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Synthesis and Structural Analysis of (±)-*Threo*-ritalinic Acid

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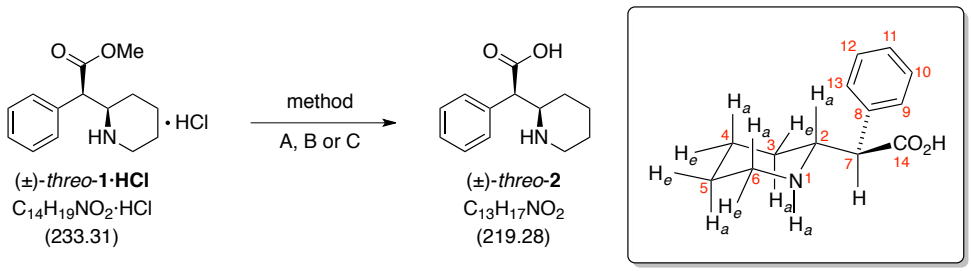
Supporting Information: Experimental Procedures

General techniques: All chemicals were purchased from Aldrich, TCI or ABCR and used as received unless otherwise noted. Reported density values are for ambient temperature. (±)-*Threo*-methylphenidate was obtained from Ciba-Geigy.

^{1}H and ^{13}C NMR spectra were recorded in Fourier transform mode at the field strength specified on Bruker Avance FT-NMR spectrometers. Spectra were obtained from the specified deuterated solvents in 5 mm diameter tubes. Chemical shift in ppm is quoted relative to residual solvent signals calibrated as follows: **D_2O** δ_H (H_2O) = 4.79 ppm. Multiplicities in the ^{1}H NMR spectra are described as: s = singlet, d = doublet, t = triplet, q = quartet, quint. = quintet, m = multiplet, b = broad; coupling constants are reported in Hz. Numbers in parentheses following carbon atom chemical shifts refer to the number of attached hydrogen atoms as revealed by the DEPT spectral editing technique.

Chemistry



(±)-*threo*-**1**·**HCl**
$C_{14}H_{19}NO_2$·HCl
(233.31)

(±)-*threo*-**2**
$C_{13}H_{17}NO_2$
(219.28)

(±)-*Threo*-2-Phenyl-2-(piperidin-2-yl)acetic acid ((±)-*threo*-ritalinic acid, (±)-*threo*-2): *Method A*:[1] At ambient temperature, open to air one neck round bottom flask was charged with methyl 2-phenyl-2-(piperidin-2-yl)acetate (methylphenidate, 100 mg, 0.42 mmol) and hydrochloric acid (6 M, aq., 1 mL) and the resulting heterogeneous mixture was allowed to heat (oil bath temperature 130 °C) and stir over 1.3 h during which time the mixture became colourless and completely homogeneous. After this time the mixture was allowed to cool to ambient temperature and the pH was adjusted using aq. NaOH (4 M) to 3 to yield a white precipitate which was identified as the title compound (21 mg, 0.1 mmol, 21%): IR (neat) 2938, 1653, 1565, 1380, 1340, 1031, 710, 695 cm^{-1}; ^{1}H NMR (D_2O, 400 MHz) δ ppm; ^{13}C NMR (D_2O) δ ppm. 7.46-7.39 (m, 3H, Ph), 7.33-7.30 (m, 2H, Ph), 3.61 (d, J = 9.3 Hz, 1H, H7) 3.55 (ddm, J = 2.8, 9.3 Hz, 1H, H2), 3.47 (dm, J = 12.8 Hz, 1H, H6$_e$), 3.04 (td, J = 3.2, 12.8 Hz, 1H, H6$_a$), 1.87-1.80 (m, 2H, H5 and H4), 1.63-1.61 (m, 2H, H3 and H5), 1.46-1.40 (m, 2H, H3 and H4) ppm; ^{13}C NMR (D_2O, 100 MHz) δ 178.1 (0, C14), 136.8 (0, C8), 129.1 (1, 2C, C9 and C13), 128.4 (1, 2C, C10 and C12), 127.8 (1, C11), 59.2 (1, C2), 56.6 (1, C7), 44.9 (2, C6), 26.6 (2, C3), 22.0 (2, C5), 21.4 (2, C4) ppm.

