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Supporting Information

Preparation of useful building blocks, α-iodo- and bromoalkanols from cyclic ethers using the Dowex H$^+$/NaX (X=I, Br) approach

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EXPERIMENTAL SECTION

General

^{1}H and ^{13}C NMR spectra were recorded on a 500 MHz spectrometer operating at 500.1 and 125.8 MHz, respectively. The solvent residual peak was used as a standard in the ^{1}H and ^{13}C NMR measurements of $CDCl_3$ and CD_3OD (7.26 ppm or 77.16 ppm for $CDCl_3$ and 3.31 ppm or 49.00 ppm for CD_3OD, respectively)[1], in D_2O 4.79 ppm in the ^{1}H NMR measurements and trimethylsilyl propionic acid sodium salt (TSP) in the ^{13}C measurements (0.00 ppm). The $^3J_{HH}$ couplings were calculated from proton spectra and all J values are given in Hz. The Dowex H$^+$ resin was first washed with water and then oven dried for approx. 20 hours at 120°C before use. NaI was also dried in an oven at 120°C and then stored there until use. Mass spectra were recorded with a Finnigan LCQ quadrupole ion trap mass spectrometer (Finnigan MAT, San Jose, CA, USA) equipped with an electrospray ionization source and elemental analysis (C, H, N) with a Perkin Elmer 2400 Series II CHNS/O organic elemental analyzer (Perkin Elmer Inc., Waltham, MA, USA). The purity of the products was determined from ^{1}H NMR spectra and was ≥ 95 % unless stated otherwise. NOTE: Compounds **18**, **20** and **22** were collected from the silica after elution using EtOAc:MeOH (8:2), since if DCM had been used, then it proved impossible to collect the compounds from the silica and yields were 0-1%. We were unable to measure reasonable mass spectra for the compounds **12a-b**. Reasons for this might be the lack of ionization or degradation of the compounds before reaching the detector.

Preparation of 1-iodobutan-2-ol (2): Oven dried NaI (348 mg, 2.32 mmol), oven dried Dowex 50W-X8 ion exchange resin (H$^+$-form, 1.5 g) and dry acetone (8 ml) were stirred for 15 minutes at room temperature before 1,2-epoxybutane (200 µl, 167 mg, 2.32 mmol) was added in 4 portions and the reaction mixture was stirred for overnight at 50°C. The Dowex was filtered off and washed with DCM and the combined DCM fractions evaporated *in vacuo*. The crude product was dissolved in DCM (5 ml) and washed with 10% $Na_2S_2O_3$ (sodium thiosulfate, 3 ml), the DCM layer was separated, aqueous phase was extracted with DCM (5ml), DCM was separated and the combined DCM layers dried with $MgSO_4$ and removed by evaporation *in vacuo*. 1-Iodobutan-2-ol (253 mg, 55%) was obtained as a crude product with ≥ 90% purity. The crude product (92 mg) was purified by TLC using ethyl acetate/hexane (15:85) as eluent. 1-Iodobutan-2-ol (45 mg, 27%) was obtained as a colorless oil with R_f 0.50. All ^{1}H NMR data were comparable with those reported elsewhere.[2] ^{1}H NMR ($CDCl_3$): δ 3.48-3.41 (m, 1H), 3.41-3.37 (m, 1H), 3.27-3.21 (m, 1H), 1.98 (br, -OH) 1.66-1.54 (m, 2H) 0.97 (t, 3H, $^3J_{HH} = 7.5$). ^{13}C NMR ($CDCl_3$): δ 72.5, 29.7, 16.3, 10.1.

Preparation of 3-iodopropan-1-ol (4a): Oven dried NaI (414 mg, 2.76 mmol), oven dried Dowex 50W-X8 ion exchange resin (H^+-form, 1.5 g) and dry acetonitrile (6 ml) were stirred for 15 minutes at room temperature before trimethylene oxide (180 µl, 161 mg, 2.76 mmol) was added and the reaction mixture were stirred overnight at 50°C. The Dowex was filtered off and washed with DCM which was combined with the reaction mixture and evaporated *in vacuo*. The crude product was dissolved in DCM (10 ml) and washed with 10% $Na_2S_2O_3$ (sodium thiosulfate, 3 ml), DCM layer was separated, aqueous phase was extracted with DCM, DCM was separated and combined DCM layers dried with $MgSO_4$ and removed by evaporation *in vacuo*. The residue was purified by silica column chromatography using ethyl acetate/hexane (3:2) as eluent. 3-Iodopropan-1-ol (267 mg, 53%) was obtained as a colorless oil. All ^1H NMR data were comparable with those reported elsewhere.[3] ^1H NMR ($CDCl_3$): δ 3.74 (t, 2H, $^3J_{HH}$ = 6.0), 3.30 (t, 2H, $^3J_{HH}$ = 7.0), 2.05 (qv, 2H), 1.45 (br, -OH). ^{13}C NMR ($CDCl_3$): δ 62.5, 35.7, 3.1.

Preparation of 3-bromopropan-1-ol (4b): Oven dried NaBr (285 mg, 2.77 mmol), oven dried Dowex 50W-X8 ion exchange resin (H^+-form, 1.0 g) and dry 2-propanol (6 ml) were stirred 15 minutes at room temperature before trimethylene oxide (180 µl, 161 mg, 2.76 mmol) was added and the reaction mixture were stirred for overnight at 50°C. The Dowex was filtered off and washed with DCM which was combined with the reaction mixture and evaporated *in vacuo*. The crude product was dissolved in DCM (10 ml) and washed with 10% $Na_2S_2O_3$ (sodium thiosulfate, 3 ml), the DCM layer was separated, aqueous phase was extracted with DCM, DCM was separated and combined DCM layers dried with $MgSO_4$ and removed by evaporation *in vacuo*. The residue was purified by silica column chromatography using ethyl acetate/hexane (2:1) as eluent. 3-Bromopropan-1-ol (110 mg, 29%) was obtained as a colorless oil. All ^1H and ^{13}C NMR data were comparable with those reported elsewhere.[4] ^1H NMR ($CDCl_3$): δ 3.80 (t, 2H, $^3J_{HH}$ = 5.5), 3.54 (t, 2H, $^3J_{HH}$ = 6.5), 2.10 (qv, 2H), 1.50 (br, -OH). ^{13}C NMR ($CDCl_3$): δ 60.6, 35.2, 30.4.

Preparation of 4-iodobutan-1-ol (6a): Oven dried NaI (173 mg, 1.15 mmol), oven dried Dowex 50W-X8 ion exchange resin (H^+-form, 600 mg) and dry THF (5 ml) were refluxed overnight. The Dowex was filtered off and the filtrate evaporated to dryness *in vacuo*. The residue was dissolved in EtOAc (10 ml) and washed with 10% $Na_2S_2O_3$ (sodium thiosulfate, 3 ml), The EtOAc layer was separated, dried with $MgSO_4$ and removed by evaporation *in vacuo*. 4-Iodobutan-1-ol (198 mg, 86%) was obtained without further purifications as a slightly yellow oil. All ^{1}H NMR data were comparable with those reported elsewhere.[5] ^{1}H NMR ($CDCl_3$) δ 3.69 (t, 2H, $^3J_{HH}$ = 6.5), 3.24 (t, 2H, $^3J_{HH}$ = 6.5), 1.94 (qv, 2H), 1.68 (qv, 2H), 1.41 (br, 1H). ^{13}C NMR ($CDCl_3$) δ 61.8, 33.5, 29.9, 6.6.

Preparation of 4-bromobutan-1-ol (6b): Oven dried NaBr (400 mg, 2.76 mmol), oven dried Dowex 50W-X8 ion exchange resin (H^+-form, 2.0 g) and dry THF (5 ml) were refluxed over the weekend. The Dowex was filtered off and washed with DCM which was combined with the reaction mixture and evaporated *in vacuo*. The residue was purified by silica column chromatography using ethyl acetate/hexane (1:1) as the eluent. 4-Bromobutan-1-ol (202 mg, 34%) was obtained as a colorless oil. All ^{1}H NMR data were comparable with those reported elsewhere.[6] ^{1}H NMR ($CDCl_3$): δ 3.69 (t, 2H, $^3J_{HH}$ = 6.5), 3.46 (t, 2H, $^3J_{HH}$ = 7.0), 2.01-1.93 (m, 2H), 1.75-1.68 (m, 2H) 1.39 (br, -OH). ^{13}C NMR ($CDCl_3$): δ 62.1, 33.7, 31.3, 29.4.

Preparation of 5-iodopentan-1-ol (8): Oven dried NaI (400 mg, 2.67 mmol), tetrahydropyran (15 ml), and oven dried Dowex 50W-X8 ion exchange resin (H^+-form, 2 g) were refluxed overnight in the dark. The Dowex was filtered off and washed with DCM which was combined with the reaction mixture and evaporated *in vacuo*. The crude product was dissolved in DCM (10 ml) and washed with 10% $Na_2S_2O_3$ (sodium thiosulfate, 3 ml), the DCM layer was separated, dried with $MgSO_4$ and removed by evaporation *in vacuo*. The residue was purified by silica column chromatography using ethyl acetate/hexane (1:1) as eluent. 5-Iodopentan-1-ol (269 mg, 47%) was obtained as a very slightly yellow oil. All ^{1}H and ^{13}C NMR data were comparable with those that we have reported elsewhere.[7] ^{1}H NMR ($CDCl_3$): δ 3.66 (t, 2H, $^3J_{HH}$ = 7.0), 3.20 (t, 2H, $^3J_{HH}$ = 7.0), 1.86 (qv, 2H), 1.63-1.56 (m, 2H), 1.52-1.45 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 62.9, 33.5, 31.8, 27.0, 7.0.

Preparation of 2-(2-iodo-ethoxy)-ethanol (10): Prepared as we have reported elsewhere.[7] Oven dried NaI (1 g, 6.67 mmol), distilled 1,4-dioxane (20 ml), and oven dried Dowex 50W-X8 ion exchange resin (H^+-form, 4 g) were refluxed overnight. The Dowex was filtered off, washed with DCM and the reaction mixture with DCM was evaporated *in vacuo*. The crude product was dissolved in DCM (20 ml) and washed with 10% $Na_2S_2O_3$ (sodium thiosulfate, 6 ml), the DCM layer was separated, dried with $MgSO_4$ and removed by evaporation *in vacuo*. The residue was purified by silica column chromatography using ethyl acetate as eluent. 2-(2-Iodo-ethoxy)-ethanol (980 mg, 68%) was obtained as a very slightly yellow oil. All ^{1}H and ^{13}C NMR data were comparable with those that we have reported elsewhere.[7] ^{1}H NMR ($CDCl_3$): δ 3.79-3.73 (m, 4H), 3.62 (virtual t, 2H), 3.29 (t, 2H, $^3J_{HH} = 6.5$) 2.00 (t, -OH, $^3J_{HH} = 6.5$). ^{13}C NMR ($CDCl_3$): δ 71.7, 71.5, 61.9, 3.1.

