Supplementary Material (ESI) for Organic & Biomolecular Chemistry

SUPPORTING INFORMATION

Synthesis of Polyfunctional Quinolizidine Alkaloids: Development towards Selective Glycosidase Inhibitors

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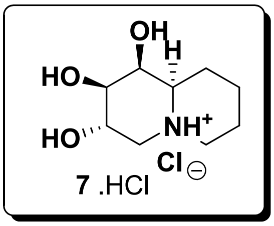
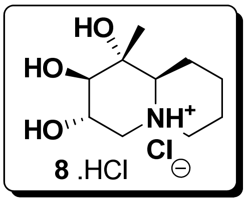
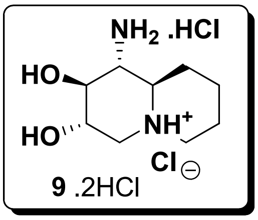
Experimental and spectroscopic data for compounds 7. HCl, 8. HCl, 9. 2HCl, 10. 2HCl, 11. 2HCl, 12. 2HCl and 29



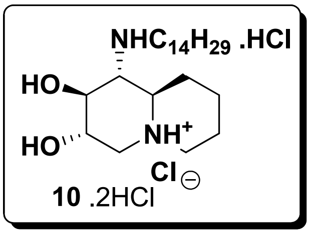
(1*S*,2*R*,3*S*,9a*R*)-1,2,3-trihydroxydecahydroquinolizinium chloride (7 .HCl). Compound **25** (20 mg, 0.087 mmol) was subjected to acetonide deprotection in presence of 1N HCl (1 mL) to provide **7** in the form of its hydrochloride salt quantitatively. $[\alpha]_D^{25} = +7.75$ (*c* 0.5, MeOH). Anal. Calcd. for $C_9H_{18}ClNO_3$: C, 48.32; H, 8.11; N, 6.26; Found: C, 48.43; H, 8.17; N, 6.21. δ_H (400 MHz, D_2O) 1.44-1.63 (2H, m, 8ax-H, 9ax-H), 1.68-1.84 (4H, m, 7ax-H, 7eq-H, 8eq-H, 9eq-H), 2.79 (1H, t, $^3J_{3ax,4ax}$ = 11.92, 4ax-H), 2.95 (1H, dt, $^3J_{6ax,7ax}$ = 12.55, $^3J_{6ax,7eq}$ = 2.5, 6ax-H), 3.16 (1H, dd, $^3J_{9ax,9a\text{-}ax}$ = 9.79, $^3J_{9eq,9a\text{-}ax}$ = 5.27, 9a-ax-H), 3.33-3.42 (2H, m, 4eq-H, 6eq-H), 3.56 (1H, dd, $^3J_{2ax,3ax}$ = 9.79, $^3J_{1eq,2ax}$ = 3.03, 2ax-H), 3.89 (1H, d, $^3J_{1eq,9a\text{-}ax}$ = 2.51, 1eq-H), 3.98 (1H, ddd, 3ax-H). δ_C (100 MHz, D_2O) 20.9 (C-8), 22.6 (C-7), 25.7 (C-9), 55.0 (C-6), 56.1 (C-4), 64.3 (C-9a), 64.8 (C-1), 69.8 (C-3), 72.9 (C-2). Mass (ESI): *m/z* 188 (M^++H).



(1*R*,2*R*,3*S*,9a*R*)-1,2,3-trihydroxy-1-methyldecahydroquinolizinium chloride (8 .HCl). Compound **27** (0.031 g, 0.136 mmol) upon acetonide deprotection using aqueous 1N HCl (1 mL) provided hydrochloride salt of **8** quantitatively. $[\alpha]_D^{27}$ = + 27.8 (*c* 1.1, MeOH). Anal. Calcd. for $C_{10}H_{20}ClNO_3$: C, 50.52; H, 8.48; N, 5.89; Found: C, 50.69; H, 8.39; N, 5.94. δ_H (400 MHz, D_2O) 1.12 (3H, s, 1-Me), 1.36-1.67 (3H, m, 7ax-H, 8ax-H, 9ax-H), 1.86 (2H, br d, $^2J_{H,H}$ = 14.4, 7eq-H, 8eq-H), 2.13 (1H, br d, $^2J_{H,H}$ = 13.78, 9eq-H), 2.88 (1H, t, $^3J_{3ax,4ax}$ = 12.05, 4ax-H), 2.95-3.03 (2H, m, 6ax-H, 9a-ax-H), 3.39-3.48 (3H, m, 2ax-H, 4eq-H, 6eq-H), 3.65 (1H, ddd, $^3J_{2ax,3ax}$ = 10.16, $^3J_{3ax,4eq}$ = 5.14, 3ax-H). δ_C (100 MHz, D_2O) 13.7 (1-Me), 21.2, 22.70, 22.8 (C-7, C-8, C-9), 56.2 (C-6), 56.7 (C-4), 64.8 (C-3), 68.2 (C-9a), 72.6 (C-1), 78.2 (C-2). Mass (ESI): *m/z* 202 (M^++H), 224 (M^++Na).

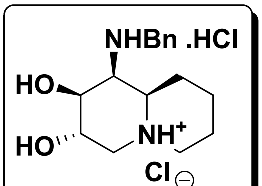


(1*R*,2*S*,3*S*,9a*R*)-1-amino-2,3-dihydroxydecahydroquinolizinium chloride hydrochloride (9 .2HCl): Compound **31** (0.023 g, 0.01 mmol) was subjected to acetonide deprotection in presence of aqueous 1N HCl (1 mL) to provide dihydrochloride salt of **9** quantitatively. $[\alpha]_D^{28}$ = + 7.29 (*c* 1.4, MeOH). Anal.Calcd. for $C_9H_{20}Cl_2N_2O_2$: C, 41.71; H, 7.78; N, 10.81; Found: C, 41.83; H, 7.83; N, 10.77. δ_H (400 MHz, D_2O) 1.43-1.56 (2H, m, 8ax-H, 9ax-H), 1.62-1.72 (1H, m, 7ax-H), 1.89 (2H, br d, $^2J_{H,H}$ = 12.80, 7eq-H, 8eq-H), 2.14 (1H, br d, $^2J_{H,H}$ = 13.3, 9eq-H), 3.01 (1H, t, $^3J_{3ax,4ax}$ = 12.05, 4ax-H), 3.06 (1H, dt, $^3J_{6ax,7ax}$ = 12.90, $^3J_{6ax,7eq}$ = 2.51, 6ax-H), 3.22 (1H, t, $^3J_{1ax,2ax}$ = 10.79, 1ax-H), 3.38 (1H, dt, $^3J_{9ax,9a\text{-}ax}$ = 11.54, $^3J_{9eq,9a\text{-}ax}$ = 3.01, 9a-ax-H), 3.50-3.54 (2H, m, 4eq-H, 6eq-H), 3.61 (1H, t, $^3J_{2ax,3ax}$ = 10.04, 2ax-H), 3.76 (1H, ddd, 3ax-H). δ_C (100 MHz, D_2O) 20.3, 22.2, 26.0 (C-7, C-8, C-9), 53.8 (C-9a), 55.7 (C-4, C-6), 61.7 (C-1), 66.5 (C-3), 71.8 (C-2). Mass (ESI): *m/*z = 187 (M^++H), 209 (M^++Na).



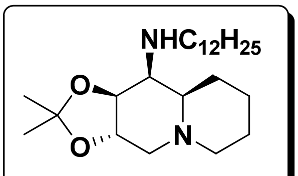
(1*R*,2*S*,3*S*,9a*R*)-2,3-dihydroxy-1-(tetradecylamino)decahydroquinolizinium chloride hydrochloride (10 .2HCl): To a stirring solution of **31** (0.025 g, 0.11 mmol) in dry CH_3CN and THF (3:1), (2 mL) was added tetradecyl bromide (0.031 g, 0.11 mmol) followed by K_2CO_3 (0.029 g, 0.22 mmol) and refluxed for 12 h. Water (5mL) was added and the reaction mixture was extracted in ethyl acetate (2 × 5 mL). After drying over Na_2SO_4 the reaction mixture was concentrated and purified by column chromatography (pet. ether/ethyl acetate, 7:3) to get alkylated amine (0.030 g, 65%) as yellow liquid. This amine upon acetonide deprotection with aqueous 1N HCl (1 mL) produced dihydrochloride salt of **10** in quantitative amount. $[\alpha]_D^{26}$ = + 5.4 (*c* 0.3, MeOH). Anal.Calcd. for $C_{23}H_{48}Cl_2N_2O_2$: C, 60.64; H, 10.62; N, 6.15; Found: C, 60.78; H, 10.69; N, 6.11. δ_H (500 MHz, CD_3OD) 0.81

(1H, t, J = 6.90, CH_2CH_3), 1.20-1.35 (24H, m, $NHCH_2(CH_2)_{12}CH_3$), 1.68-1.91 (5H, m, 7ax-H, 7eq- H, 8ax-H, 8eq-H, 9ax-H), 2.02-2.11 (1H, m, 9eq-H), 2.95-3.08 (4H, m, 1ax-H, 4ax-H, 6ax-H, 9a-ax-H), 3.33-3.40 (2H, m, $NHCH_2$), 3.52 (1H, br d, $^2J_{H,H}$ = 11.87, 6eq-H), 3.68-3.72 (2H, m, 2ax-H, 4eq-H), 3.84-3.95 (1H, m, 3ax-H). δ_C (125 MHz, CD_3OD) 14.6 (CH_2CH_3), 22.2, 23.7, 23.9, 27.6, 27.7, 30.3, 30.4, 30.6, 30.7, 30.8, 30.90, 30.92, 33.2 ($NHCH_2(CH_2)_{12}CH_3$, C-7, C-8, C-9), 46.2 (CH_2NH), 57.0 (C-6), 57.7 (C-4), 61.2, 61.9 (C-1, C-9a), 68.2 (C-3), 71.8 (C-2). Mass (ESI): *m/z* 383 (M^++H).



11 .2HCl

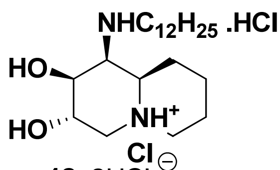
(1*S*,2*S*,3*S*,9a*R*)-1-(benzylamino)octahydro-1H-quinolizine-2,3-diol (11 .2HCl). Compound **28** (0.032 g, 0.01 mmol) under acetonide deprotection condition using aqueous 1N HCl (1 mL) provided **11** quantitatively, in the form of its dihydrochloride salt. $[\alpha]_D^{26}$ = + 5.2 (*c* 1.1, MeOH). Anal.Calcd. for : $C_{16}H_{26}Cl_2N_2O_2$: C, 55.02; H, 7.50; N, 8.02; Found: C, 54.89; H, 7.55; N, 8.09. δ_H (400 MHz, D_2O) 1.33-1.44 (1H, m, 8ax-H), 1.70-1.89 (4H, m, 7ax-H, 7eq-H, 8eq-H, 9ax-H), 2.23-2.34 (1H, m, 9eq-H), 3.03 (1H, d, $^3J_{9ax,9a\text{-}ax}$ = 13.3, 9a-ax-H), 3.23-3.32 (2H, m, 4ax-H, 6ax-H), 3.73-3.81 (2H, m, 4eq-H, 6eq-H), 3.97 (1H, d, $^3J_{2ax,3ax}$ = 13.30, 2ax-H), 4.16-4.18 (2H, m, 1eq-H, 3ax-H), 4.25, 4.35 (1H each, 2 d, $^2J_{H,H}$ = 13.25, CH_2Ph), 7.40-7.46 (5H, m, H-arom). δ_C (100 MHz, D_2O) 20.0, 22.0, 24.0 (C-7, C-8, C-9), 48.2 (CH_2Ph), 51.4 (C-6), 55.3 (C-1), 56.6 (C-4), 59.1 (C-9a), 65.6 (C-3), 68.5 (C-2), 131.9, 132.0, 132.5, 132.7 (C-arom). Mass (ESI): *m/z* 277 (M^++H).



29

(3a*S*,9a*R*,10*S*,10a*S*)-N-dodecyl-2,2-dimethyloctahydro-3aH-[1,3]dioxolo[4,5-b]quinolizin-10-amine (29). Ketone **24** (0.084 g, 0.373 mmol) under similar reductive amination condition as described earlier with dodecyl amine (0.072 g, 0.391 mmol) gave **29** (0.096 g, 65 %) as a white solid. $[\alpha]_D^{25}$ = + 17.19 (*c* 0.8, $CHCl_3$). Anal. Calcd. for $C_{24}H_{46}N_2O_2$: C, 73.04; H, 11.75; N, 7.10; Found: C, 73.18; H, 11.69; N, 7.06. IR ν_{max} cm^{-1} in $CHCl_3$ 3397 (NH), 2144, 1531, 1265. δ_H (500 MHz, $CDCl_3$) 0.86 (3H, t, J = 6.84,

CH_2CH_3), 1.24-1.27 (20H, m, $NHCH_2(CH_2)_{10}CH_3$), 1.42, 1.43 (3H each, 2 s, $C(CH_3)_2$), 1.50-1.57 (4H, m, 7ax-H, 7eq-H, 8ax-H, 9ax-H), 1.67-1.79 (2H, m, 8eq-H, 9eq-H), 1.92 (1H, d, $^3J_{9ax,9a\text{-}ax}$ = 11.01, 9a-ax-H), 2.08-2.13 (2H, m, 4ax-H, 6ax-H), 2.62-2.72 (2H, m, $NHCH_2$), 2.90-2.92 (2H, m, 6eq-H, 10eq-H), 3.15 (1H, dd, $^2J_{H,H}$ = 9.94, $^3J_{3a\text{-}ax,4eq}$ = 4.16, 4eq-H), 3.37 (1H, dd, $^3J_{3a\text{-}ax,10a\text{-}ax}$ = 9.40, $^3J_{10eq,10a\text{-}ax}$ = 3.52, 10a-ax-H), 3.89 (1H, dt, $^3J_{3a\text{-}ax,4ax}$ = 9.73, 3a-ax-H). δ_C (100 MHz, $CDCl_3$) 14.1 (CH_2CH_3), 26.6, 26.9 ($C(CH_3)_2$), 22.7, 24.4, 25.5, 27.2, 29.3, 29.51, 29.58, 29.6, 30.5, 31.9 (C-7, C-8, C-9, $NHCH_2(CH_2)_{10}CH_3$), 51.6 ($NHCH_2$), 56.8 (C-6), 58.3 (C-4), 59.7 (C-9a), 65.2 (C-10), 70.9 (C-3a), 82.4 (C-10a), 109.7 ($C(CH_3)_2$). Mass (ESI): *m/z* 395 (M^++H), 417 (M^++Na).



12 .2HCl

(1*S*,2*S*,3*S*,9a*R*)-1-(dodecylamino)-2,3-dihydroxydecahydroquinolizinium chloride hydrochloride (12 .2HCl): Compound **29** (0.054 g, 0.137 mmol) upon acetonide deprotection in aqueous 1N HCl (1 mL) provided dihydrochloride salt of **12** quantitatively. $[\alpha]_D^{25}$ = + 20.3 (*c* 0.3, MeOH). Anal.Calcd. for $C_{21}H_{44}Cl_2N_2O_2$: C, 59.00; H, 10.37; N, 6.55; Found: C, 59.17; H, 10.41; N, 6.58. δ_H (400 MHz, D_2O) 0.76 (1H, t, *J* = 6.23,CH_2CH_3), 1.18-1.45 (20H, m, $NHCH_2(CH_2)_{10}CH_3$)) 1.65-1.89 (5H, m, 7ax-H, 7eq-H, 8ax-H, 8eq-H, 9ax-H), 2.22-2.31 (1H, m, 9eq-H), 2.96-3.11 (3H, m, 4ax-H, 6ax-H, 9a-ax-H), 3.25-3.33 (2H, m, $NHCH_2$), 3.74-3.84 (2H, m, 1eq-H, 2ax-H), 3.96 (1H, d, $^2J_{H,H}$ = 13.48, 6eq-H), 4.11-4.16 (2H, m, 3ax-H, 4eq-H). δ_C (100 MHz, D_2O) 13.4 (CH_2CH_3), 17.5, 19.4, 21.5, 22.0, 25.3, 25.7, 25.8, 28.1, 28.2, 28.5, 28.7, 28.9, 31.2 (C-7, C-8, C-9, $NHCH_2(CH_2)_{10}CH_3$), 45.7 (C-4, C-6), 53.5 (C-9a), 54.1 ($NHCH_2$), 56.5, 63.1, 66.0 (C-1, C-2, C-3). Mass (ESI): *m/z* 355 (M^++H).

Optical rotation of enantiomeric compounds.

Compound	**Optical rotation** $[\alpha]_D^T$
22b	$[\alpha]_D^{27}$ = -56.4 (*c* 0.95, CH_2Cl_2)
Ent-**23**	$[\alpha]_D^{28}$ = -26.3 (*c* 1.1, DCM)
13. HCl	$[\alpha]_D^{25}$ = -25.8 (*c* 1.1, MeOH)
Ent-**25**	$[\alpha]_D^{27}$ = -15.37 (*c* 1.25, DCM)
14. HCl	$[\alpha]_D^{26}$ = -8.91 (*c* 0.8, MeOH)
Ent-**26**	$[\alpha]_D^{27}$ = -51.02 (*c* 1.05, $CHCl_3$)
Ent-**27**	$[\alpha]_D^{29}$ = -37.3 (*c* 1.05, $CHCl_3$)
15. HCl	$[\alpha]_D^{29}$ = -28.7 (*c* 1.15, MeOH)
Ent-**28**	$[\alpha]_D^{27}$ = -17.63 (*c* 1.15, $CHCl_3$)
18. 2HCl	$[\alpha]_D^{25}$ = -5.6 (*c* 1.0, MeOH)
Ent-**30**	$[\alpha]_D^{26}$ = -61.11 (*c* 1.15, $CHCl_3$)
Ent-**31**	$[\alpha]_D^{28}$ = -40.13 (*c* 0.85, $CHCl_3$)
16. 2HCl	$[\alpha]_D^{26}$ = -7.89 (*c* 1.1, MeOH)
17. 2HCl	$[\alpha]_D^{29}$ = - 5.88 (*c* 0.55, MeOH)

X-ray crystal structure analysis for compounds 23 and 25.

Crystal Data: Data for both the compounds were collected at T = 296 K, on SMART APEX CCD Single Crystal X-ray diffractometer using Mo-Kα radiation (λ = 0.7107 Å) to a maximum θ range of 25.00°. The structures were solved by direct methods using SHELXTL. All the data were corrected for Lorentzian, polarisation and absorption effects. SHELX-97 (ShelxTL)[1] was used for structure solution and full matrix least squares refinement on F^2. Hydrogen atoms were included in the refinement as per the riding model. The refinements were carried out using SHELXL-97.

$C_{13}H_{23}NO_4$ compound 23: Single crystals of the complex were grown by slow evaporation of the solution a mixture of hexanes and ethylacetate. Colourless needle crystal of approximate size 0.22 x 0.07 x 0.01 mm^3, was used for data collection. Crystal to detector distance 6.05 cm, 512 x 512 pixels / frame, Multirun data acquisition. Total scans = 4, total frames = 2424, Oscillation / frame -0.3º, exposure / frame = 20.0 sec / frame, maximum detector swing angle = –30.0º, beam center = (260.2, 252.5), in plane spot width = 1.24, SAINT integration, θ range = 1.68 to 25.0 º, completeness to θ of 25.0 º is 100.0 %. SADABS correction applied, $C_{13}H_{23}NO_4$, M = 257.32. Crystals belong to orthorhombic, space group $P2_12_12_1$, a = 5.3743(4), b = 10.2506 (7), c = 24.311(2) Å, V = 1339.27(16) $Å^3$, Z = 4, D_c = 1.276 g /cc, μ (Mo–Kα) = 0.094 mm^{-1}, 12741, reflections measured, 2369 unique [I>2σ(I)], R value 0.0358, wR2 = 0.0823. Largest diff. peak and hole 0.153 and -0.200 e. $Å^{-3}$.

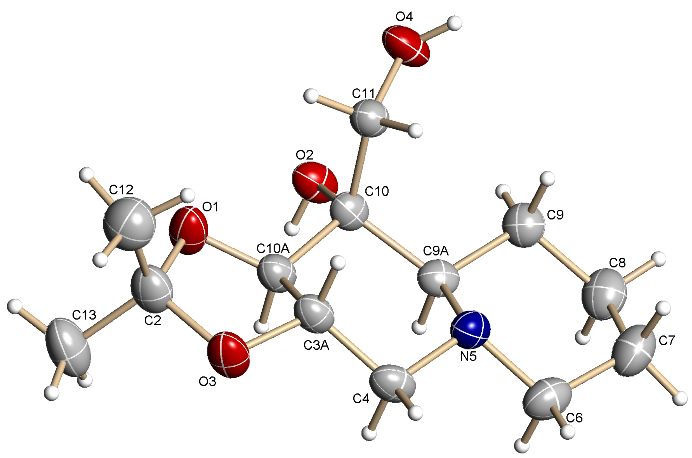


Fig. 1 ORTEP diagram of **23**. Ellipsoids are drawn at 50% probability.

[1]G. M. Sheldrick, SHELX-97 program for crystal structure solution and refinement, University of Gottingen, Germany, 1997

$C_{12}H_{21}NO_3$ compound 25: Single crystals of the complex were grown by slow evaporation of the solution a mixture of hexanes and ethylacetate. Colourless needle of approximate size 0.20 x 0.05 x 0.01 mm^3, was used for data collection. Crystal to detector distance 6.05 cm, 512 x 512 pixels / frame, Multirun data acquisition. Total scans = 5, total frames = 2101, Oscillation / frame -0.3º, exposure / frame = 25.0 sec / frame, maximum detector swing angle = –30.0º, beam center = (260.2, 252.5), in plane spot width = 1.24, SAINT integration, θ range = 2.00 to 24.99 º, completeness to θ of 24.99 º is 100.0 % SADABS correction applied, $C_{12}H_{21}NO_3$, M = 227.30. Crystals belong to orthorhombic, space group $P2_12_12_1$, a = 9.725 (1), b = 6.4790(7), c = 20.325(2) Å, V = 1280.6(2) $Å^3$, Z = 4, D_c = 1.179 g/cc, μ (Mo–Kα) = 0.084 mm^{-1}, 10685 reflections measured, 2250 unique [I>2σ(I)], R value 0.0480, wR2 = 0.0864. Largest diff. peak and hole 0.101 and -0.101 e. $Å^{-3}$.

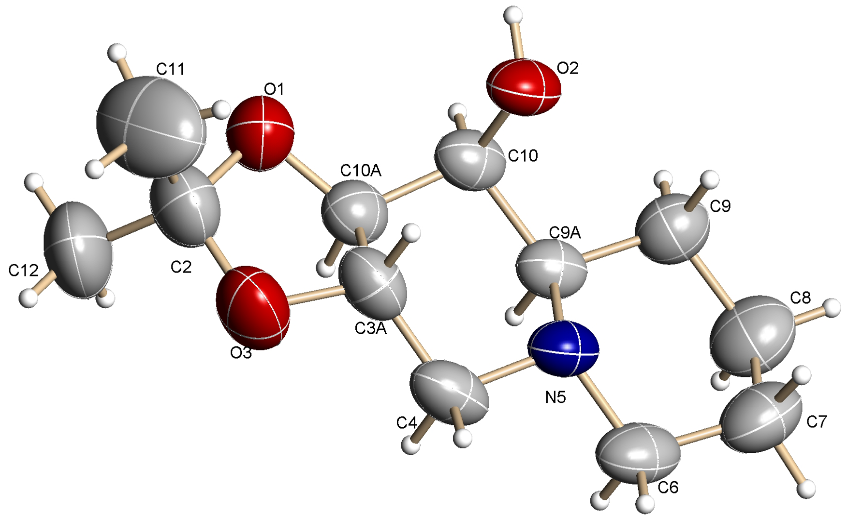
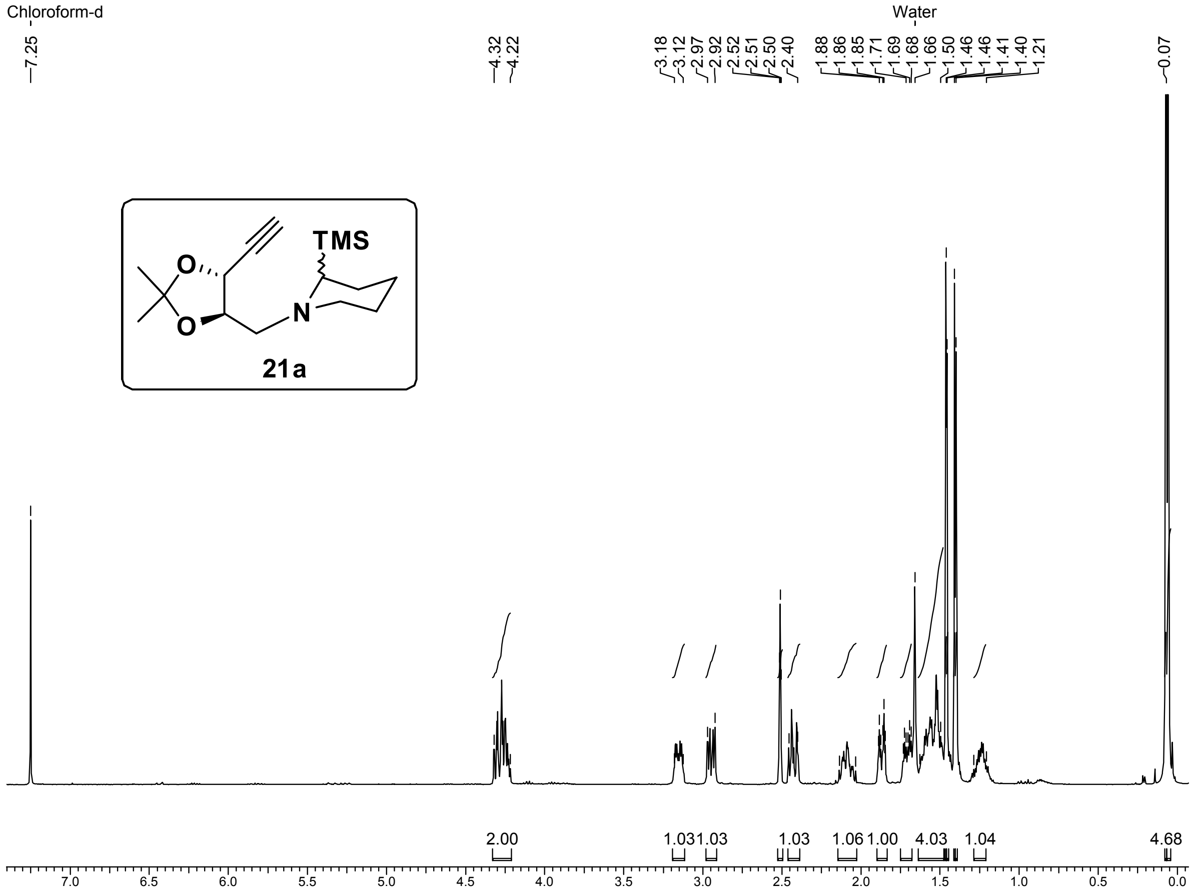