^{1}H NMR (NaOD/D_2O, 400 MHz) δ 7.34-7.25 (m, 5H, Ph), 3.22 (d, J = 10.3 Hz, 1H, H7), 2.95 (ddm, J = 2.3, 10.4 Hz, 2H, H2 and H6$_e$ overlapped), 2.59 (td, J = 2.8, 11.9 Hz, 1H, H6$_a$), 1.60-1.49 (m, 2H, H4 and H5), 1.35-1.22 (m, 1H, H5), 1.20-1.07 (m, 2H, H3 and H4), 0.94-0.81 (m, 1H, H3) ppm; ^{13}C NMR (NaOD/D_2O, 100 MHz) δ 180.5 (0, C14), 139.1 (0,

C8), 128.6 (1, 2C, C9 and C13), 128.4 (1, 2C, C10 and C12), 127.0 (1, C11), 61.6 (1, C7), 58.5 (1, C2), 45.8 (2, C6), 28.6 (2, C3), 24.6 (2, C5), 23.7 (2, C4) ppm.

Method B:[2] A round bottom flask was at ambient temperature open to air charged with 2-phenyl-2-(piperidin-2-yl)acetate (methylphenidate, 104 mg, 0.44 mmol) and ethanol (absolute, 0.95 mL) and the heterogeneous mixture was treated with aq. KOH (20% wt, 0.95 mL) to give clear mixture which was allowed to further stir for 19.3 h after which time the EtOH was removed and the crude mixture treated with hydrochloric acid (4 M, aq.) dropwise until the precipitate started forming at pH 5. Precipitate was washed with ice-cold water and dried to afford the title compound (39.5 mg, 0.18 mmol, 40%) as colourless prisms.

Method C:[3] A round bottom flask was at ambient temperature open to air charged with 2-phenyl-2-(piperidin-2-yl)acetate (methylphenidate, 151 mg, 0.64 mmol) and tetrahydrofuran:water (7.5:1) mixture (1 mL) was added followed by lithium hydroxide monohydrate (105 mg, 2.5 mmol) and the resulting heterogeneous mixture was allowed to further stir for 19.3 h during which time mixture formed two phases. After this time THF was removed and the crude mixture was diluted with water (1 mL) and then treated with hydrochloric acid (4 M, aq.) to adjust pH to 7. After ca. 5 min precipitate started forming. The colorless prisms were collected, washed with ice-cold water and dried to afford the title compound (50.8 mg, 0.23 mmol, 36%). These crystals were used for the crystal structure analysis.

References

(1) Misra, M.; Shi, Q.; Ye, X.; Gruszecka-Kowalik, E.; Bu, W.; Liu, Z.; Schweri, M. M.; Deutsch, H. M.; Venanzi, C. A. Quantitative structure-activity relationship studies of *threo*-methylphenidate analogs. *Bioorg. Med. Chem.* **2010**, *18*, 7221-7238.