Preparation of 4-iodocyclohexanol (12a): Oven dried NaI (222 mg, 1.48 mmol), oven dried Dowex 50W-X8 ion exchange resin (H^+-form, 800 mg), 7-oxabicyclo(2,2,1)heptane (150 µl, 145 mg, 1.48 mmol) and dry acetone (5ml) were refluxed overnight. The Dowex was filtered off and washed with DCM which was combined with the reaction mixture and evaporated *in vacuo*. The crude product was dissolved in DCM (10 ml) and washed with 10% $Na_2S_2O_3$ (sodium thiosulfate, 3 ml), DCM layer was separated, aqueous phase was extracted with DCM, DCM was separated and combined DCM layers dried with $MgSO_4$ and removed by evaporation *in vacuo*. The residue was purified by silica column chromatography using ethyl acetate/hexane (1:1) as eluent. 4-Iodocyclohexanol (248 mg, 75%) was obtained as a colorless oil which solidified in the freezer to become a white solid. Mp. 75 ºC. ^{1}H NMR ($CDCl_3$, 500.1 MHz) δ 4.20 (m, 1H), 3.71 (m, 1H), 2.32-2.27 (m, 2H), 1.99-1.90 (m, 2H), 1.88-1.84 (m, 2H), 1.43-1.34 (m, 2H). ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 67.9, 36.7 (2C), 35.8 (2C), 29.2. Anal. Calcd for $C_6H_{11}IO\cdot0.03$ HI: C, 33.69; H, 5.20. Found: C, 33.56; H, 5.21.

Preparation of 4-bromocyclohexanol (12b): Oven dried NaBr (153 mg, 1.48 mmol), oven dried Dowex 50W-X8 ion exchange resin (H^+-form, 800 mg), 7-oxabicyclo(2,2,1)heptane (150 µl, 145 mg, 1.48 mmol) and dry acetone (5ml) were refluxed for overnight. The Dowex was filtered off and washed with DCM which was combined with the reaction mixture and evaporated *in vacuo*. The crude product was purified by silica column chromatography using ethyl acetate/hexane (1:1) as eluent. 4-Bromocyclohexanol (154 mg, 59%) was obtained as a white solid. Mp. 85 ºC. ^{1}H NMR ($CDCl_3$, 500.1 MHz) δ 4.14 (m, 1H), 3.78 (m, 1H), 2.31-2.27 (m, 2H), 2.04-1.98 (m, 2H), 1.88-1.80 (m, 2H), 1.47-1.39 (m, 2H). ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 68.1, 51.2, 34.3 (2C), 34.0 (2C). Anal. Calcd for $C_6H_{11}BrO \cdot 0.17$ HBr: C, 37.38; H, 5.84. Found: C, 37.45; H, 5.80.

Preparation of 2-(2-iodoethyl)phenol (14): Oven dried NaI (320 mg, 2.13 mmol), oven dried Dowex 50W-X8 ion exchange resin (H^+-form, 2.0 g), 2,3-dihydrobenzofuran and butyronitrile (8 ml) were refluxed overnight (ca. 18 h) before the NMR-sample was taken and dried *in vacuo*. The ^1H NMR spectrum demonstrated that there had been 100% conversion to the desired product. Subsequently, the Dowex was filtered off and washed with a small amount of butyronitrile and the filtrates were evaporated to dryness *in vacuo* to give 454 mg of expected product. Surprisingly, the measured ^1H NMR spectrum revealed that ca. 30% of product had in some way reacted back to the starting material (2,3-dihydrobenzofuran). The crude product (89 mg) was purified by TLC using ethyl acetate/hexane (1:9) as the eluent. 2-(2-iodoethyl)phenol (31 mg, 36%) was obtained as a colorless oil with R_f 0.39. All ^1H and ^{13}C NMR data were comparable with those reported elsewhere.[8] ^1H NMR ($CDCl_3$, 500.1 MHz) δ 7.19-7.11 (m, 2H), 6.91 (t, 1H, $^3J_{HH} = 7.0$), 6.74 (d, 1H, $^3J_{HH} = 8.0$), 4.80 (s, -OH), 3.41 (t, 2H, $^3J_{HH} = 8.0$) 3.22 (t, 2H, $^3J_{HH} = 8.0$). ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 153.4, 130.8, 128.4, 127.2, 121.2, 115.6, 35.3, 5.0.

Preparation of 4-Iodobutanoic acid (16): Oven dried NaI (588 mg, 3.92 mmol), oven dried Dowex 50W-X8 ion exchange resin (H^+-form, 3 g), γ-butyrolactone (200 µl, 224 mg, 2.60 mmol) and xylene (8 ml) were refluxed for 24 h before the NMR-sample was taken and dried *in vacuo*. The ^1H NMR spectrum showed ca. 95% conversion to desired product. The Dowex was filtered off and washed with DCM which was combined with the reaction mixture and evaporated *in vacuo*. The crude product was purified by silica column chromatography using EtOAc/hexane (3:1) as the eluent. 4-Iodobutanoic acid (182 mg, 33%) was obtained as a white translucent solid. All ^1H NMR data were comparable with those reported elsewhere.[9] ^1H NMR ($CDCl_3$) δ 3.26 (t, 2H, $^3J_{HH} = 6.8$), 2.52 (t, 2H, $^3J_{HH} = 7.3$), 2.15 (qv, 2H). ^{13}C NMR ($CDCl_3$) δ 177.5, 34.5, 28.3, 5.1.

Preparation of 2-{2-[2-(2-Iodo-ethoxy)-ethoxy]-ethoxy}-ethanol (18): Oven dried NaI (224 mg, 1.49 mmol), oven dried Dowex 50W-X8 ion exchange resin (H^+-form, 1.6 g), 12-

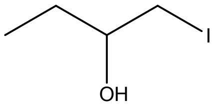
Crown-4 ether (200 µl, 218 mg, 1.24 mmol) and xylene (8 ml) were refluxed for 24 h. The Dowex was filtered off and washed with DCM which was combined with the reaction mixture and evaporated *in vacuo*. The residue was dissolved in 10% $Na_2S_2O_3$ (sodium thiosulfate, 2-3 ml) and evaporated to dryness. The residue was dissolved in DCM (5 ml) and all the solids were filtered off and DCM evaporated *in vacuo* to give crude product (321 mg). The crude product (83 mg) was purified by TLC using EtOAc/MeOH (98:2) as eluent. Product **18** (30.9 mg, 32%) was obtained as a colorless viscous oil with R_f 0.51. All ^1H and ^{13}C NMR data were comparable with those reported elsewhere.[10] ^1H NMR ($CDCl_3$, 500.1 MHz) δ 3.75 (t, 2H, $^3J_{HH}$ = 7.0), 3.73-3.70 (m, 2H), 3.69-3.63 (m, 8H), 3.62-3.59 (m, 2H) 3.25 (t, 2H, $^3J_{HH}$ = 7.0) 2.46 (br, 1H). ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 72.6, 72.1, 70.8, 70.7, 70.5, 70.3, 61.9, 2.9.

Preparation of 14-iodo-3,6,9,12-tetraoxatetradecan-1-ol (20): Oven dried NaI (182 mg, 1.21 mmol), oven dried Dowex 50W-X8 ion exchange resin (H^+-form, 1.6 g), 15-Crown-5 ether (200 µl, 223 mg, 1.01 mmol) and xylene (8 ml) were refluxed for 24 h. The Dowex was filtered off and washed with DCM which was combined with the reaction mixture and evaporated *in vacuo*. The residue was dissolved in 10% $Na_2S_2O_3$ (sodium thiosulfate, 2-3 ml) and evaporated to dryness. The residue was dissolved in DCM (5 ml) and any solids were filtered off and DCM evaporated *in vacuo* to give crude product (329 mg). The crude product (85 mg) was purified by TLC using EtOAc/MeOH (98:2) as eluent. Product **20** (20.1 mg, 22%) was obtained as a colorless viscous oil with R_f 0.32. ^1H NMR ($CDCl_3$, 500.1 MHz) δ 3.76 (t, 2H, $^3J_{HH}$ = 7.0), 3.73-3.70 (m, 2H), 3.69-3.64 (m, 12H), 3.63-3.60 (m, 2H) 3.26 (t, 2H, $^3J_{HH}$ = 7.0) 2.51 (br, 1H). ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 72.7, 72.2, 70.82, 70.81 (2C), 70.77, 70.5, 70.4, 61.9, 3.0. MS (ESI$^+$) calcd. for $C_{10}H_{22}IO_5$ $[M+H]^+$ 349.0512, found: 349.0516.

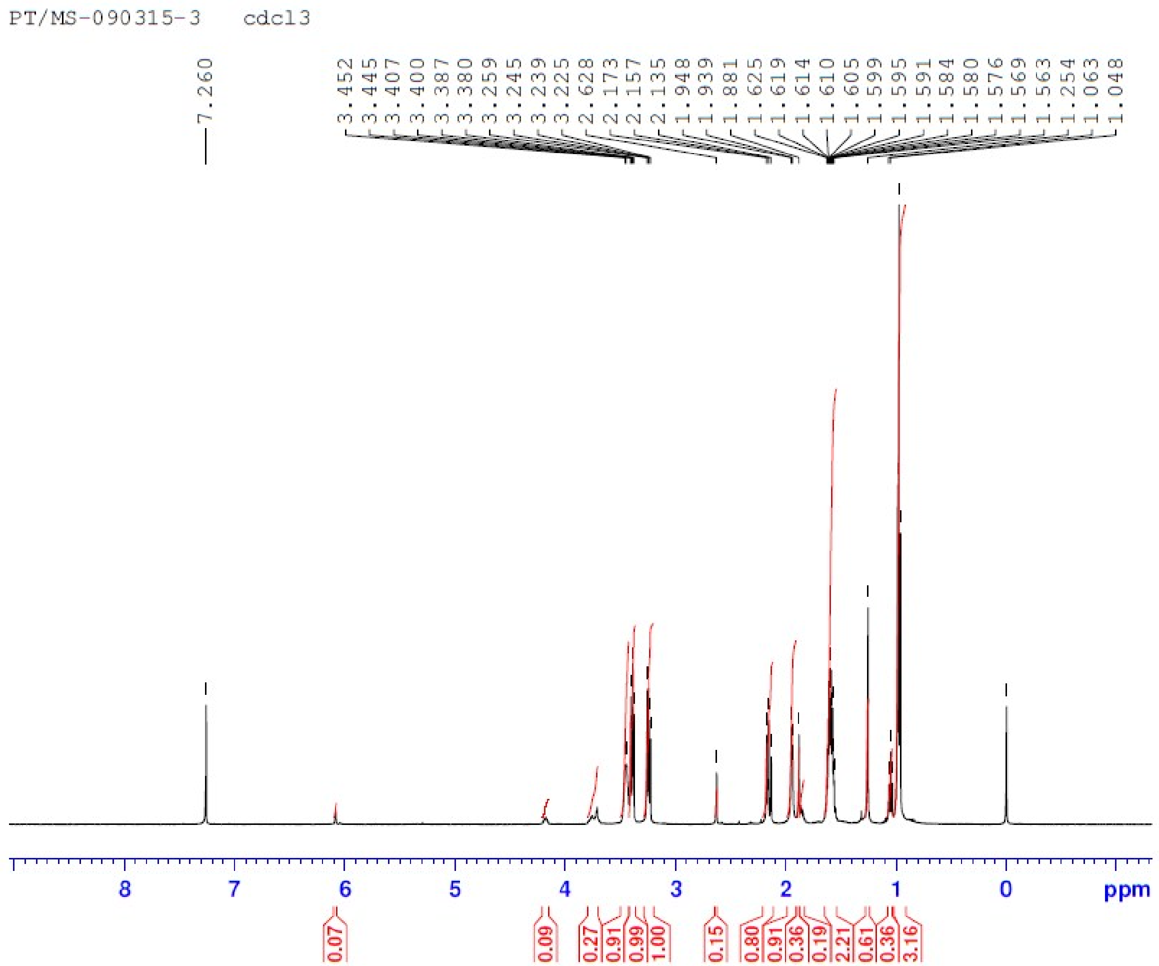
17-iodo-3,6,9,12,15-pentaoxaheptadecan-1-ol (22): Oven dried NaI (137 mg, 0.91 mmol), oven dried Dowex 50W-X8 ion exchange resin (H^+-form, 1.6 g), 18-Crown-6 ether (200 mg, 0.76 mmol) and xylene (5 ml) were refluxed for 24 h. The Dowex was filtered off and washed with DCM and the combined DCM fractions were evaporated *in vacuo*. The residue was dissolved in 10% $Na_2S_2O_3$ (sodium thiosulfate, 2-3 ml) and evaporated to dryness. The residue was dissolved in DCM (5 ml) and all the solids were filtered off and DCM evaporated *in vacuo* to give crude product (260 mg). The crude product (100 mg) was purified by TLC using EtOAc/MeOH (95:5) as eluent. Product **18** (15.5 mg, 14%) was obtained as a colorless viscous oil with R_f 0.32. ^{1}H NMR ($CDCl_3$, 500.1 MHz) δ 3.75 (t, 2H, $^3J_{HH}$ = 7.0), 3.73-3.70 (m, 2H), 3.69-3.63 (m, 16H), 3.62-3.59 (m, 2H) 3.26 (t, 2H, $^3J_{HH}$ = 7.0) 2.60 (t, 1H, $^3J_{HH}$ = 7.0). ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 72.6, 72.1, 70.8, 70.74, 70.72 (3C), 70.69, 70.5, 70.4, 61.9, 3.1. MS (ESI$^+$) calcd. for $C_{12}H_{25}IO_6Na$ [M+Na]$^+$ 415.0594, found: 415.0597.