Fig. 2 ORTEP diagram of **25**. Ellipsoids are drawn at 50% probability.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2.92
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2.51
2.50
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1.88
1.86
1.85
1.71
1.69
1.68
1.66
1.50
1.46
1.41
1.40
1.21
0.07
TMS
N
O
O
21a
2.00
1.03
1.03
1.03
1.06
1.00
4.03
1.04
4.68
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6.5
6.0
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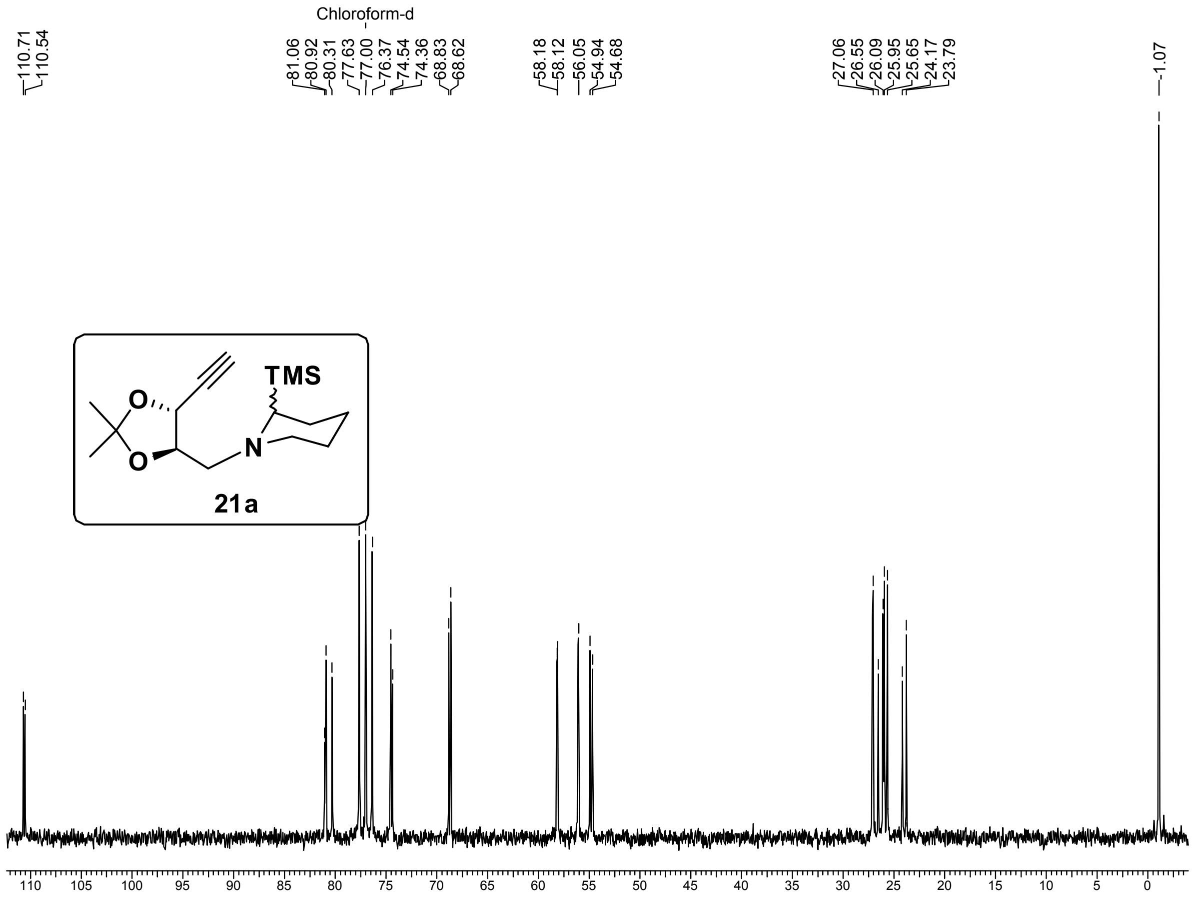
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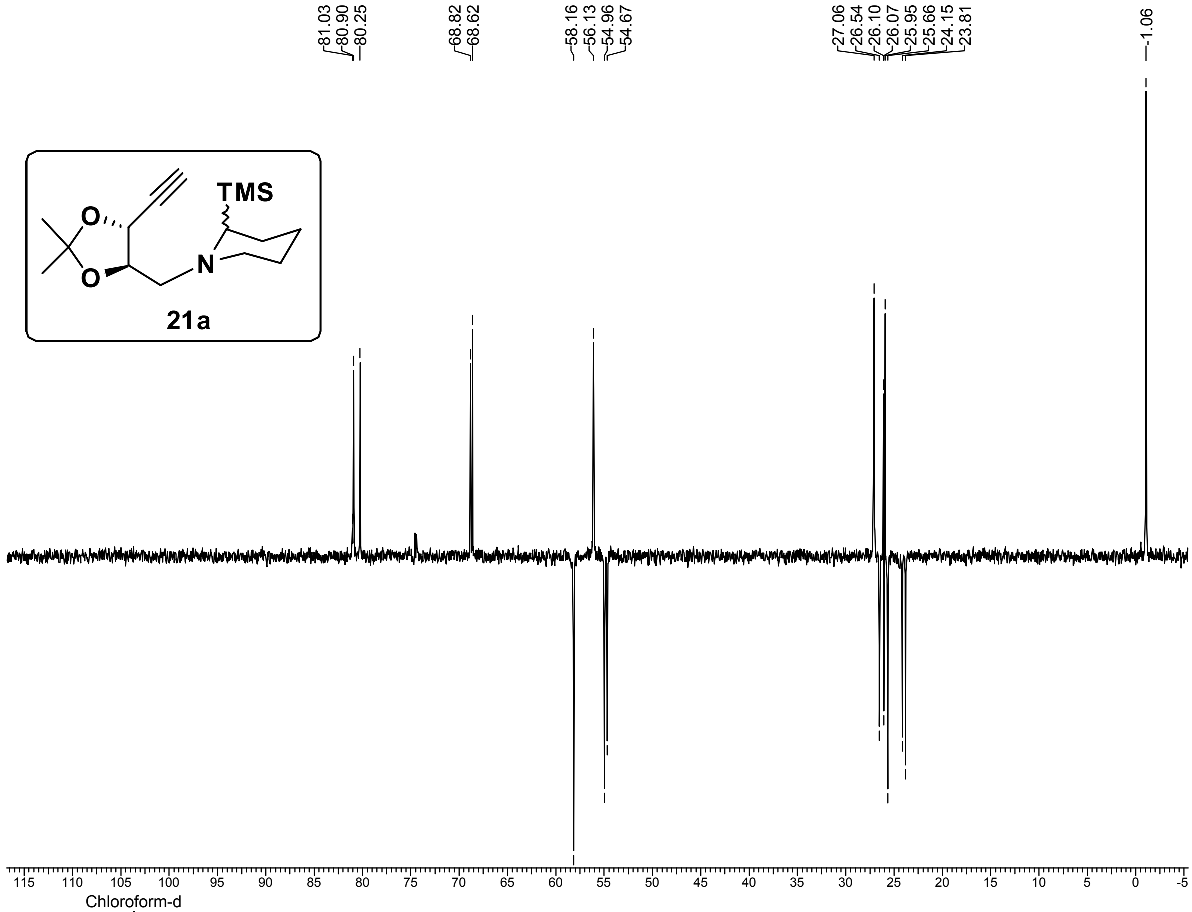
TMS
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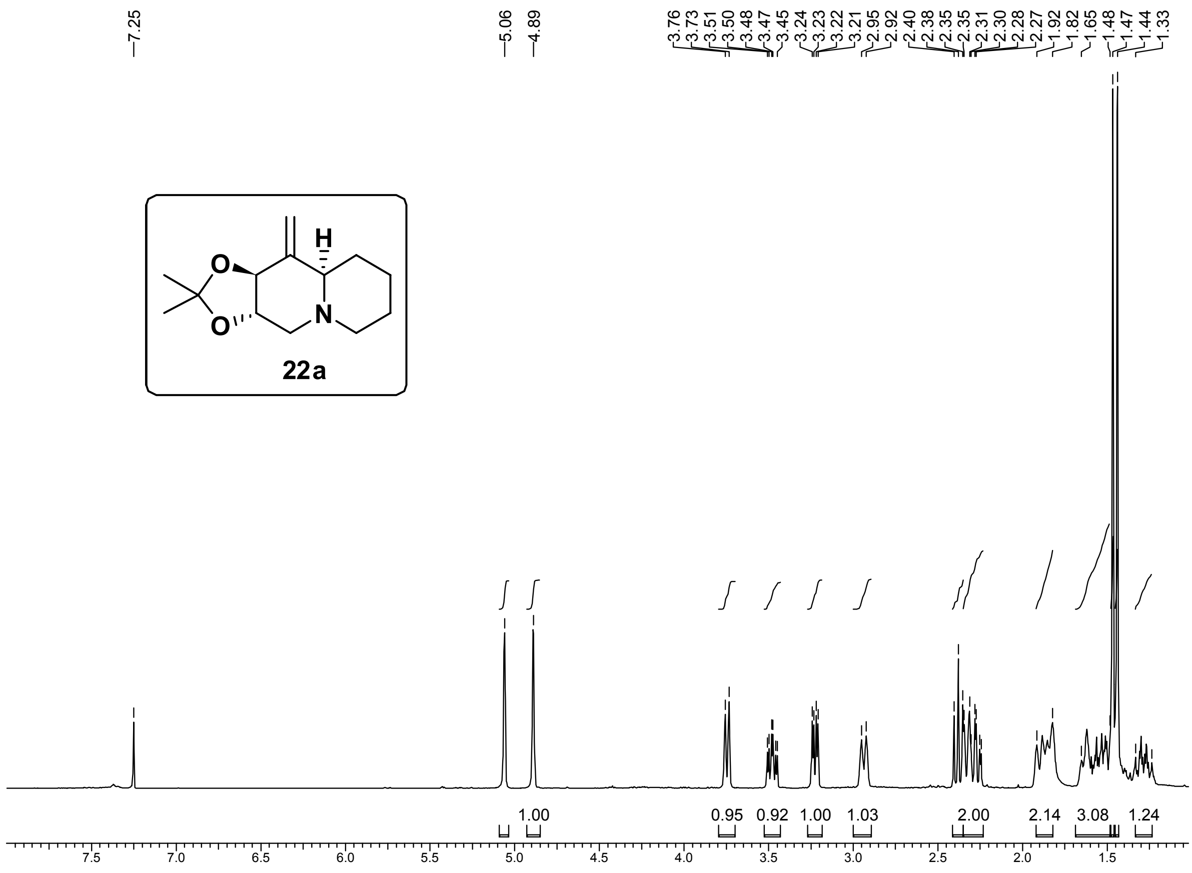
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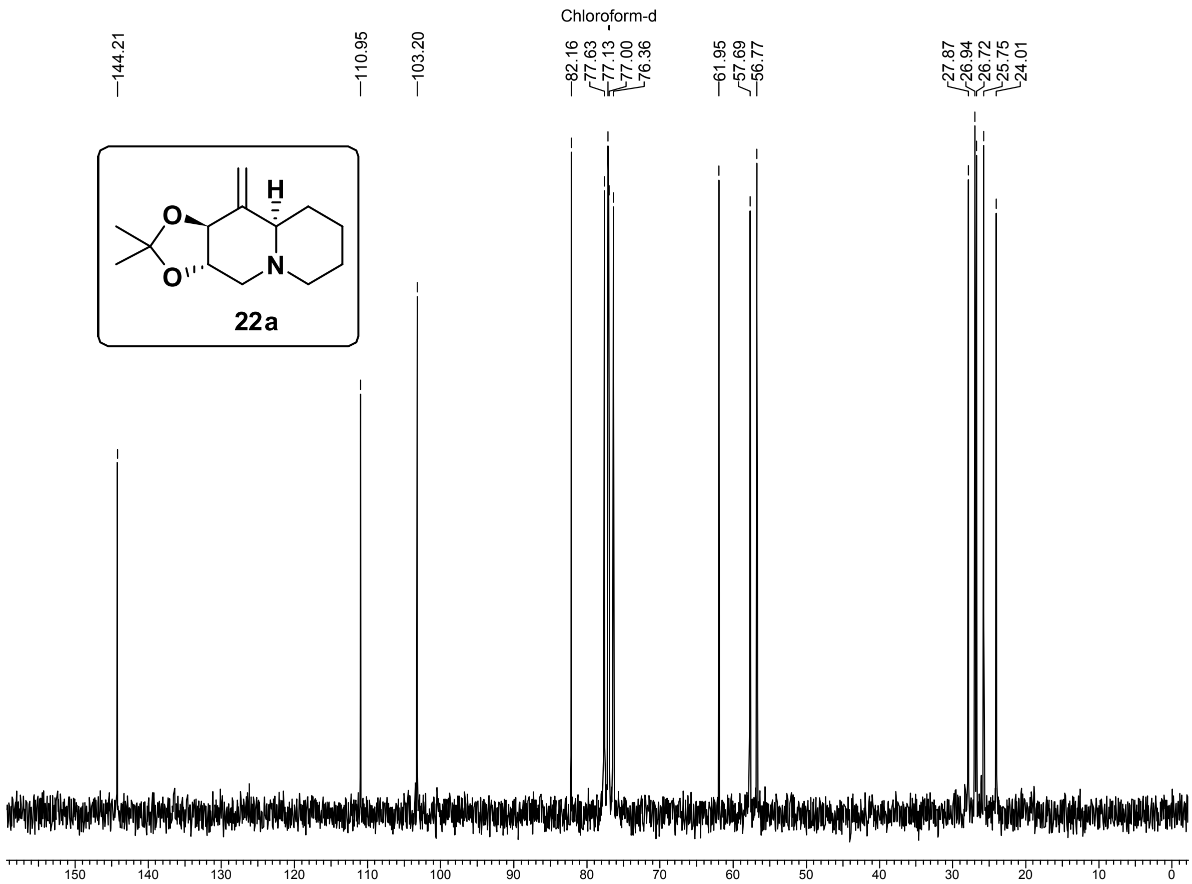
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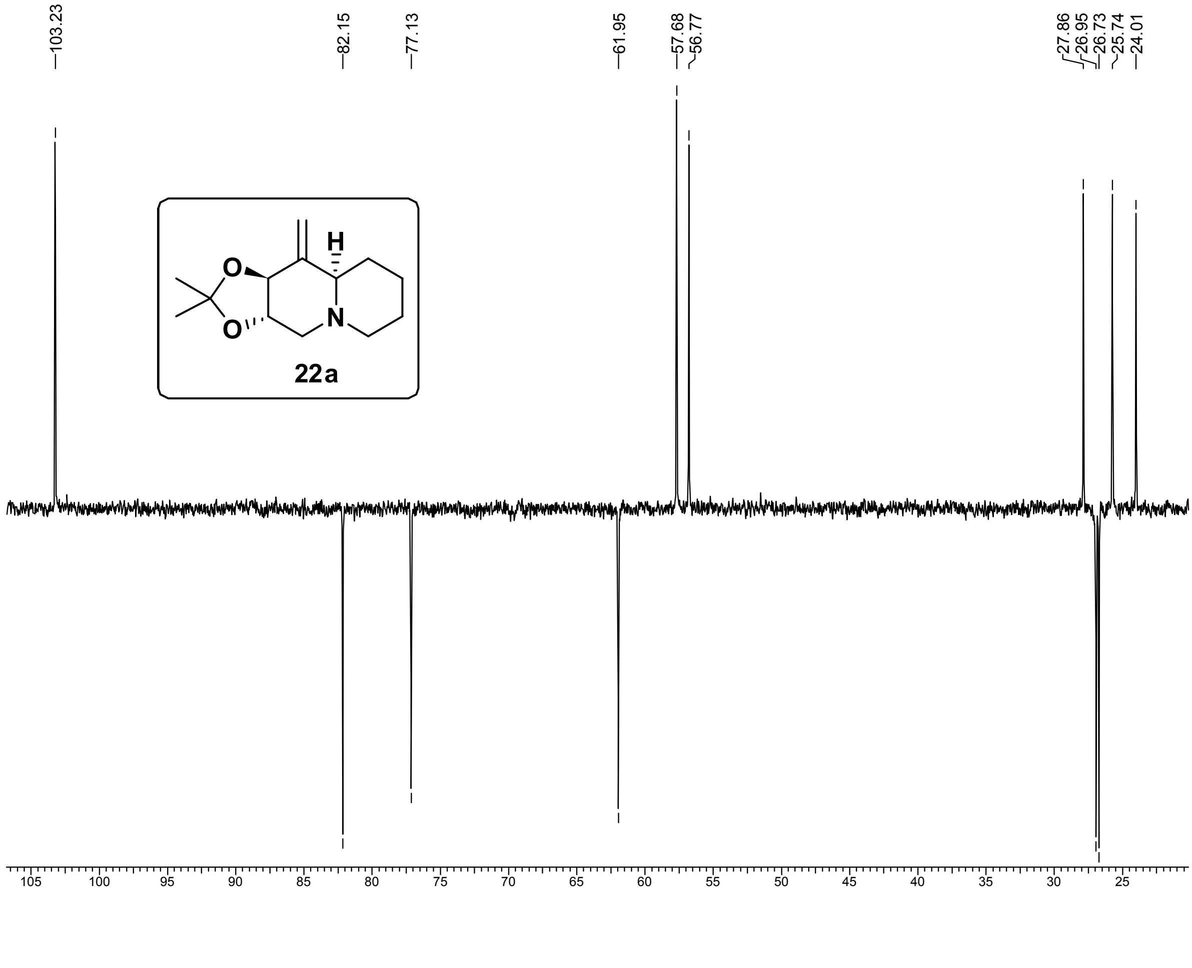
103.20
82.16
77.63
77.13
77.00
76.36
61.95
57.69
56.77
27.87
26.94
26.72
25.75
24.01
O
O
H
N
22a
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0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82.15
77.13
61.95
57.68
56.77
27.86
26.95
26.73
25.74
24.01
O
O
H
N
22a
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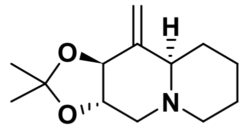
COSY



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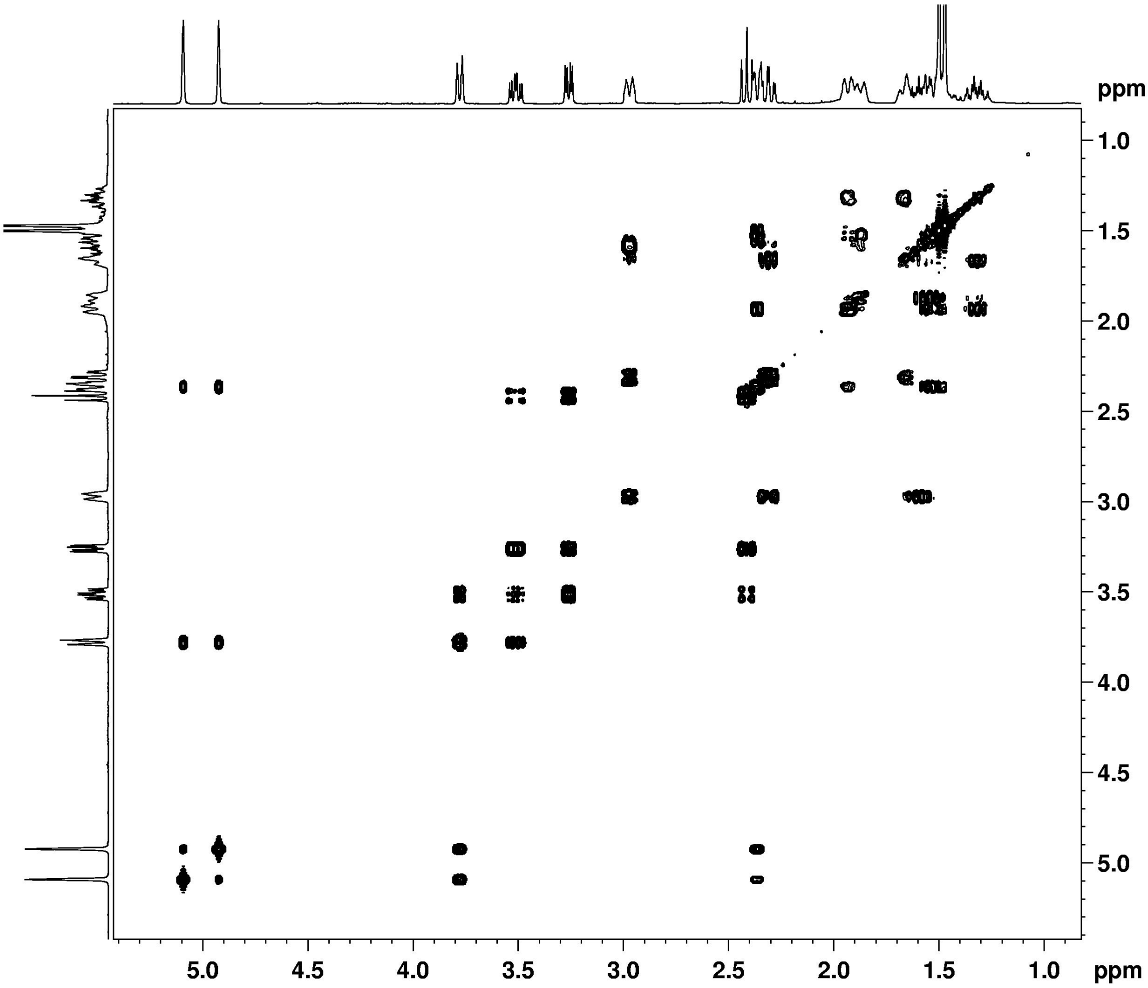

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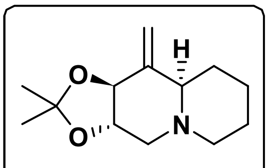

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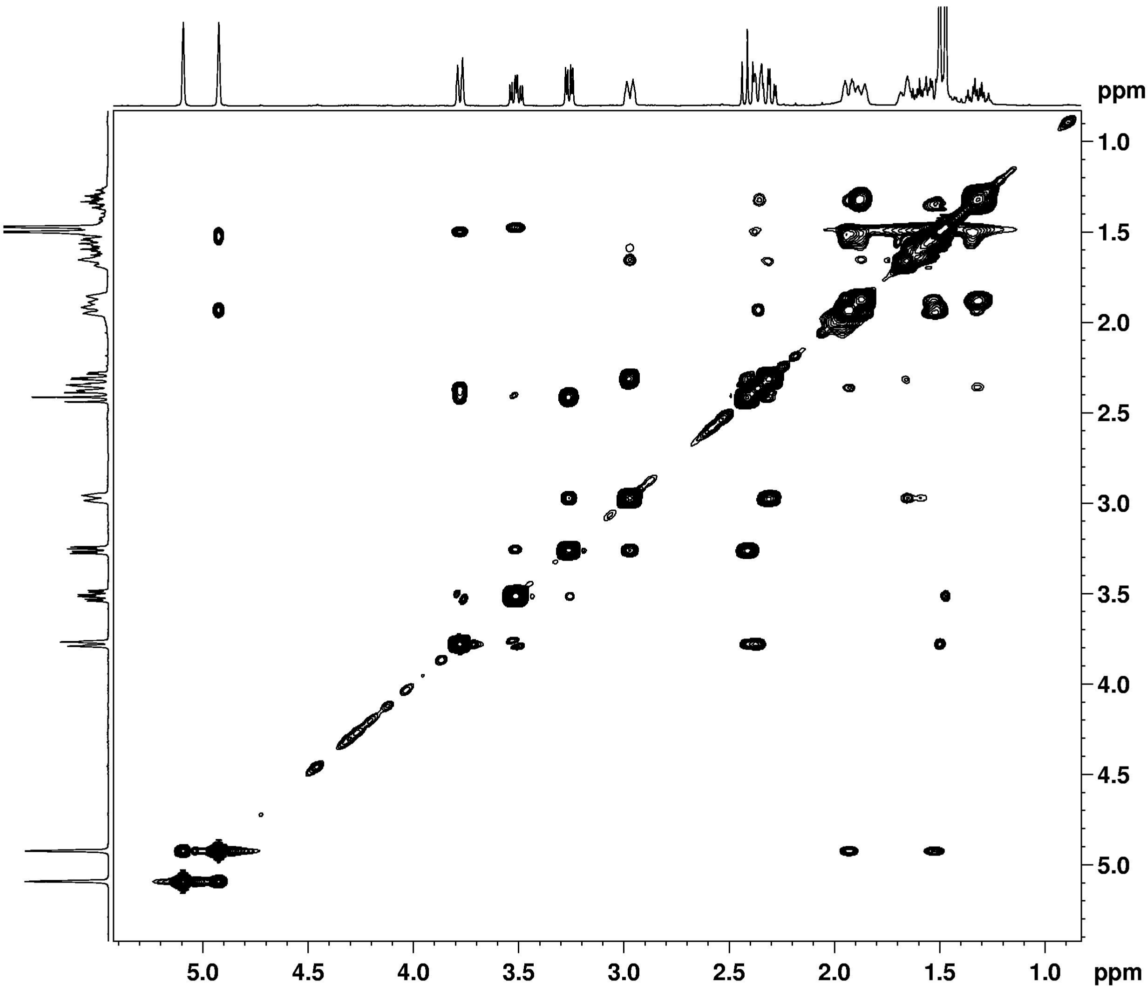

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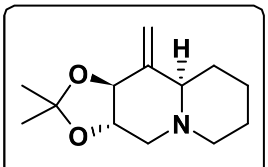

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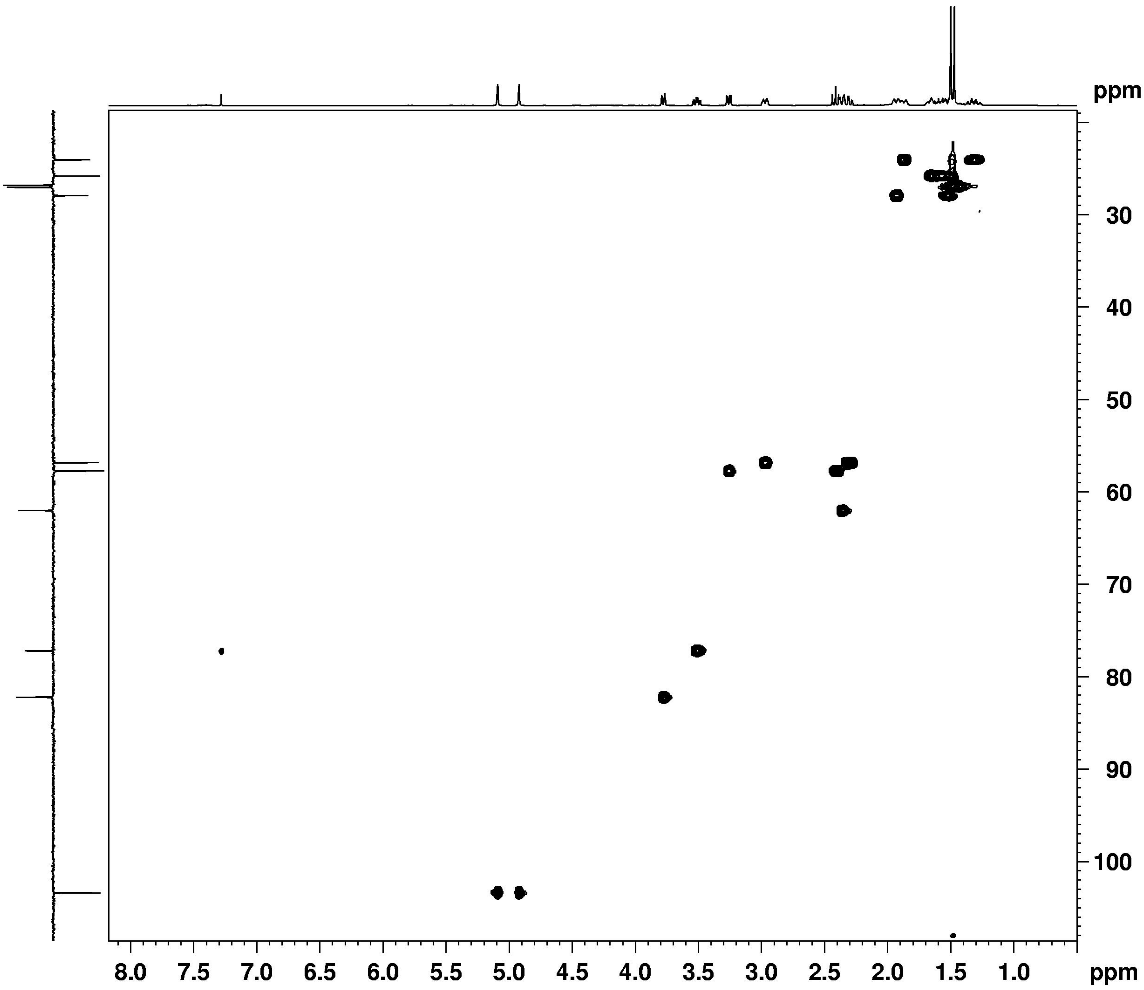

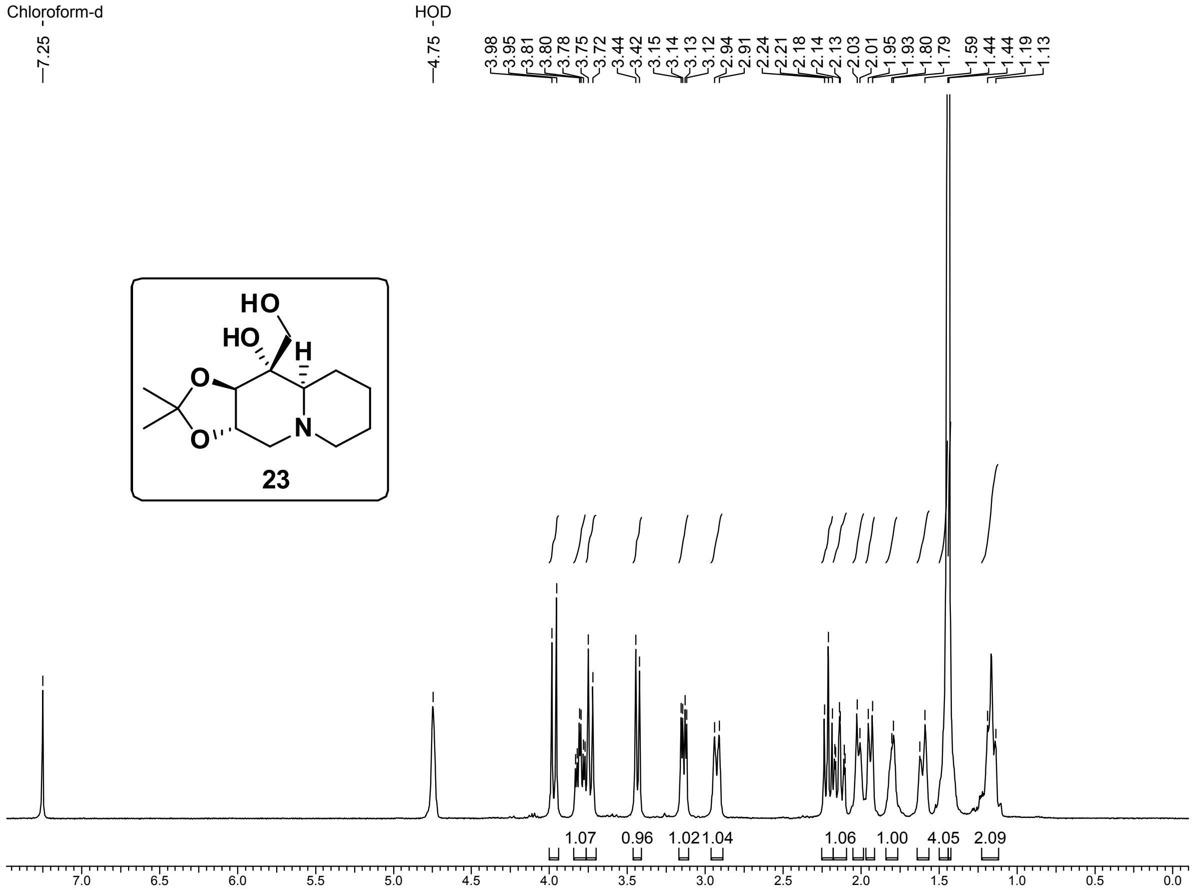
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HOD
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3.80
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3.42
3.15
3.14
3.13
3.12
2.94
2.91
2.24
2.21
2.18
2.14
2.13
2.03
2.01
1.95
1.93
1.80
1.79
1.59
1.44
1.44
1.19
1.13
HO
HO
H
O
O
N
23
1.07
0.96
1.02
1.04
1.06
1.00
4.05
2.09
7.0
6.5
6.0
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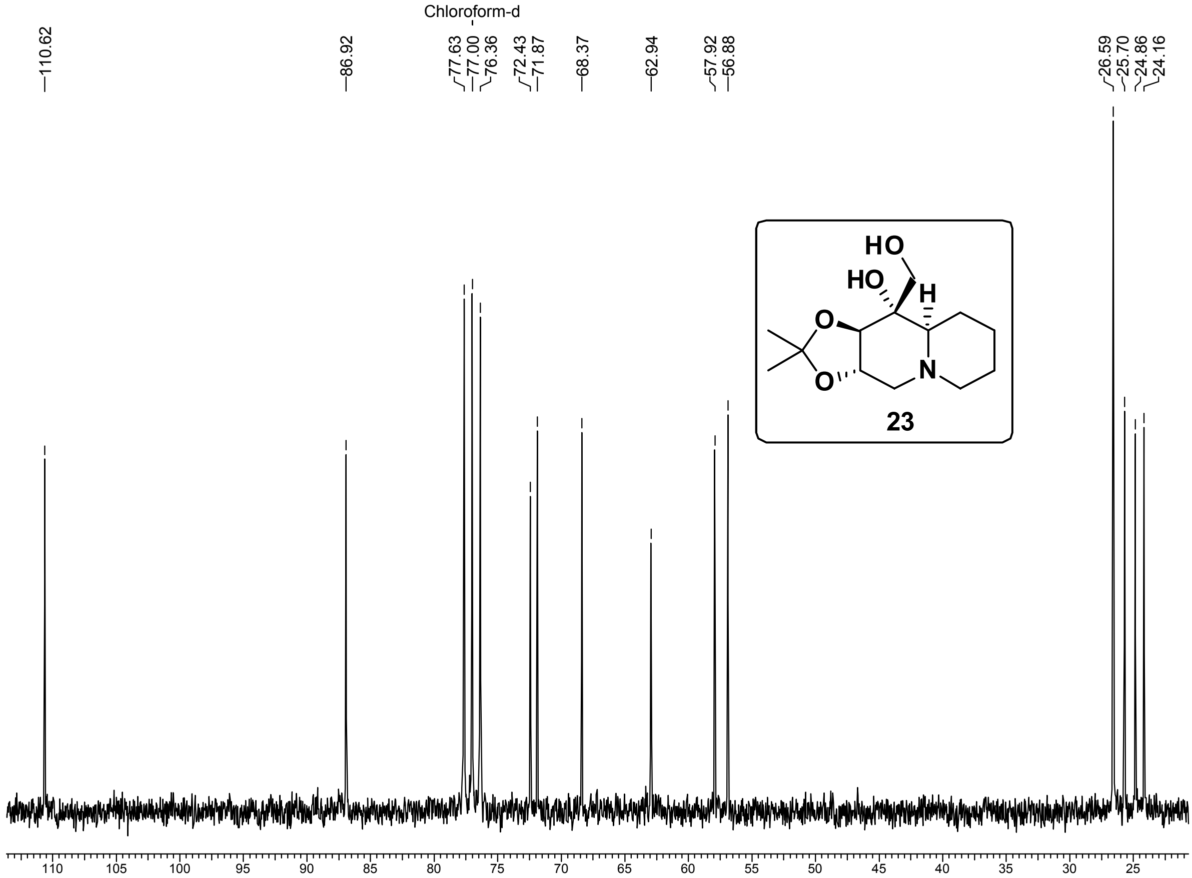
Chloroform-d
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86.92
77.63
77.00
76.36
72.43
71.87
68.37
62.94
57.92
56.88
26.59
25.70
24.86
24.16
HO
HO
H
O
O
N
23
110
105
100
95
90
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70
65
60
55
50
45
40
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30
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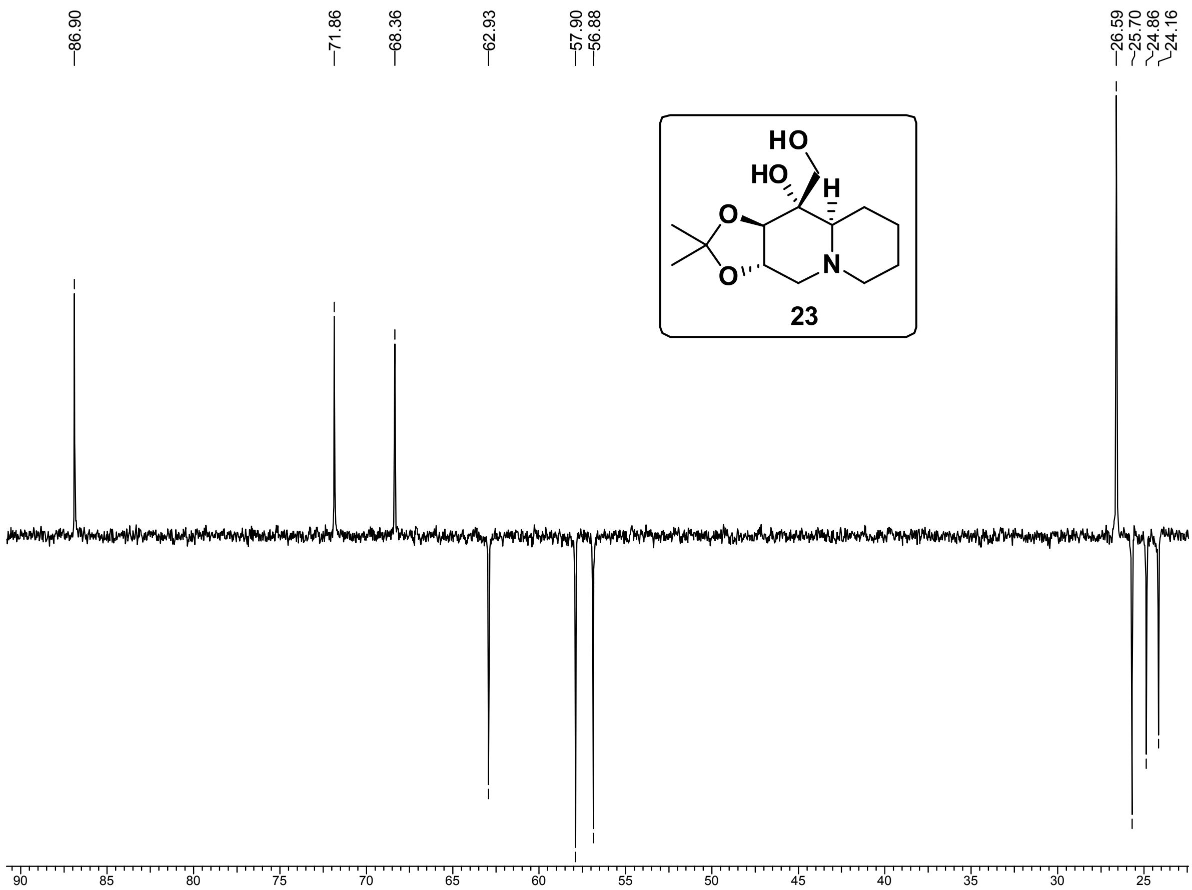
86.90
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68.36
62.93
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56.88
26.59
25.70
24.86
24.16
HO
HO
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90
85
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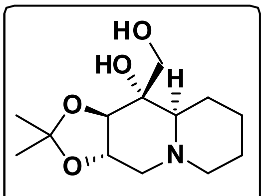
30
25