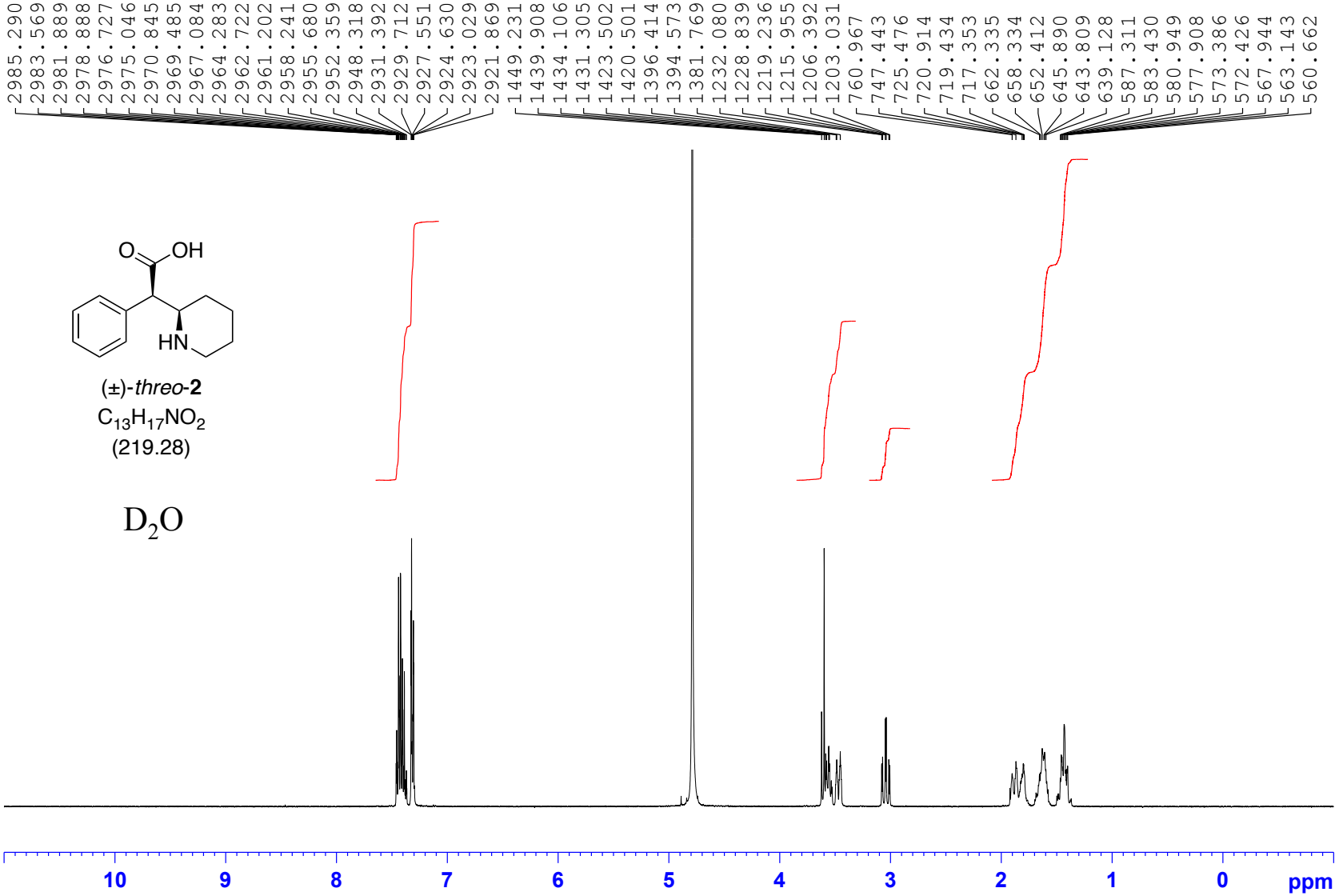
(2) Kato, D.; Mitsuda, S.; Ohta, H. Microbal deracemization of alpha-substituted carboxylic acids: substrate specificity and mechanistic investigation. *J. Org. Chem.* **2003**, *68*, 7234-7242.

(3) Iliev, B.; Linden, A.; Kunz, R.; Heimgartner, H. 14-Membered cyclodepsipeptides with alternating beta-hydroxy and alpha-amino acids by cyclodimerization. *Tetrahedron* **2006**, *62*, 1079-1094.

Supporting Information: ^{1}H and ^{13}C NMR Spectra

^{1}H NMR spectra were recorded in Fourier transform mode at the field strength specified using standard 5 mm diameter tubes. Chemical shifts in ppm is quoted relative to residual solvent signals calibrated as follows: D_2O δ_H (H_2O) = 4.79 ppm. Unless otherwise stated spectra were collected at ambient temperature.

SDM-V-033CR, D2O, 400MHz, 24.08.2012.



