |
| Formula | |
| Decision | |

| # | Peak Name | CH | tR [min] | Area [µV·sec] | Height [µV] | Area% | Height% | Quantity | NTP | Resolution | Symmetry Factor | Warning |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Unknown | 9 | 13.800 | 6012872 | 262624 | 49.762 | 56.824 | N/A | 8623 | 1.561 | 3.041 | |
| 2 | Unknown | 9 | 14.873 | 6070387 | 199546 | 50.238 | 43.176 | N/A | 5759 | N/A | 3.466 | |



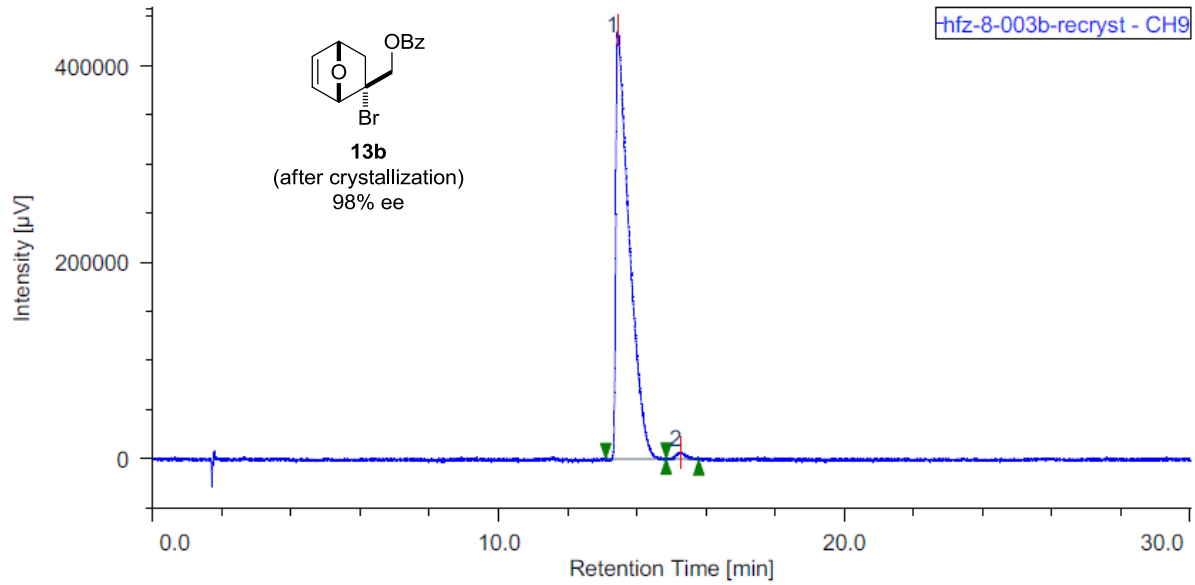

Chromatogram Information

| | |
|---|---|
| User Name | sfc |
| Date Modified | 31.10.2013 23:13:39 |
| Description | |
| HPLC System Name | Jasco SFC |
| Injection Date | 31.10.2013 22:42:03 |
| Volume | 10.00 [µL] |
| Sample Number | 112 |
| Project Name | EMC-SFC |
| Acquisition Time | 30.0 [min] |
| Acquisition Sequence | hfz-8-003b |
| Control Method | column5-99CO2-25C-flow2-30min |
| Peak ID Table | |
| Calibration Method | |
| Additional Information | |

**Channel & Peak Information Table**

| | |
|---|---|
| Chromatogram Name | hfz-8-003b-crude-CH9 |
| Sample Name | |
| Channel Name | 225.0nm |
| Sampling Interval | 400 [msec] |
| Peak Method | (Manual) |
| Formula | |
| Decision | |

| # | Peak Name | CH | tR [min] | Area [µV·sec] | Height [µV] | Area% | Height% | Quantity | NTP | Resolution | Symmetry Factor | Warning |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Unknown | 9 | 13.413 | 13656770 | 487338 | 92.383 | 90.669 | N/A | 5437 | 2.477 | 3.969 | |
| 2 | Unknown | 9 | 15.040 | 1126034 | 50151 | 7.617 | 9.331 | N/A | 10419 | N/A | 2.055 | |