2-(2-(2-iodoethoxy)ethoxy)ethanol (23): Isolated from the reaction mixture of **19**. ^{1}H NMR ($CDCl_3$, 500.1 MHz) δ 3.79-3.72 (m, 4H), 3.71-3.65 (m, 4H), 3.65-3.60 (m, 2H), 3.27 (t, 2H, $^3J_{HH}$ = 6.5), 2.19 (br, 1H). ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 72.6, 72.1, 70.6, 70.4, 62.0, 2.8. MS (ESI$^+$) calcd. for $C_6H_{14}IO_3$ [M+H]$^+$ 260.9988, found: 260.9984.

1,14-diiodo-3,6,9,12-tetraoxatetradecane (24): Isolated from the reaction mixture of **19**. ^{1}H NMR ($CDCl_3$, 500.1 MHz) δ 3.76 (t, 4H, $^3J_{HH}$ = 7.0), 3.74-3.61 (m, 12H), 3.26 (t, 4H, $^3J_{HH}$ = 7.0). ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 72.2, 70.9, 70.8, 70.4, 3.0. MS (ESI$^+$) calcd. for $C_{10}H_{20}I_2O_4Na$ [M+Na]$^+$ 480.9349, found: 480.9350.



compd. 2 conversion -see the ^{1}H NMR characterization data for compound **2** in page 2.



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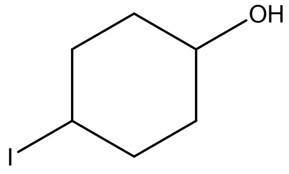

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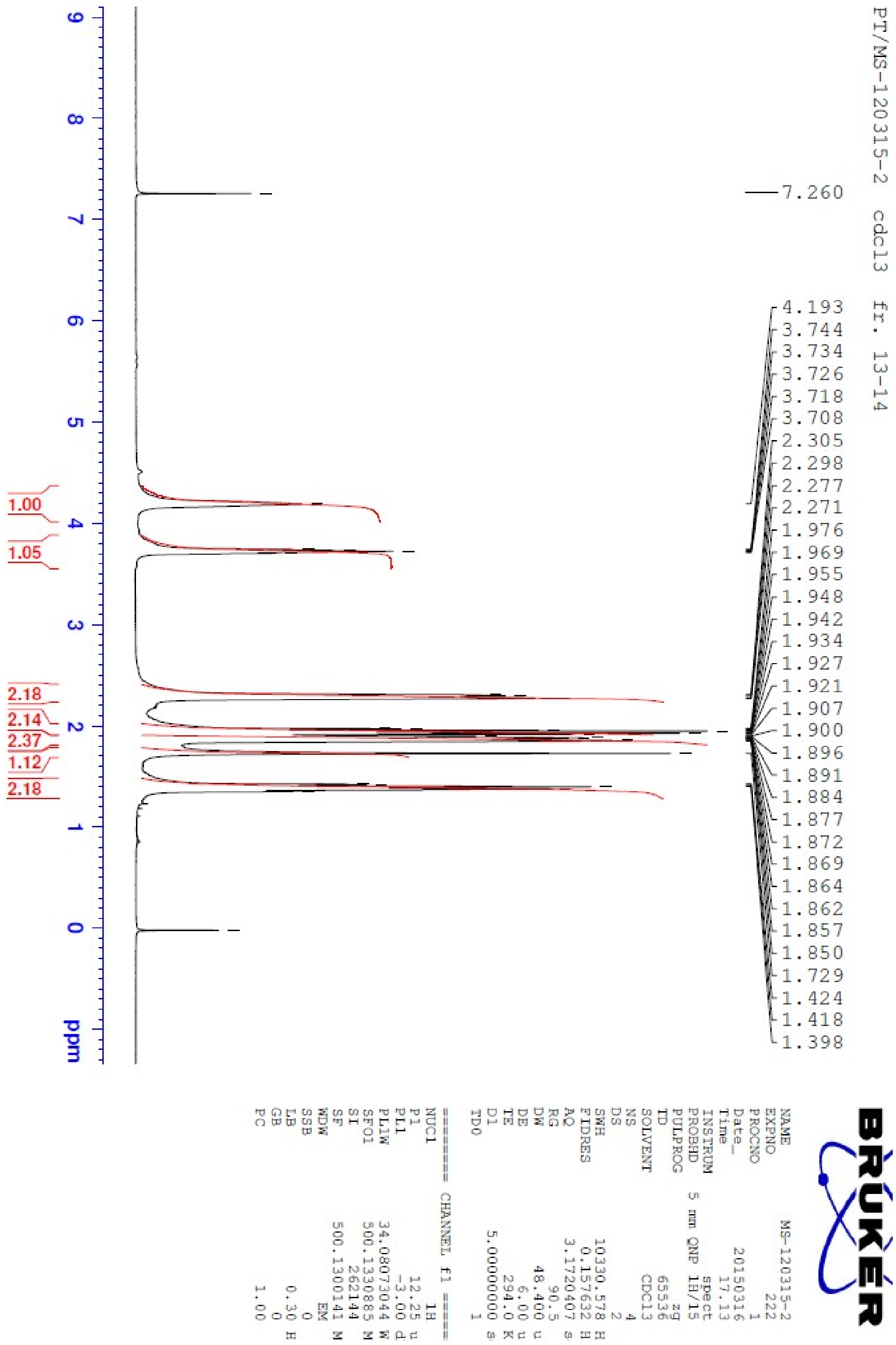
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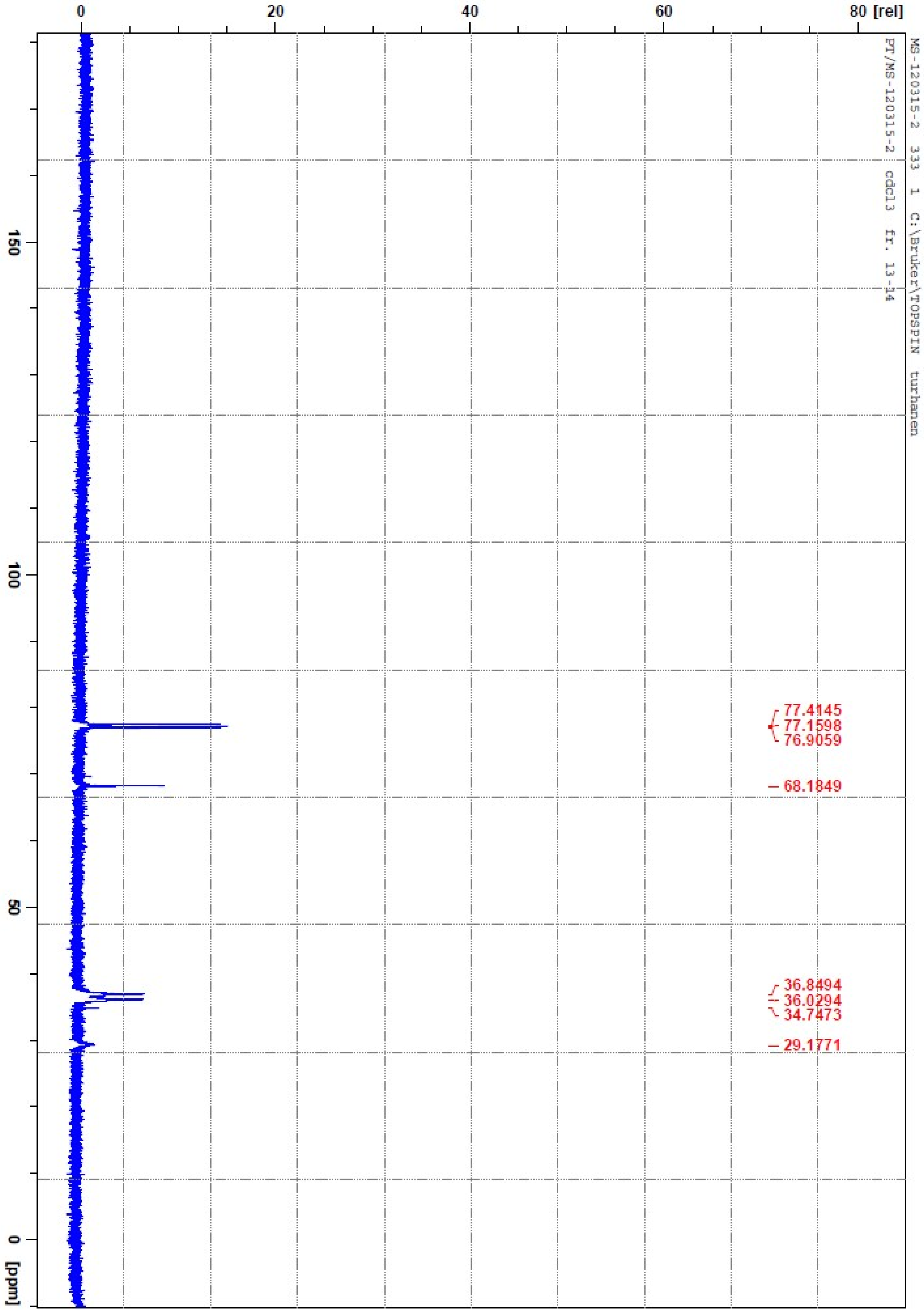
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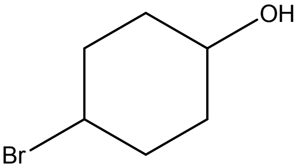