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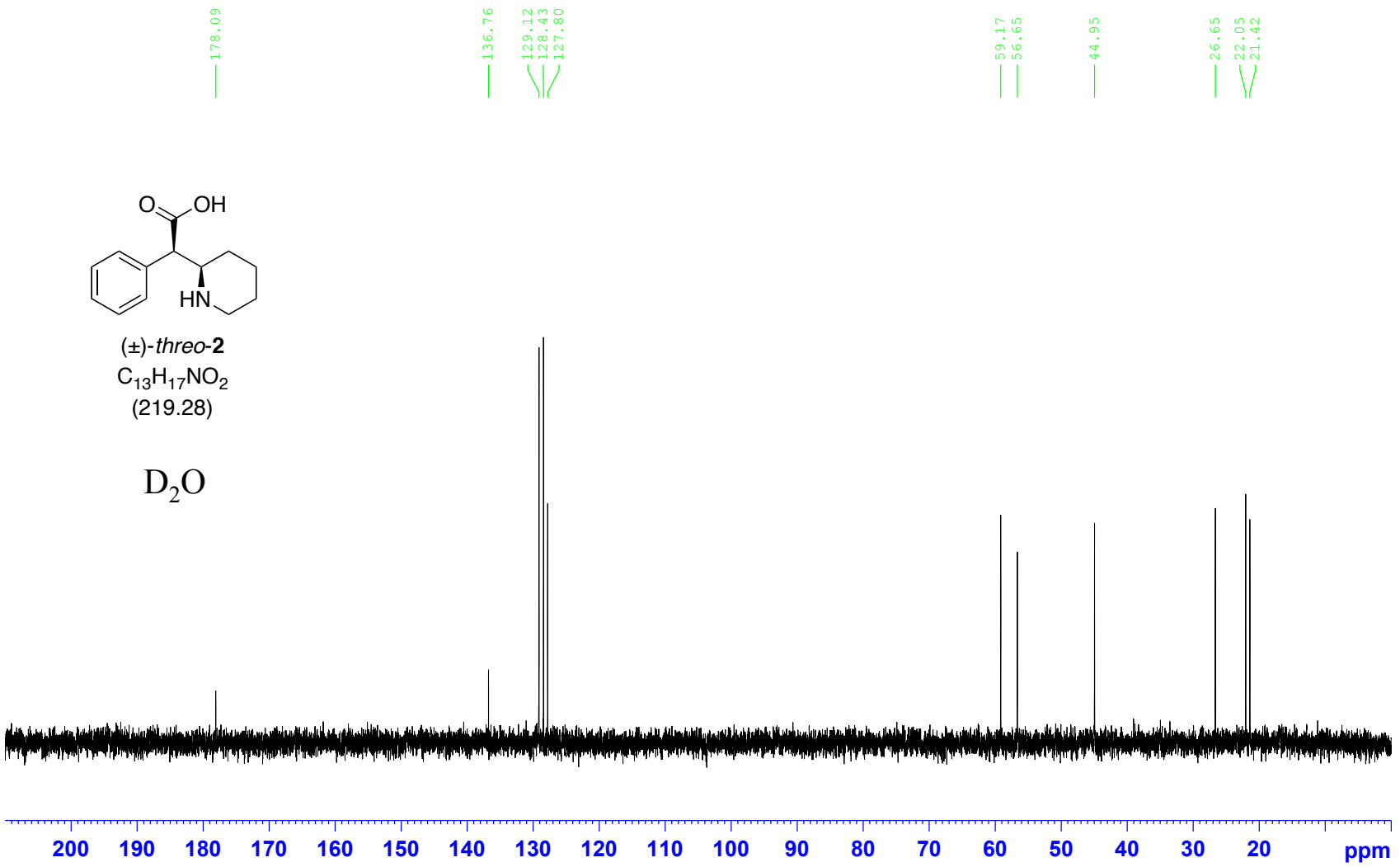