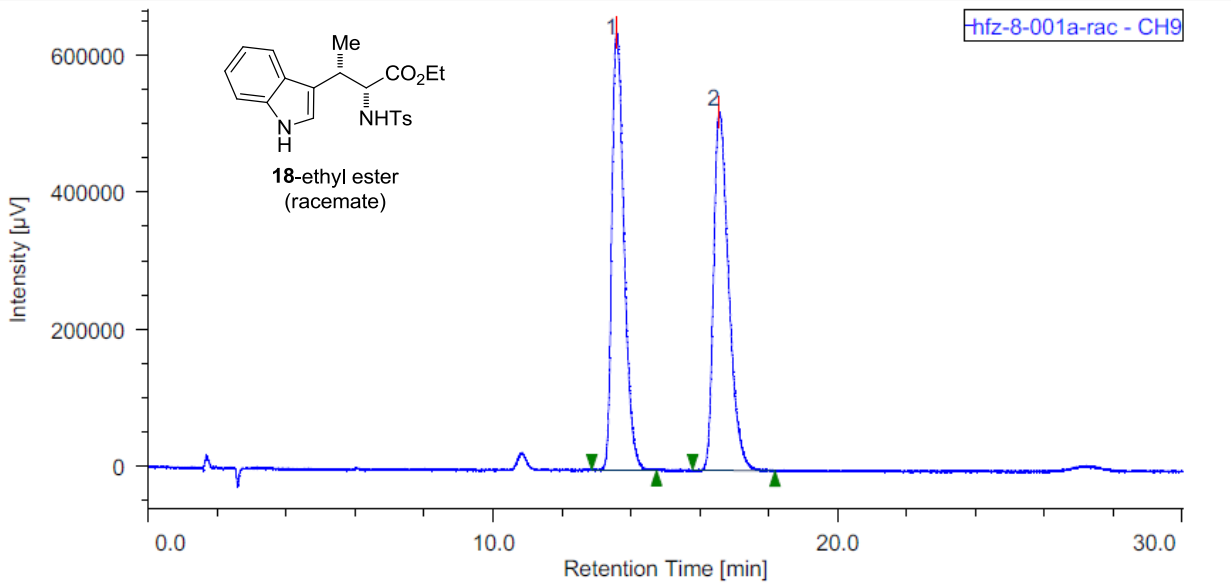



| | |
|---|---|
| Chromatogram Information | |
| User Name | sfc |
| Date Modified | 31.10.2013 23:43:43 |
| Description | |
| HPLC System Name | Jasco SFC |
| Injection Date | 31.10.2013 23:13:43 |
| Volume | 10.00 [µL] |
| Sample Number | 113 |
| Project Name | EMC-SFC |
| Acquisition Time | 30.0 [min] |
| Acquisition Sequence | hfz-8-003b |
| Control Method | column5-99CO2-25C-flow2-30min |
| Peak ID Table | |
| Calibration Method | |
| Additional Information | |

**Channel & Peak Information Table**

| | |
|---|---|
| Chromatogram Name | hfz-8-003b-recryst-CH9 |
| Sample Name | |
| Channel Name | 225.0nm |
| Sampling Interval | 400 [msec] |
| Peak Method | (Manual) |
| Formula | |
| Decision | |

| # | Peak Name | CH | tR [min] | Area [µV·sec] | Height [µV] | Area% | Height% | Quantity | NTP | Resolution | Symmetry Factor | Warning |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Unknown | 9 | 13.453 | 11804788 | 435570 | 98.967 | 98.424 | N/A | 5881 | 2.889 | 3.908 | |
| 2 | Unknown | 9 | 15.287 | 123264 | 6976 | 1.033 | 1.576 | N/A | 11468 | N/A | 1.121 | |