COSY



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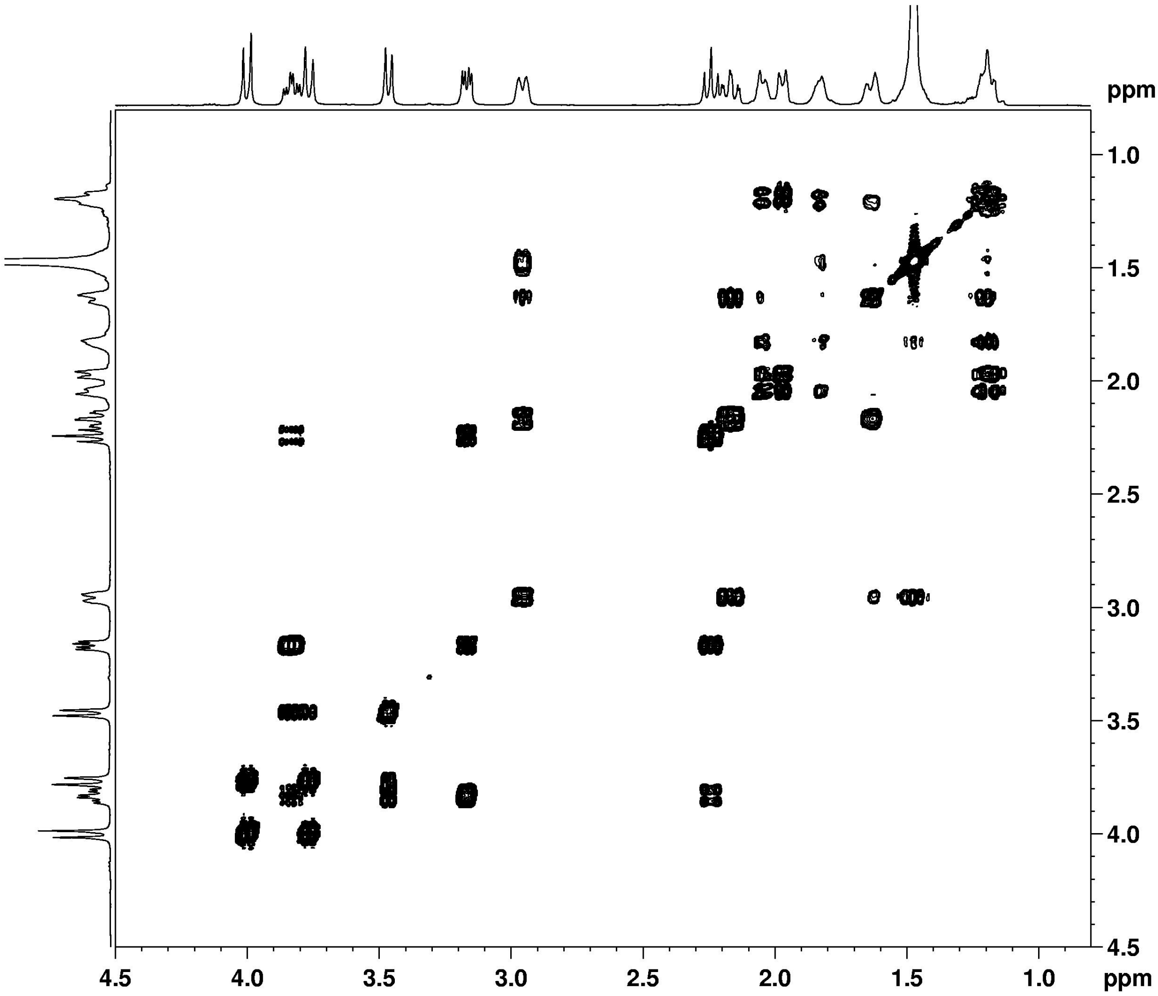

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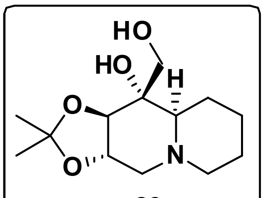

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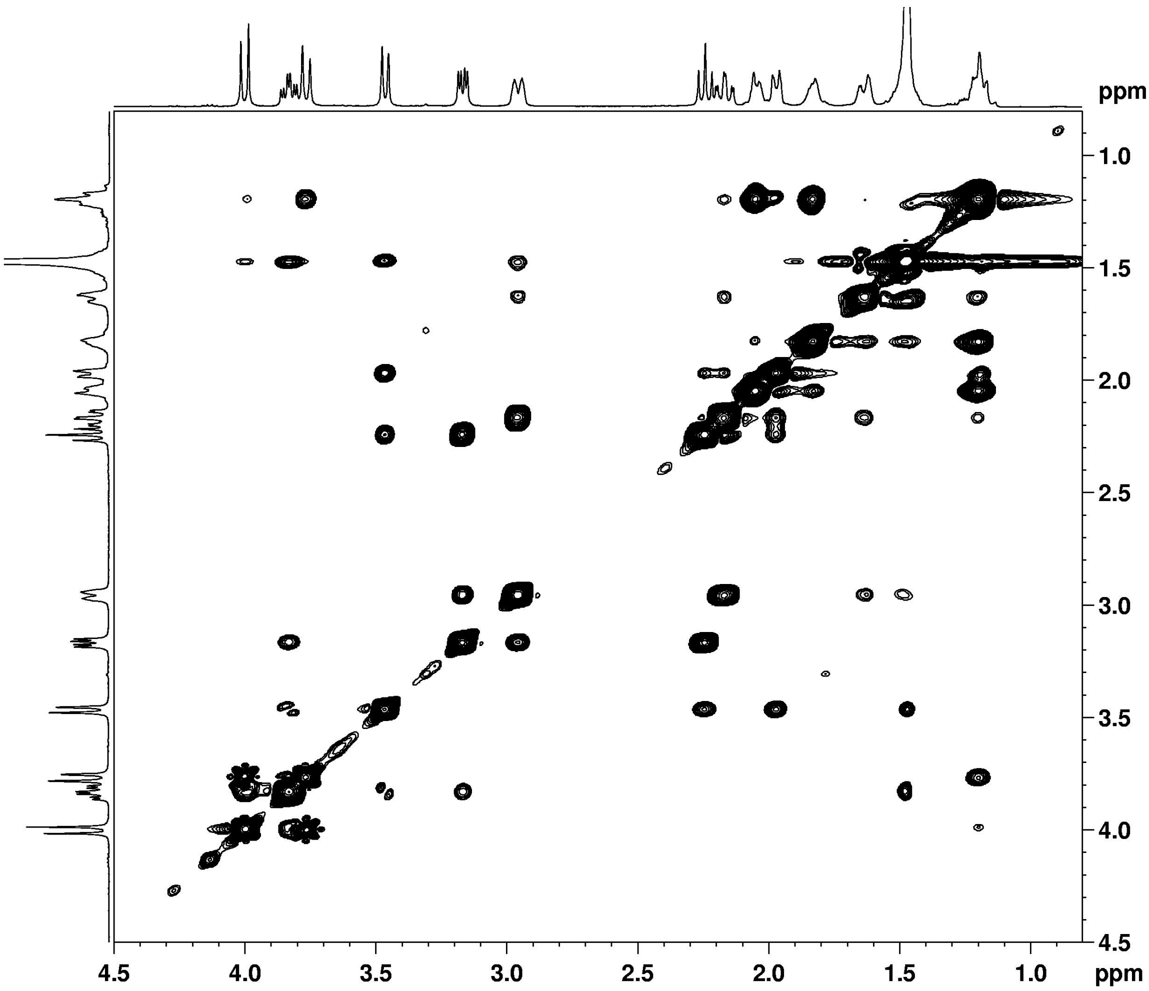

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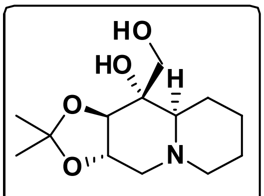

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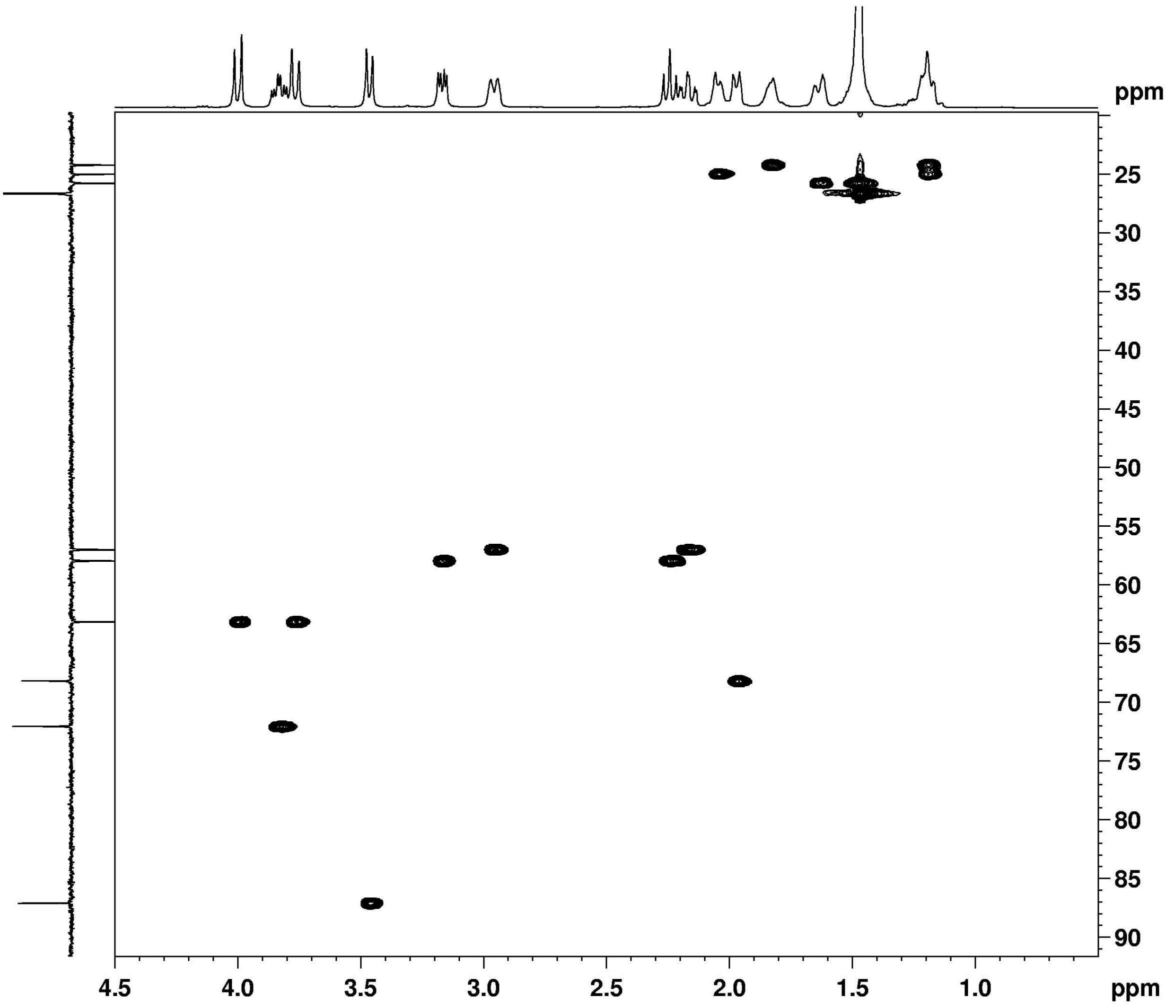

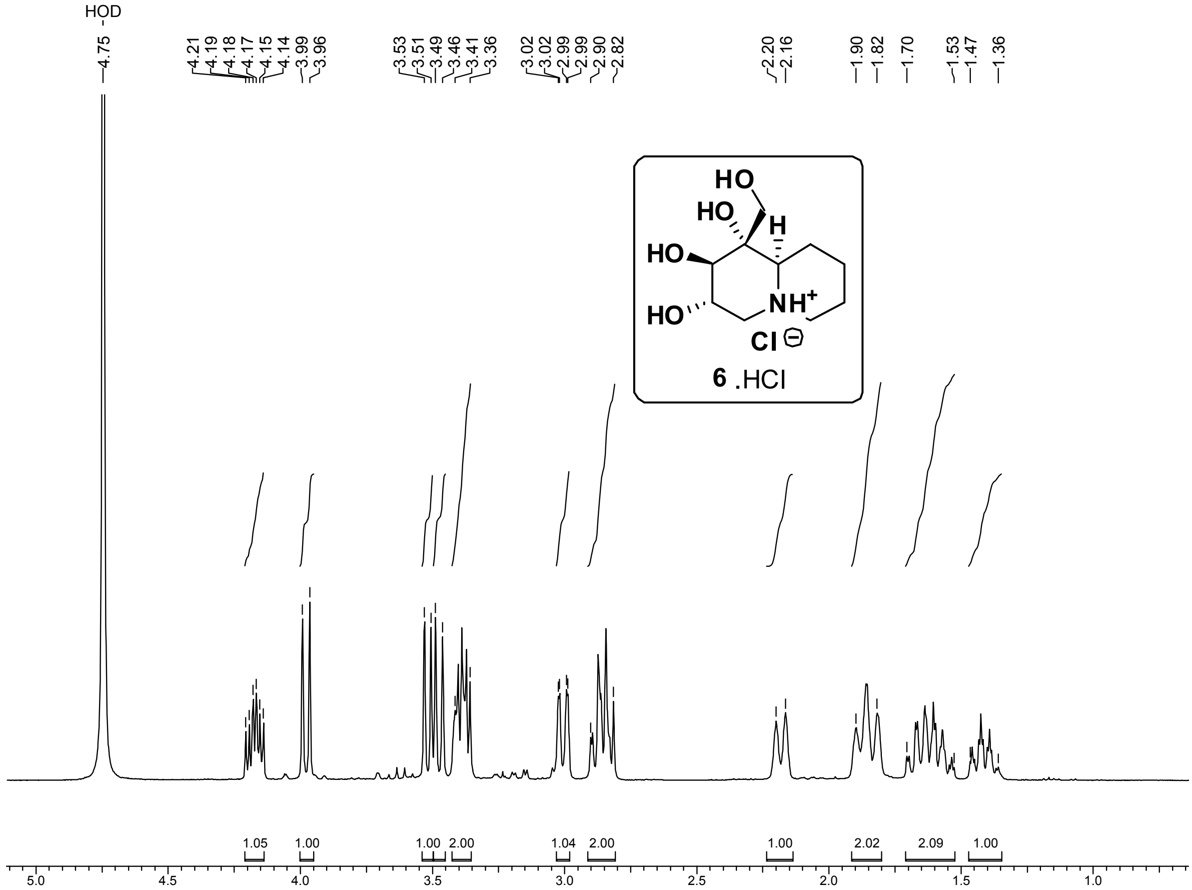
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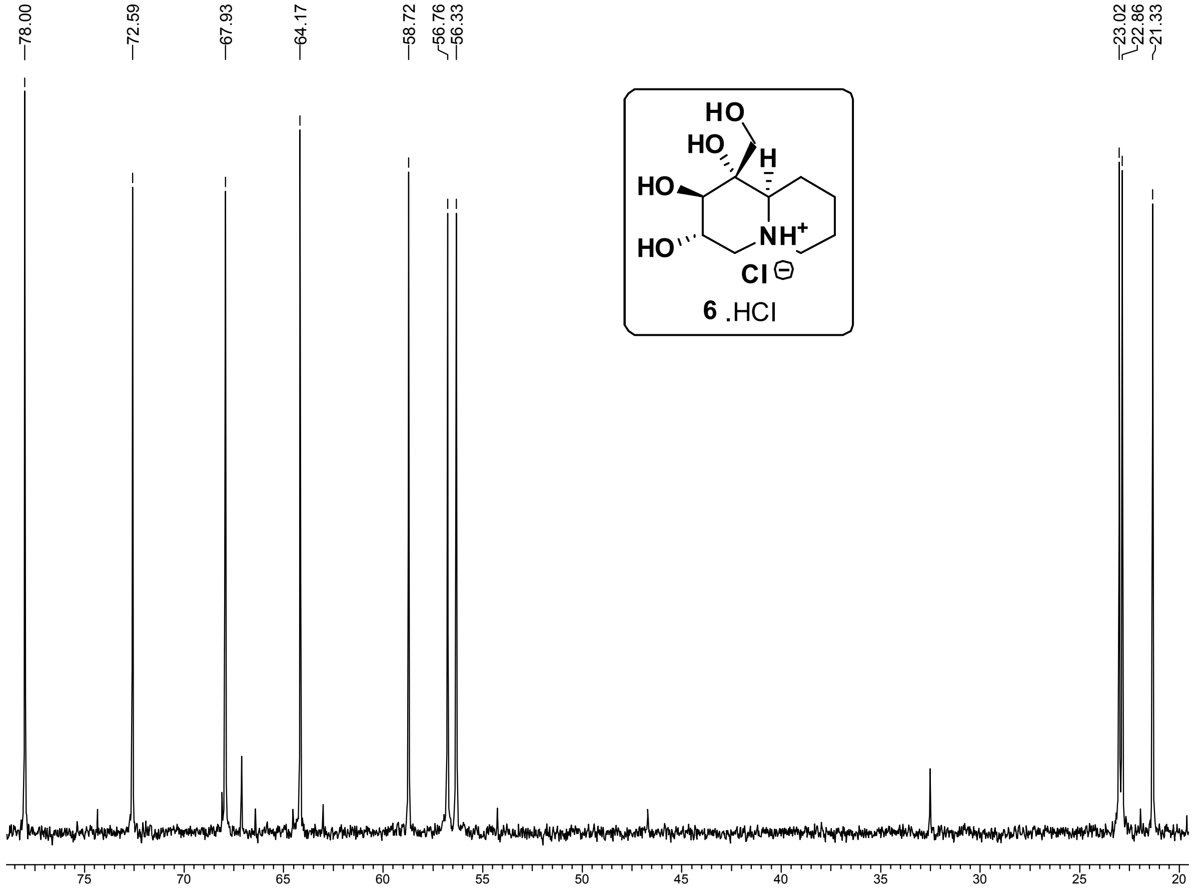
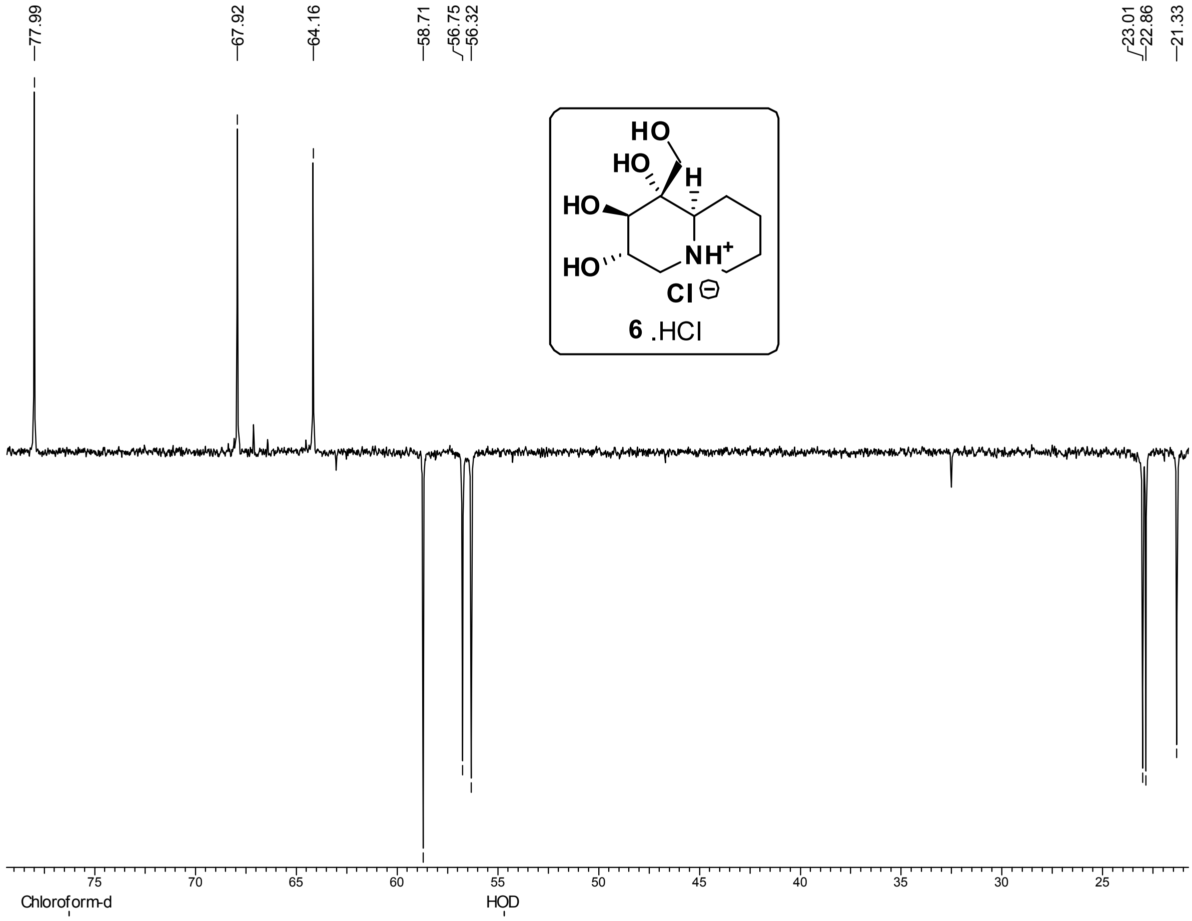
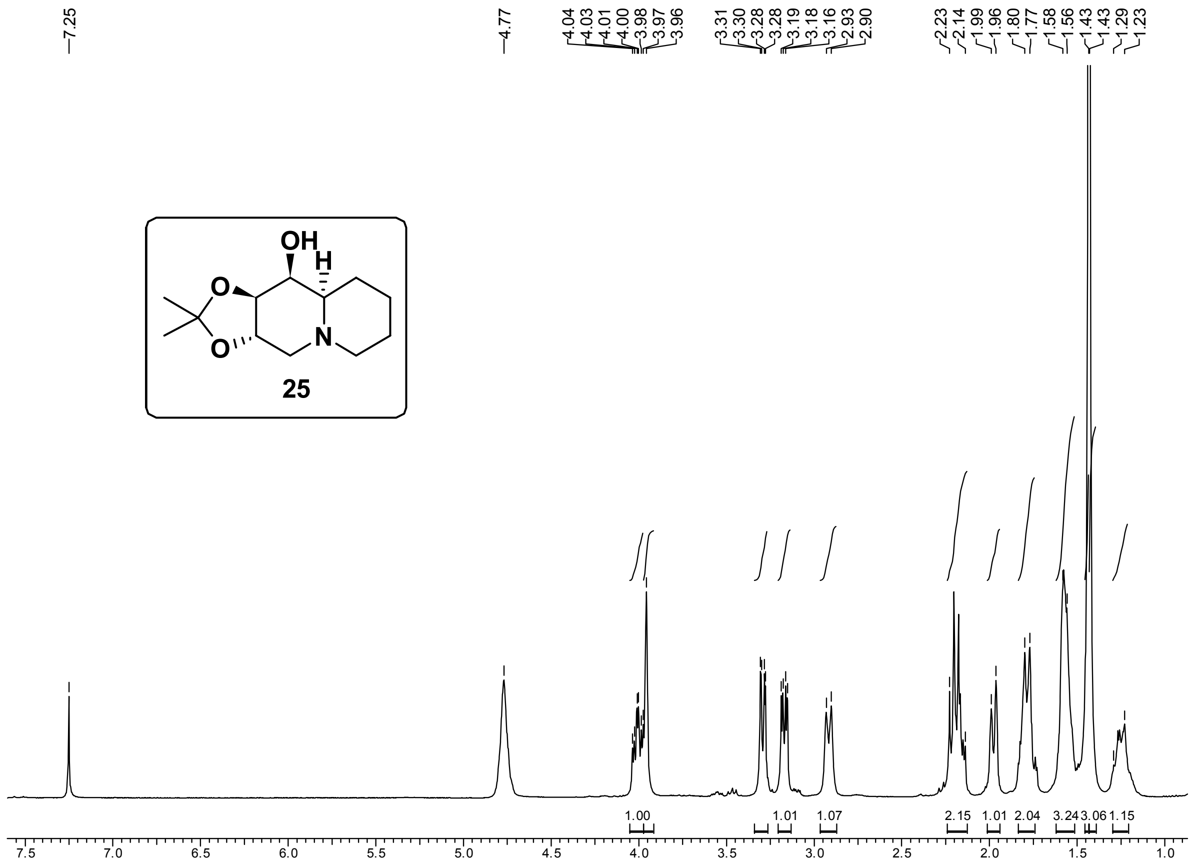
4.75
4.21 4.19 4.18 4.17 4.15 4.14 3.99 3.96
3.53 3.51 3.49 3.46 3.41 3.36
3.02 3.02 2.99 2.99 2.90 2.82
2.20 2.16
1.90 1.82 1.70 1.53 1.47 1.36
HO
HO
H
HO
HO
NH+
Cl ⊖
6 .HCl
1.05 1.00 1.00 2.00 1.04 2.00 1.00 2.02 2.09 1.00
5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0


78.00 72.59 67.93 64.17 58.72 56.76 56.33 23.02 22.86 21.33
HO
HO
H
HO
HO
NH+
Cl ⊖
6 .HCl
75 70 65 60 55 50 45 40 35 30 25 20


77.99
67.92
64.16
58.71
56.75
56.32
23.01
22.86
21.33
HO
HO
H
HO
NH+
HO
Cl
6 .HCl
75
70
65
60
55
50
45
40
35
30
25


Chloroform-d
7.25
HOD
4.77
4.04
4.03
4.01
4.00
3.98
3.97
3.96
3.31
3.30
3.28
3.28
3.19
3.18
3.16
2.93
2.90
2.23
2.14
1.99
1.96
1.80
1.77
1.58
1.56
1.43
1.43
1.29
1.23
OH
H
O
O
N
25
1.00
1.01
1.07
2.15
1.01
2.04
3.24
3.06
1.15
7.5
7.0
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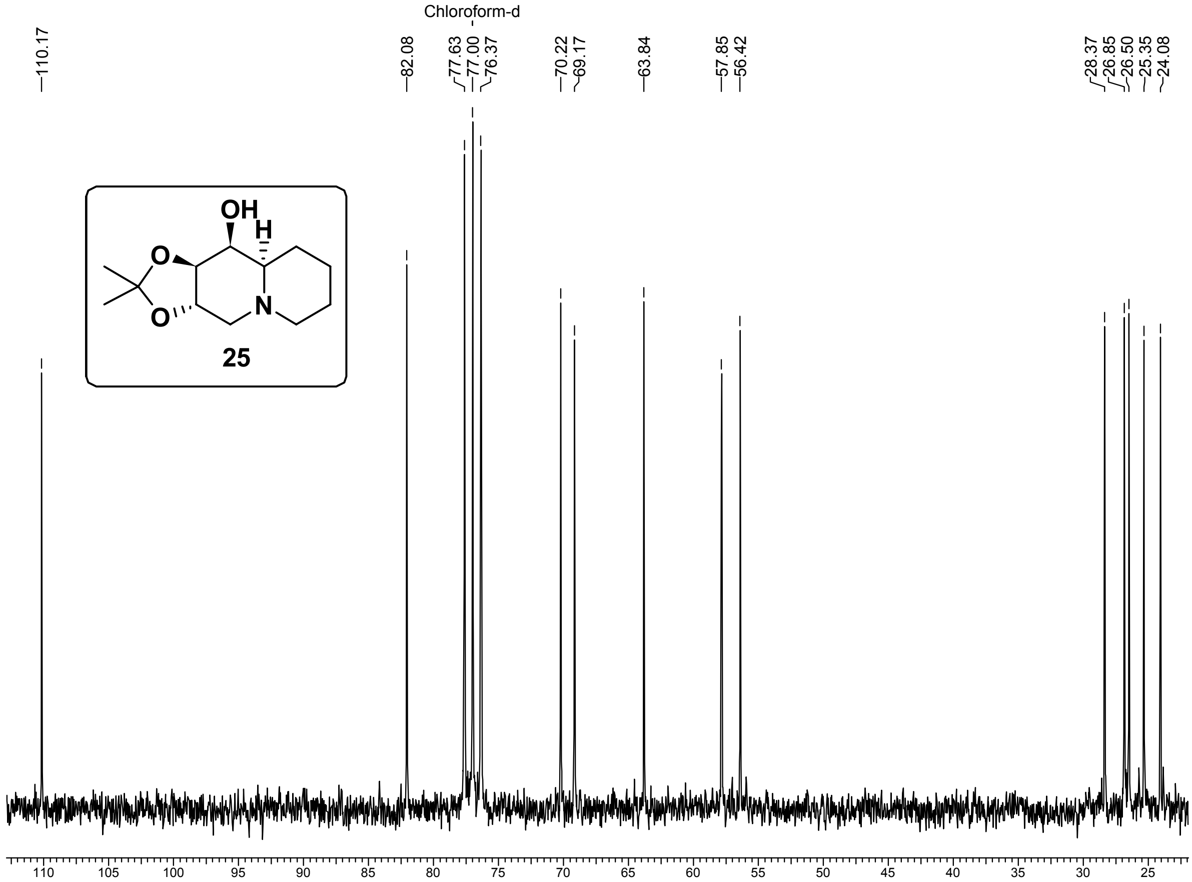
1.0