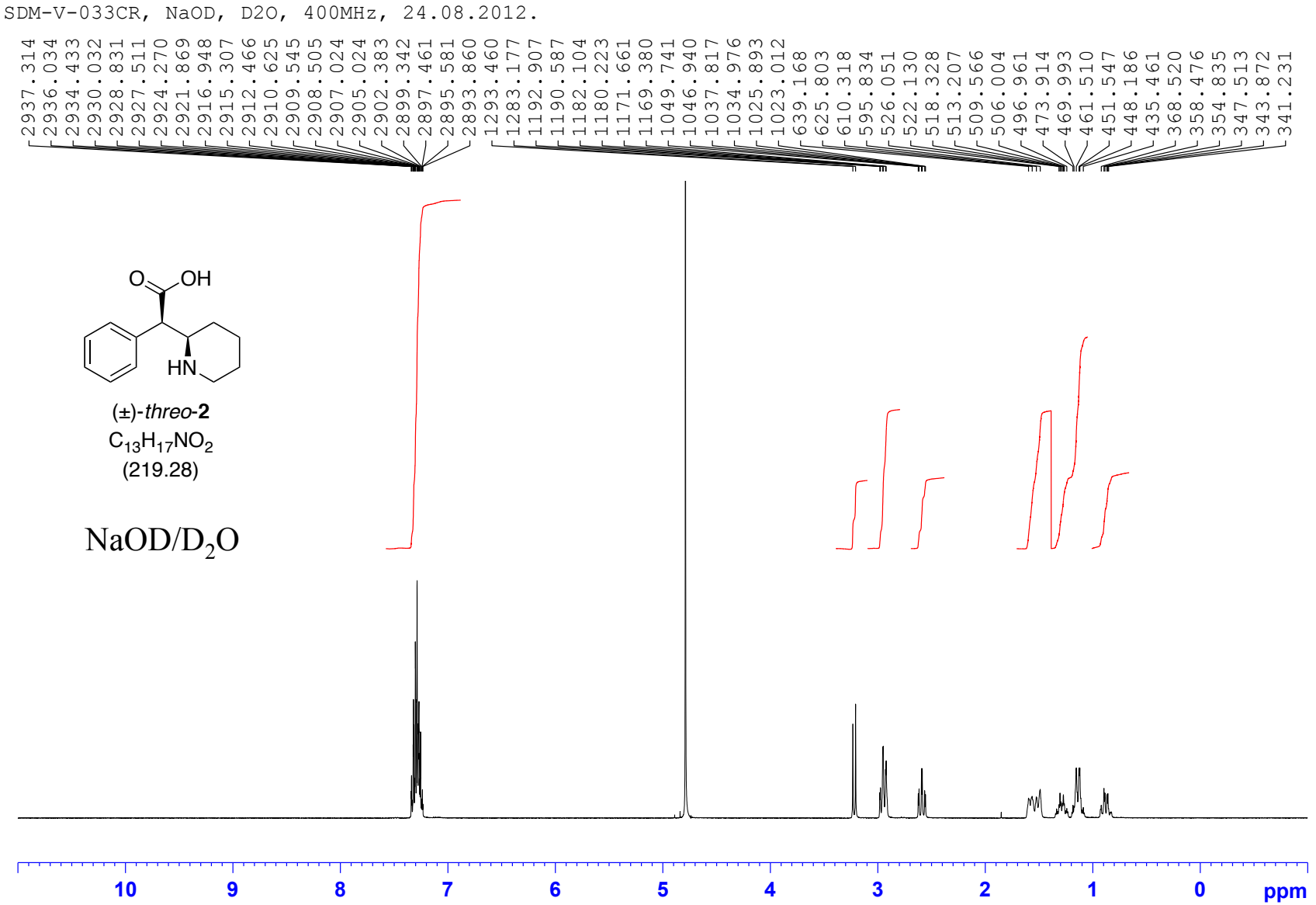
SDM-V-033CR, NaOD, D2O, 400MHz, 24.08.2012.
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2930.032
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2924.270
2921.869
2916.948
2915.307
2912.466
2910.625
2909.545
2908.505
2907.024
2905.024
2902.383
2899.342