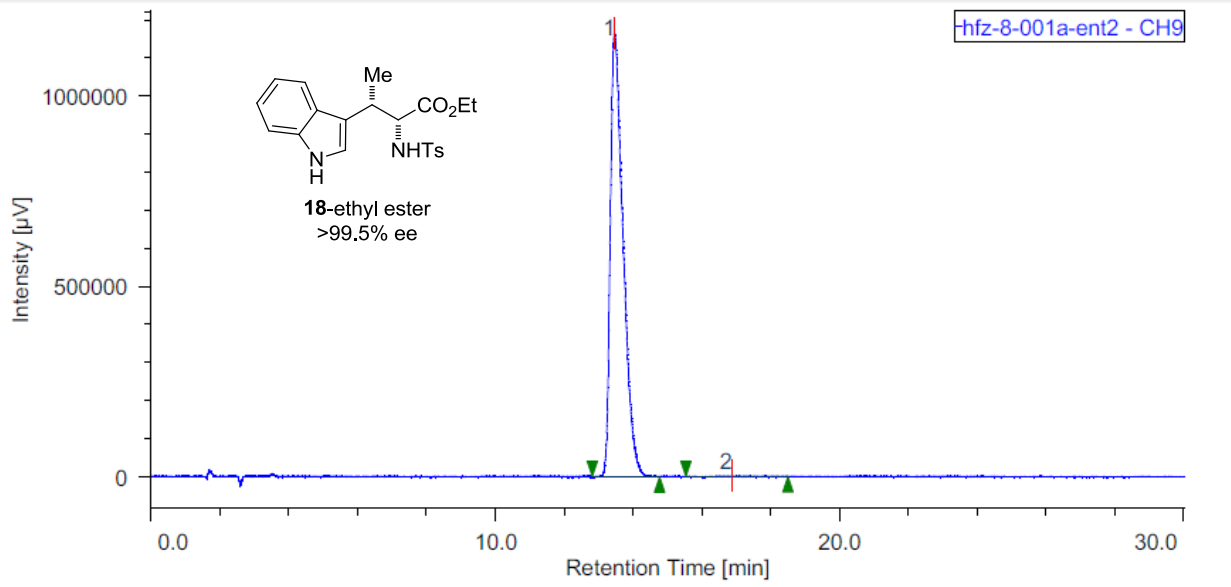



| | |
|---|---|
| Chromatogram Information | |
| User Name | sfc |
| Date Modified | 28.10.2013 15:03:29 |
| Description | |
| HPLC System Name | Jasco SFC |
| Injection Date | 28.10.2013 14:33:27 |
| Volume | 10.00 [µL] |
| Sample Number | 111 |
| Project Name | EMC-SFC |
| Acquisition Time | 30.0 [min] |
| Acquisition Sequence | hfz-8-001a-recrystallized |
| Control Method | column1-85CO2-25C-flow2-30min |
| Peak ID Table | |
| Calibration Method | |
| Additional Information | |

**Channel & Peak Information Table**

| | |
|---|---|
| Chromatogram Name | hfz-8-001a-rac-CH9 |
| Sample Name | |
| Channel Name | 220.0nm |
| Sampling Interval | 400 [msec] |
| Peak Method | (Manual) |
| Formula | |
| Decision | |

| # | Peak Name | CH | tR [min] | Area [µV·sec] | Height [µV] | Area% | Height% | Quantity | NTP | Resolution | Symmetry Factor | Warning |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Unknown | 9 | 13.587 | 15763738 | 637406 | 49.779 | 54.996 | N/A | 7195 | 4.182 | 1.436 | |
| 2 | Unknown | 9 | 16.560 | 15903616 | 521604 | 50.221 | 45.004 | N/A | 7118 | N/A | 1.516 | |




| | |
|---|---|
| Chromatogram Information | |
| User Name | sfc |
| Date Modified | 28.10.2013 15:35:07 |
| Description | |
| HPLC System Name | Jasco SFC |
| Injection Date | 28.10.2013 15:05:06 |
| Volume | 10.00 [µL] |
| Sample Number | 112 |
| Project Name | EMC-SFC |
| Acquisition Time | 30.0 [min] |
| Acquisition Sequence | hfz-8-001a-recrystallized |
| Control Method | column1-85CO2-25C-flow2-30min |
| Peak ID Table | |
| Calibration Method | |
| Additional Information | |

**Channel & Peak Information Table**

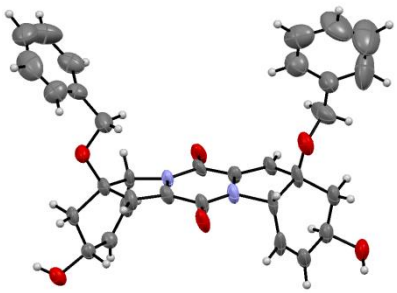
| | |
|---|---|
| Chromatogram Name | hfz-8-001a-ent2-CH9 |
| Sample Name | |
| Channel Name | 220.0nm |
| Sampling Interval | 400 [msec] |
| Peak Method | (Manual) |
| Formula | |
| Decision | |

| # | Peak Name | CH | tR [min] | Area [µV·sec] | Height [µV] | Area% | Height% | Quantity | NTP | Resolution | Symmetry Factor | Warning |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Unknown | 9 | 13.467 | 30424996 | 1163586 | 99.978 | 99.920 | N/A | 5874 | 1.479 | 1.679 | |
| 2 | Unknown | 9 | 16.860 | 6699 | 936 | 0.022 | 0.080 | N/A | 299 | N/A | 1.116 | |