Chloroform-d
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82.08
77.63
77.00
76.37
70.22
69.17
63.84
57.85
56.42
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26.85
26.50
25.35
24.08
OH
H
O
O
N
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100
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75
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60
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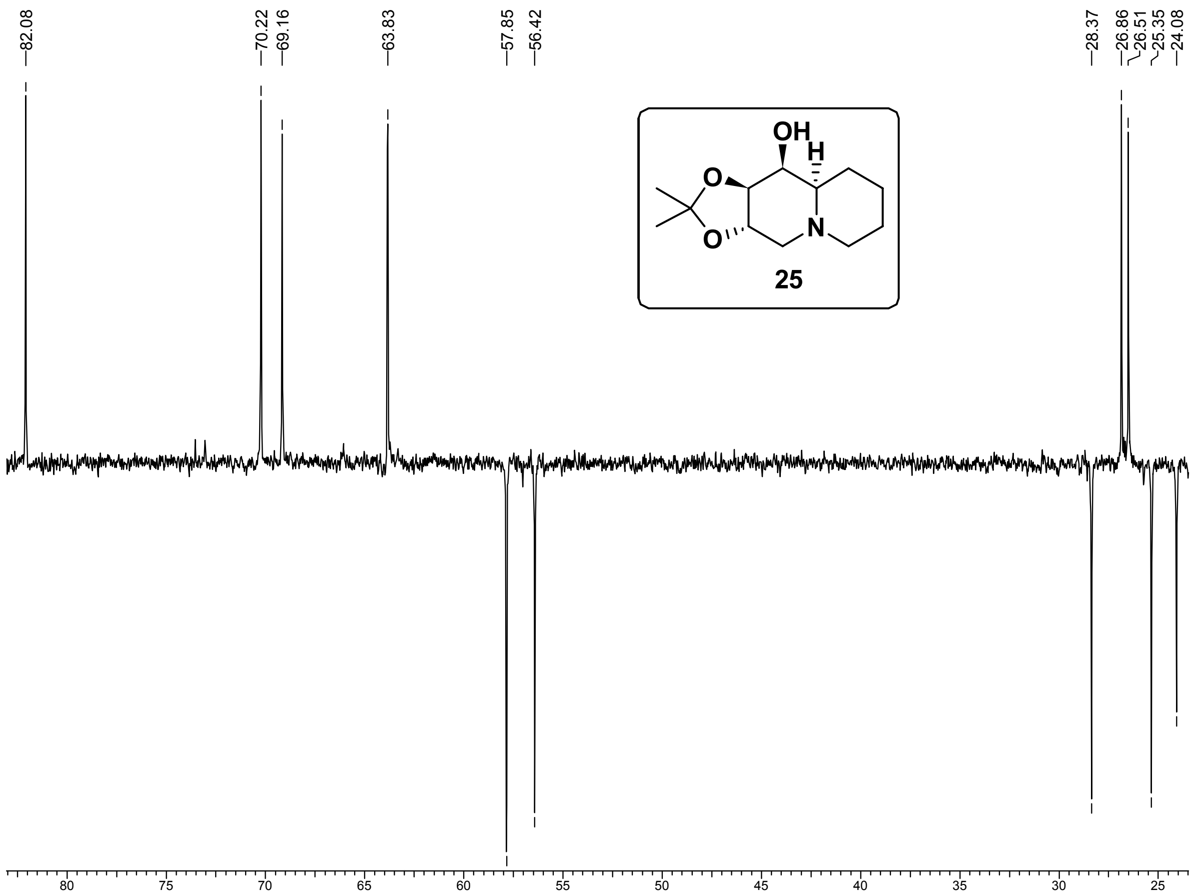
30
25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56.42
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26.86
26.51
25.35
24.08
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N
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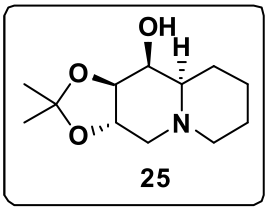
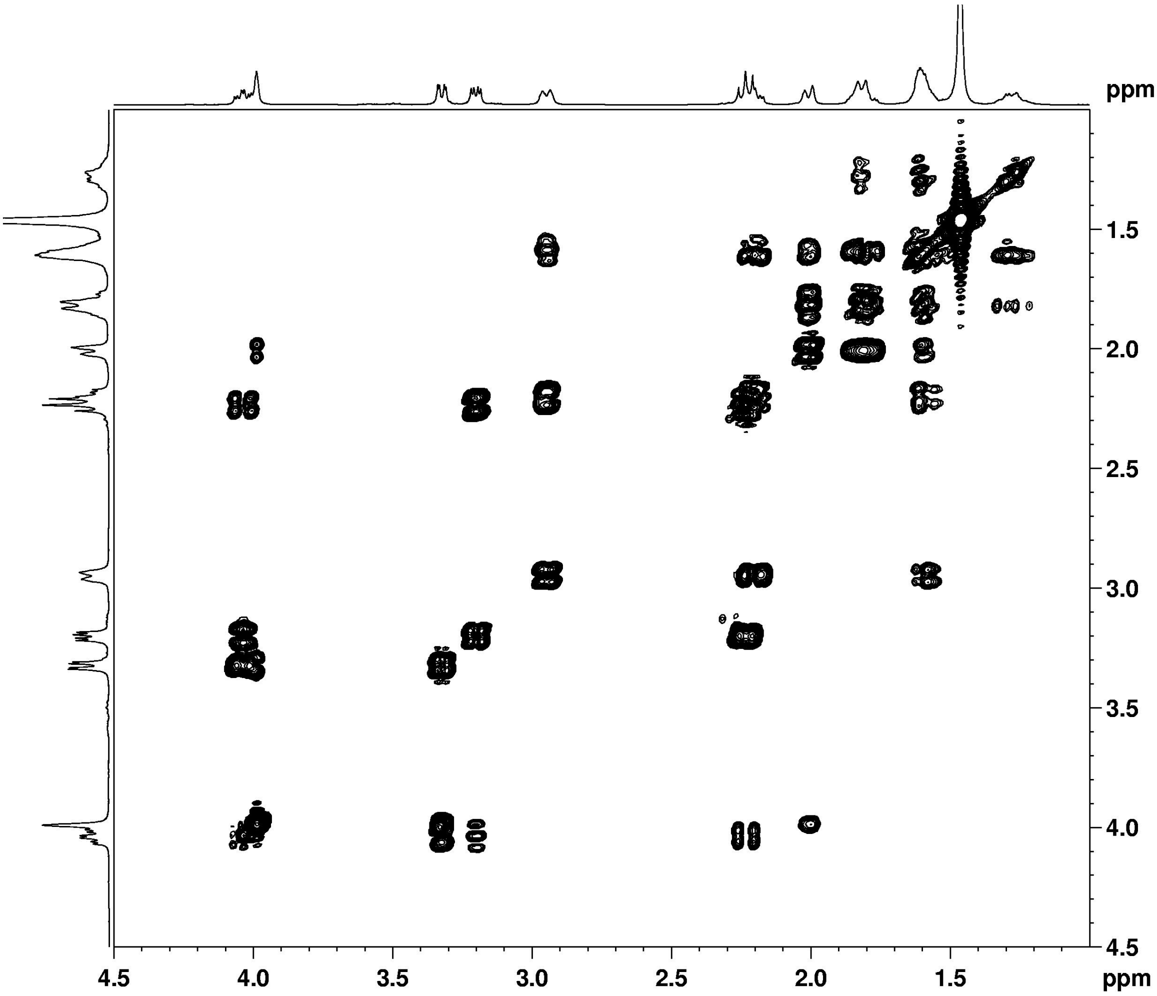
25

COSY





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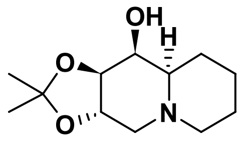

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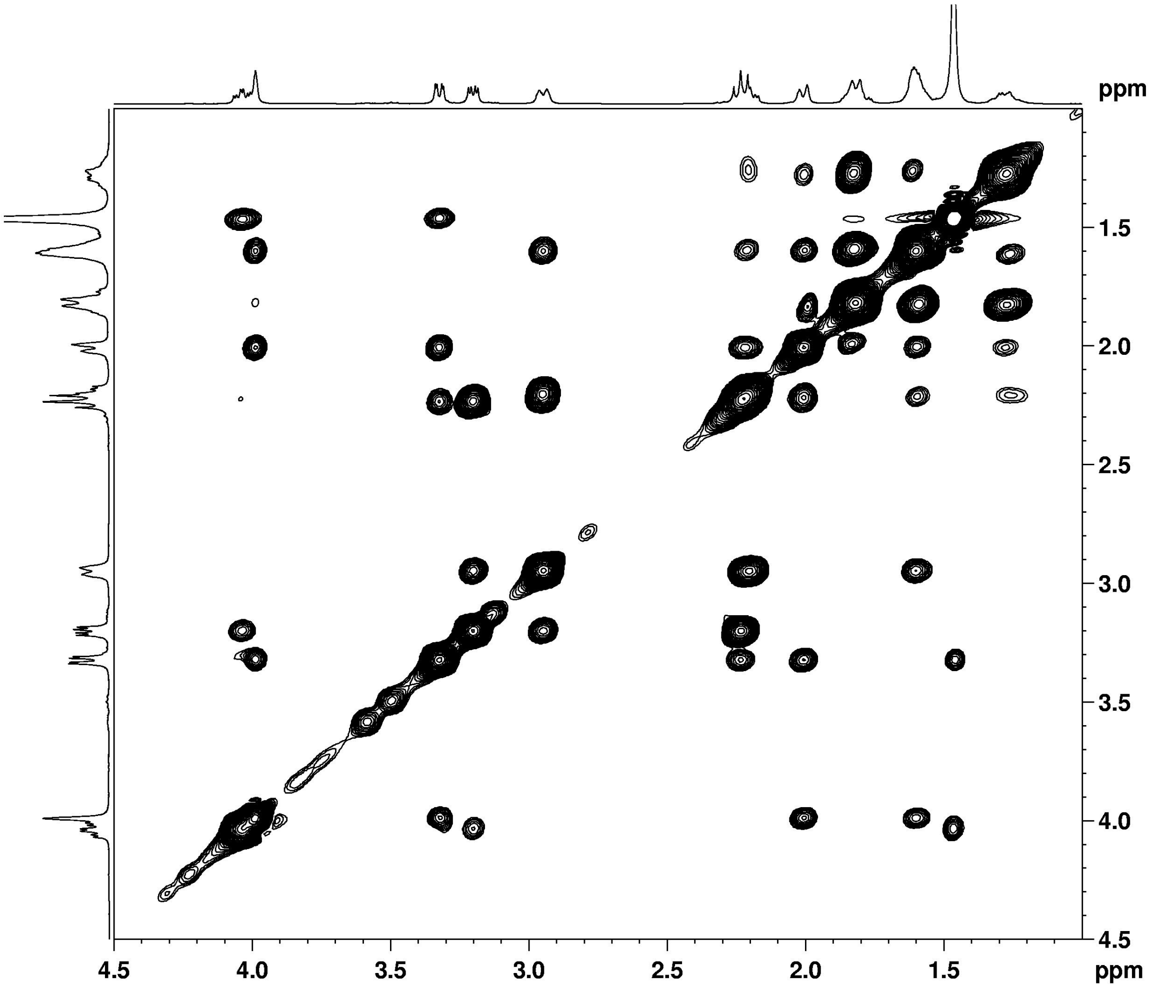

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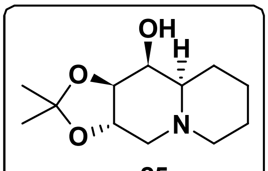

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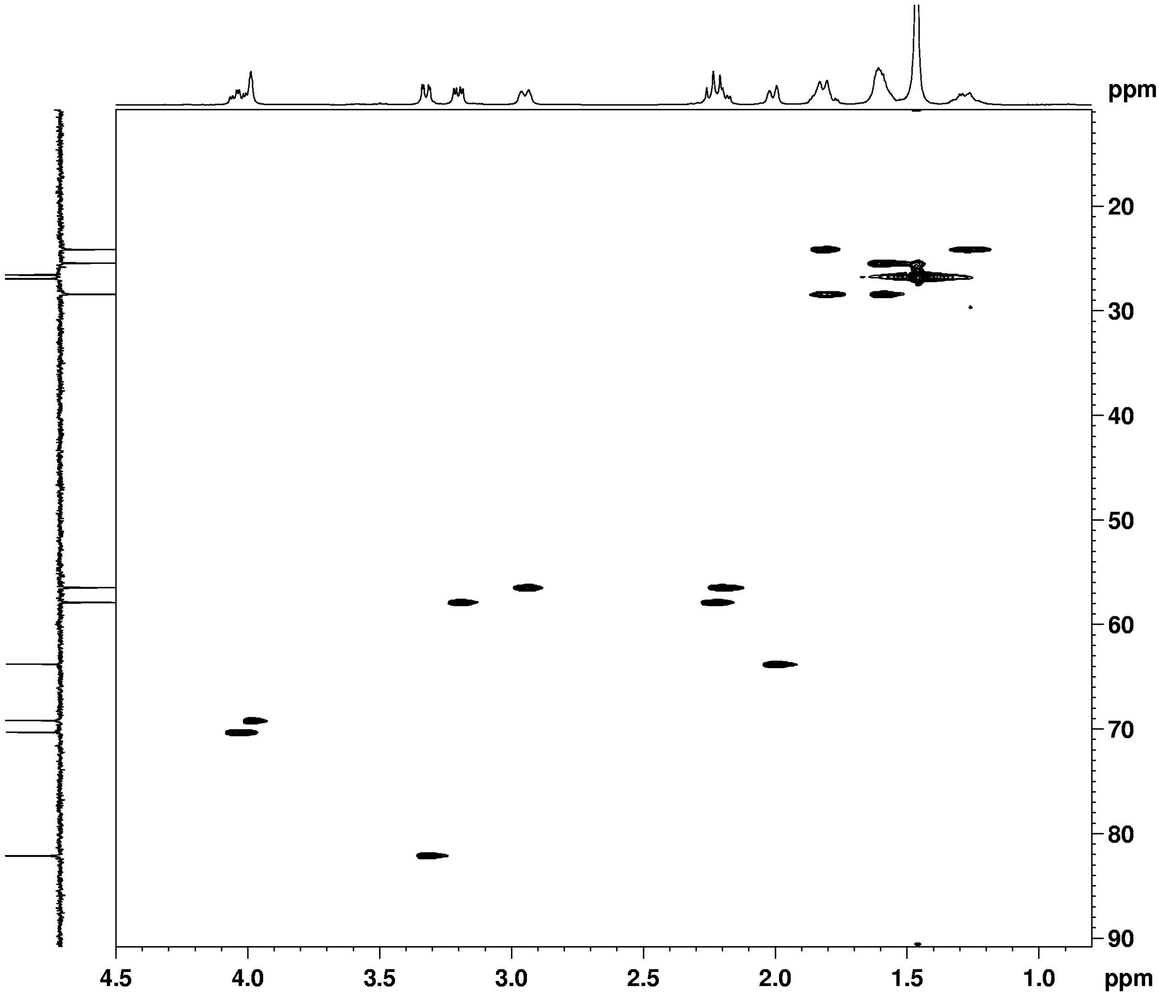

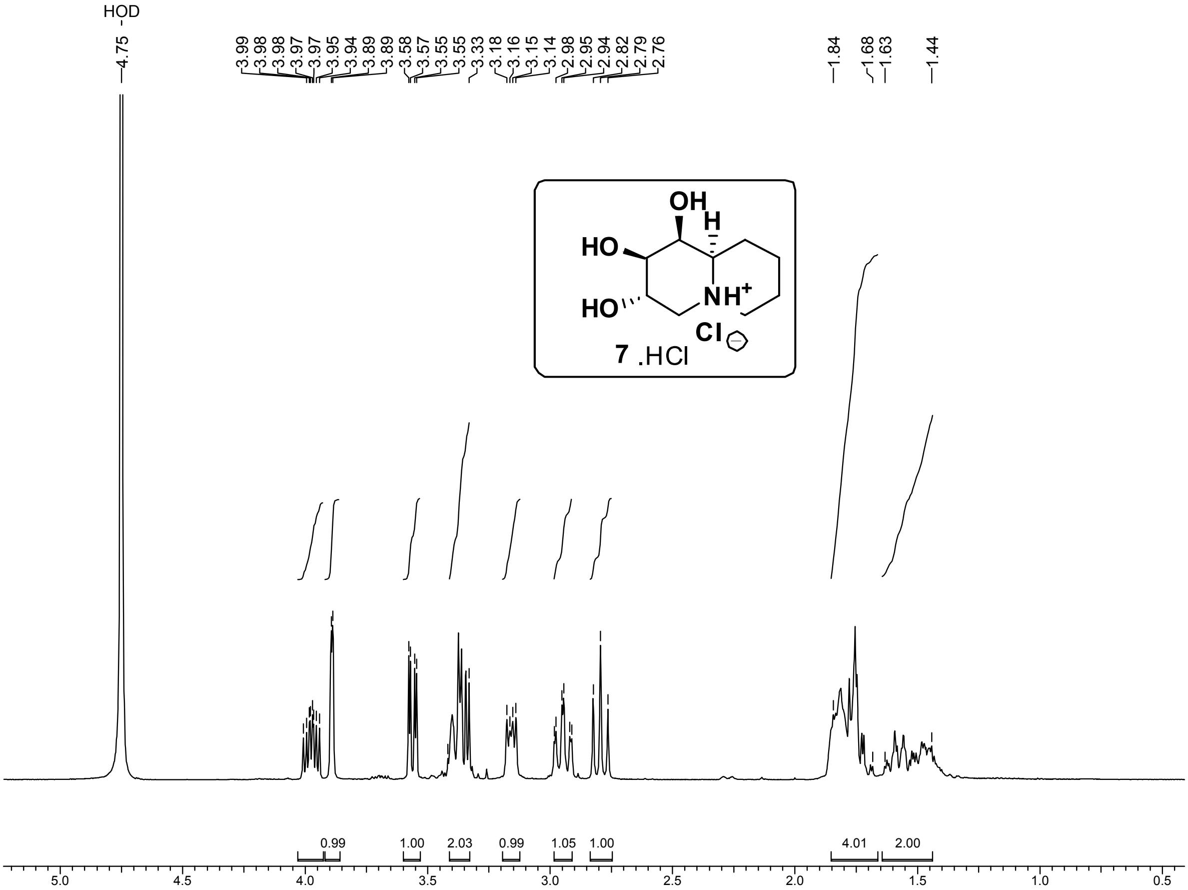
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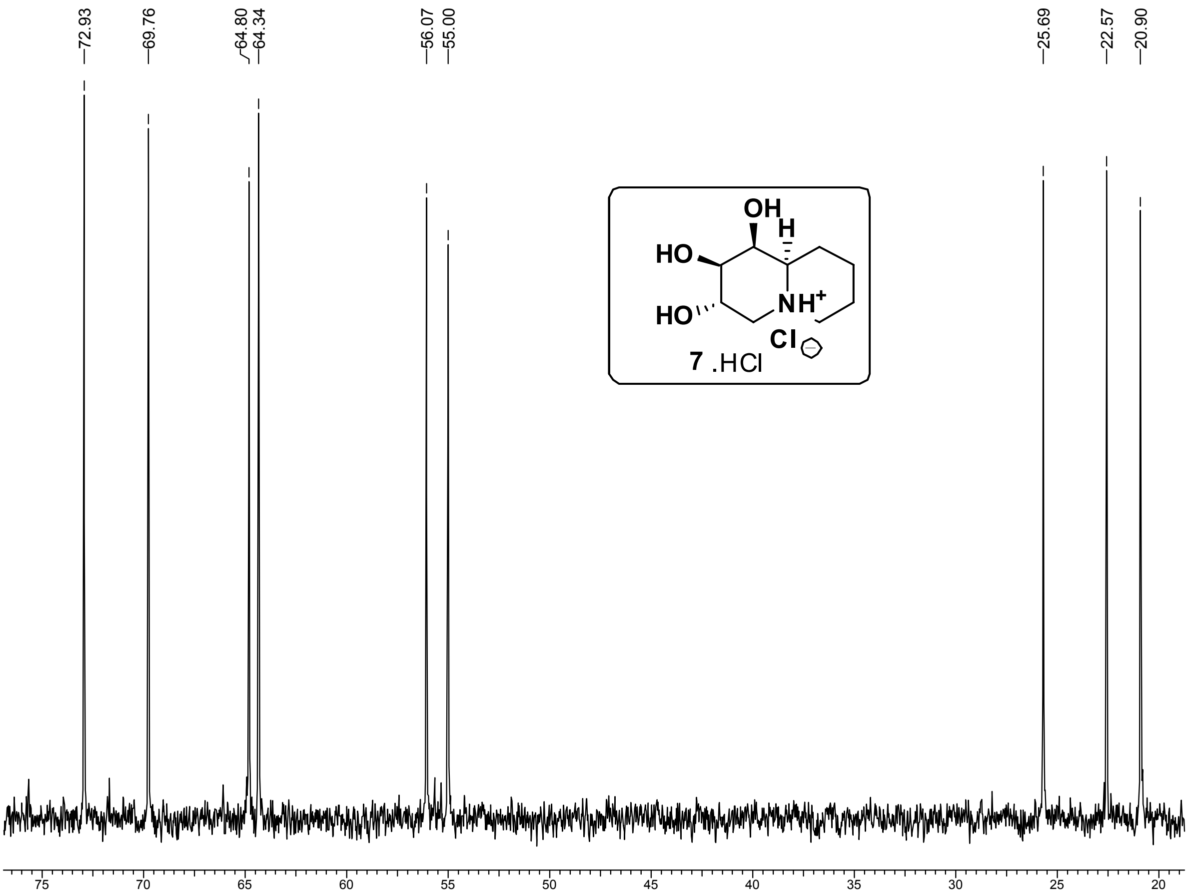
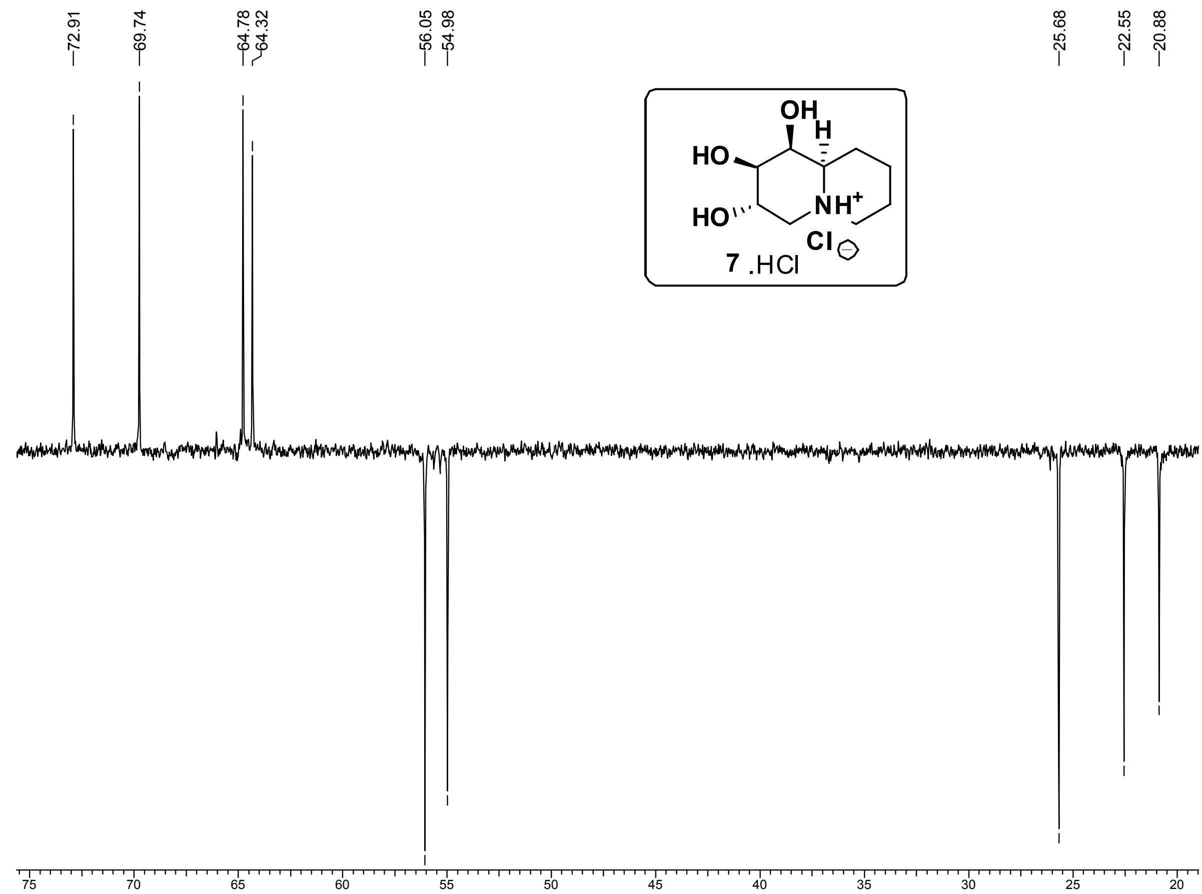
3.98
3.98
3.97
3.97
3.95
3.94
3.89
3.89
3.58
3.57
3.55
3.55
3.33
3.18
3.16
3.15
3.14
2.98
2.95
2.94
2.82
2.79
2.76
1.84
1.68
1.63
1.44
OH
H
HO
HO
NH+
Cl
7 .HCl
0.99
1.00
2.03
0.99
1.05
1.00
4.01
2.00
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5


72.93
69.76
64.80
64.34
56.07
55.00
25.69
22.57
20.90
OH
H
HO
HO
NH+
Cl
7 .HCl
75
70
65
60
55
50
45
40
35
30
25
20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69.74
64.78
64.32
56.05
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25.68
22.55
20.88
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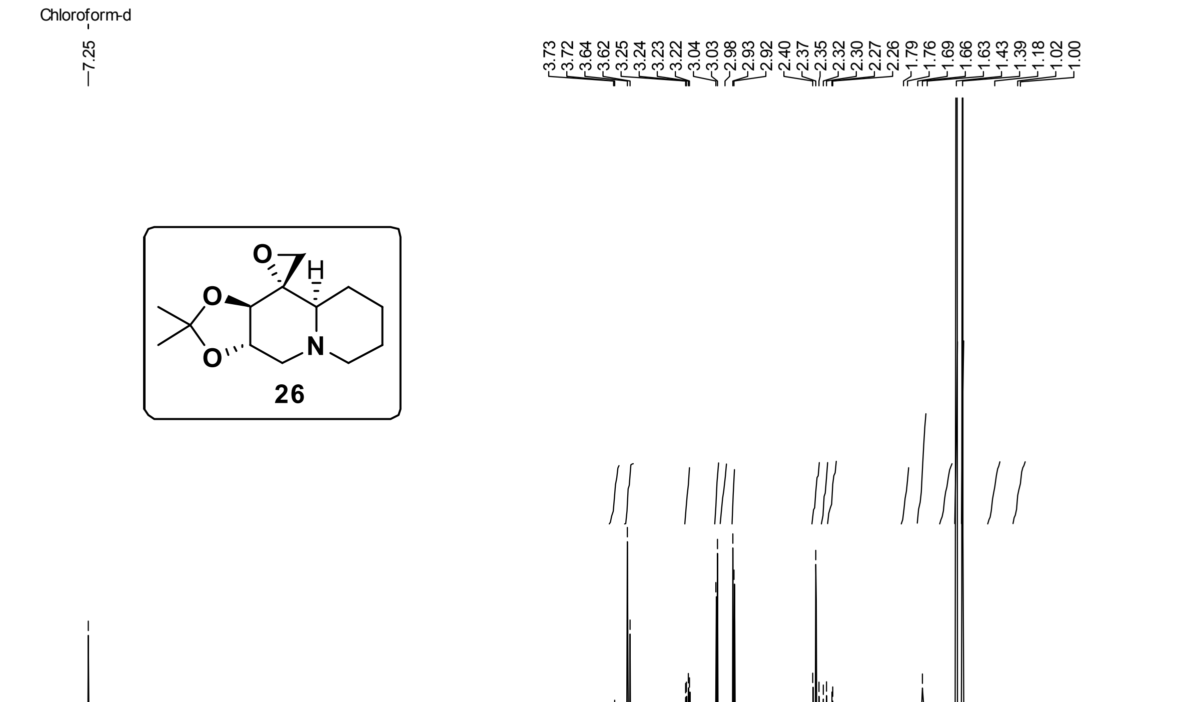
H
HO
HO
NH+
Cl
7 .HCl
75
70
65
60
55
50
45
40
35
30
25
20


Chloroform-d
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3.73
3.72
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3.25
3.24
3.23
3.22
3.04
3.03
2.98
2.93
2.92
2.40
2.37
2.35
2.32
2.30
2.27
2.26
1.79
1.76
1.69
1.66
1.63
1.43
1.39
1.18
1.02
1.00
O
H
O
O
N
26
0.99
1.00
1.01
1.05
2.05
3.03
1.04
1.02
7.5
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6.5
6.0
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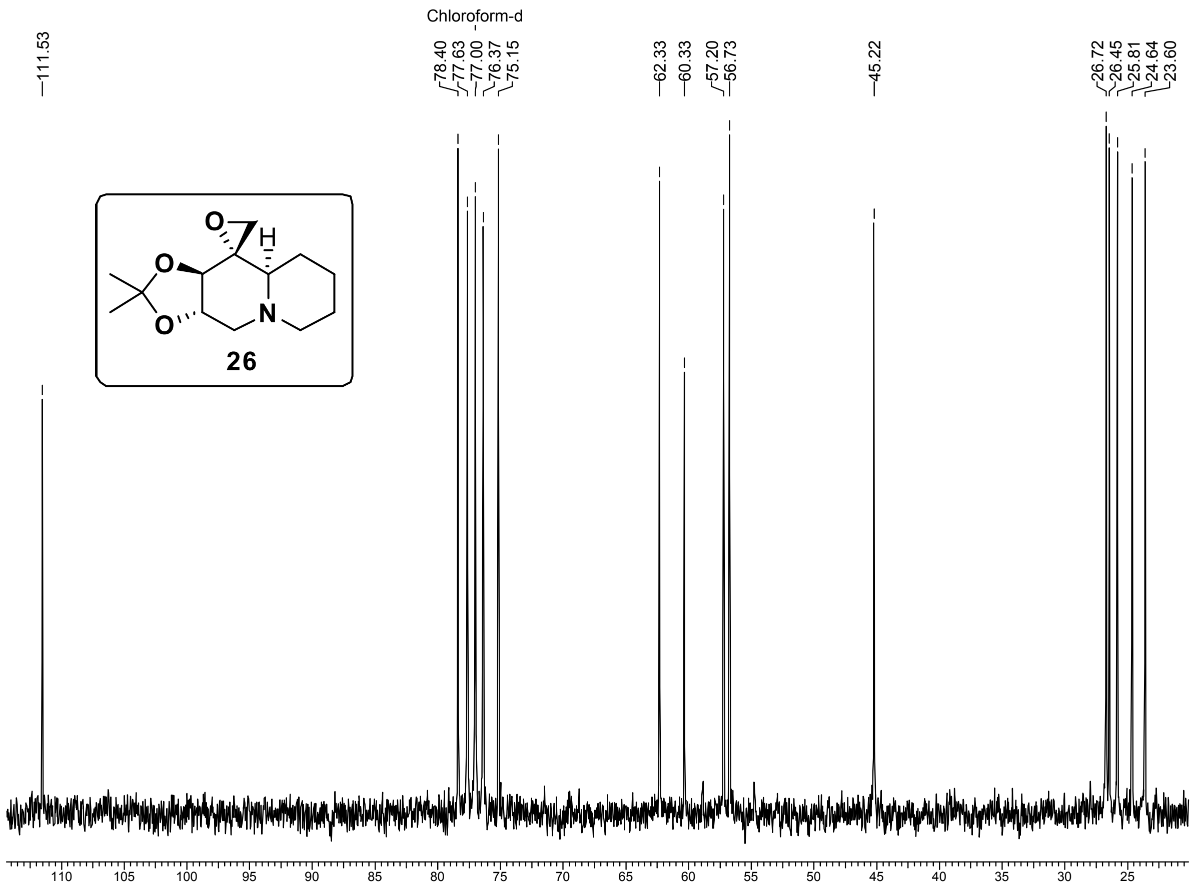
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60.33
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26
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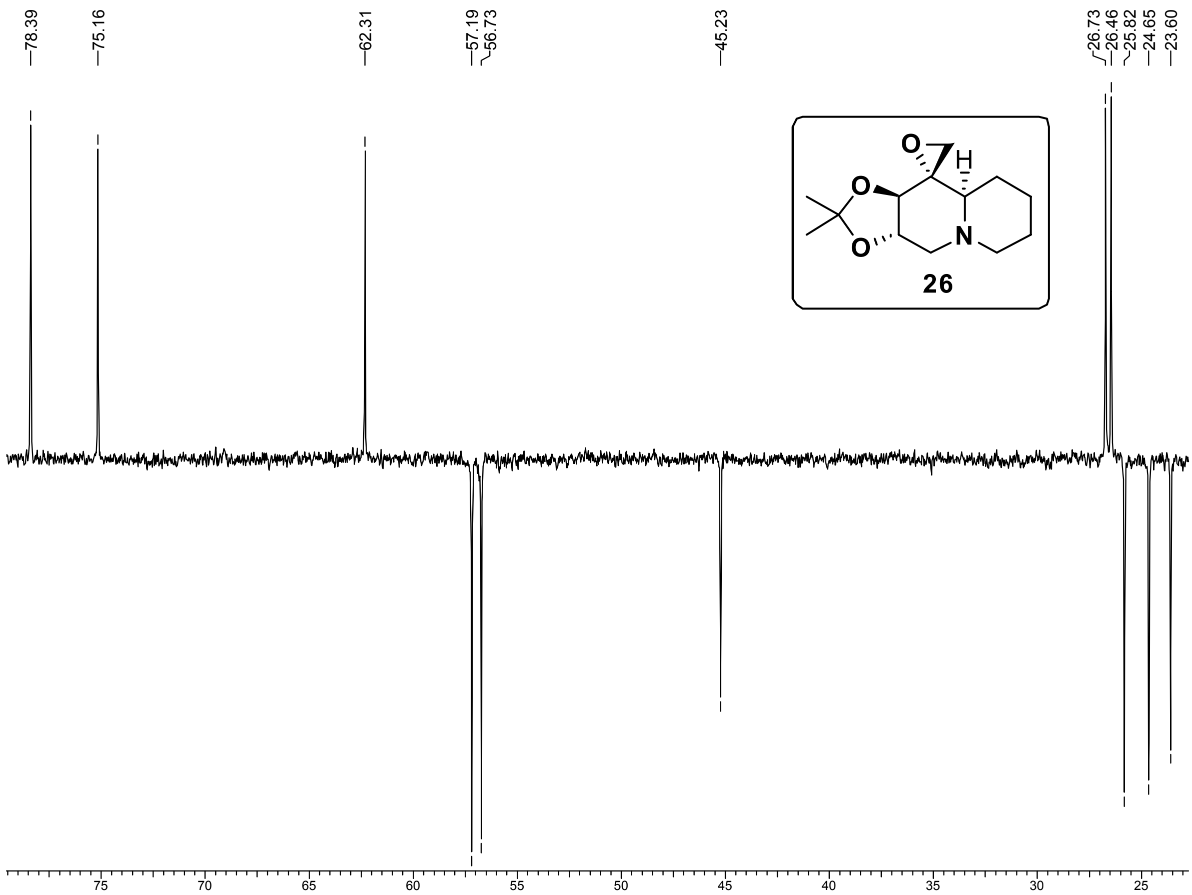
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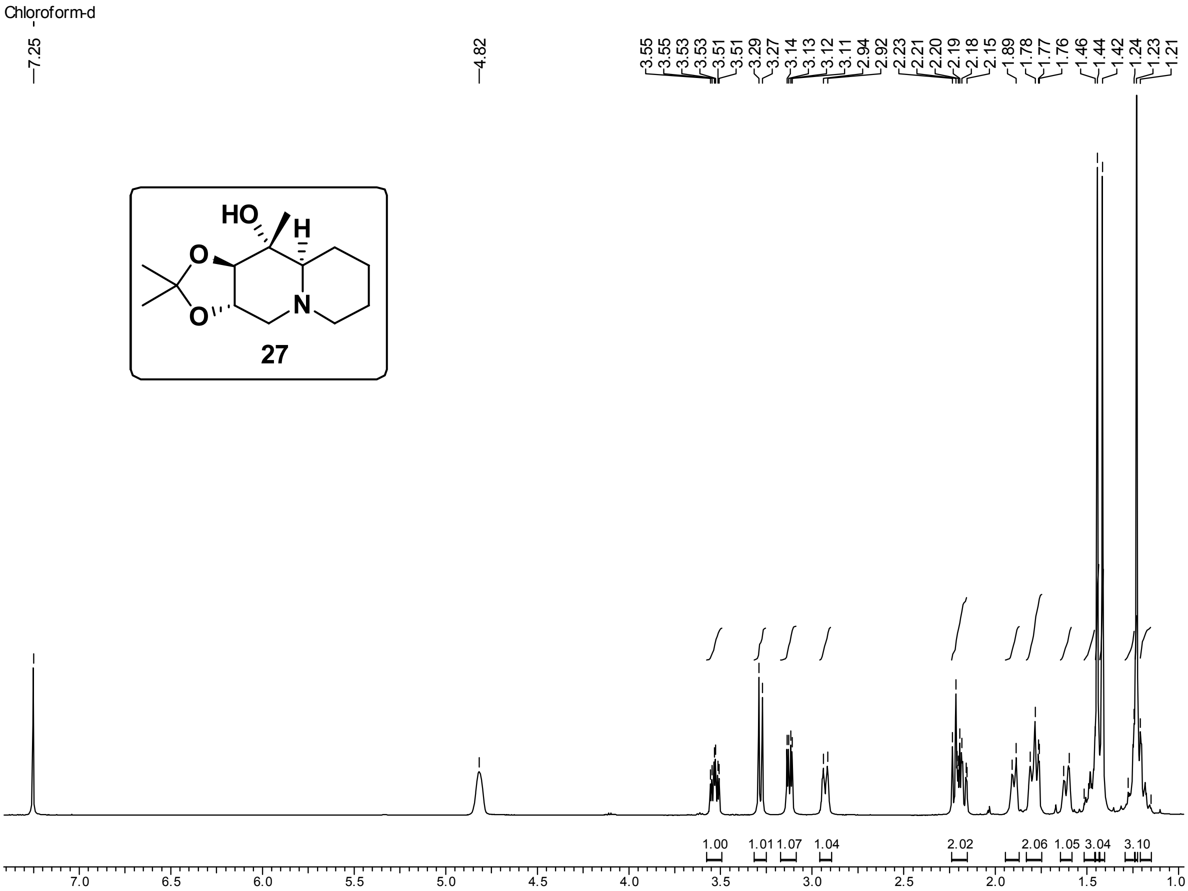
75 70 65 60 55 50 45 40 35 30 25