2897.461
2895.581
2893.860
1293.460
1283.177
1192.907
1190.587
1182.104
1180.223
1171.661
1169.380
1049.741
1046.940
1037.817
1034.976
1025.893
1023.012
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625.803
610.318
595.834
526.051
522.130
518.328
513.207
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473.914
469.993
461.510
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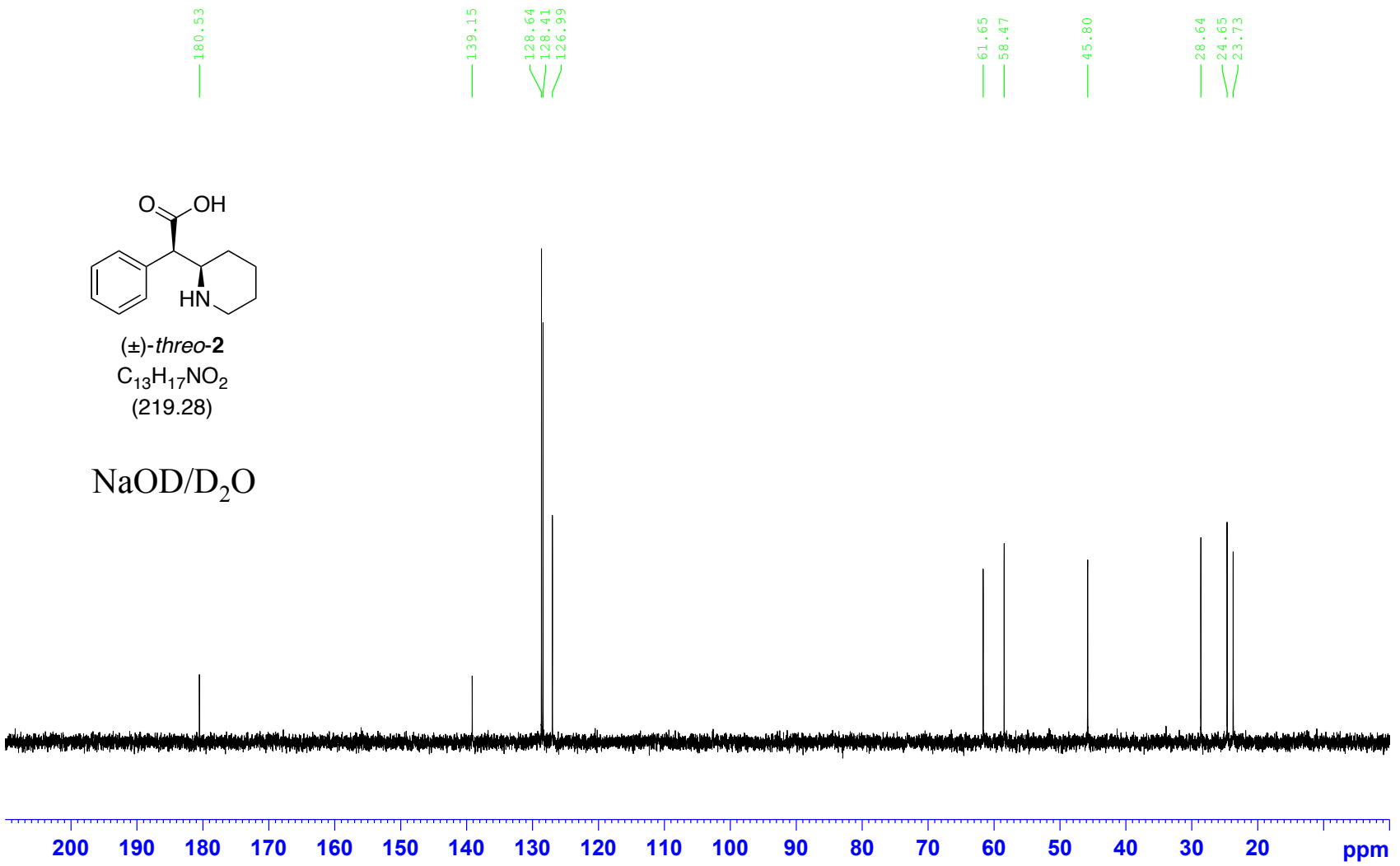
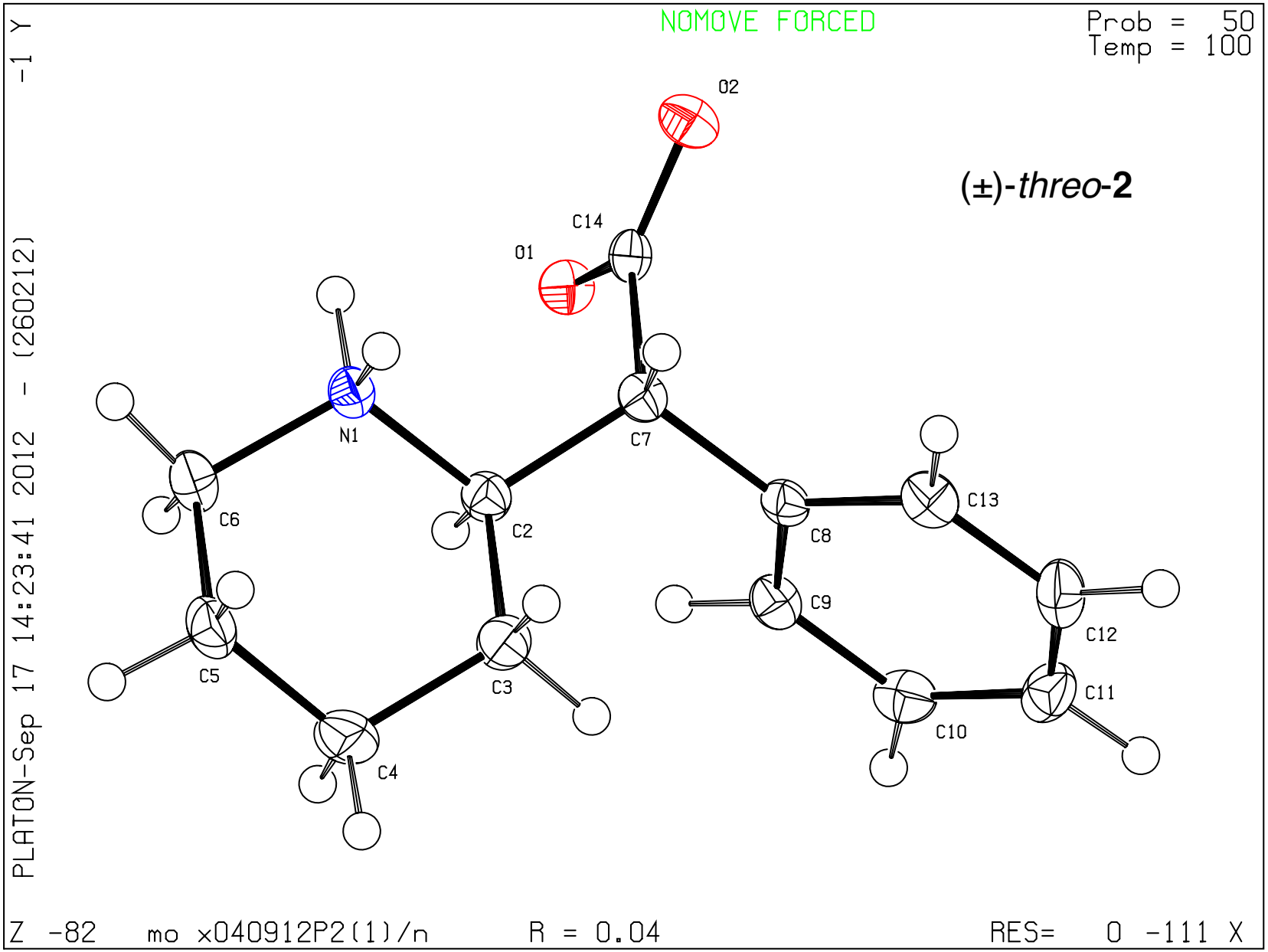
448.186
435.461
368.520
358.476
354.835
347.513
343.872
341.231
O
OH
HN
(±)-threo-2
C13H17NO2
(219.28)
NaOD/D2O
10
9
8
7
6
5
4
3
2
1
0
ppm

