Supplementary information

for

Asymmetric synthesis of 2-azabicyclo[3.3.1]nonanes by a microwave-assisted organocatalyzed tandem desymmetrization and intramolecular aldolization

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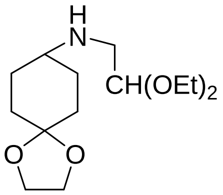
Contents

I) Experimental section

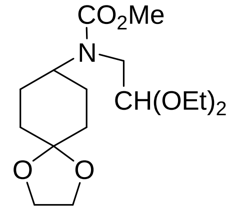
General procedures. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution. Chemical shifts are reported as δ values (ppm) relative to internal Me_4Si. Infrared spectra were recorded on a Nicolet 320 FT-IR spectrophotometer. TLC was performed on SiO_2 (silica gel 60 F_{254}, Merck). The spots were located by UV light, a 1% $KMnO_4$ aqueous solution or a 1.5% K_2PtCl_6 aqueous solution. Chromatography refers to flash chromatography and was achieved on SiO_2 (silica gel 60, SDS, 230–400 mesh). All reactions were carried out under an argon atmosphere. Drying of the organic extracts during the work-up of reactions was performed over anhydrous Na_2SO_4. HPLC analyses for the determination of enantiomeric excess were carried out using a DAICEL CHIRALPAK IC column (250×4.6 mm I.D., 5 µm; Chiral Technologies Europe) on a Waters model 2487 Dual Absorbance Detector and set at the wavelength of 290 nm. The chromatog. resoln. of compound **4** was achieved using CH_2Cl_2/MeOH 99: 1 as the mobile phase in an isocratic run. Microwave irradiation experiments were performed using a single-mode Discover System from CEM Corporation using standard Pyrex vessel (capacity 10 mL).

N-(2,2-Diethoxyethyl)-4-aminocyclohexanone ethylene acetal (2)



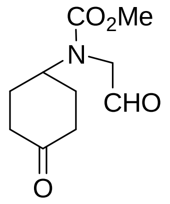
A mixture of cyclohexanedione monoethylene acetal (5 g, 31.05 mmol), 2,2-diethoxyethylamine (5.70 mL, 38.42 mmol) and molecular sieves (8 g) in CH_2Cl_2 (60 mL) was stirred at rt for 4 h. The reaction mixture was filtered on a celite pad and concentrated to yield the corresponding imine. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 1.22 (t, 6H, *J* = 7.1 Hz, CH_3), 1.84 (m, 4H), 2.46 (m, 4H), 3.50 (d, 2H, J = 5.40 Hz), 358 (m, 2H), 3.72 (m, 2H), 3.99 (s, 4H), 4.74 (t, 1H, *J* = 5.4 Hz); **^{13}C NMR (**$CDCl_3$, 75 MHz): δ 15.3 (CH_3), 25.3 (CH_2), 34.0 (CH_2), 34.9 (CH_2), 36.2 (CH_2), 54.3 (CH_2), 62.5 (CH_2), 64.3 (CH_2), 102.8 (CH), 107.9 (C), 172.6 (C=N). The residue was dissolved in MeOH (100 mL) and treated with $NaBH_4$ (2.3 g, 62.09 mmol) at 0 ºC then at rt overnight. Finally the mixture was concentrated, brine was added and the aqueous extracted with CH_2Cl_2. The organics were dried and concentrated to yield amine **2** in a quantitative yield and enough pure to be used in the next step without further purification. An analytical sample was obtained by chromatography (CH_2Cl_2-CH_2Cl_2/MeOH 97:3). **2**: **IR** (NaCl, neat): 3325, 2973, 2935, 2877, 1446, 1376, 1343, 1275, 1237, 1107, 1063, 1036, 922, 854, 733, 664 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 1.21 (t, 6H, *J* = 7.2 Hz, CH_3), 1.37 (brs, 1H, NH), 1.45 (m, 2H), 1.55 (td, 2H, *J* = 12.6, 3.6 Hz), 1.77 (m, 2H), 1.87 (m, 2H), 2.54 (tt, 1H, *J* = 9.6, 3.6 Hz), 2.74 (d, 2H, *J* = 5.6 Hz), 3.54 (dq, 2H, *J* = 9.2, 7.2 Hz), 3.70 (dq, 2H, *J* = 9.2, 7.2 Hz), 3.93 (s, 4H), 4.58 (t, 1H, *J* = 5.6 Hz); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 15.3 (CH_3), 30.1 (CH_2), 32.9 (CH_2), 49.5 (CH_2), 55.0 (CH), 62.2 (CH_2), 64.1 (CH_2), 64.2 (CH_2), 102.4 (CH), 108.6 (C). **HRMS** (ESI-TOF): Calcd for $C_{14}H_{28}NO_4$ 274.2012 (M^++1). Found 274.2012.