## 5. X-Ray Crystallographic Data

### 5.1 Compound *ent*-1

**Table 1:** Crystal data and structure refinement for compound *ent*-**1**



*Crystal Data*

| | | |
|---|---|---|
| Empirical Formula: | $C_{65}H_{62}Cl_2N_4O_{12}$ | |
| Formula Weight: | 1162.08 | |
| Temperature: | 100.0(2) K | |
| Radiation: | CuKα (λ = 1.54178 Å) | |
| Crystal System, Space Group: | Monoclinic, $C_2$ | |
| Unit Cell Dimensions: | a = 43.265(2) Å | α = 90° |
| | b = 15.055(1) Å | β = 93.976(3)° |
| | c = 10.237(1) Å | γ = 90° |
| Volume: | 6651.5(5) $Å^3$ | |
| Z: | 4 | |
| Calculated Density: | 1.160 $mg/mm^3$ | |
| Absorption Coefficient: | 1.365 $mm^{-1}$ | |
| F(000): | 2440.0 | |
| Crystal Size: | (0.260 × 0.080 × 0.015) $mm^3$ | |

*Data Collection*

| | |
|---|---|
| 2Θ Range for Data Collection: | 8.66–135.6° |
| Index Ranges: | $-50 \le h \le 51$, $-17 \le k \le 15$, $-12 \le l \le 8$ |
| Reflections Collected / Unique: | 19920 / 8767[R(int) = 0.0481] |
| Completeness to 2Θ = 135.6°: | 94.4% |

*Solution Refinement*

| | |
|---|---|
| Refinement Method: | least squares minimization |
| Data / Restraints / Parameters: | 8767 / 1 / 709 |
| Goodness-of-Fit on $F^2$: | 1.023 |
| Final R Indexes [I>=2σ (I)]: | $R_1$ = 0.0773, $wR_2$ = 0.2051 |
| Final R Indexes (all Data): | $R_1$ = 0.0869, $wR_2$ = 0.2159 |
| Largest Diff. Peak and Hole: | 0.52 and –0.66 e $Å^{-3}$ |
| Flack Parameter: | 0.15(3) |

*Experimental*

Single crystals of compound *ent*-**1** were crystallized from $CH_2Cl_2$. A suitable crystal was selected under a microscope using polarized light and tip-mounted on a BRUKER ApexII Duo diffractometer. The crystal was kept at 100.0(2) K during data collection. Using OLEX2[10], the structure was solved with the Superflip[11] structure solution program using charge flipping and refined with the SHELXL[11] refinement package using least squares minimization.

[10] Dolomanov, O.V.; Bourhis, L.J.; Gildea, R.J.; Howard, J.A.K.; Puschmann, H. *J. Appl. Cryst.* **2009**, *42*, 339-341.
[11] SHELXS-97, SHELXL-97: Sheldrick, G.M. *Acta Cryst.* **2008**, *A64*, 112-122.

## 5.2 Compound 13

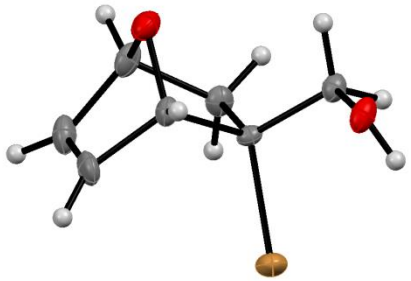


**Table 2:** Crystal data and structure refinement for compound **13**

*Crystal Data*

| | | |
|---|---|---|
| Empirical Formula: | $C_7H_9BrO_2$ | |
| Formula Weight: | 205.05 | |
| Temperature: | 100.0(2) K | |
| Radiation: | MoKα (λ = 0.71073 Å) | |
| Crystal System, Space Group: | Trigonal, $P3_2$ | |
| Unit Cell Dimensions: | a = 17.812(2) Å | α = 90° |
| | b = 17.812(2) Å | β = 90° |
| | c = 6.2589(5) Å | γ = 120° |
| Volume: | 1719.7(3) $Å^3$ | |
| Z: | 9 | |
| Calculated Density: | 1.782 $mg/mm^3$ | |
| Absorption Coefficient: | 5.313 $mm^{-1}$ | |
| F(000): | 918.0 | |
| Crystal Size: | (0.32 × 0.08 × 0.05) $mm^3$ | |