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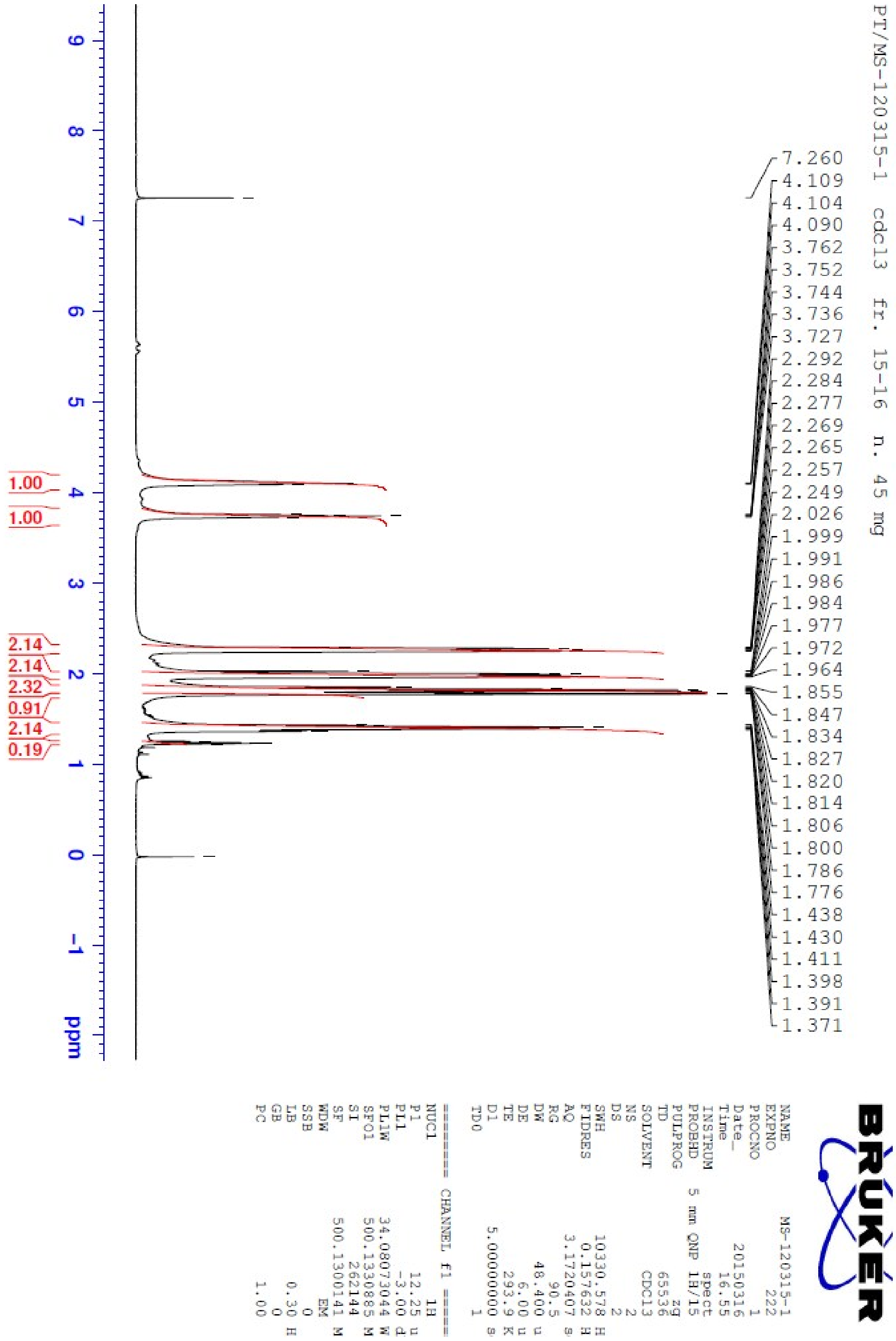
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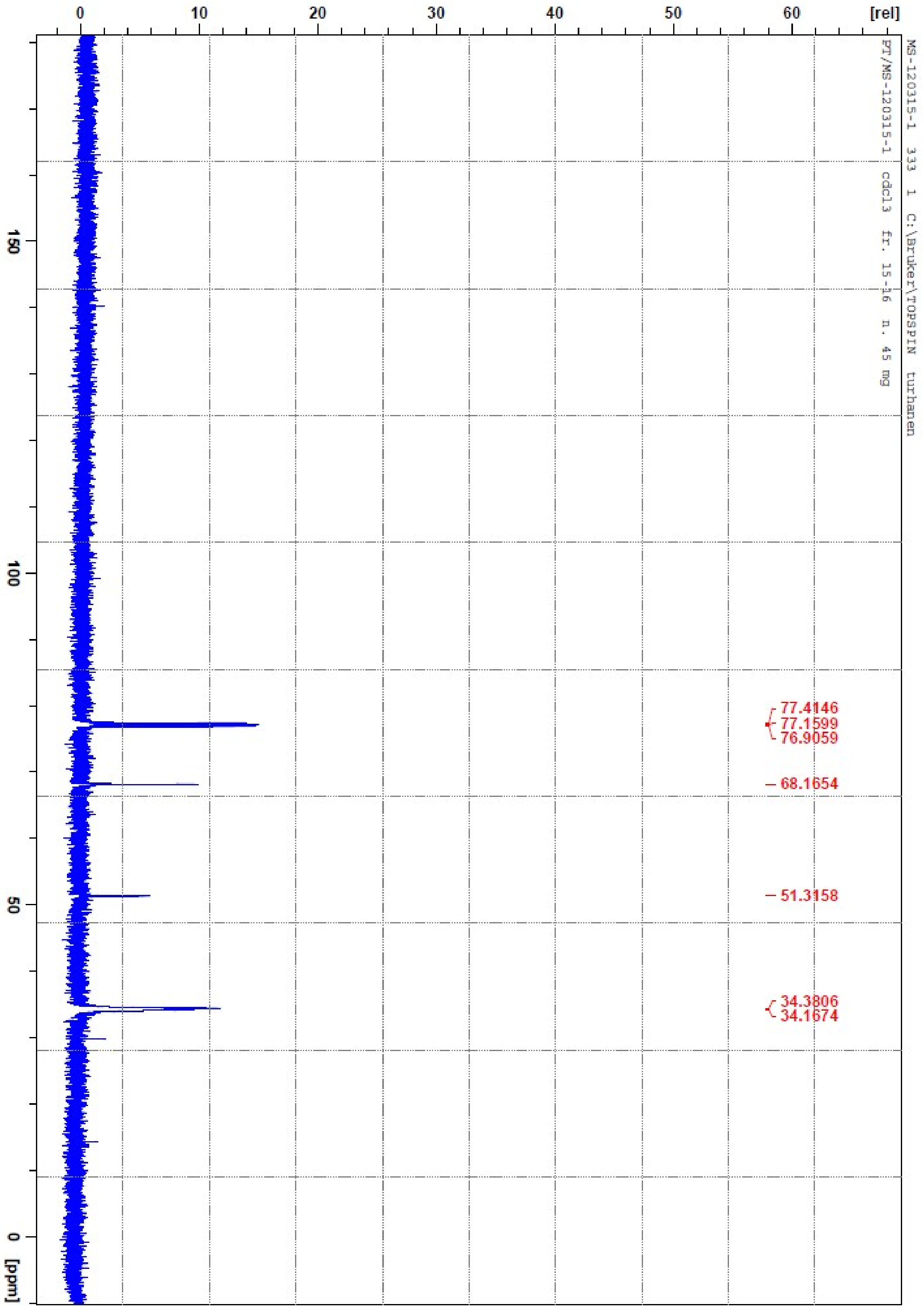
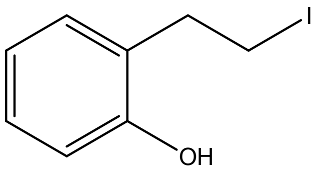
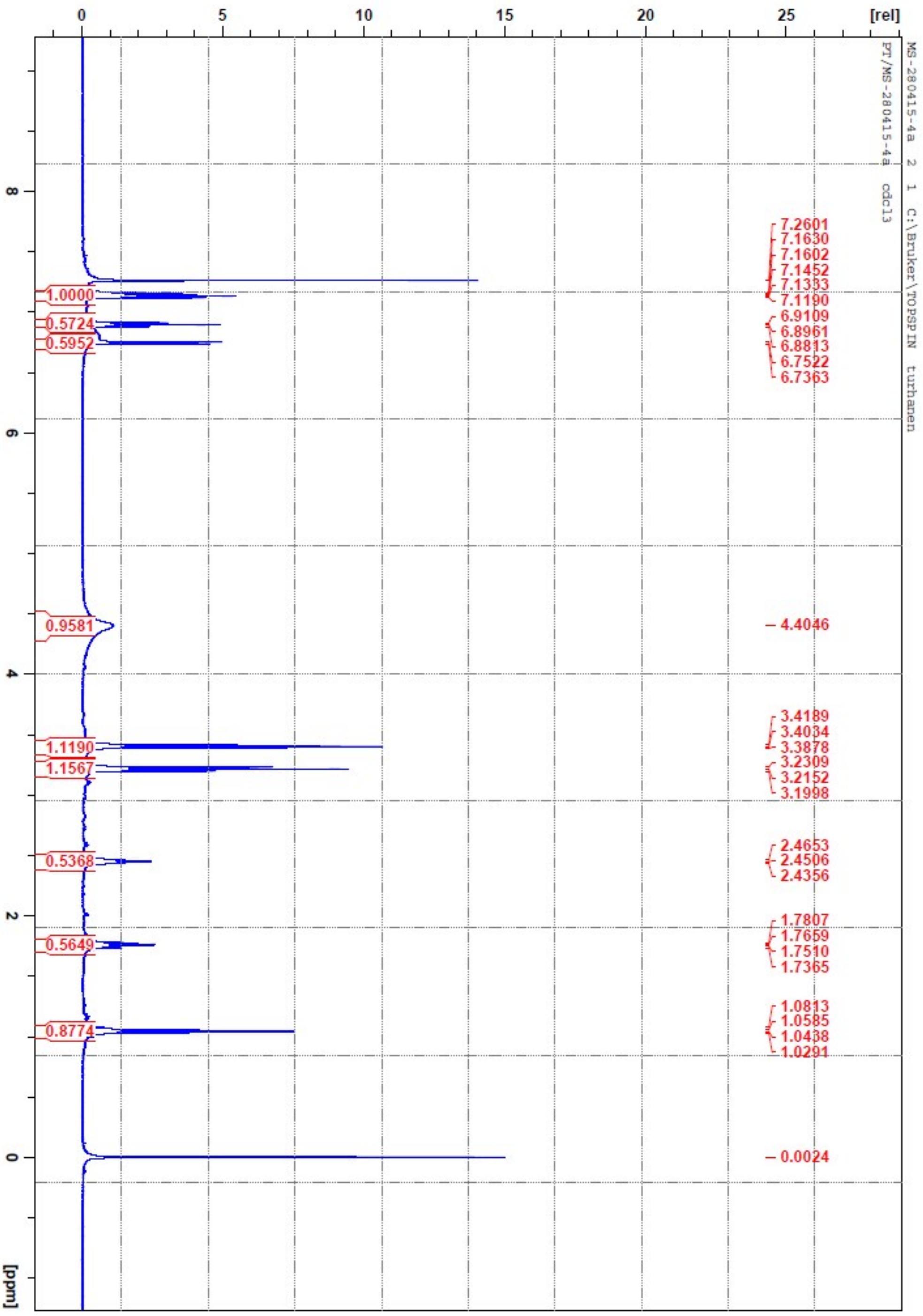
1.398
1.391
1.371
1.00
1.00
2.14
2.14
2.32
0.91
2.14
0.19
9
8
7
6
5
4
3
2
1
0
-1
ppm
NAME MS-120315-1
EXPNO 222
PROCNO 1
Date_ 20150316
Time 16.55
INSTRUM spect
PROBHD 5 mm QNP 1H/15
PULPROG zg
TD 65536
SOLVENT CDCl3
NS 2
DS 2
SWH 10330.578 H
FIDRES 0.157632 H
AQ 3.1720407 s
RG 90.5
DW 48.400 u
DE 6.00 u
TE 293.9 K
D1 5.00000000 s
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 12.25 u
PL1 -3.00 d
PL1W 34.08073044 W
SFO1 500.1330885 M
SI 262144
SF 500.1300141 M
WDW EM
SSB 0
LB 0.30 H
GB 0
PC 1.00