SDM-V-033CR, NaOD/D2O, 100MHz, 27.08.2012., not calibrated

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Temp = 100
(±)-threo-2
O2
C14
O1
N1
C7
C6
C2
C8
C13
C9
C12
C5
C3
C11
C10
C4
-1 Y
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Z -82 mo x040912P2(1)/n R = 0.04
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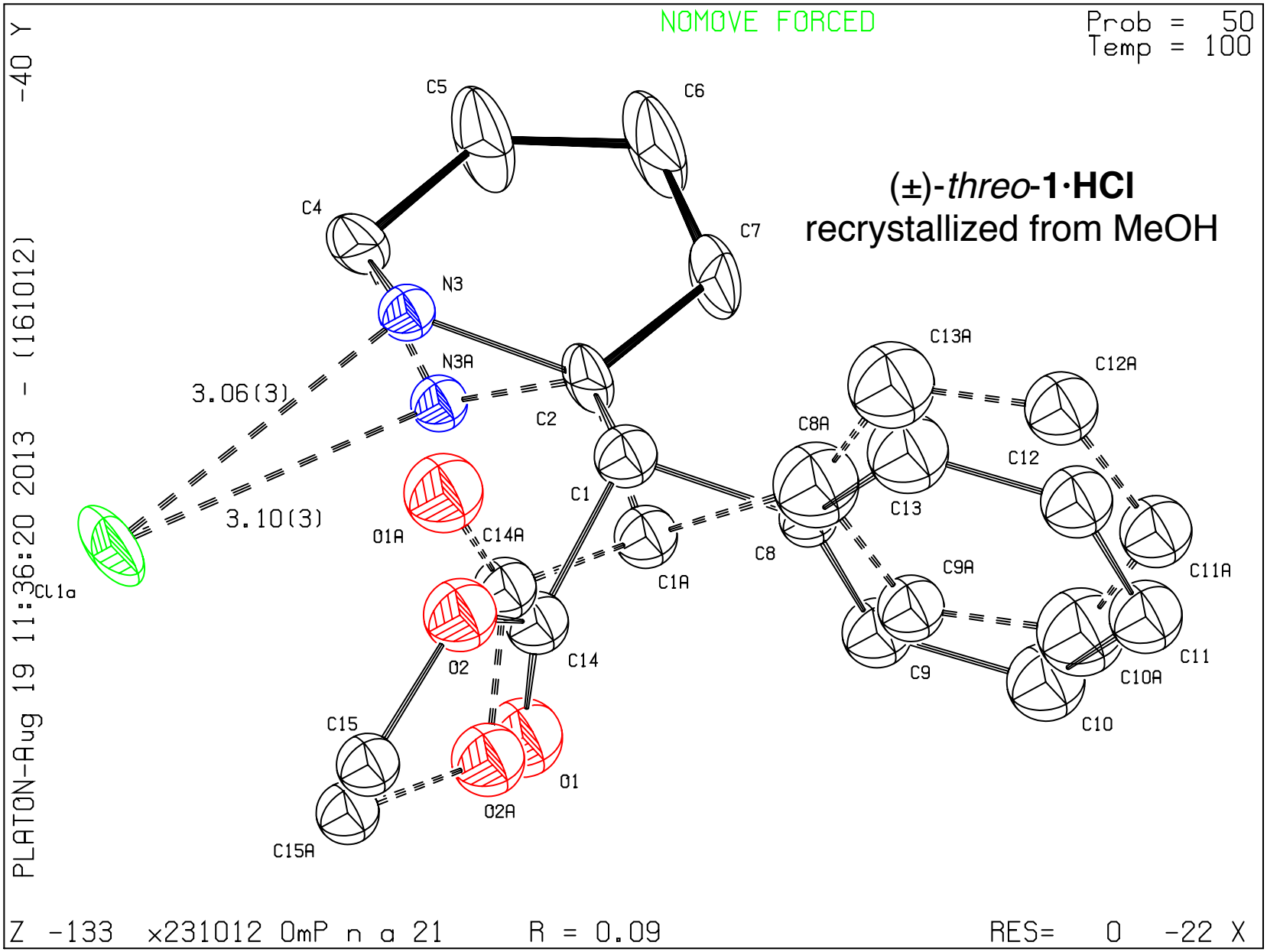
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(±)-*threo*-**1**·**HCl**
recrystallized from MeOH
PLATON-Aug 19 11:36:20 2013 - (161012)
-40 Y
C5
C6
C4
C7
N3
N3A
3.06(3)
3.10(3)
C2
C1
C13A
C12A
C8A
C12
C13
C1A
C8
C9A
C11A
Cl1a
O1A
C14A
C9
C11
C10A
O2
C14
C10
C15
O1
O2A
C15A
Z -133 x231012 0mP n a 21
R = 0.09
RES= 0 -22 X

(±)-*threo*-**1·HCl**