Chloroform-d
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3.29
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3.14
3.13
3.12
3.11
2.94
2.92
2.23
2.21
2.20
2.19
2.18
2.15
1.89
1.78
1.77
1.76
1.46
1.44
1.42
1.24
1.23
1.21
HO
H
O
O
N
27
1.00
1.01
1.07
1.04
2.02
2.06
1.05
3.04
3.10
7.0
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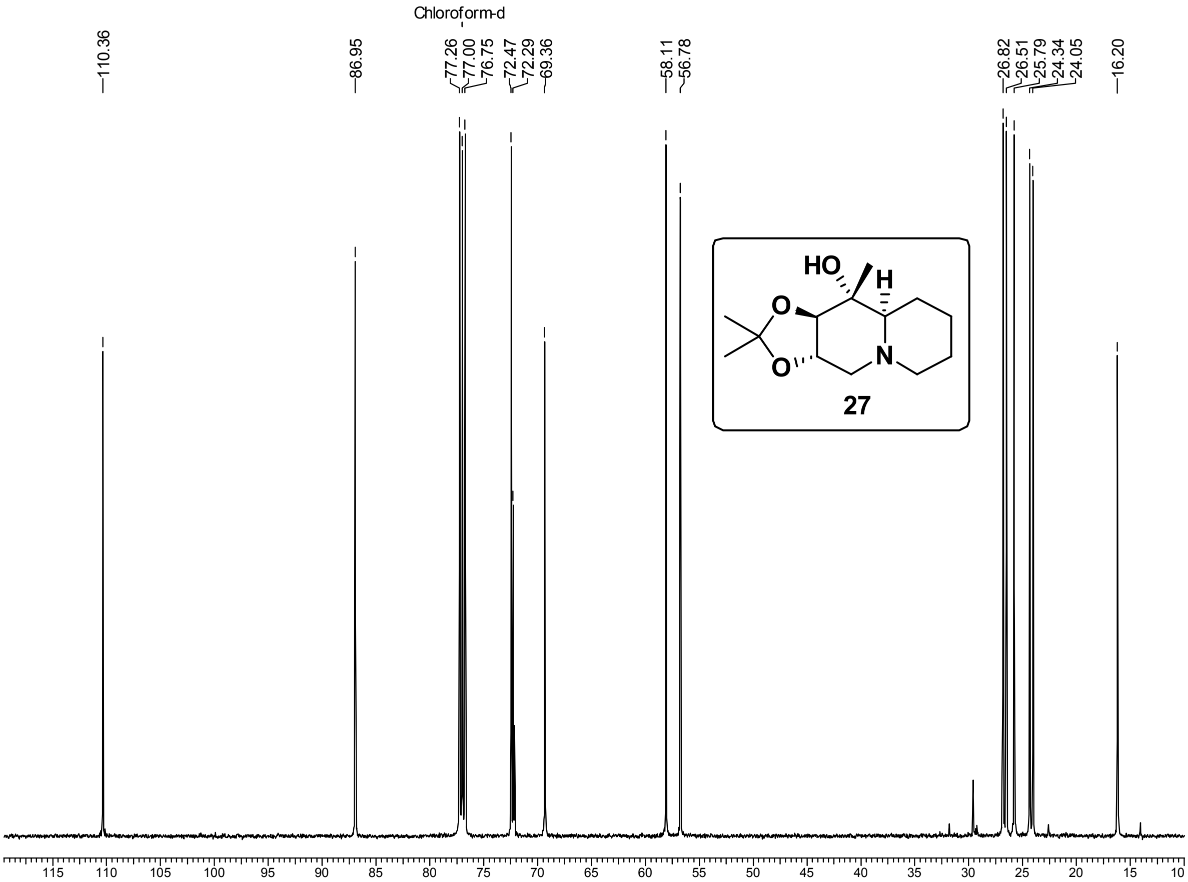
Chloroform-d
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26.82
26.51
25.79
24.34
24.05
16.20
HO
H
O
O
N
27
115
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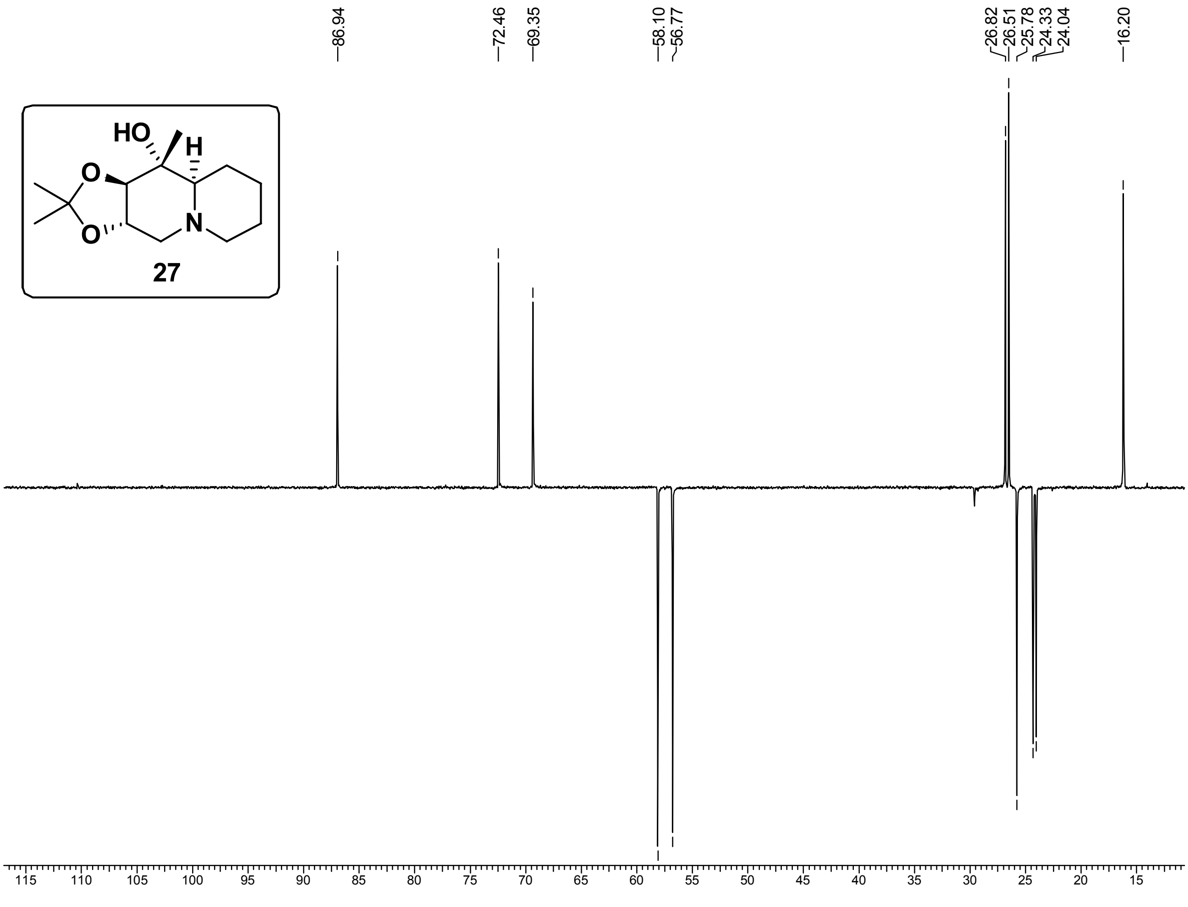
86.94
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69.35
58.10
56.77
26.82
26.51
25.78
24.33
24.04
16.20
HO
H
O
O
N
27
115
110
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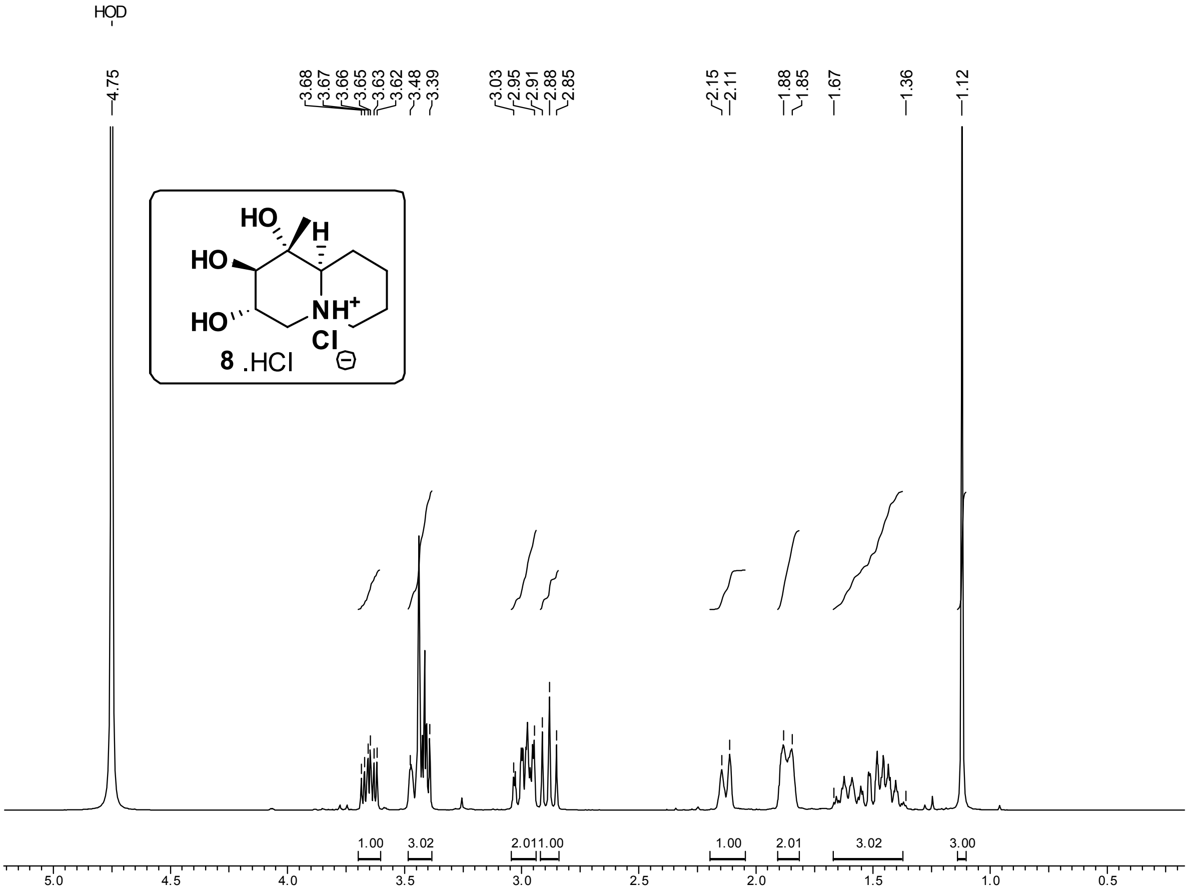
HOD
4.75
3.68
3.67
3.66
3.65
3.63
3.62
3.48
3.39
3.03
2.95
2.91
2.88
2.85
2.15
2.11
1.88
1.85
1.67
1.36
1.12
HO
H
HO
HO
NH+
Cl
8 .HCl
1.00
3.02
2.01
1.00
1.00
2.01
3.02
3.00
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4.5
4.0
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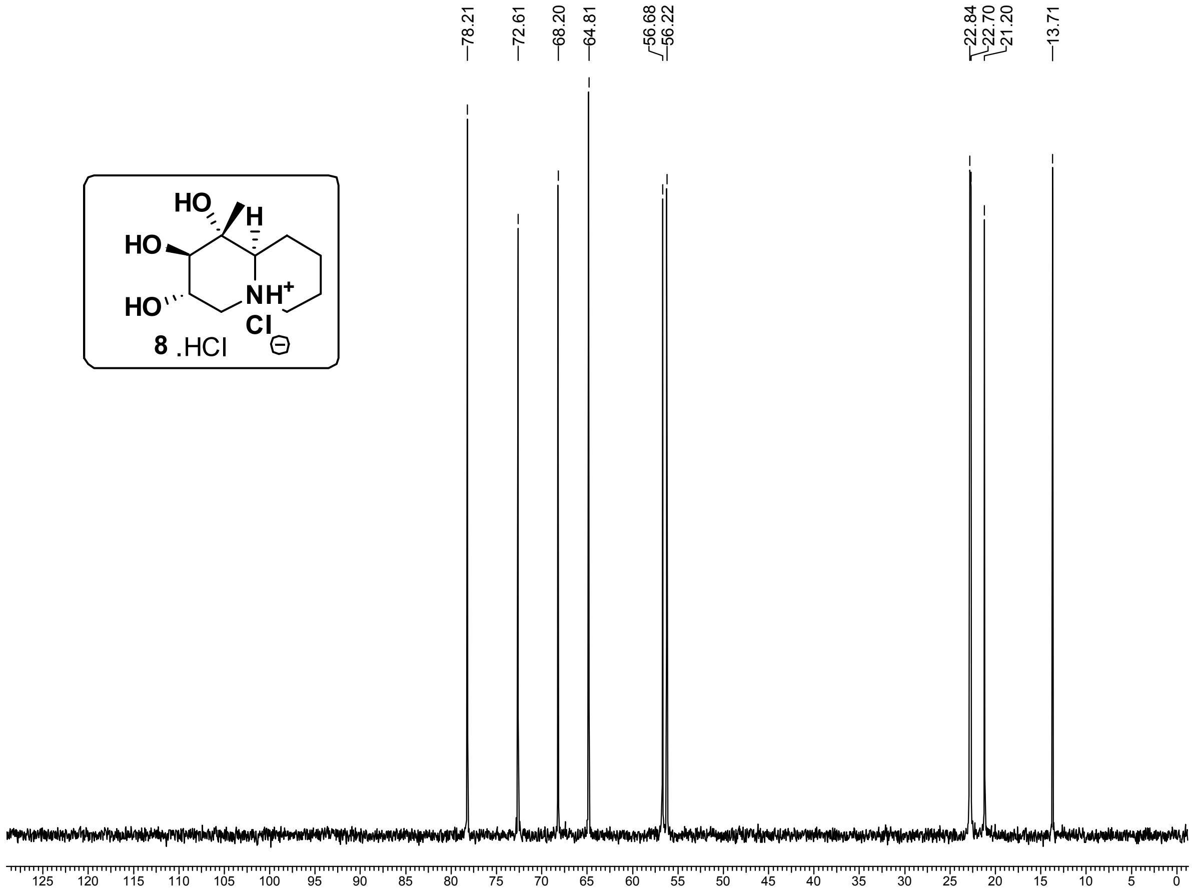
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72.61
68.20
64.81
56.68
56.22
22.84
22.70
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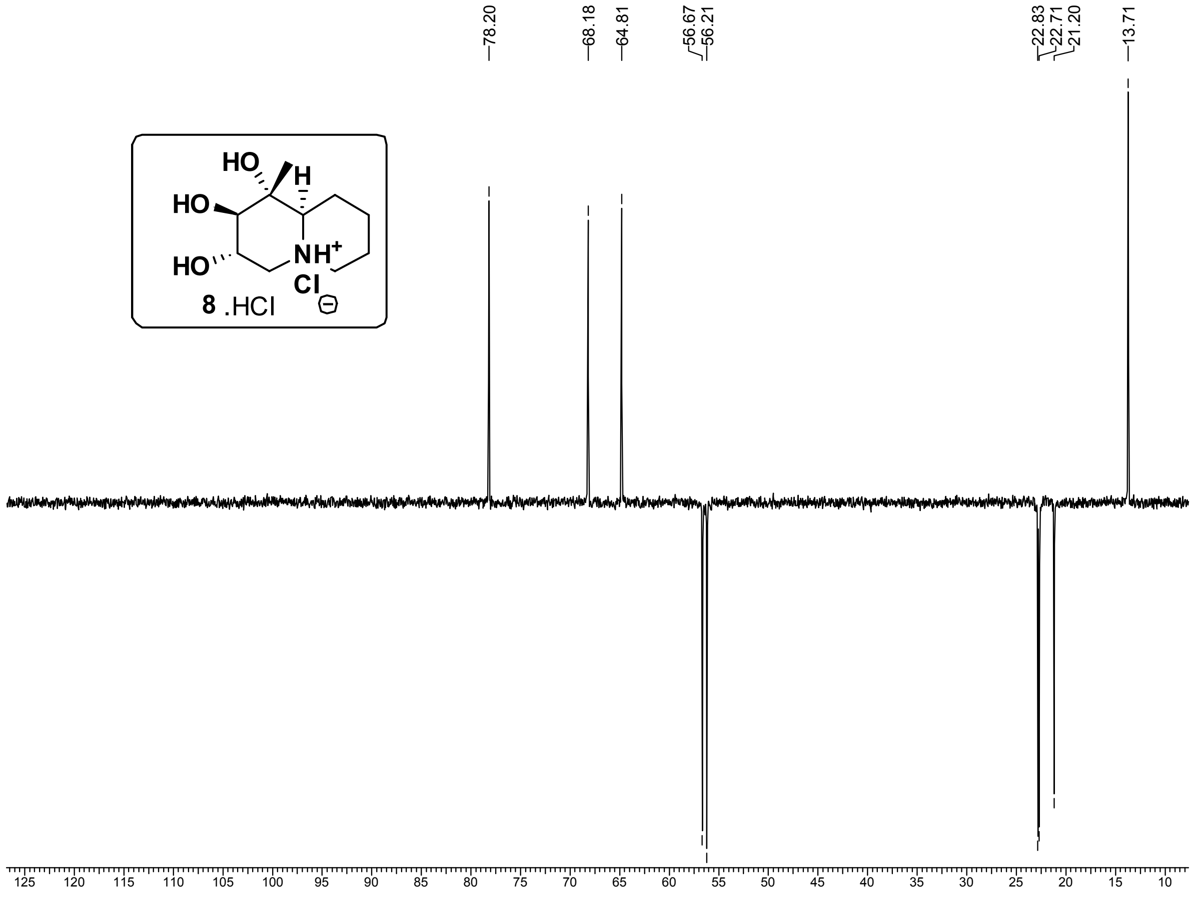
H
HO
HO
NH+
Cl
8 .HCl
125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0


78.20
68.18
64.81
56.67
56.21
22.83
22.71
21.20
13.71
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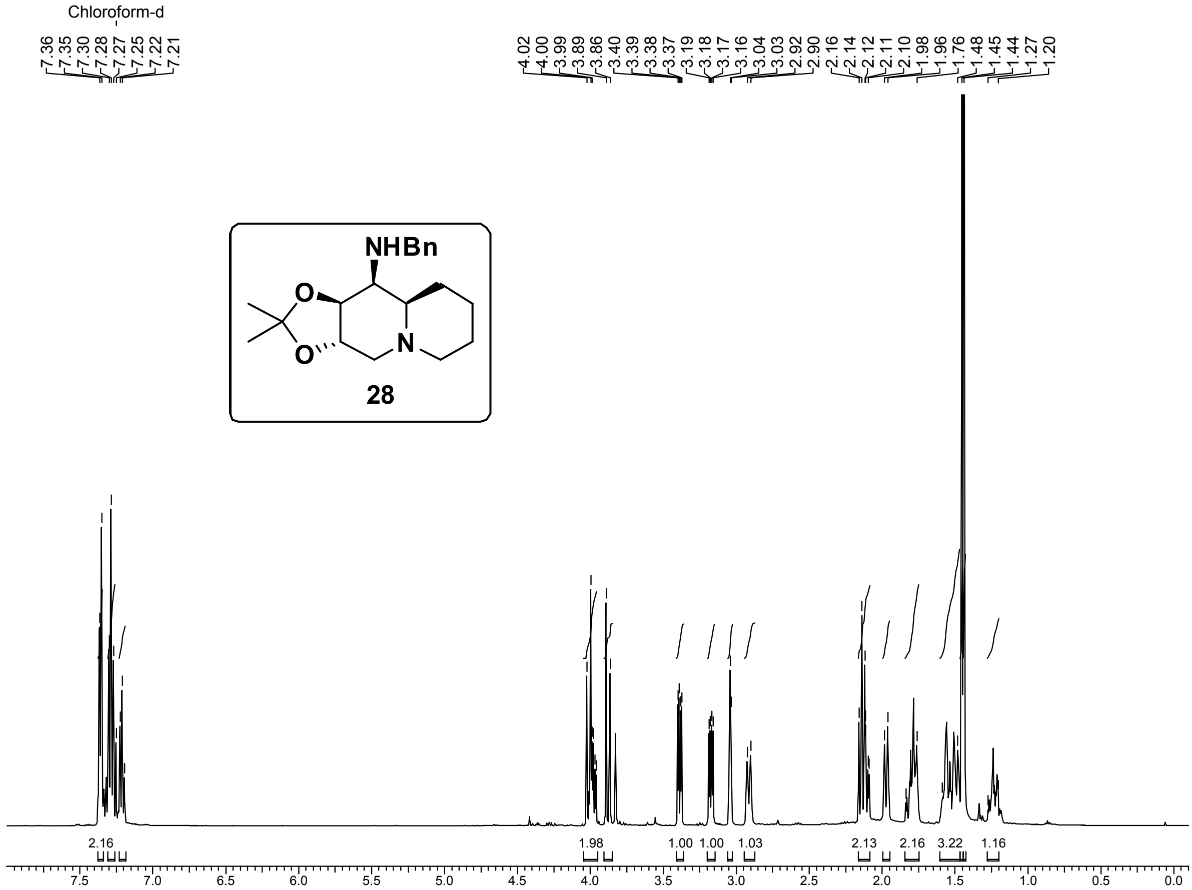
H
HO
HO
NH+
Cl
8 .HCl
125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10


Chloroform-d
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4.02 4.00 3.99 3.89 3.86 3.40 3.39 3.38 3.37 3.19 3.18 3.17 3.16 3.04 3.03 2.92 2.90 2.16 2.14 2.12 2.11 2.10 1.98 1.96 1.76 1.48 1.45 1.44 1.27 1.20
NHBn
O
O
N
28
2.16 1.98 1.00 1.00 1.03 2.13 2.16 3.22 1.16
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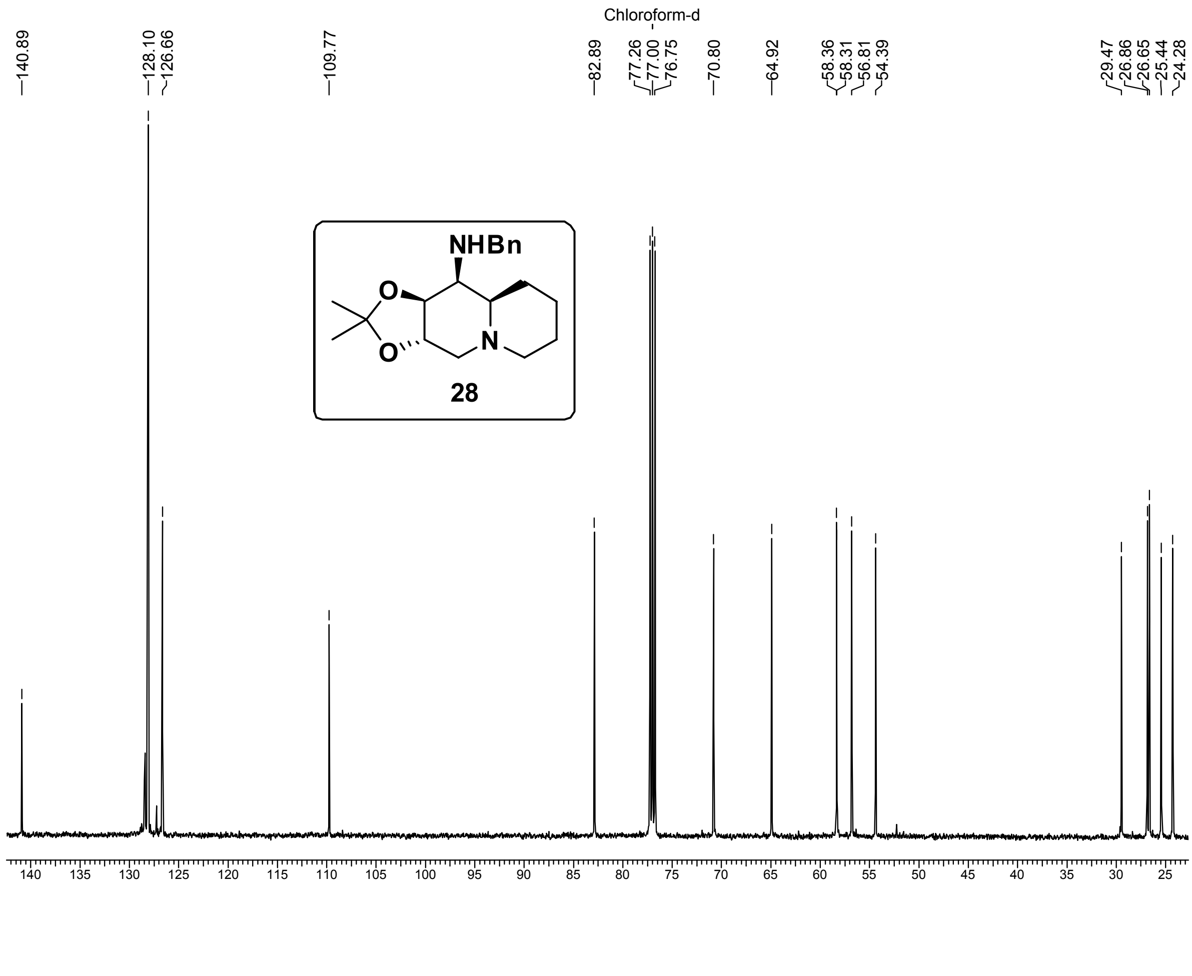
Chloroform-d
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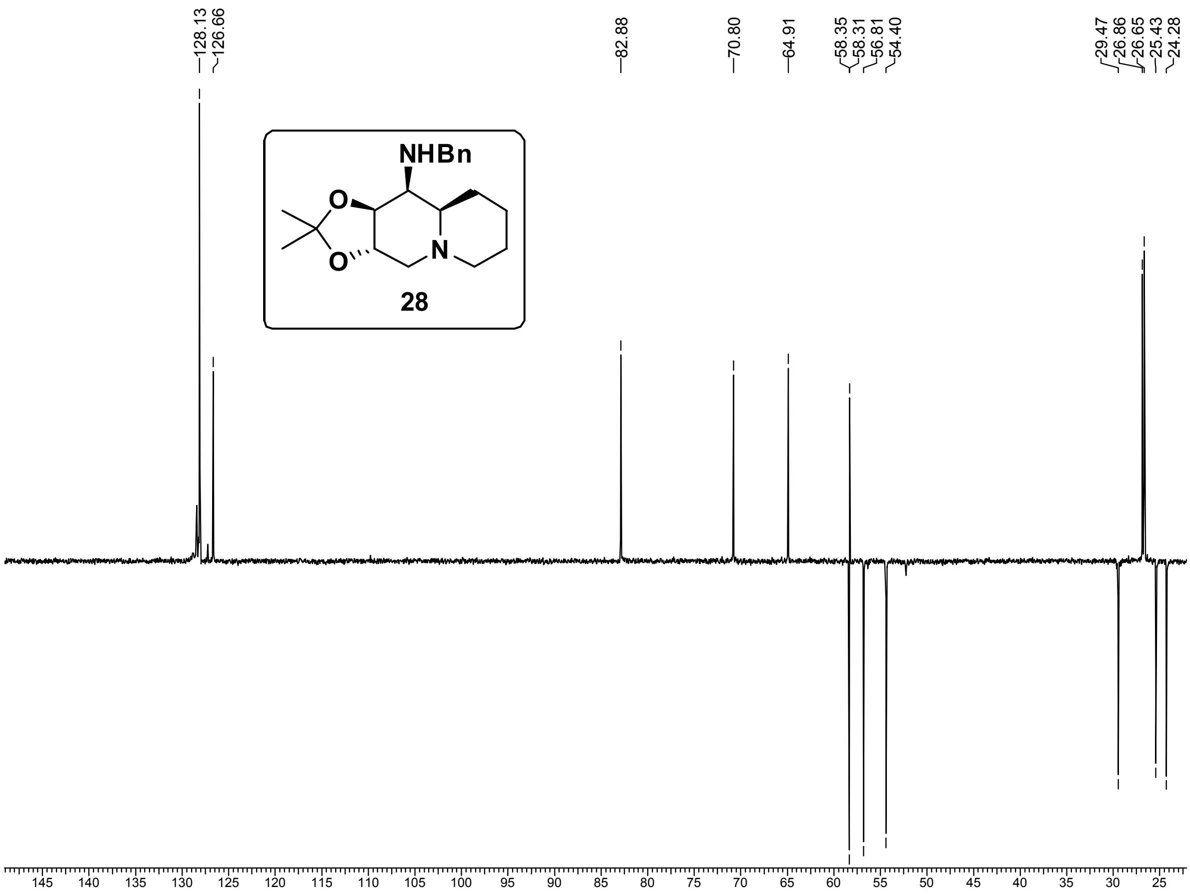
NHBn
O
O
N
28
140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25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126.66
82.88
70.80
64.91
58.35
58.31
56.81
54.40
29.47
26.86
26.65
25.43
24.28
NHBn
O
O
N
28
145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25

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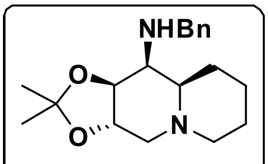
COSY