N-(2,2-Diethoxyethyl)-*N*-(methoxycarbonyl)-4-aminocyclohexanone ethylene acetal (3)



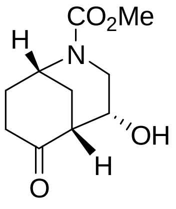
A mixture of amine **2** (8.5 g, 31.05 mmol), methyl chloroformate (4.85 mL, 62.1 mmol) and K_2CO_3 (8.58 g, 62.1 mmol) in CH_3CN (200 mL) was stirred at rt overnight. The solvent was then removed, brine was added and the aqueous extracted with CH_2Cl_2. The organics were dried, concentrated and the residue purified by chromatography (CH_2Cl_2-CH_2Cl_2/MeOH 99:1) to yield **3** as a colourless oil (8.74 g, 85%). **IR**: (NaCl, neat): 2974, 2947, 2879, 1700, 1452, 1402, 1372, 1344, 1287, 1247, 1158, 1100, 1064, 982, 930,812, 774 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 1.20 (t, 3H, *J* = 7.0 Hz, CH_3), 1.54-1.94 (m, 8H), 3.25 (brs, 2H), 3.52 (brs, 2H), 3.71 (brs, 5H), 3.92 (s, 4H), 4.62 (brs, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 15.3 (CH_3), 27.5 and 27.9 (CH_2), 34.0 (CH_2), 46.9 and 48.0 (CH_2), 52.4 (CH_3), 55.7 (CH), 63.3 (CH_2), 64.3 (CH_2),101.5 and 102.0 (CH), 107.8 (C), 156.6 (CO). **HRMS** (ESI-TOF) Calcd for $C_{16}H_{29}NO_6Na$ 354.1887 (M^++Na). Found 354.1887.

N-(Methoxycarbonyl)-N-(2-oxoethyl)-4-aminocyclohexanone (1)



A solution of carbamate **3** (2 g, 6 mmol), THF (30 mL) and 5% HCl (60 mL) was stirred at rt for 10 min then it was extracted with CH_2Cl_2. The organics were dried and concentrated to yield ketoaldehyde **1** (1.2 g, 95%) enough pure to be used in the next step without further purification. An analytical sample was obtained by chromatography (CH_2Cl_2/AcOEt 1:1). **IR** (NaCl, neat): 2956, 2875, 2832, 2717, 1700, 1453, 1406, 1369, 1328, 1296, 1222, 1191, 1134, 1097, 997, 953, 775 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 1.74 (brs, 2H), 2.09 (m, 2H), 2.39-2.60 (m, 4H), 3.72 and 3.80 (2s, 3H, CH_3), 3.90 and 3.97 (2s, 2H), 4.41 and 4.63 (2brs, 1H), 9.56 (s, 1H, CHO); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 29.7 and 30.1 (CH_2), 39.6 (CH_2), 52.2 and 52.6 (CH_2), 53.1 (CH_3), 53.1 and 53.4 (CH), 156.0 and 156.6 (CO), 198.0 (CHO), 208.8 (CO); **HRMS** (ESI-TOF) Calcd for $C_{10}H_{15}NO_4Na$ 236.0893 (M^++Na). Found: 236.0893.