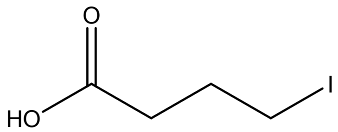


MS-120315-1 333 1 C:\Bruker\TOPSPIN turhanen
PT/MS-120315-1 cdcl3 fr. 15-16 n. 45 mg
77.4146
77.1599
76.9059
68.1654
51.3158
34.3806
34.1674
0
10
20
30
40
50
60
[rel]
150
100
50
0
[ppm]

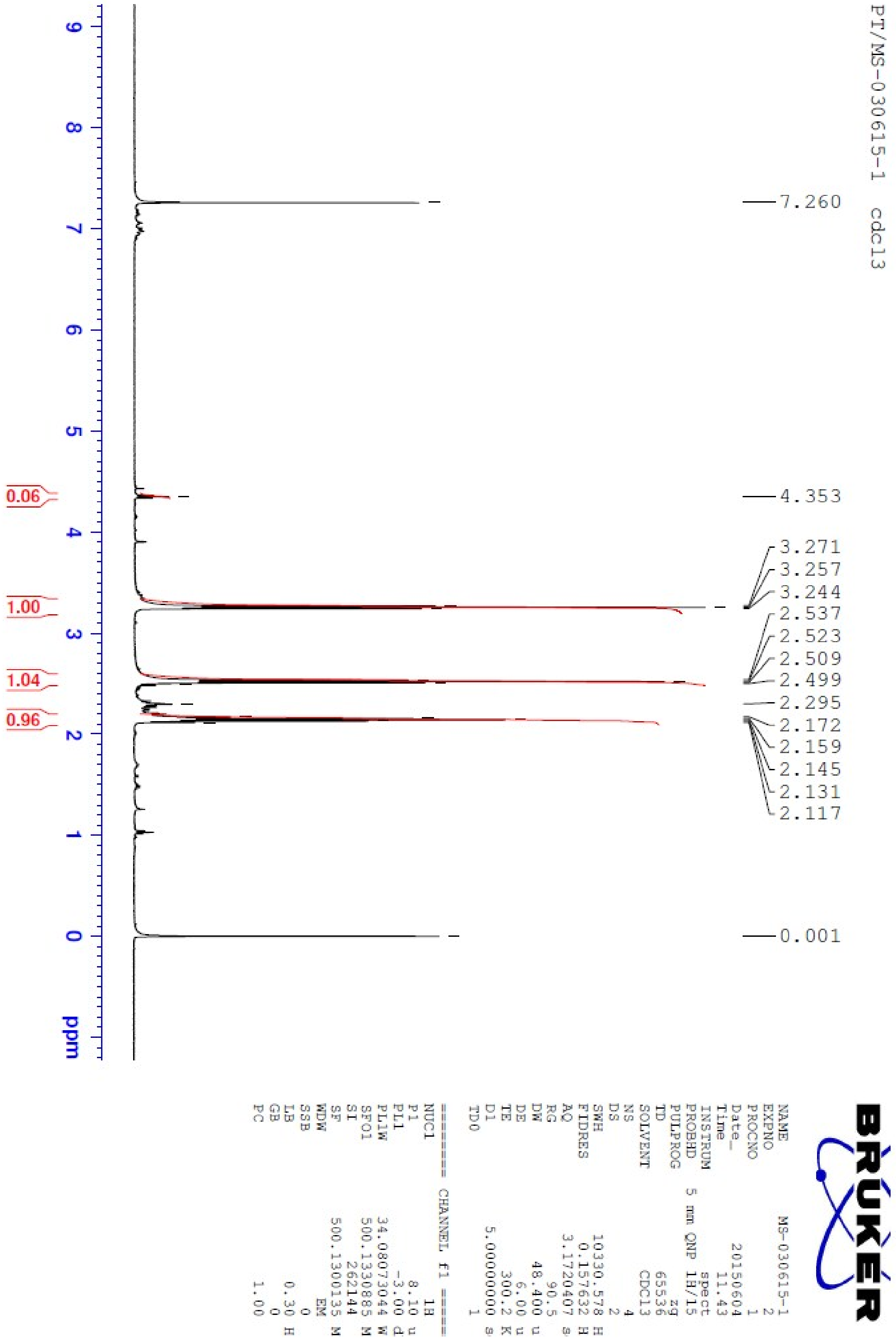


compd. 14 conversion; peaks at 2.45, 1.76 and 1.04 ppm belongs to used solvent: butyronitrile



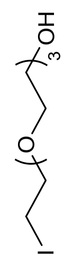


compd. 16 conversion



```
NAME          MS-030615-1
EXPNO                   2
PROCNO                  1
Date_            20150604
Time                11.43
INSTRUM             spect
PROBHD   5 mm QNP 1H/15
PULPROG                zg
TD                  65536
SOLVENT             CDCl3
NS                      4
DS                      2
SWH             10330.578 Hz
FIDRES           0.157632 Hz
AQ              3.1720407 sec
RG                   90.5
DW                 48.400 usec
DE                   6.00 usec
TE                  300.2 K
D1             5.00000000 sec
TD0                     1

======== CHANNEL f1 ========
NUC1                   1H
P1                   8.10 usec
PL1                 -3.00 dB
PL1W          34.08073044 W
SFO1          500.1330885 MHz
SI                 262144
SF            500.1300135 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.00
```



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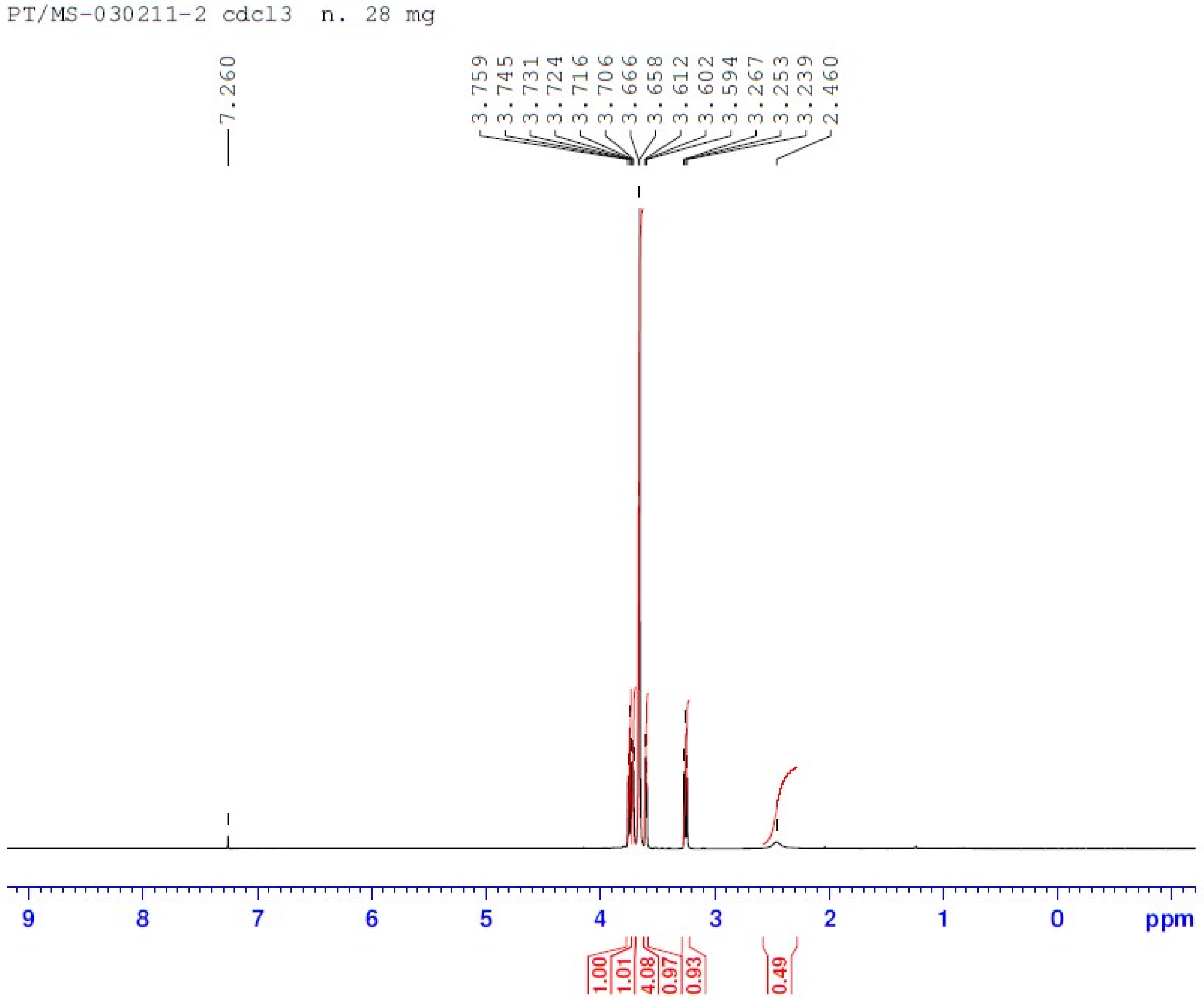
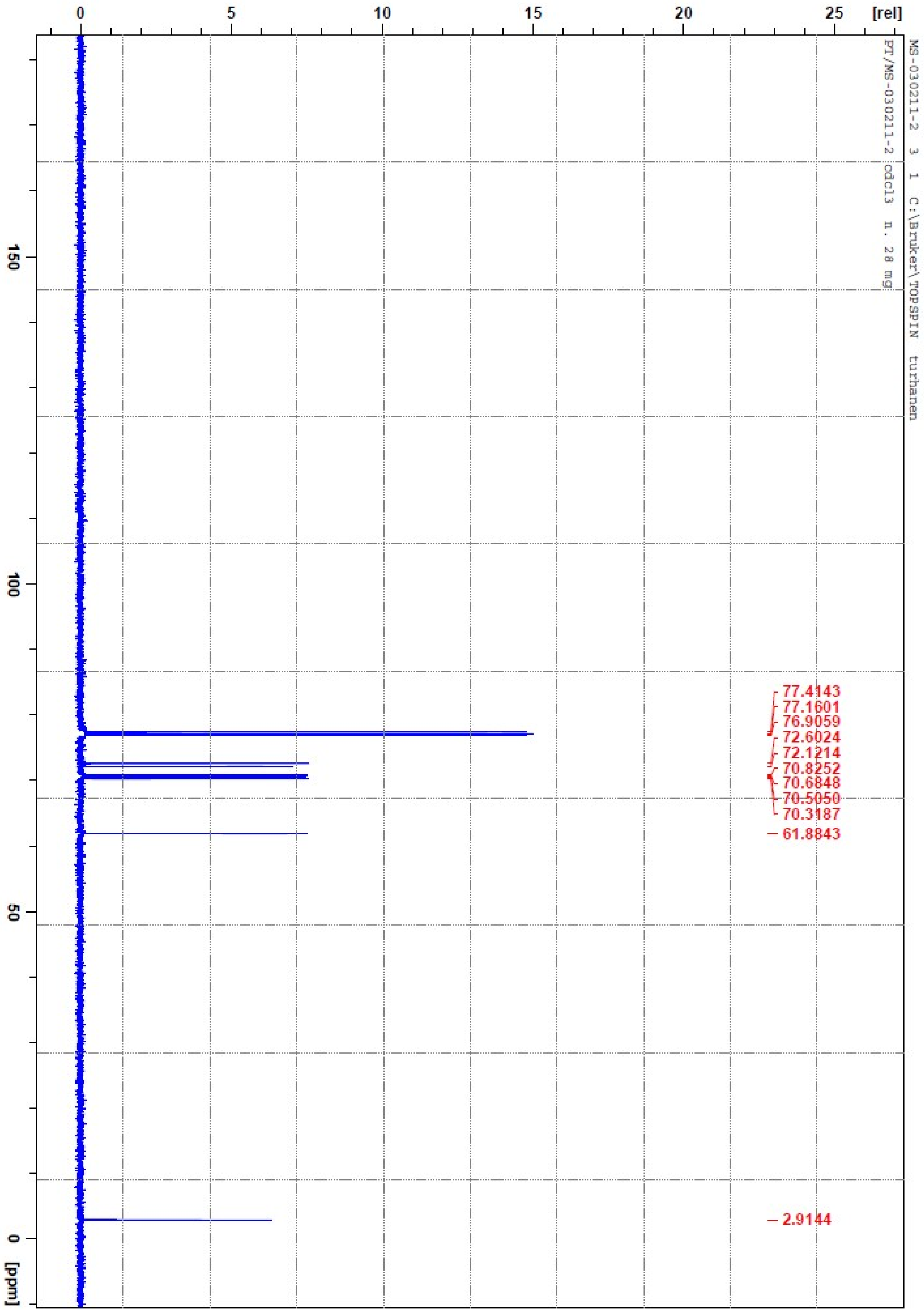
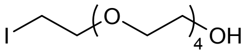