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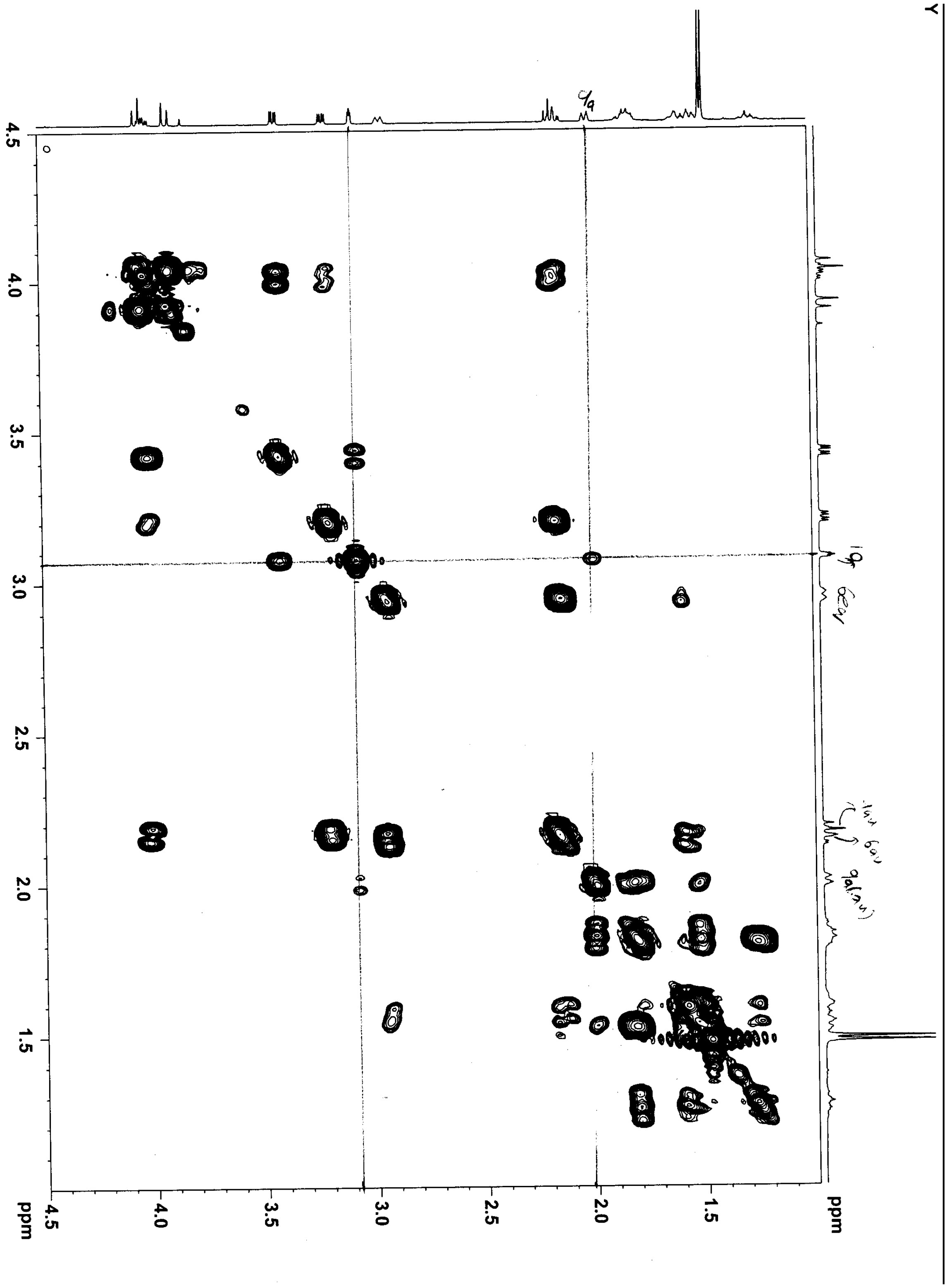

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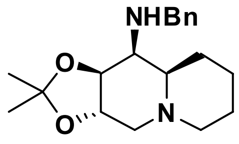

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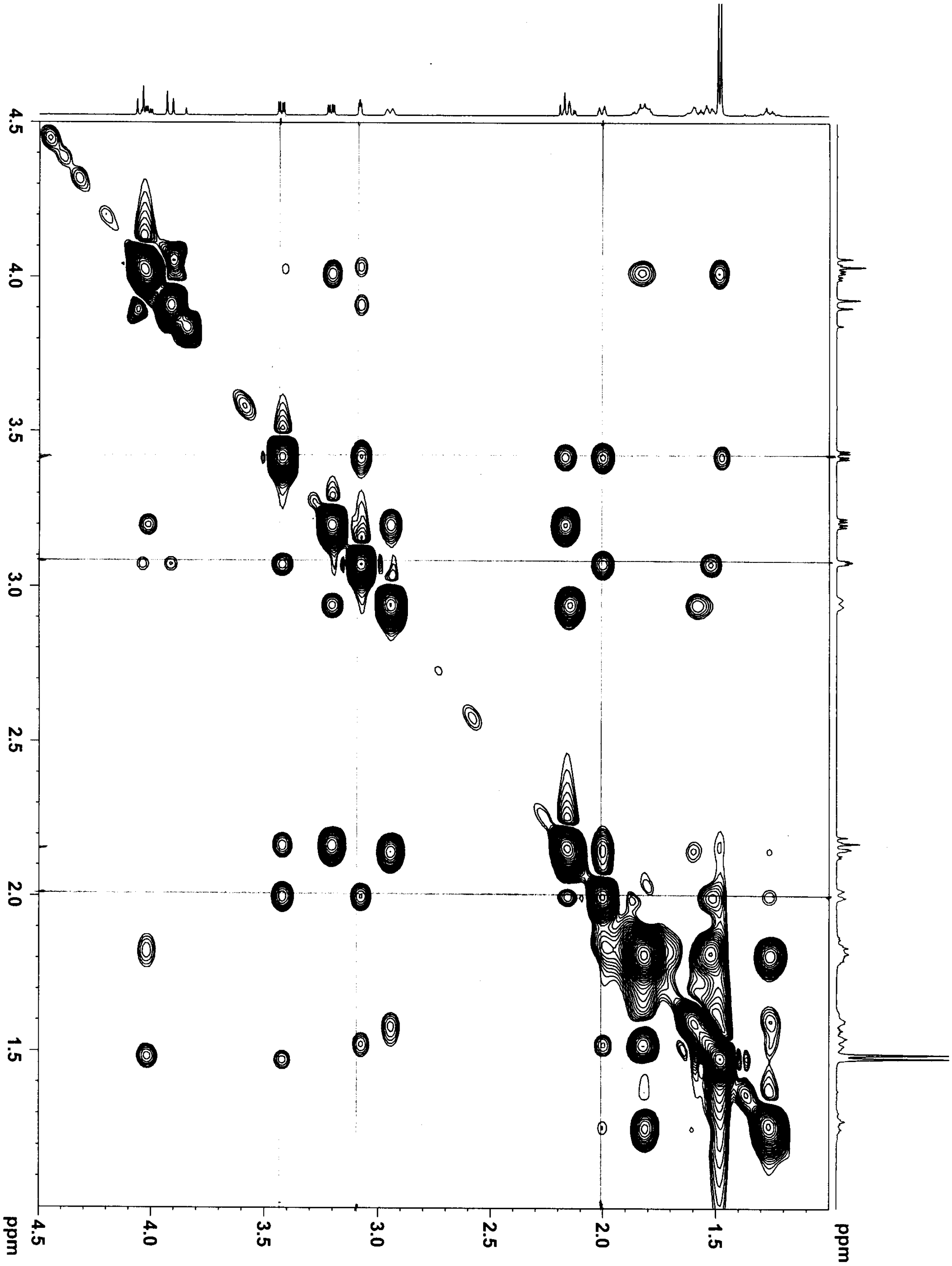

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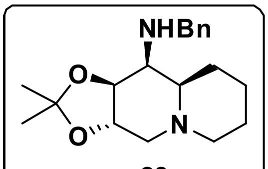

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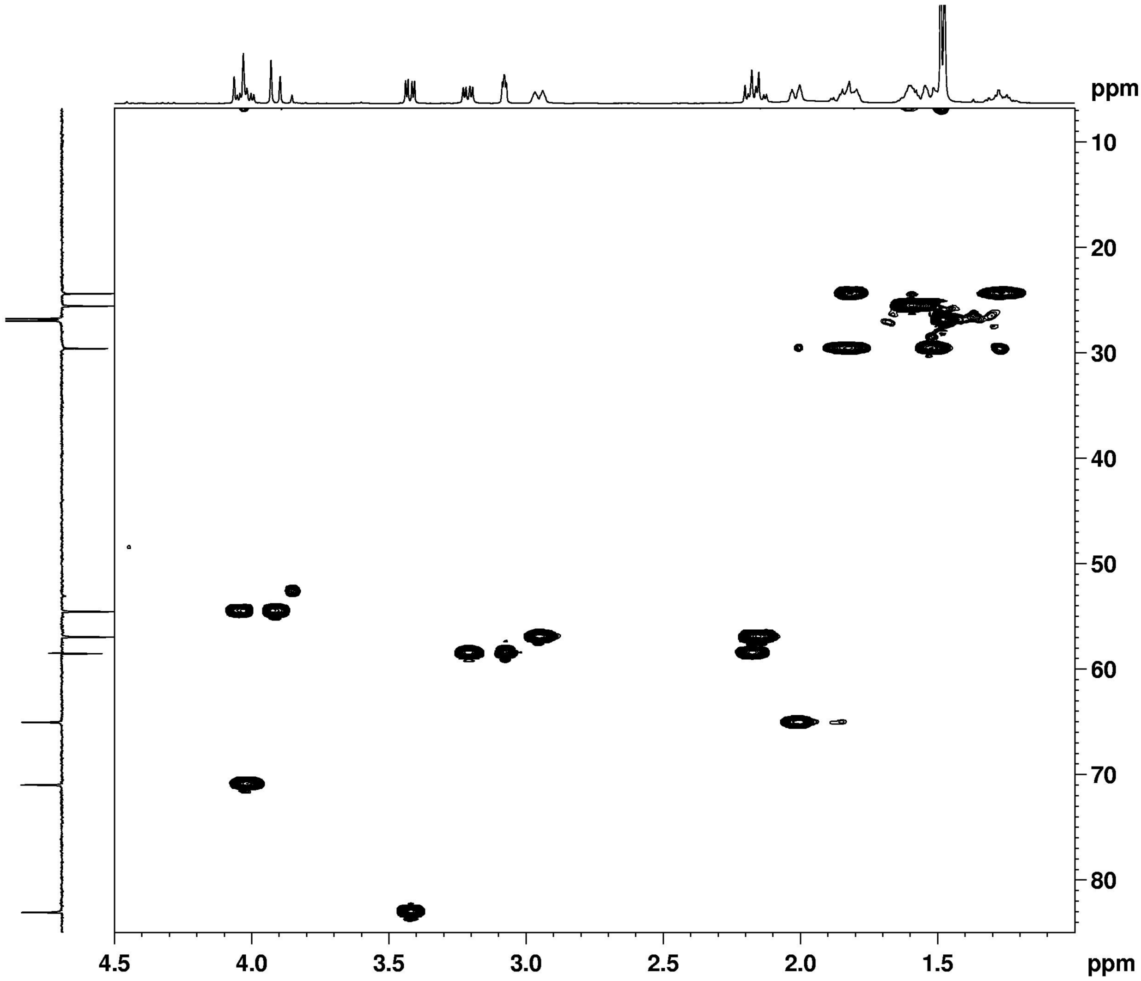

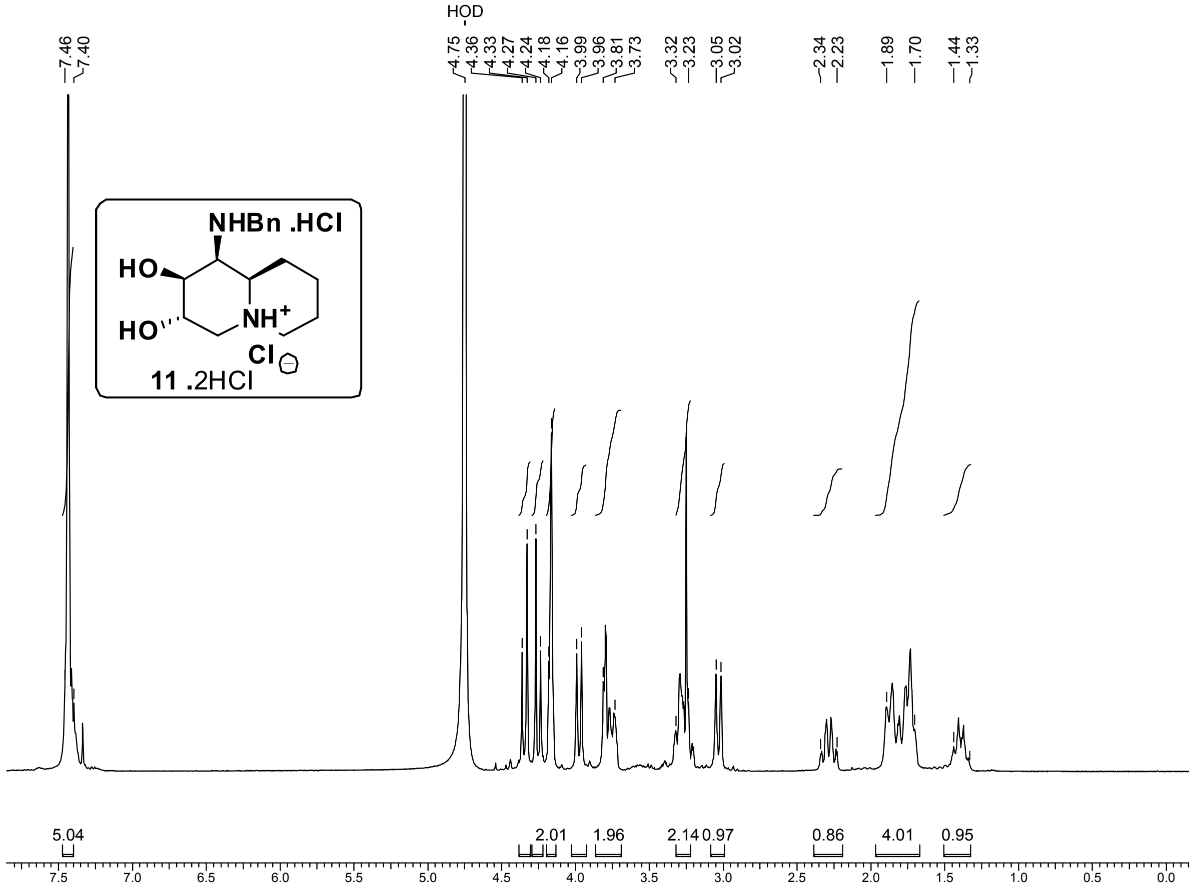
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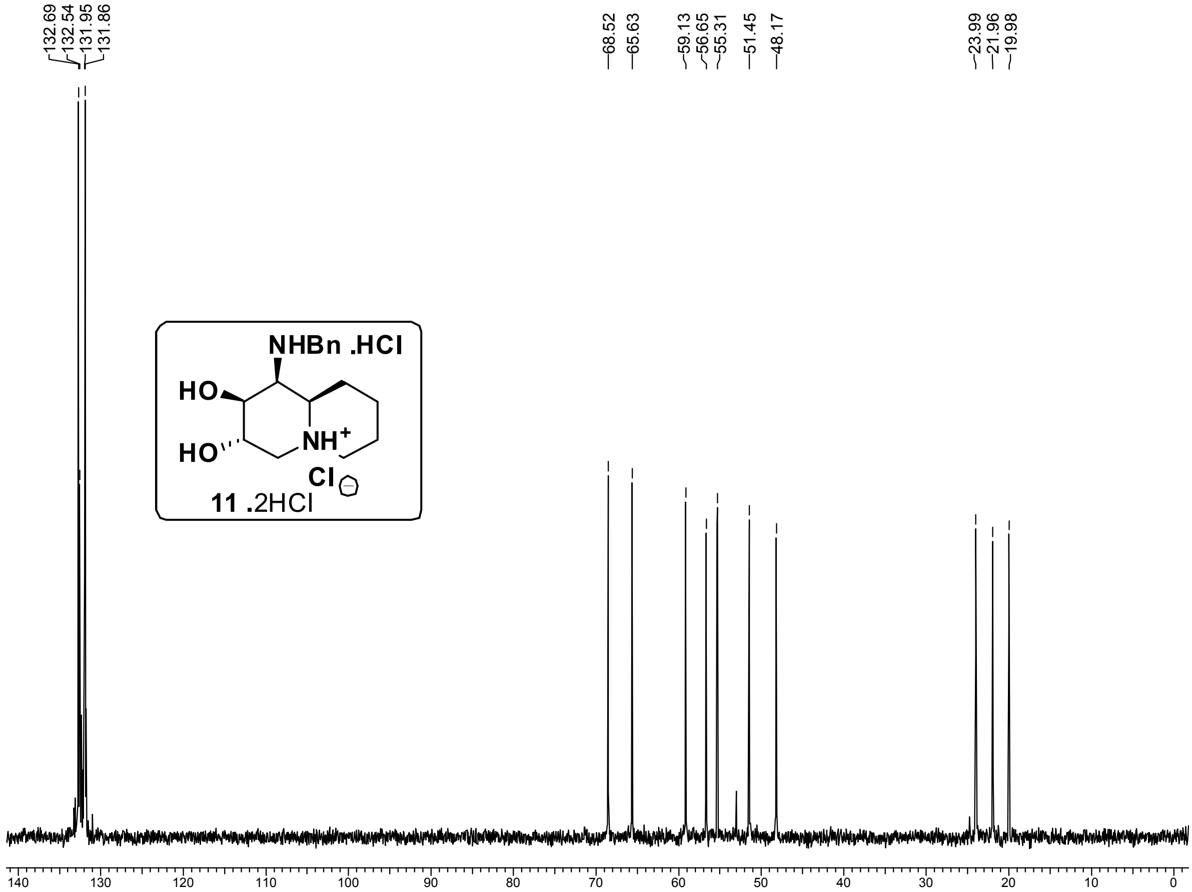
7.40
4.75
4.36
4.33
4.27
4.24
4.18
4.16
3.99
3.96
3.81
3.73
3.32
3.23
3.05
3.02
2.34
2.23
1.89
1.70
1.44
1.33
NHBn .HCl
HO
HO
NH+
Cl
11 .2HCl
5.04
2.01
1.96
2.14
0.97
0.86
4.01
0.95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59.13
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21.96
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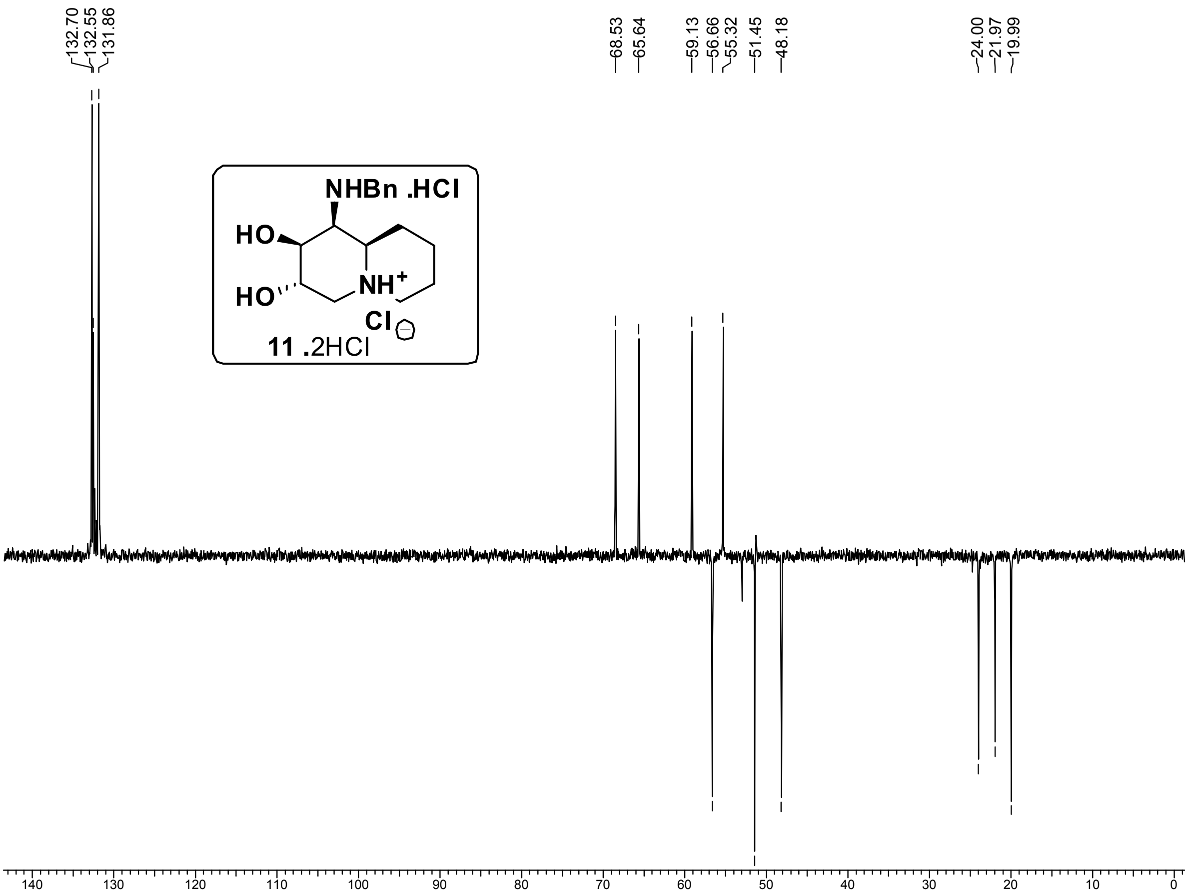
HO
NH+
Cl
11 .2HCl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HO
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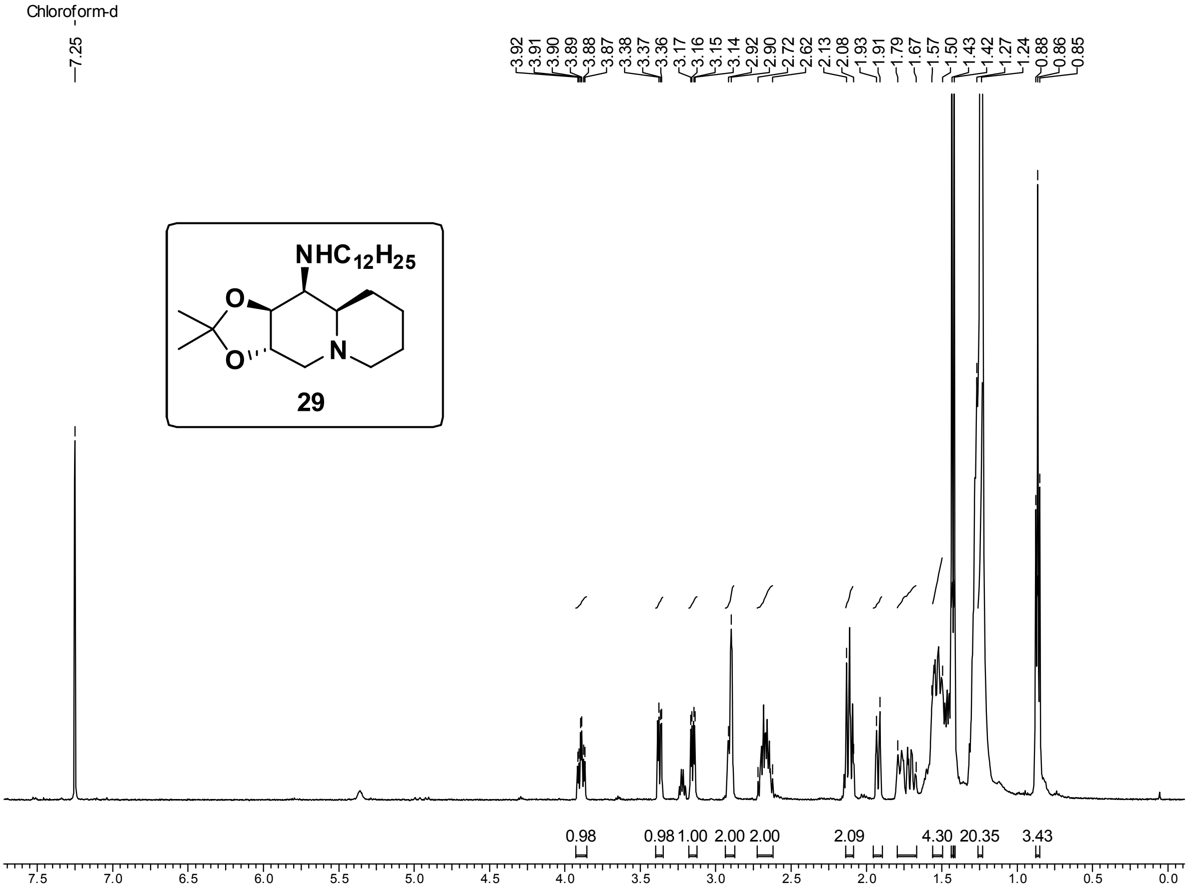
NH+
Cl
11 .2HCl