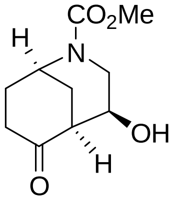
(1*RS*,4*SR*,5*SR*)-4-Hydroxy-2-methoxycarbonyl-2-azabicyclo[3.3.1]nonan-6-one (*rac*-4)



A solution of carbamate **3** (1 g, 3 mmol), THF (20 mL) and 10% HCl (40 mL) was stirred at rt for 4 h. The mixture was then extracted with CH_2Cl_2, the organics were dried and the solvent removed to yield ***rac*-4** (0.56 g, 87%). An analytical sample was obtained by chromatography (CH_2Cl_2/AcOEt 1:1). **IR** (NaCl, neat): 3413, 3008, 2953, 2926, 2872, 1698, 1450, 1403, 1341, 1300, 1263, 1217, 1192, 1121, 1106, 1087, 1070, 1037, 978, 942, 753 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz, gCOSY): δ 1.90-2.24 (m, 4H), 2.46 (dt, 1H, *J* = 18, 8.4 Hz, H-7ax), 2.59 (ddd, 1H, *J* = 18, 9.2, 4.8 Hz, H-7eq), 2.82 (brs, 1H, H-5), 2.89 (t, 1H, *J* = 12.4 Hz, H-3ax), 3.24 and 3.27 (2d, 1H, *J* = 5.6 Hz, OH), 3.73 (s, 3H, CH_3), 3.98 (brs, 1H, H-4), 4.23 and 4.37 (2dd, 1H, *J* = 13.2, 6 Hz, H-3eq), 4.45 and

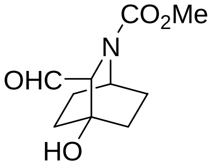
4.61 (2brs, 1H, H-1); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 27.7 and 28.6 (C-9), 29.4 and 29.9 (C-8), 38.3 (C-7), 43.4 and 43.7 (C-1), 45.9 and 46.1 (C-3), 49.4 (C-5), 52.8 (CH_3), 67.4 and 67.7 (C-4), 156.0 (CO), 212.3 and 213.2 (C-6). **HRMS** (ESI-TOF) Calcd for $C_{10}H_{16}NO_4$ 214.1073 (M^++H). Found 214.1074.

(1*R*,4*S*,5*S*)-4-Hydroxy-2-methoxycarbonyl-2-azabicyclo[3.3.1]nonan-6-one (4).



In a 10 mL vessel was placed ketoaldehyde **1** (0.1 g, 0.47 mmol), catalyst C (43 mg, 0.12 mmol, 25%), acetonitrile (1ml) and water (0.08 mL, 4.4 mmol). The mixture was subsequently heated with stirring to 100 ºC using microwave irradiation for 15 min. After concentration, the reaction mixture was purified by chromatography (CH_2Cl_2/AcOEt 1:1) to give **4** (70 mg, 70%) as a viscous colourless oil: HPLC (Daicel Chiralpak IC, CH_2Cl_2/MeOH 99:1, 1 mL min^{-1}, λ = 290 nm; major isomer t = 8.48 min, minor isomer 9.63 min, 70% ee). **4**: $[\alpha]_D^{23}$ = -74 (c = 1.7, $CHCl_3$).

Methyl 3-Formyl-4-hydroxy-2-azabicyclo[2.2.2]octane-2-carboxylate (*rac*-5).

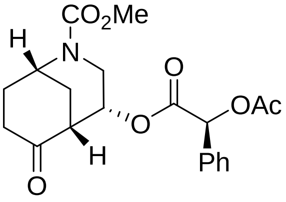


A mixture of ketoaldehyde **1** (0.1 g, 0.47 mmol), CH_2Cl_2 (25 mL), K_2CO_3 (0.2 g, 3.6 mmol), THF (10 mL) and H_2O (25 ml) was shaken for about 4 minutes then it was extracted with CH_2Cl_2. The organics were dried and concentrated to yield pure isoquinuclidine ***rac*-5** as a colourless viscous oil (88 mg, 88%). An analytical sample was obtained by chromatography (CH_2Cl_2/AcOEt 1:1). **IR** (NaCl, neat): 3416, 2954, 2917, 2872, 2722, 1733, 1680, 1453, 1396, 1336, 1249, 1193, 1141, 1104, 1037, 1007, 957, 772, 734 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz, gCOSY): δ 1.50-2.16 (m, 8H), 2.62 and 2.79 (2brs, 1H, OH), 3.70 and 3.75 (2s, 3H, CH_3), 3.94 and 4.03 (2brs, 1H, H-3), 4.10 and 4.24 (2brs, 1H, H-1), 9.71 and 9.72 (2d, 1H, *J* = 1.2 Hz, CHO); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 25.9 and 26.3 (CH_2), 26.4 and 26.6 (CH_2), 28.9 and 29.0 (CH_2), 33.0 and 33.3 (CH_2), 43.7 and 44.3 (C-1), 52.8 and 52.9 (CH_3), 68.4 and 68.8 (C-3), 71.3 and 71.4 (C-4), 154.9 and 155.9 (CO), 204.2 and 204.4 (CHO); **HRMS** (ESI-TOF) Calcd for $C_{10}H_{15}NO_4Na$ 236.0893 (M^++Na). Found 236.0893.