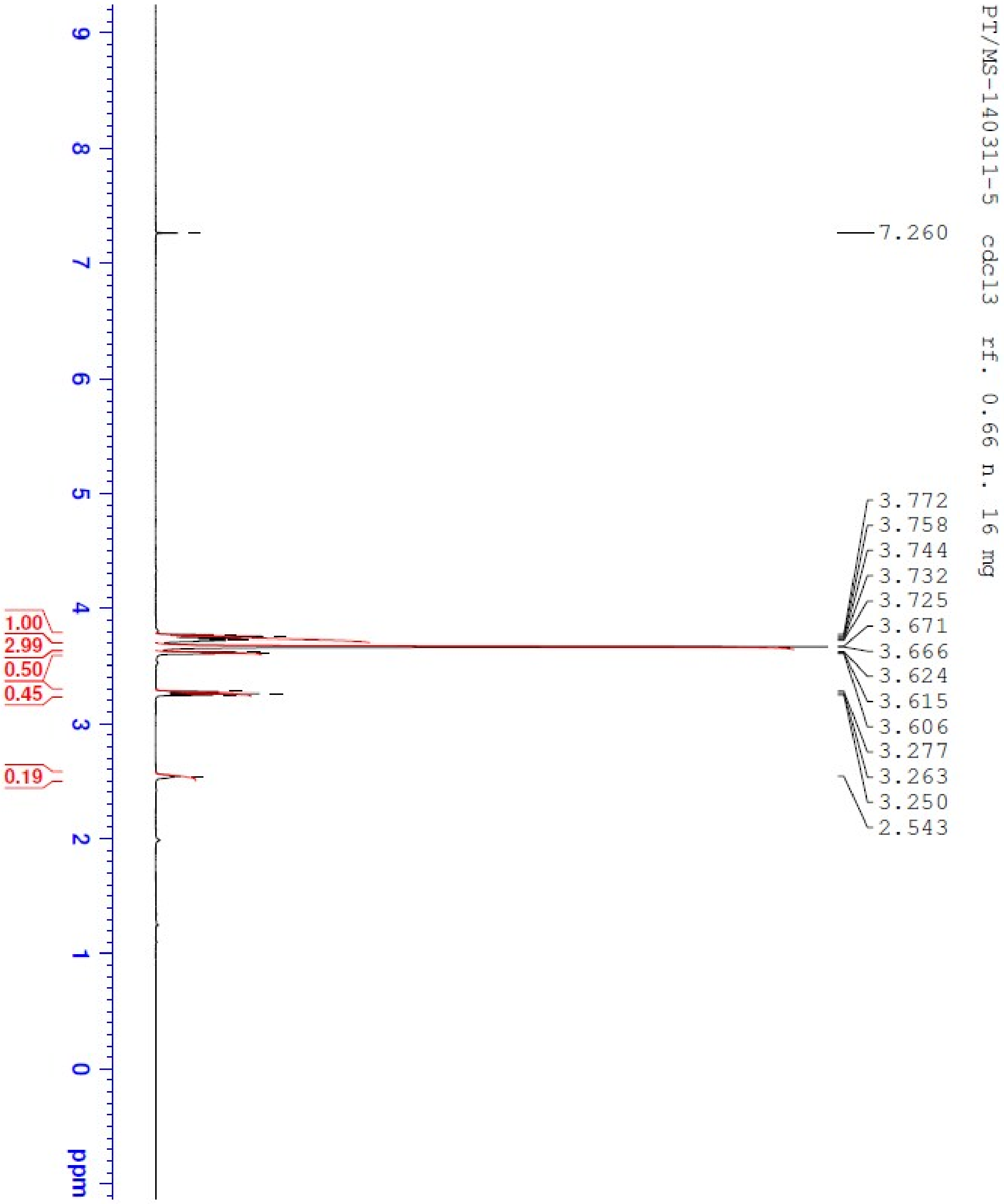
```
NAME          MS-030211-2
EXPNO                   2
PROCNO                  1
Date_            20110207
Time                12.24
INSTRUM             spect
PROBHD   5 mm QNP   1H/1
PULPROG                zg
TD                  65536
SOLVENT             CDCl3
NS                      4
DS                      0
SWH             10000.000 H
FIDRES           0.152588 H
AQ              3.2769001 s
RG                     64
DW                 50.000 u
DE                   6.00 u
TE                  300.0 K
D1             1.50000000 s
TD0                     1

======== CHANNEL f1 =====
NUC1                   1H
P1                   9.38 u
PL1                 -1.00 d
SFO1          500.1340010 M
SI                 262144
SF            500.1300137 M
WDW                    EM
SSB                     0
LB                   0.30 H
GB                      0
PC                   2.00
```


MS-030211-2 3 1 C:\Bruker\TOPSPIN turhanen
PT/MS-030211-2 cdcl3 n. 28 mg
0
5
10
15
20
25
[rel]
150
100
50
0
[ppm]
77.4143
77.1601
76.9059
72.6024
72.1214
70.8252
70.6848
70.5050
70.3187
61.8843
2.9144

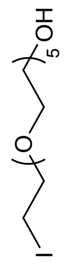


20



```
NAME         MS-140311-5
EXPNO                  2
PROCNO                 1
Date_           20110318
Time               11.35
INSTRUM            spect
PROBHD   5 mm QNP 1H/1
PULPROG               zg
TD                 65536
SOLVENT            CDCl3
NS                     8
DS                     0
SWH         10000.000 H
FIDRES       0.152588 H
AQ          3.2769001 s
RG                    64
DW             50.000 u
DE               6.00 u
TE              300.0 K
D1         1.50000000 s
TD0                    1

======== CHANNEL f1 ========
NUC1                  1H
P1               9.38 u
PL1             -1.00 d
SFO1      500.1340010 M
SI                262144
SF        500.1300135 M
WDW                   EM
SSB                    0
LB               0.30 H
GB                     0
PC                  2.00
```