Chloroform-d
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O
O
N
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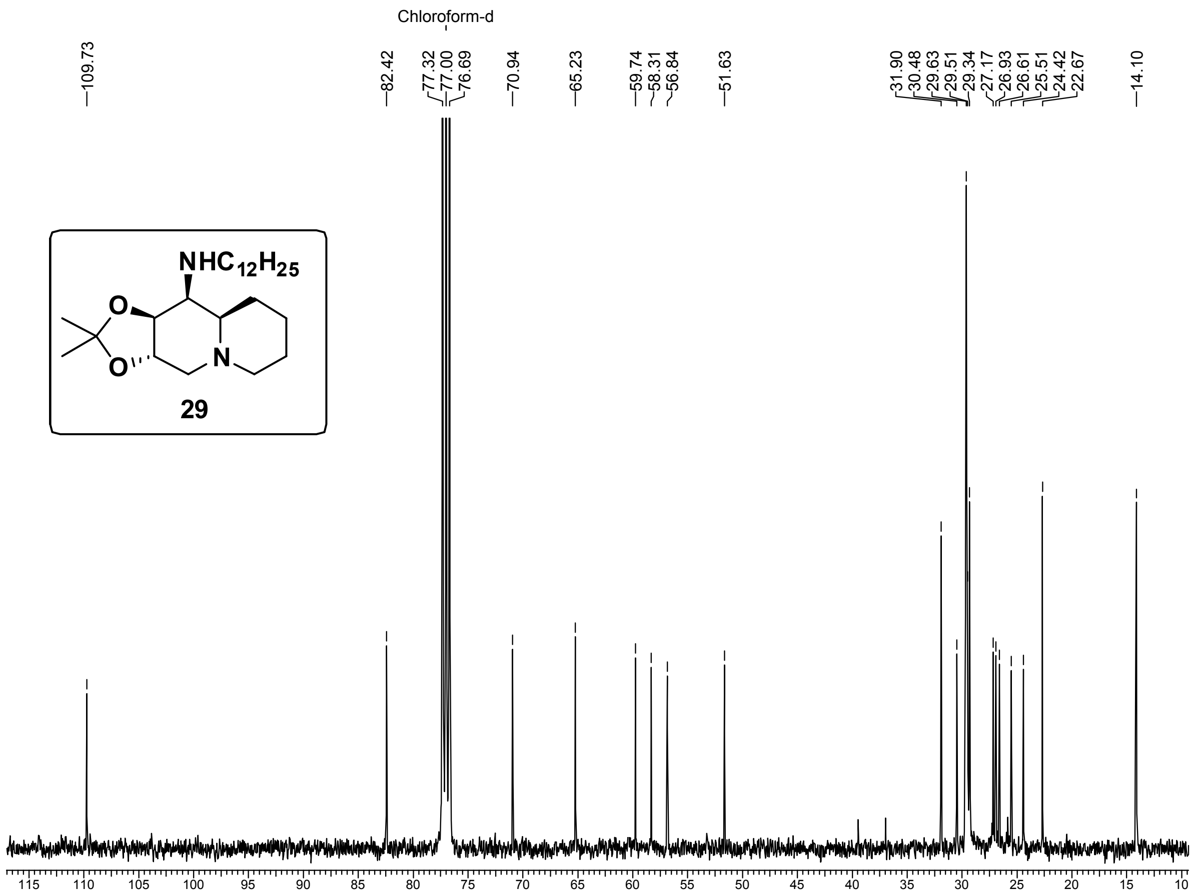
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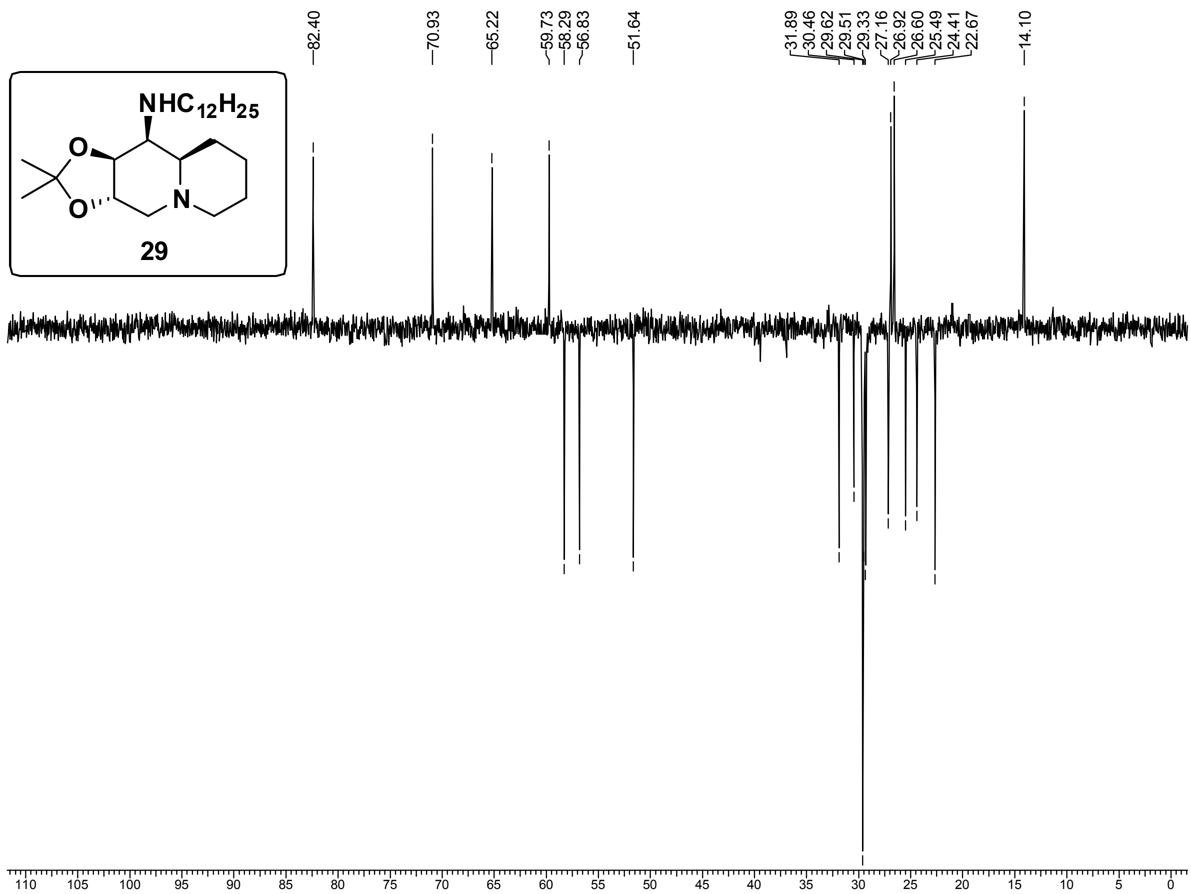
29.63
29.51
29.34
27.17
26.93
26.61
25.51
24.42
22.67
14.10
NHC12H25
O
O
N
29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31.89
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29.62
29.51
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26.60
25.49
24.41
22.67
14.10
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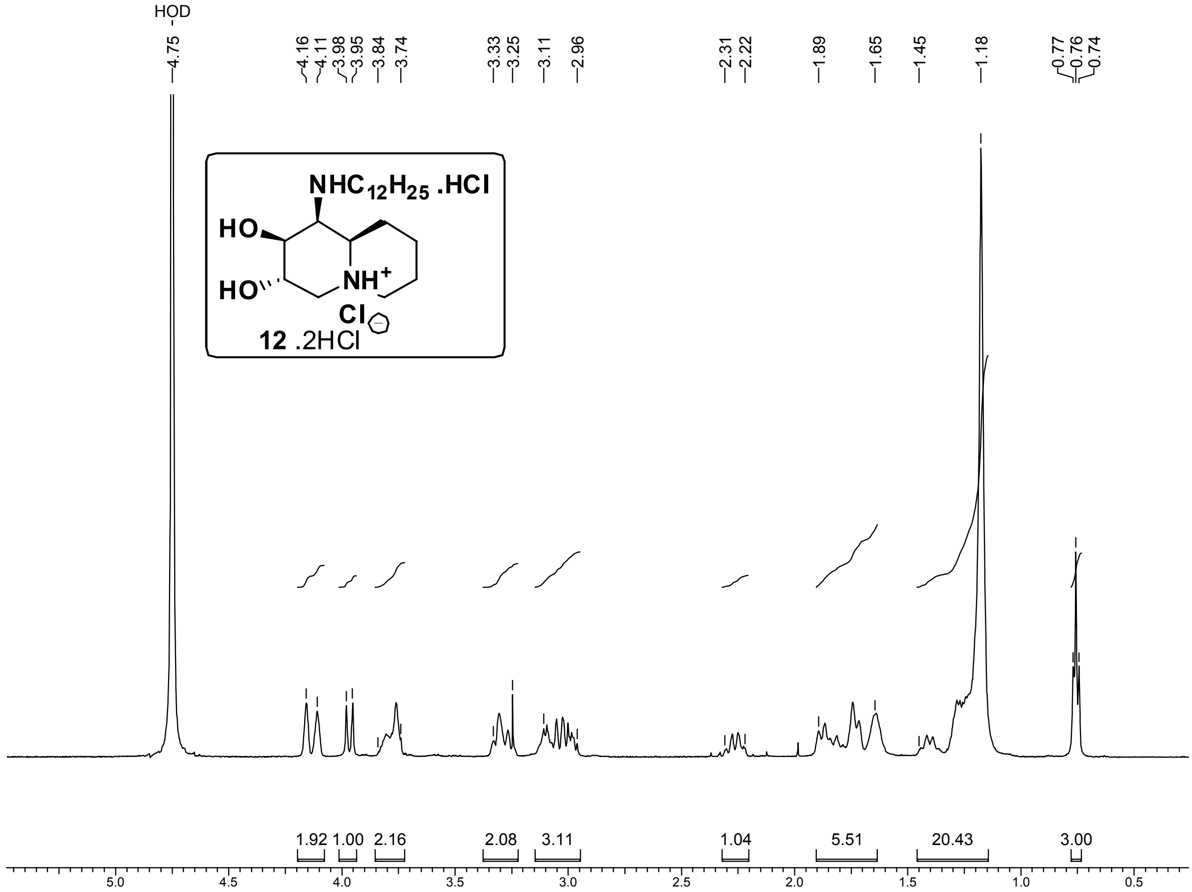
O
O
N
29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3.33 3.25 3.11 2.96
2.31 2.22
1.89 1.65 1.45 1.18
0.77 0.76 0.74
NHC12H25 .HCl
HO
HO
NH+
Cl
12 .2HCl
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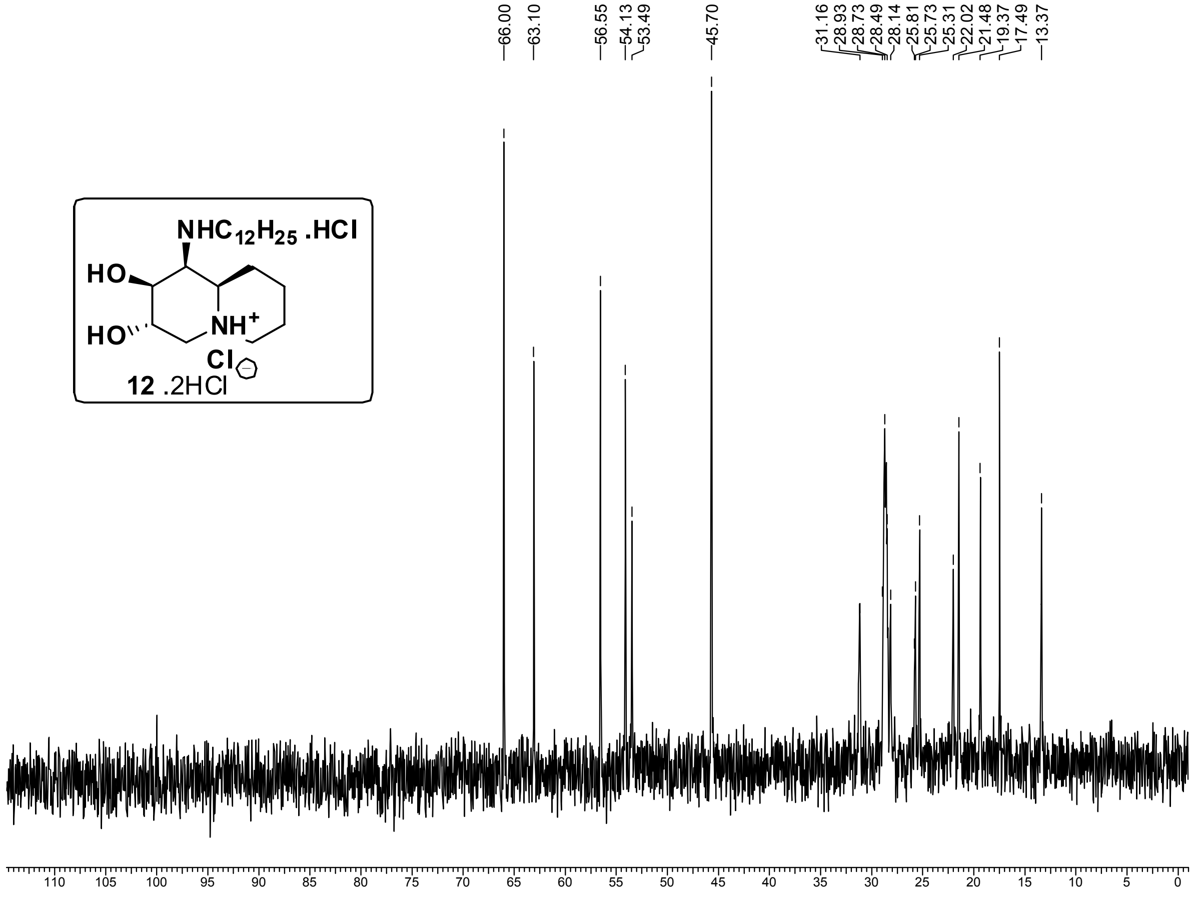
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31.16 28.93 28.73 28.49 28.14 25.81 25.73 25.31 22.02 21.48 19.37 17.49 13.37
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HO
HO
NH+
Cl
12 .2HCl
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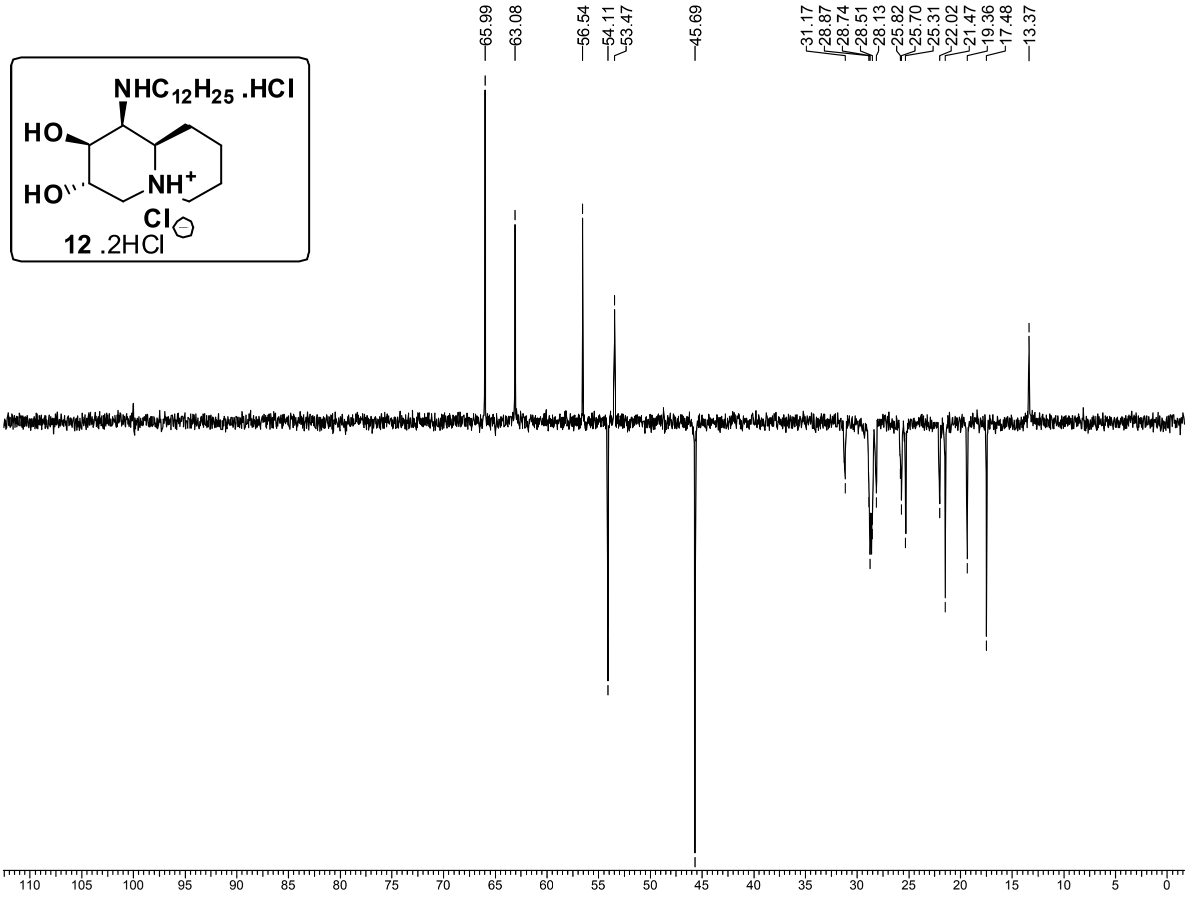
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28.51
28.13
25.82
25.70
25.31
22.02
21.47
19.36
17.48
13.37
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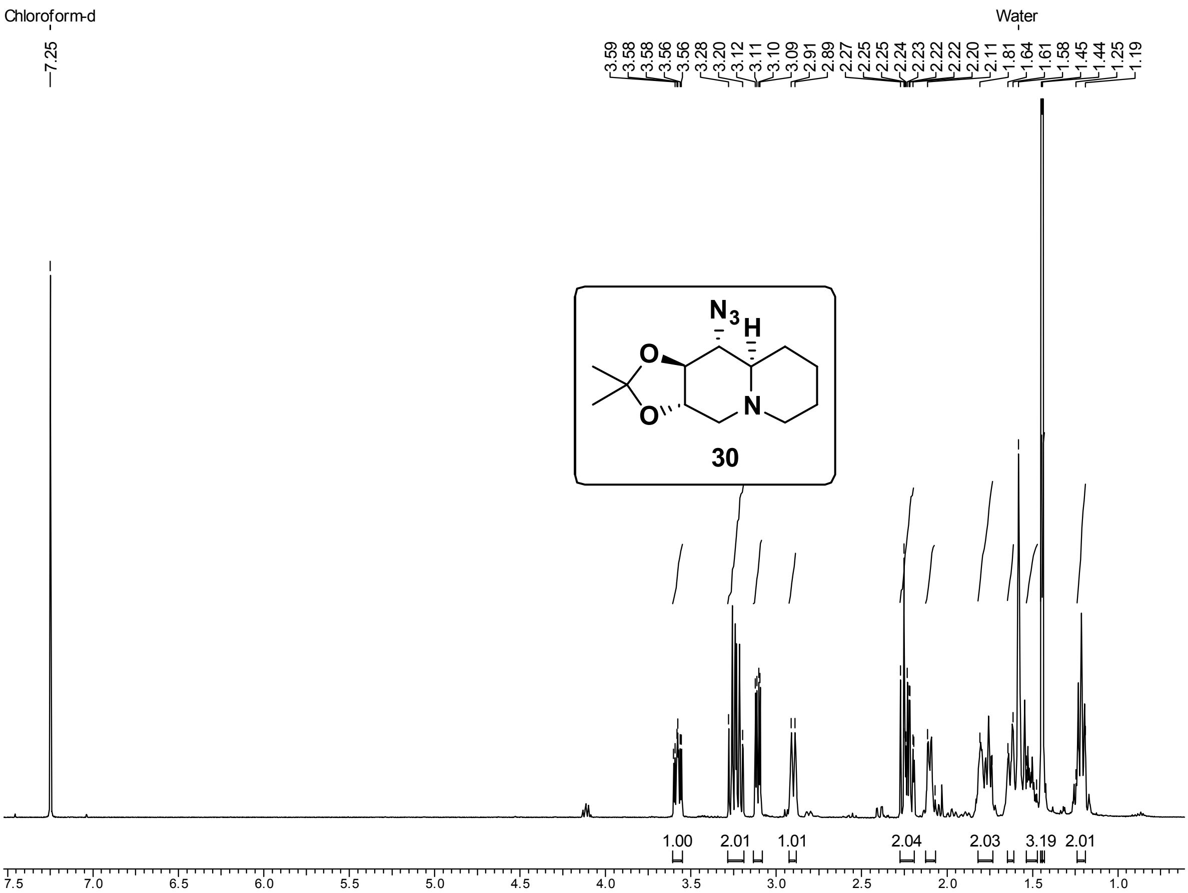
HO
HO
NH+
Cl
12 .2HCl
110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0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Water
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3.58
3.56
3.56
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3.20
3.12
3.11
3.10
3.09
2.91
2.89
2.27
2.25
2.25
2.24
2.23
2.22
2.22
2.22
2.20
2.11
1.81
1.64
1.61
1.58
1.45
1.44
1.25
1.19
N3
H
O
O
N
30
1.00 2.01 1.01 2.04 2.03 3.19 2.01
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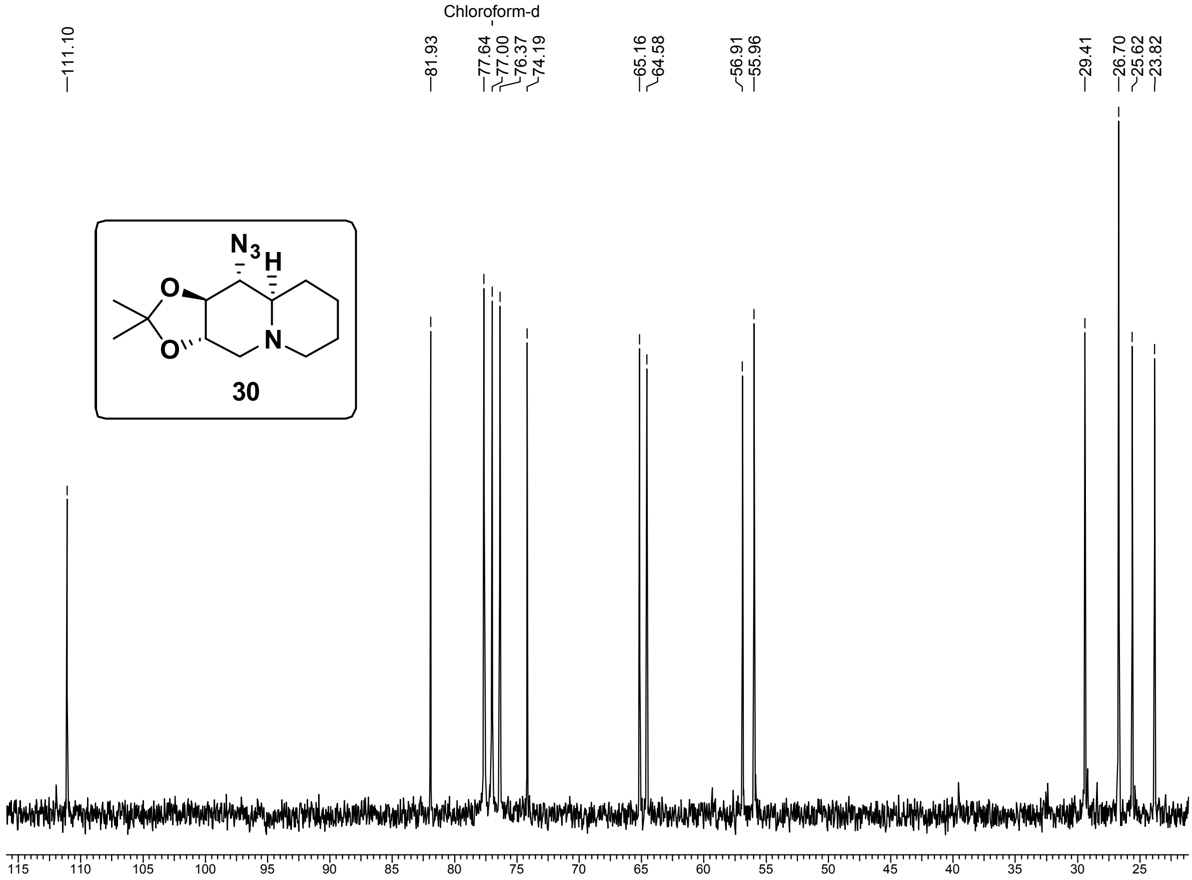
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76.37
74.19
65.16
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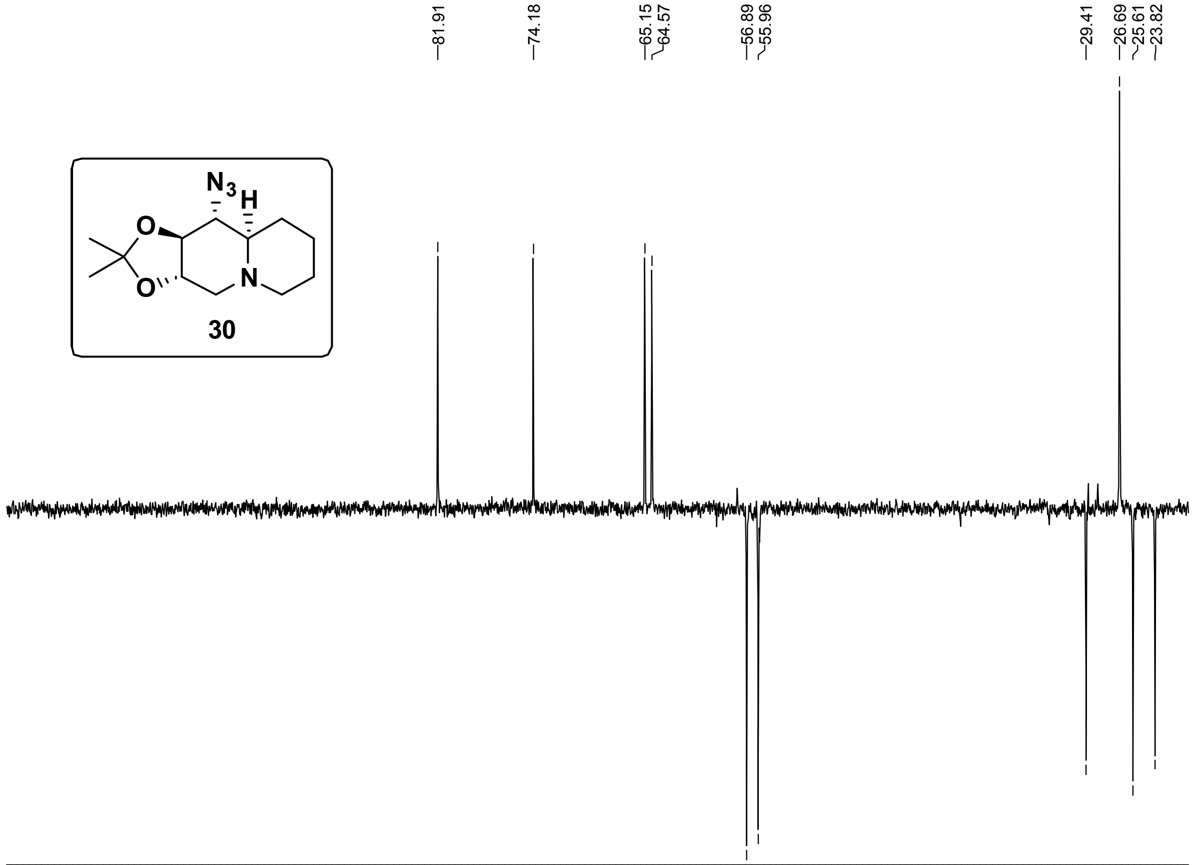
30
115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25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30
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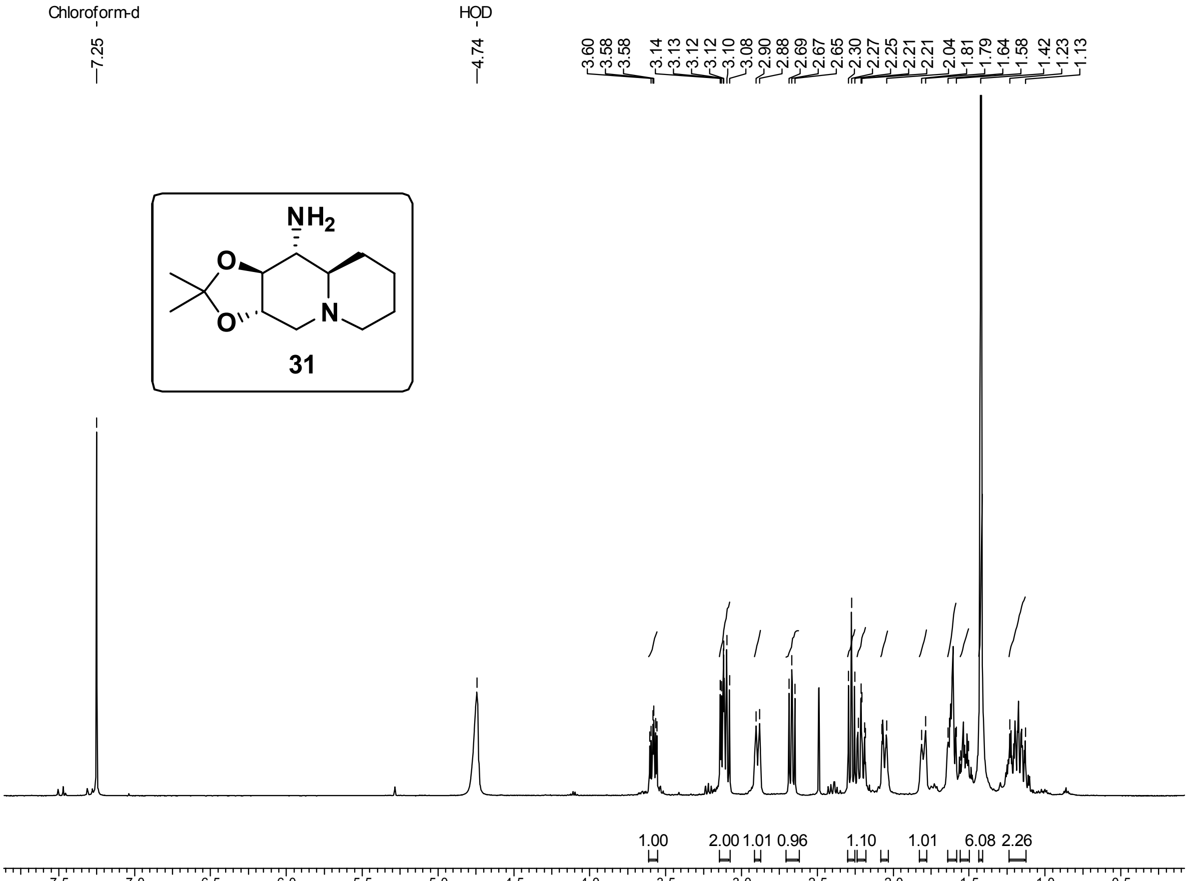
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HOD
4.74
3.60 3.58 3.58 3.14 3.13 3.12 3.12 3.10 3.08 2.90 2.88 2.69 2.67 2.65 2.30 2.27 2.25 2.21 2.21 2.04 1.81 1.79 1.64 1.58 1.42 1.23 1.13
NH_2
O
O
N
31
1.00 2.00 1.01 0.96 1.10 1.01 6.08 2.26
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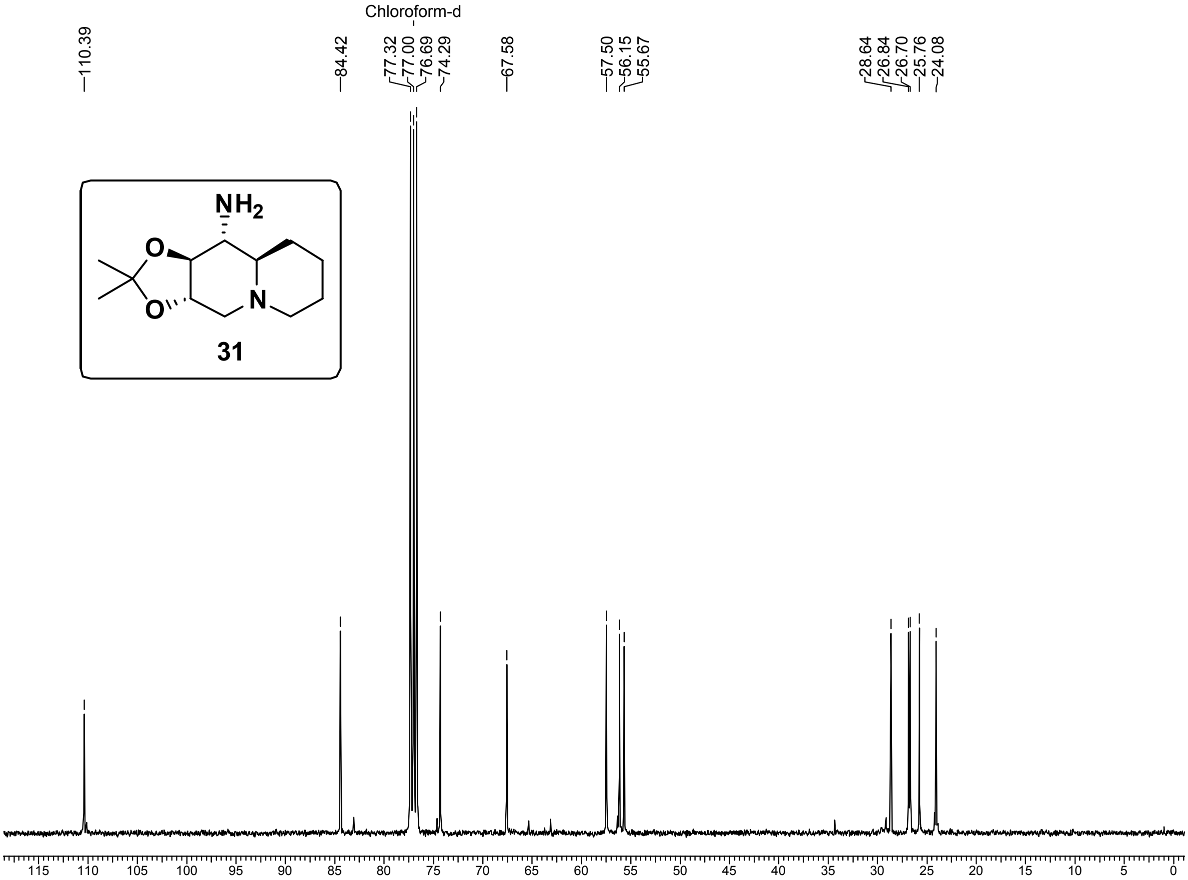
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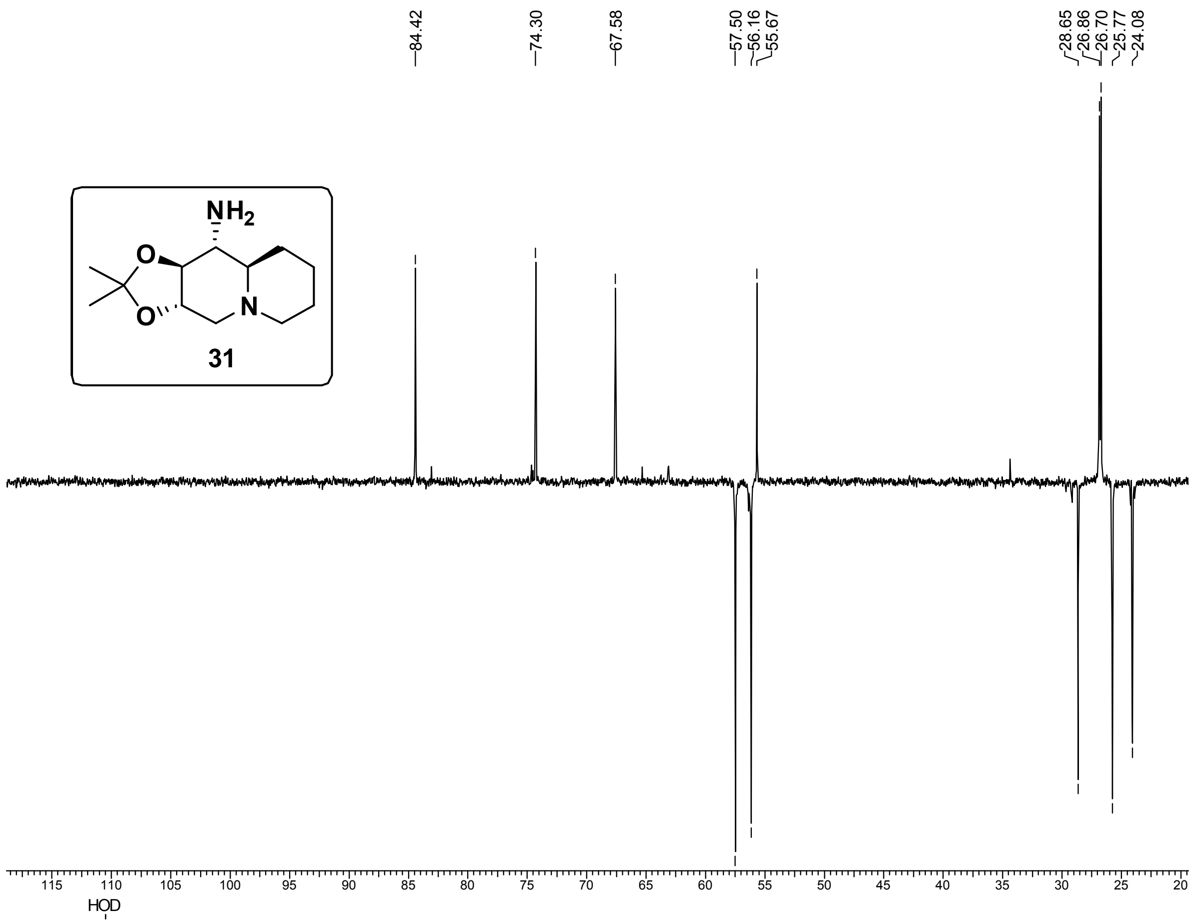
Chloroform-d
77.32 77.00 76.69 74.29
67.58
57.50 56.15 55.67
28.64 26.84 26.70 25.76 24.08
NH_2
O
O
N
31
115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0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74.30
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24.08
NH2
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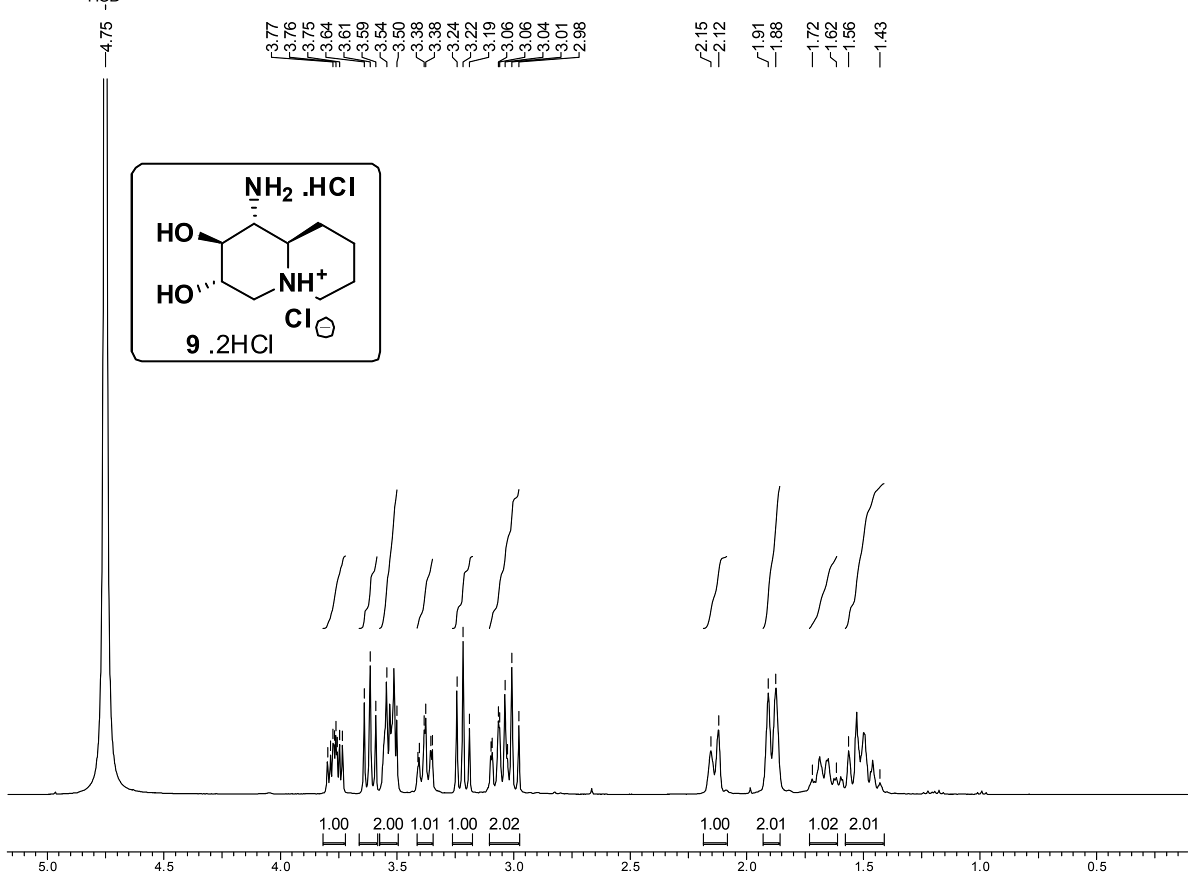
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3.75
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3.54
3.50
3.38
3.38
3.24
3.22
3.19
3.06
3.06
3.04
3.01
2.98
2.15
2.12
1.91
1.88
1.72
1.62
1.56
1.43
NH2 .HCl
HO
HO
NH+
Cl
9 .2HCl
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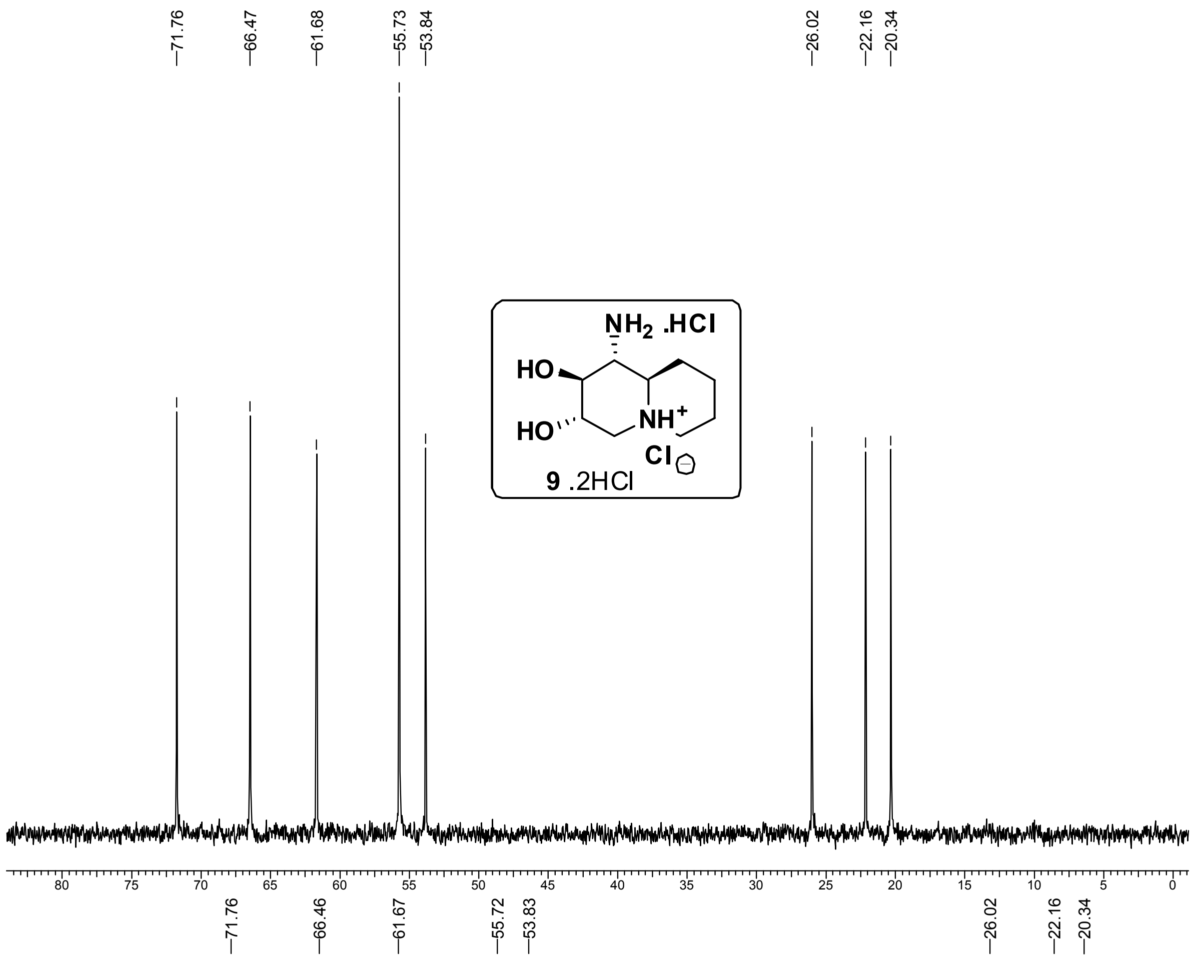
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20.34
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HO
NH+
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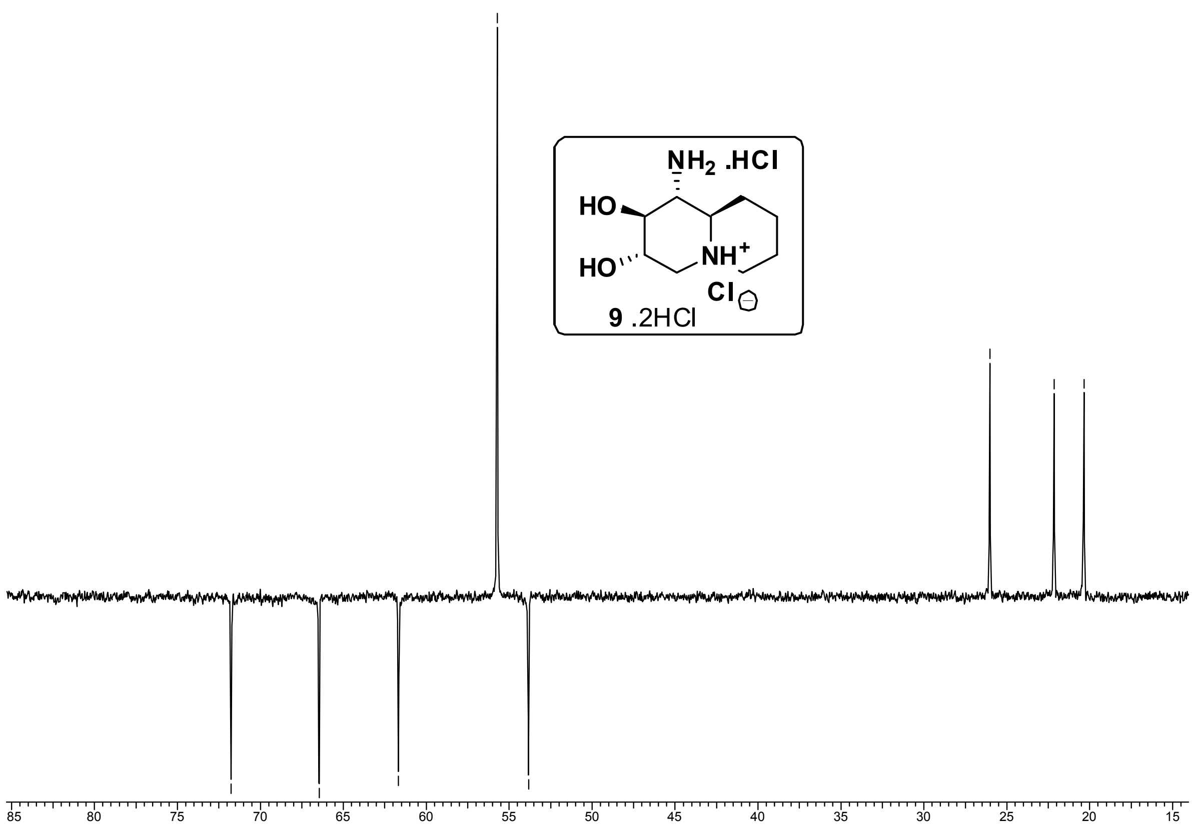
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20.34
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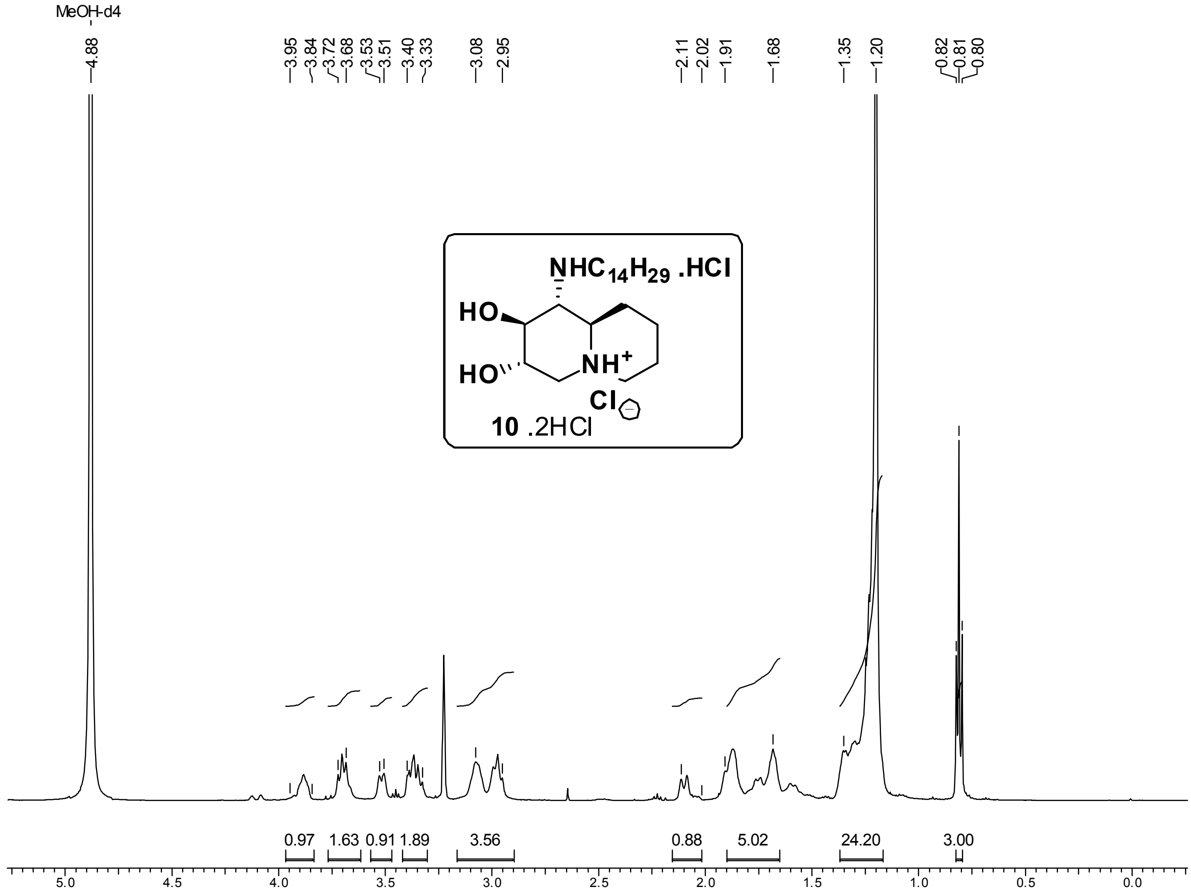
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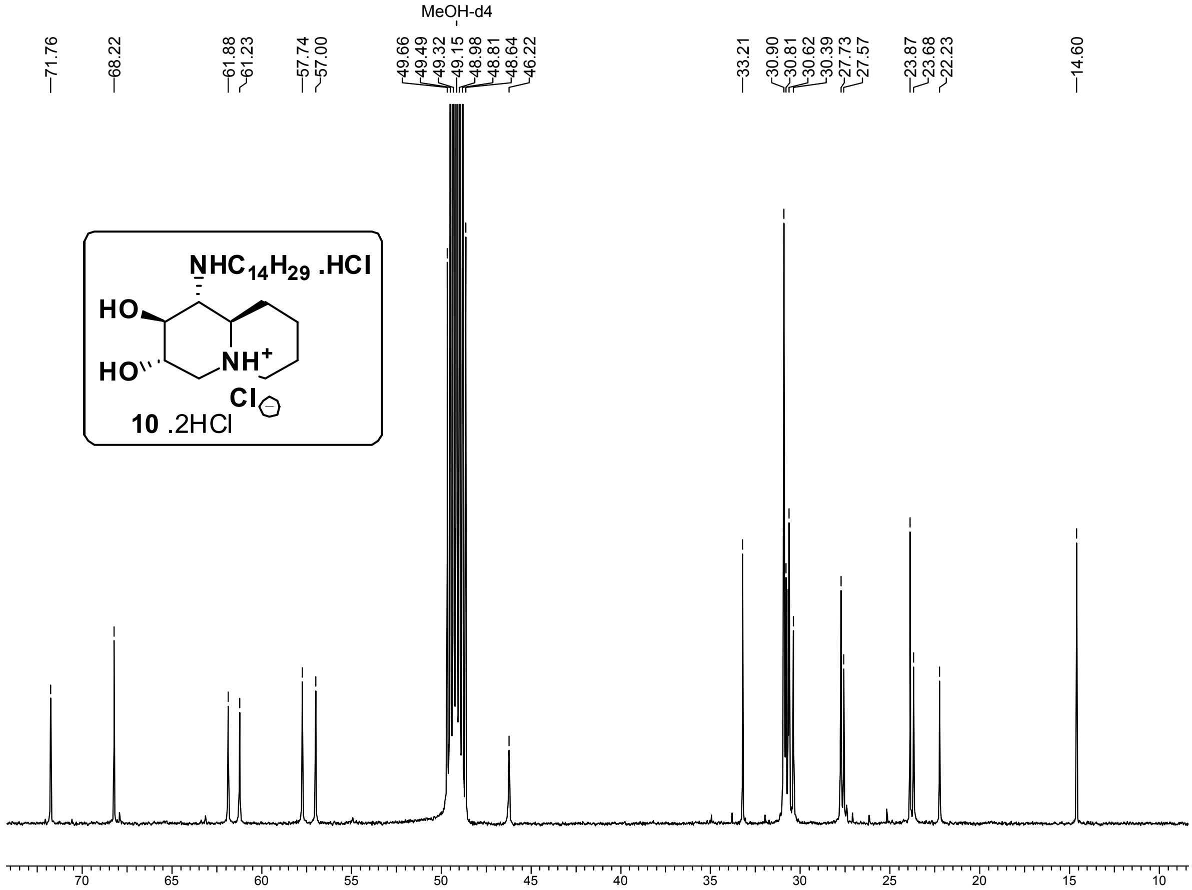
HO
HO
NH+
Cl
10 .2HCl
0.97 1.63 0.91 1.89 3.56 0.88 5.02 24.20 3.00