*Data Collection*

| | |
|---|---|
| 2Θ Range for Data Collection: | 2.64–61.0° |
| Index Ranges: | $-25 \leq h \leq 25, -25 \leq k \leq 25, -8 \leq l \leq 8$ |
| Reflections Collected / Unique: | 18642 / 6360[R(int) = 0.0301] |
| Completeness to 2Θ = 61.0°: | 100% |

*Solution Refinement*

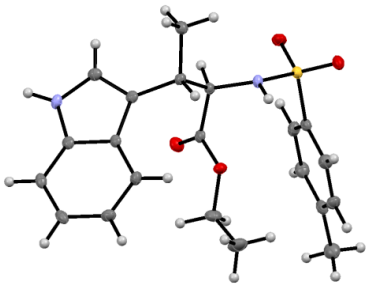
| | |
|---|---|
| Refinement Method: | least squares minimization |
| Data / Restraints / Parameters: | 6360 / 1 / 275 |
| Goodness-of-Fit on $F^2$: | 1.033 |
| Final R Indexes [I>=2σ (I)]: | $R_1 = 0.0235$, $wR_2 = 0.0456$ |
| Final R Indexes (all Data): | $R_1 = 0.0255$, $wR_2 = 0.0467$ |
| Largest Diff. Peak and Hole: | 0.74 and –0.48 e $Å^{-3}$ |
| Flack Parameter: | 0.008(5) |

*Experimental*

Single crystals of compound **13** were crystallized from a $Et_2O$/pentane mixture. A suitable crystal was selected under a microscope using polarized light and tip-mounted on a BRUKER ApexII Duo diffractometer. The crystal was kept at 100.0(2) during data collection. Using OLEX2[10], the structure was solved with the SHELXS[11] structure solution program using direct methods and refined with the SHELXL[11] refinement package using least squares minimization.

## 5.3 Compound 18-Ethyl ester

**Table 3:** Crystal data and structure refinement for compound **18**-ethyl ester



*Crystal Data*

| | | |
|---|---|---|
| Empirical Formula: | $C_{21}H_{24}N_2O_4S$ | |
| Formula Weight: | 400.48 | |
| Temperature: | 99.99K | |
| Radiation: | MoKα (λ = 0.71073 Å) | |
| Crystal System, Space Group: | Monoclinic, $P2_1$ | |
| Unit Cell Dimensions: | a = 11.639(1) Å | α = 90° |
| | b = 5.5765(3) Å | β = 106.278(3)° |
| | c = 15.545(1) Å | γ = 90° |
| Volume: | 968.48(10) $Å^3$ | |
| Z: | 2 | |
| Calculated Density: | 1.373 $mg/mm^3$ | |
| Absorption Coefficient: | 0.198 $mm^{-1}$ | |
| F(000): | 424.0 | |
| Crystal Size: | (0.240 × 0.045 × 0.015) $mm^3$ | |

*Data Collection*

| | |
|---|---|
| 2Θ Range for Data Collection: | 5.13–55.19° |
| Index Ranges: | $-15 \le h \le 15, -7 \le k \le 7, -20 \le l \le 20$ |
| Reflections Collected / Unique: | 22103 / 4487 [R(int) = 0.0442, R(sigma) = 0.0471] |
| Completeness to 2Θ = 55.19°: | 99.8% |

*Solution Refinement*

| | |
|---|---|
| Refinement Method: | least squares minimization |
| Data / Restraints / Parameters: | 4487 / 3 / 262 |
| Goodness-of-Fit on $F^2$: | 1.028 |
| Final R Indexes [I>=2σ (I)]: | $R_1$ = 0.0341, $wR_2$ = 0.0678 |
| Final R Indexes (all Data): | $R_1$ = 0.0465, $wR_2$ = 0.0720 |
| Largest Diff. Peak and Hole: | 0.23 and –0.31 e $Å^{-3}$ |
| Flack Parameter: | 0.04(3) |

*Experimental*

Single crystals of compound **18**-ethyl ester were crystallized from $CDCl_3$. A suitable crystal was selected under a microscope using polarized light and tip-mounted on a a BRUKER *Kappa ApexII* diffractometer. The crystal was kept at 100.0(2) K during data collection. Using OLEX2[10], the structure was solved with the SHELXS[11] structure solution program using direct methods and refined with the SHELXL[11] refinement package using least squares minimization.