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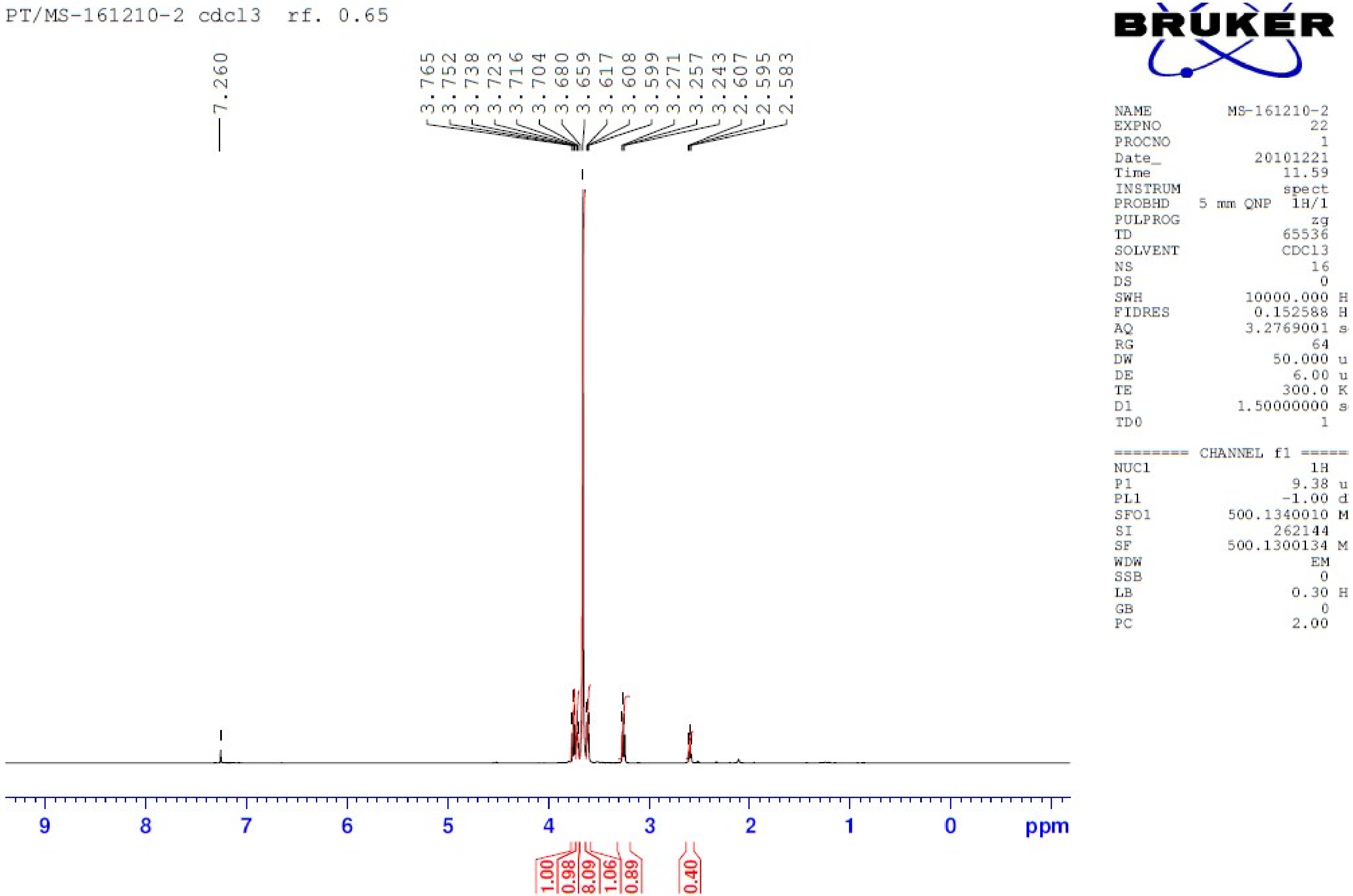
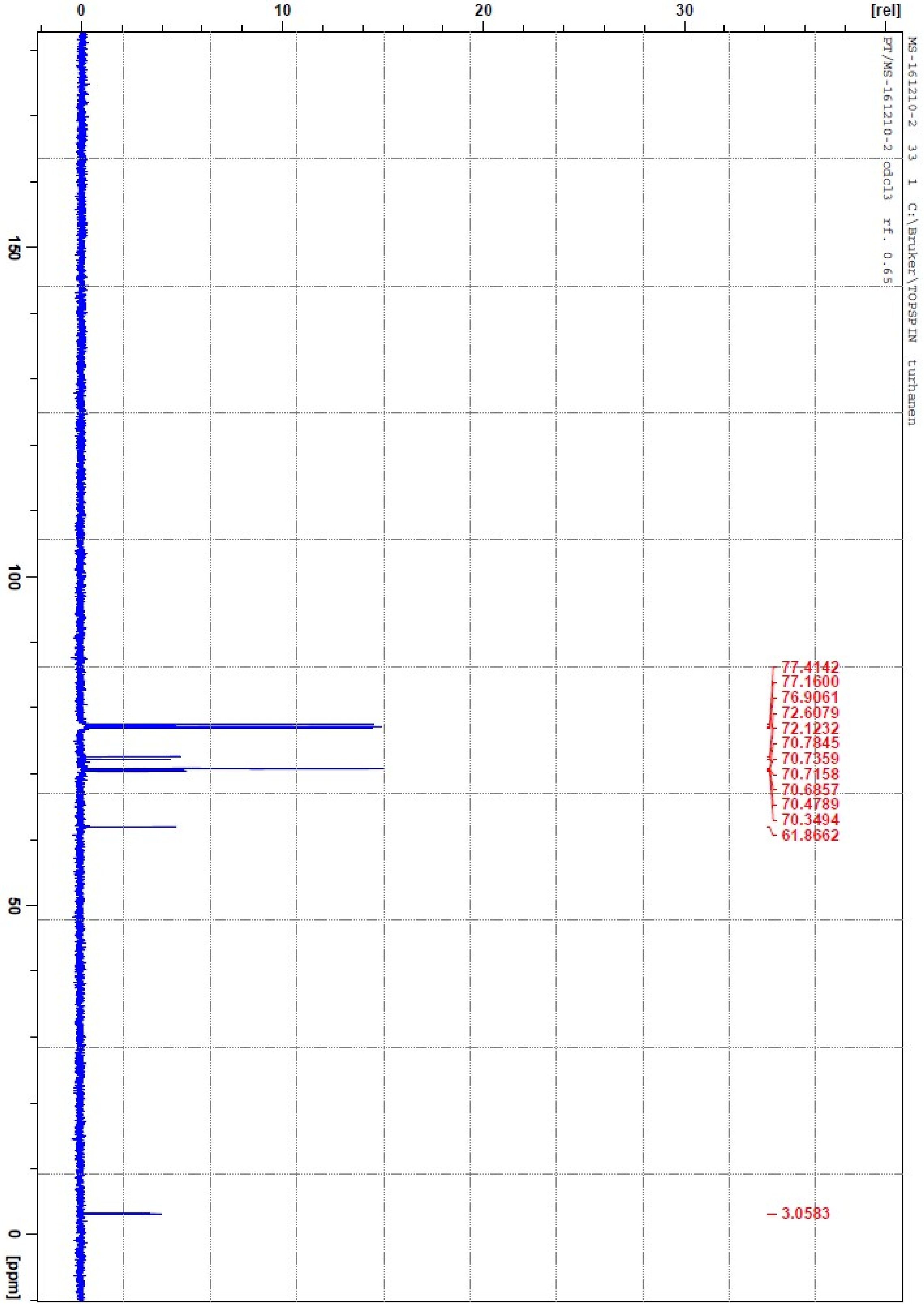
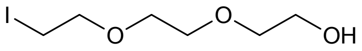
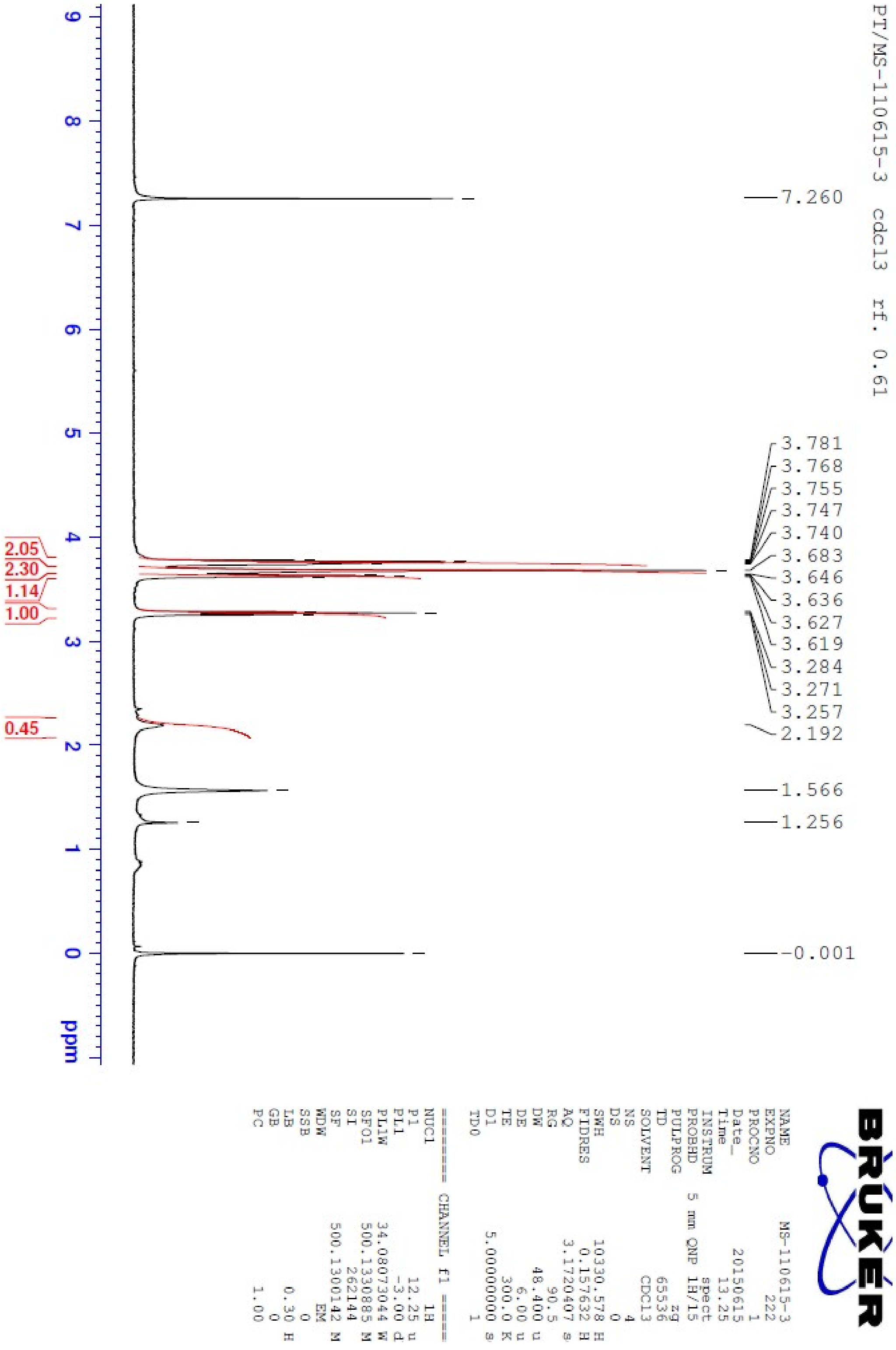


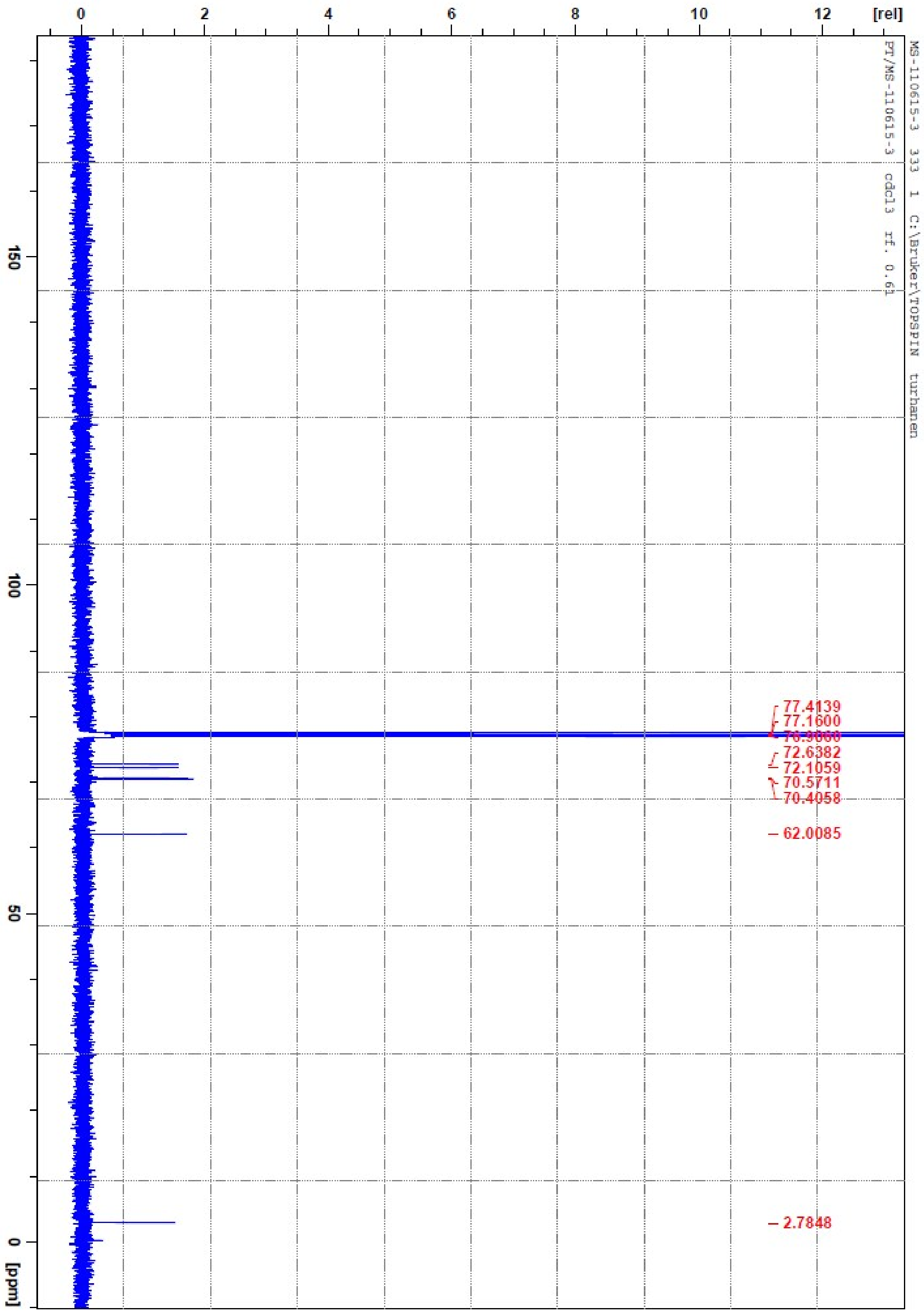
```
NAME          MS-161210-2
EXPNO                  22
PROCNO                  1
Date_            20101221
Time                11.59
INSTRUM             spect
PROBHD   5 mm QNP    1H/1
PULPROG                zg
TD                  65536
SOLVENT             CDCl3
NS                     16
DS                      0
SWH            10000.000 H
FIDRES          0.152588 H
AQ             3.2769001 s
RG                     64
DW                50.000 u
DE                  6.00 u
TE                 300.0 K
D1            1.50000000 s
TD0                     1

======== CHANNEL f1 =====
NUC1                   1H
P1                  9.38 u
PL1                -1.00 d
SFO1         500.1340010 M
SI                 262144
SF           500.1300134 M
WDW                    EM
SSB                     0
LB                  0.30 H
GB                      0
PC                   2.00
```

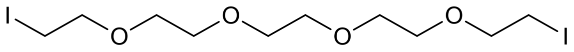

MS-161210-2 33 1 C:\Bruker\TOPSPIN turhanen
PT/MS-161210-2 cdcl3 rf. 0.65
77.4142
77.1600
76.9061
72.6079
72.1232
70.7845
70.7359
70.7158
70.6857
70.4789
70.3494
61.8662
3.0583
0
10
20
30
[rel]
150
100
50
0
[ppm]