MeOH-d4
NHC14H29 .HCl
HO
HO
NH+
Cl
10 .2HCl

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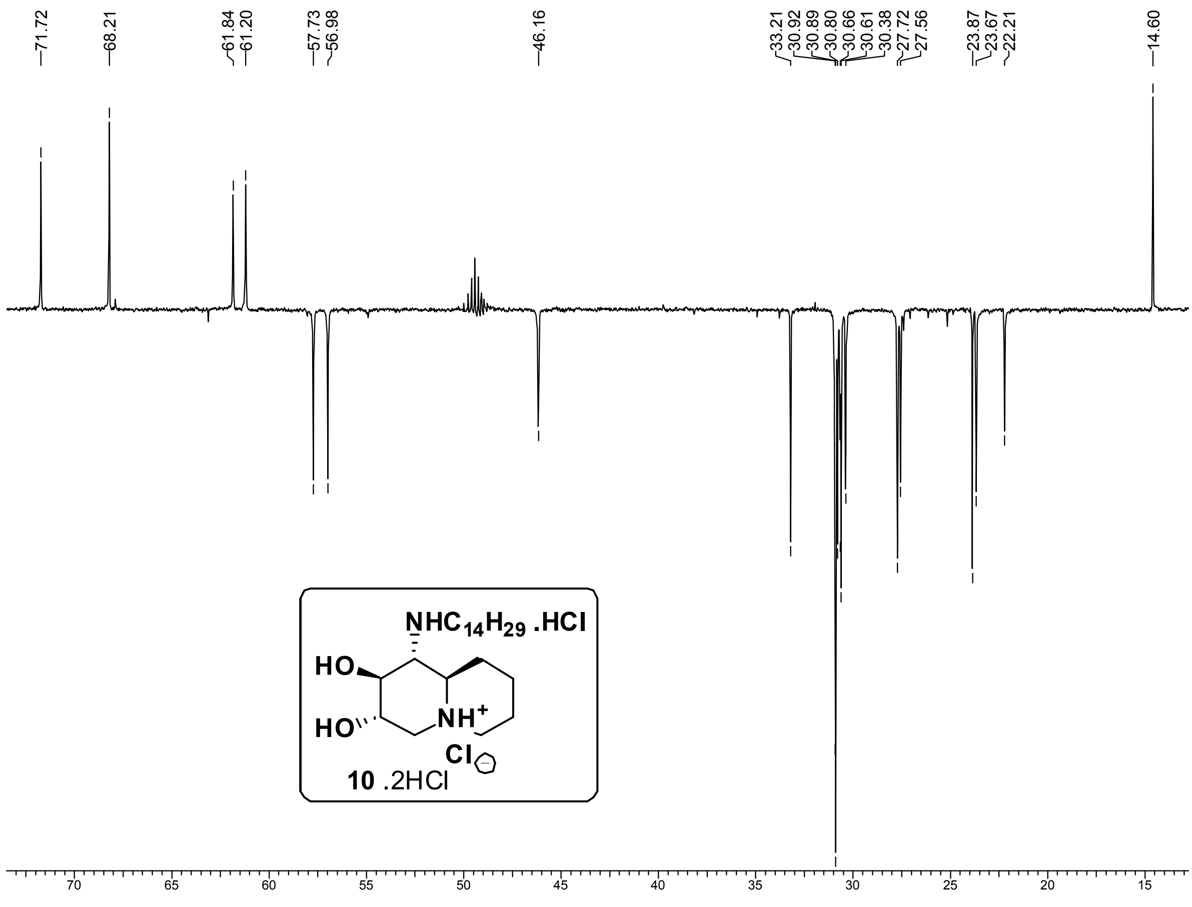


General procedure for enzyme inhibition assay:

Inhibition assay for the inhibitory potencies of the azasugars were determined by measuring the residual hydrolytic activities of the glycosidases of the corresponding *p*-nitrophenyl glycosides in the presence of azasugars spectrophotometrically. The absorbance of the resulting solution was read at 405 nm.

In the case of β-galactosidase (*Aspergillus oryzaie*) each assay was performed in citrate phosphate buffer (pH 4.5) with *p*-nitrophenyl β-D-galactpyranooside as the substrate. Varying concentrations of the substrate (100 μM, 50 μM) were employed. The reaction was initiated by the addition of 25 μL of appropriately diluted enzyme. The reaction mixture (having inhibitor) which had a final volume of 0.5 mL was incubated for 20 min at 37 °C, and then quenched by the addition of 1.0 mL of 1M Na_2CO_3solution.

In the case of α-galactosidase (Green coffee beans), the assay was performed in a potassium phosphate buffer (pH 6.5) with *p*-nitrophenyl α-D-galactopyranoside as the substrate. Varying concentrations of the substrate (100 μM, 50 μM) were employed. The reaction was initiated by the addition of 25 μL of appropriately diluted enzyme. The reaction mixture (having inhibitor) which had a final volume of 0.5 mL was incubated for 20 min at 25 °C, and then quenched by the addition of 1.0 mL of 1M Na_2CO_3 solution.

In the case of β-mannosidase (Snail), the assay was performed in a citrate phosphate buffer (pH 4.0) with *p*-nitrophenyl β-D-mannopyranoside as the substrate. Varying concentrations of the substrate (200 μM, 150 μM) were employed. The reaction was initiated by the addition of 50 μL of appropriately diluted enzyme. The reaction mixture (having inhibitor) which had a final volume of 0.5 mL was incubated for 20 min at 25 °C, and then quenched by the addition of 1.0 mL of 1M Na_2CO_3 solution.

In the case of α-mannosidae (Jack Beans), the assay was performed in citrate phosphate buffer (pH 4.5) with *p*-nitrophenyl α-D-mannpyranoside as the substrate. Varying concentrations of the substrate (50 μM, 30 μM) were employed. The reaction was initiated by the addition of 25 μL of appropriately diluted enzyme. The reaction mixture (having inhibitor) which had a final volume of 0.5 mL was incubated for 20 min at 25 °C, and then quenched by the addition of 1.0 mL of 1M Na_2CO_3 solution.

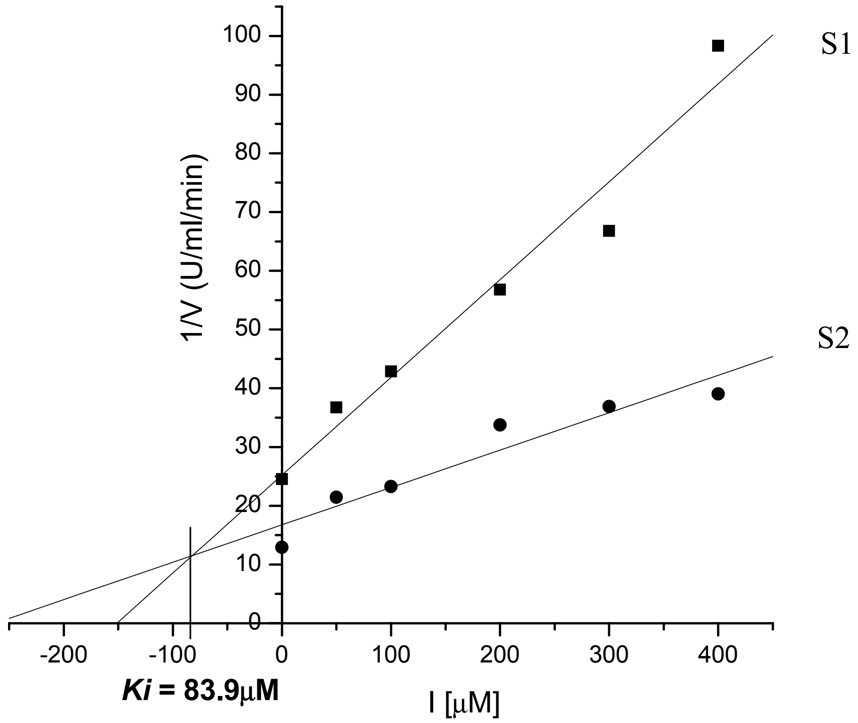
In the case of β-glucosidase (Almond), the assay was performed in a potassium phosphate buffer (pH 5.5) with *p*-nitrophenyl β-D-glucopyranoside as the substrate. Varying concentrations of the substrate (100 μM, 50 μM) were employed. The reaction was initiated by the addition of 50 μL of appropriately diluted enzyme. The reaction mixture (having inhibitor) which had a final volume of 0.5 mL was incubated for 30 min at 37 °C, and then quenched by the addition of 1.0 mL of 1M Na_2CO_3 solution

In the case of α-glucosidase (Yeast), the assay was performed in a potassium phosphate buffer (pH 6.8) with *p*-nitrophenyl α-D-glucopyranoside as the substrate. Varying concentrations of the substrate (200 μM, 100 μM) were employed (except for compound **23** and **8a** were (200 μM, 150 μM) and (300 μM, 200 μM) was used, respectively). The reaction was initiated by the addition of 50 μL of appropriately diluted enzyme. The reaction mixture (having inhibitor) which had a final volume of 0.5 mL was incubated for 20 min at 37 °C, and then quenched by the addition of 1.0 mL of 1M Na_2CO_3 solution.

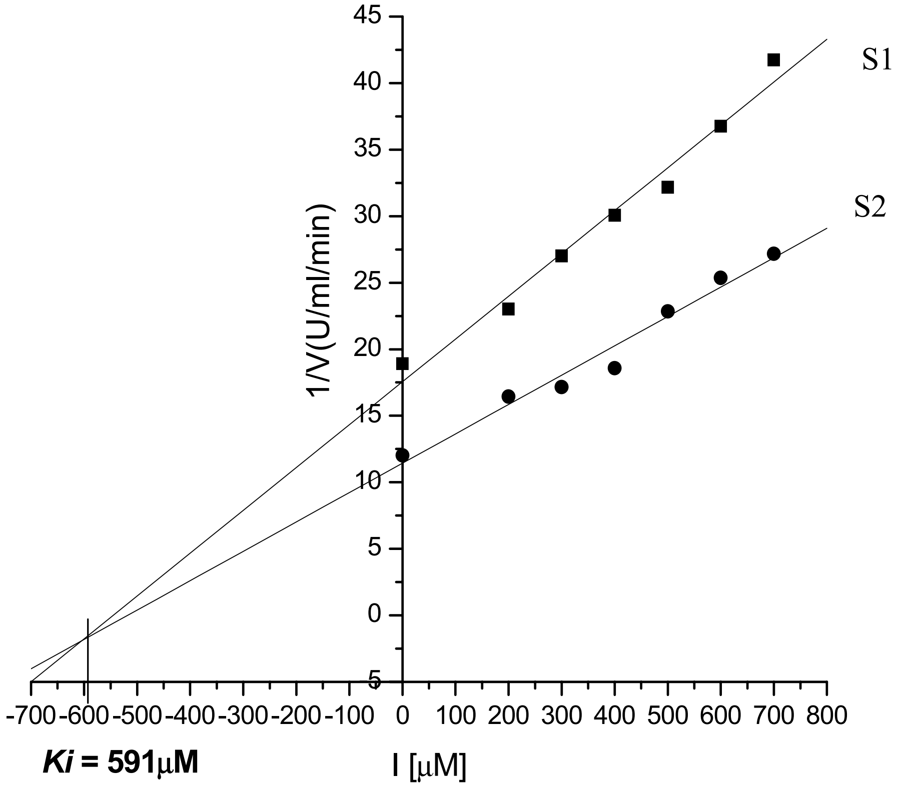
Dixon method was employed for the determination of *Ki*. In this method, hydrolytic activity of enzyme was measured in the presence of two different concentrations of substrates and varying concentrations of inhibitors. The reciprocals of substrate hydrolysis (1/V) were plotted against the inhibitor concentration and the Ki was determined by fitting the data using ORIGIN 6.1.

Lineweaver-Burke Plots:

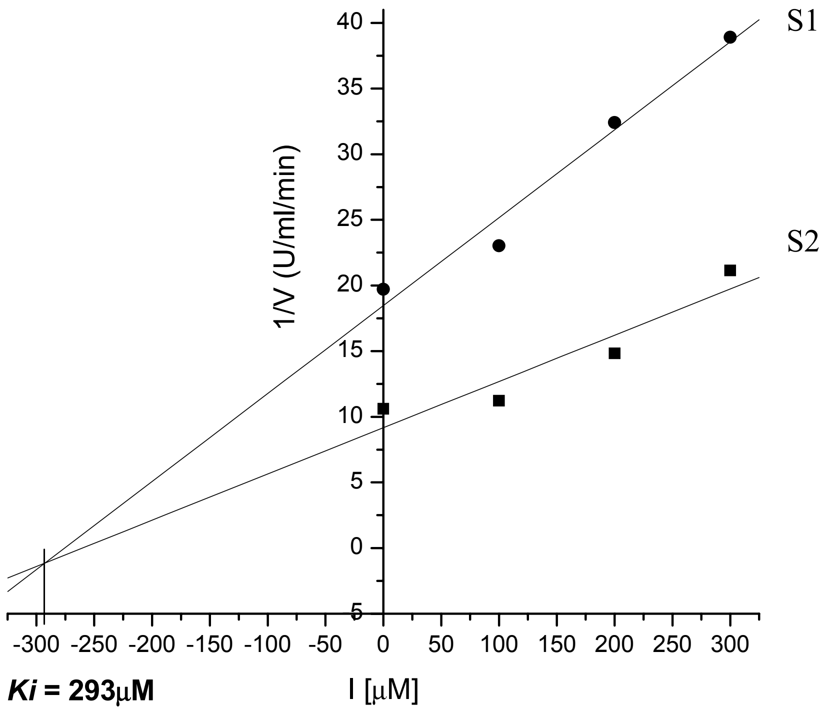
α-galactosidase inhibiton by Compound 7 (*Ki* = 83.9 μM)



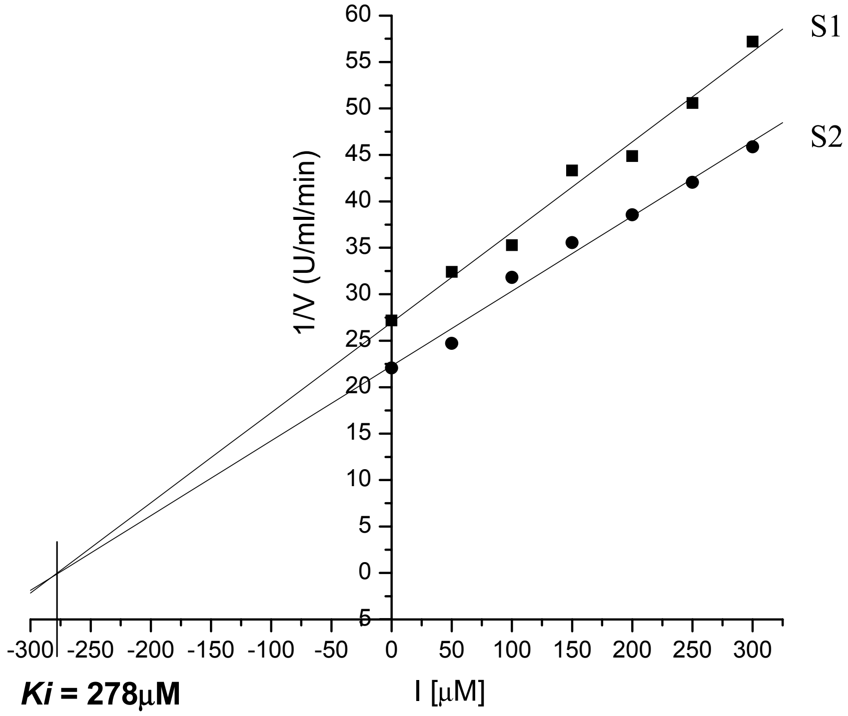
β-galactosidase inhibiton by Compound 7 (*Ki* = 591 μM)



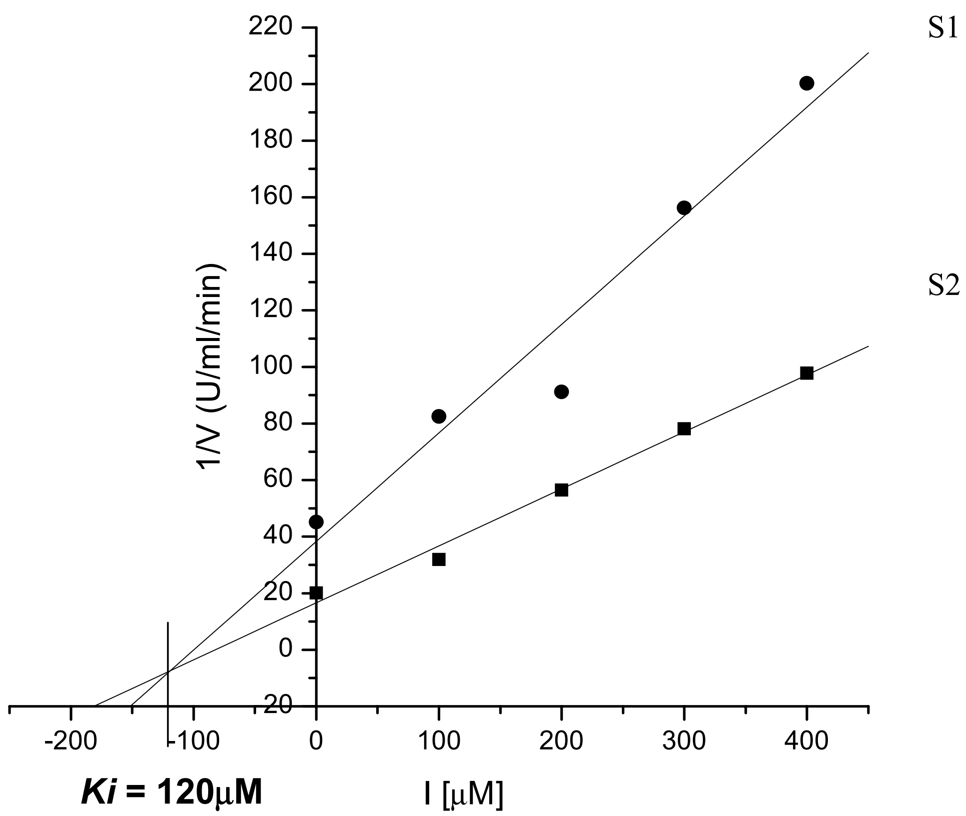
α-mannosidase inhibiton by
Compound 12 (*Ki* = 293 μM)



α-glucosidase inhibiton by
Compound 11 (*Ki* = 278 μM)



α-glucosidase inhibiton by
Compound 12 (*Ki* = 120 μM)



α-glucosidase inhibiton by
Compound 14 (*Ki* = 28 μM)