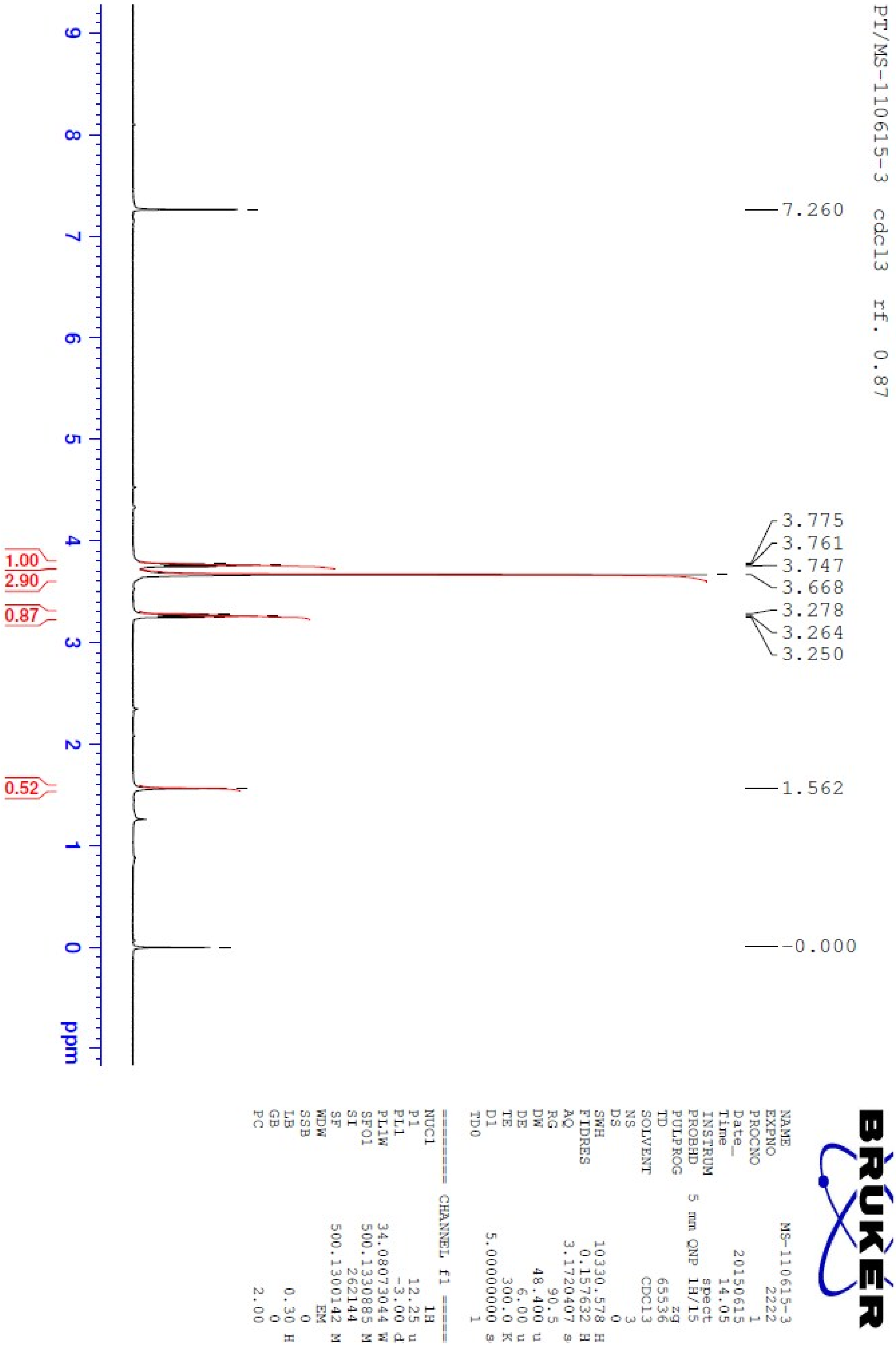
23

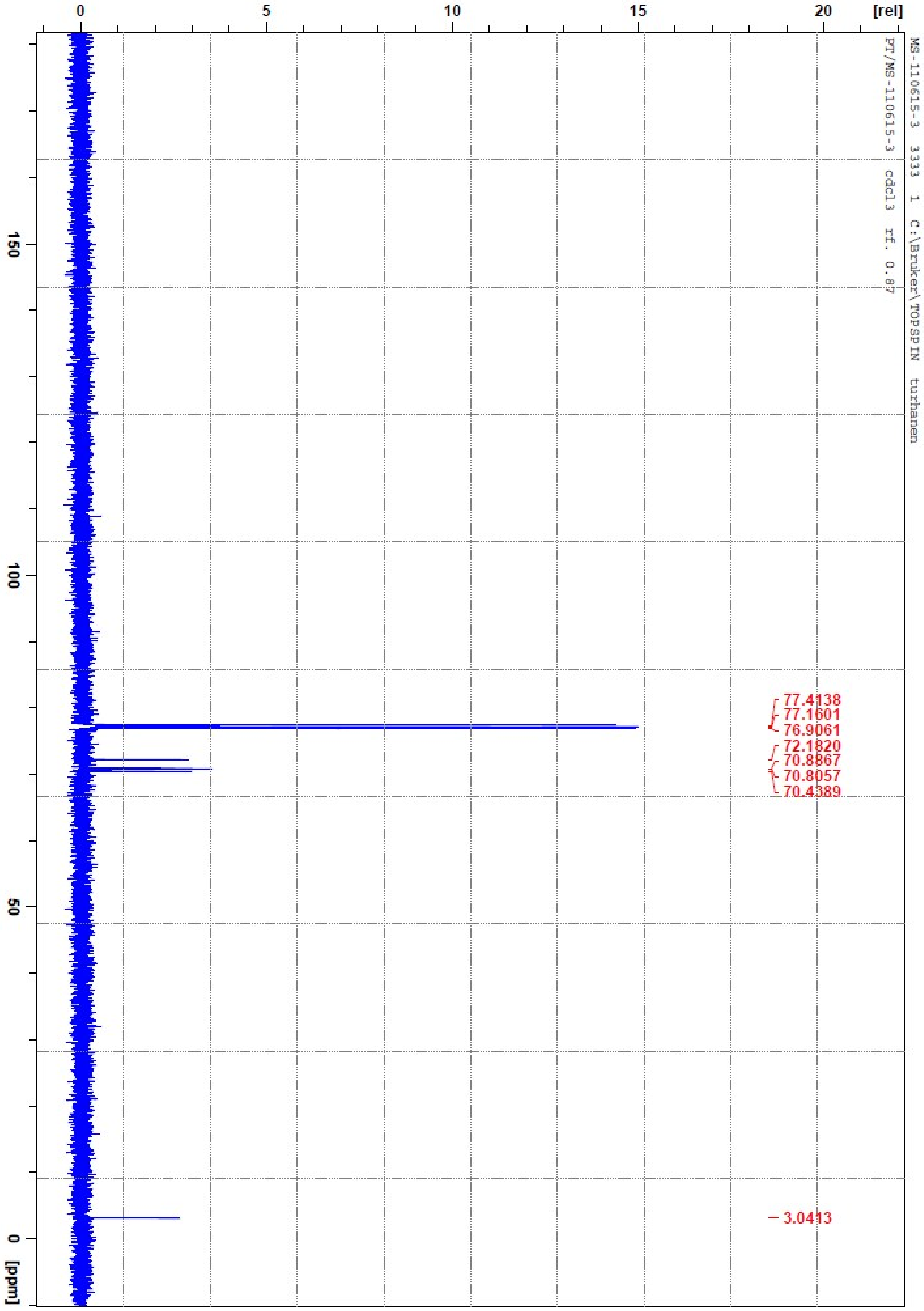

PT/MS-110615-3 cdcl3 rf. 0.61
7.260
3.781
3.768
3.755
3.747
3.740
3.683
3.646
3.636
3.627
3.619
3.284
3.271
3.257
2.192
1.566
1.256
-0.001
2.05
2.30
1.14
1.00
0.45
9
8
7
6
5
4
3
2
1
0
ppm
BRUKER
NAME MS-110615-3
EXPNO 222
PROCNO 1
Date_ 20150615
Time 13.25
INSTRUM spect
PROBHD 5 mm QNP 1H/15
PULPROG zg
TD 65536
SOLVENT CDCl3
NS 4
DS 0
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1720407 sec
RG 90.5
DW 48.400 usec
DE 6.00 usec
TE 300.0 K
D1 5.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 12.25 usec
PL1 -3.00 dB
PL1W 34.08073044 W
SFO1 500.1330885 MHz
SI 262144
SF 500.1300142 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00


MS-110615-3 333 1 C:\Bruker\TOPSPIN turhanen
PT/MS-110615-3 cdcl3 rf. 0.61
[rel]
0
2
4
6
8
10
12
150
100
50
0
[ppm]
77.4139
77.1600
76.9060
72.6382
72.1059
70.5711
70.4058
62.0085
2.7848


I
O
O
O
O
I

24


PI/MS-110615-3 cdcl3 rf. 0.87
7.260
3.775
3.761
3.747
3.668
3.278
3.264
3.250
1.562
-0.000
1.00
2.90
0.87
0.52
9
8
7
6
5
4
3
2
1
0
ppm
BRUKER
NAME MS-110615-3
EXPNO 2222
PROCNO 1
Date_ 20150615
Time 14.05
INSTRUM spect
PROBHD 5 mm QNP 1H/15
PULPROG zg
TD 65536
SOLVENT CDCl3
NS 3
DS 0
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1720407 sec
RG 90.5
DW 48.400 usec
DE 6.00 usec
TE 300.0 K
D1 5.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 12.25 usec
PL1 -3.00 dB
PL1W 34.08073044 W
SFO1 500.1330885 MHz
SI 262144
SF 500.1300142 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 2.00


MS-110615-3 3333 1 C:\Bruker\TOPSPIN turhanen
PT/MS-110615-3 cdcl3 rf. 0.87
77.4138
77.1601
76.9061
72.1820
70.8867
70.8057
70.4389
3.0413
0
5
10
15
20
[rel]
150
100
50
0
[ppm]

References

1. H.E. Gottlieb, V. Kotlyar and A. Nudelman, *J. Org. Chem.* 1997, **62**, 7512.
2. M. Arjun Reddy, K. Surendra, N. Bhanumathi and K. Rama Rao, *Tetrahedron.* 2002, **58**, 6003.
3. D. Arian, L. Kovbasyuk and A. Mokhir, *J. Am. Chem. Soc.* 2011, **133**, 3972.
4. G.A. Molander and L.N. Cavalcanti, *J. Org. Chem.* 2011, **76**, 623.
5. W. Buijs, P. Van Elburg and A. Van der Gen, *Synth. Commun.* 1983, **13**, 387.
6. J.R. Falck, G. Wallukat, N. Puli, M. Goli, C. Arnold, A. Konkel, M. Rothe, R. Fischer, D.N. Müller and W-H. Schunck, *J. Med. Chem.* 2011, **54**, 4109.
7. P.A. Turhanen and J.J. Vepsäläinen, *RSC Adv.* 2015, **5**, 26218.
8. B.M. Trost, H.C. Shen, L. Dong, J-P. Surivet and C. Sylvain, *J. Am. Chem. Soc.* 2004*,* **126***,* 11966.
9. S. Wolfe, C. Akuche, S. Ro, M-C. Wilson, C-K. Kim and Z. Shi, *Can. J. Chem.* 2003, **81**, 915.
10. W-C. Lin and S. Licht, *Biochemistry* 2008, **47**, 9163.