Resolution of (±)-*rac*-4

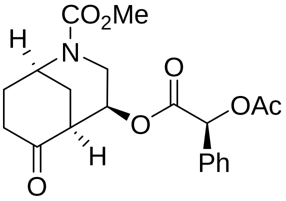
To a solution of **(±)-*rac*-4** (0.08 g, 0.35 mmol) in pyridine (2 mL) was added a solution of (S)-O-acetyl mandeloyl chloride (0.225 g, 1.06 mmol) in CH_2Cl_2 (2mL) dropwise at -5 ºC and the mixture was stirred at this temperature for 3h. The reaction mixture was then quenched with water, extracted with CH_2Cl_2 and the organics were dried and concentrated. After chromatography (hexane/AcOEt 1:1) the two diastereomers were obtained almost pure with other intermediate fractions, overall yield 82%.

(1*S*,4*R*,5*R*)-4.AcMA (less polar)

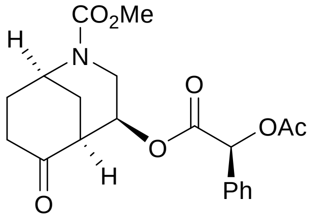


IR (NaCl, neat): 3067, 3016, 2953, 2873, 1747, 1700, 1495, 1448, 1409, 1374, 1342, 1300, 1230, 1107, 1047, 957, 754, 698 cm^{-1}; **^{1}H NMR** (CDCl$_3$, 400 MHz, 55 ºC, gCOSY): δ 1.90-2.07 (m, 3H), 2.18 (m, 1H), 2.20 (s, 3H, CH$_3$), 2.43 (ddd, 1H, *J* = 18, 11.2, 8.4 Hz, H-7ax), 2.52 (dd, 1H, *J* = 18, 8 Hz, H-7eq), 2.83 (brs, 1H, H-5), 3.23 (dd, 1H, *J* = 14, 10 Hz, H-3ax), 3.73 (s, 3H, CH$_3$), 4.31 (brs, 1H, H-3eq), 4.44 (brs, 1H, H-1), 5.10 (dt, 1H, *J* = 9.2, 7.2 Hz, H-4), 5.85 (s, 1H, CHAr), 7.34-7.45 (m, 5H, ArH); **^{13}C NMR** (CDCl$_3$, 100 MHz): δ 20.5 (CH$_3$), 29.9 (C-8), 30.7 (C-9), 38.7 (C-7), 43.7 (C-3), 44.3 (C-1), 47.2 (C-5), 52.9 (CH$_3$), 69.2 (C-4), 74.5 (CHAr), 127.5, 128.8, 129.3 (CHAr), 133.3 (ipso-C), 156.0 (CO), 167.8 (CO), 170.3 (CO), 206.8 (C-6); **HRMS** (ESI-TOF) calcd for $C_{20}H_{23}NO_7Na$ 412.1367 (M$^+$+Na). Found 412.1364.

(1*R*,4*S*,5*S*)-4.AcMA (more polar)



IR (NaCl, neat): 3067, 3012, 2953, 2874, 1752, 1700, 1448, 1408, 1374, 1341, 1300, 1234, 1106, 1084, 1047, 958, 752, 698 cm^{-1}; **^{1}H NMR** (CDCl$_3$, 400 MHz, 55 ºC, gCOSY): δ 1.90-2.08 (m, 3H), 2.15 (m, 1H), 2.15 (s, 3H, CH$_3$), 2.33 (ddd, 1H, *J* = 17.6, 12, 8.8 Hz, H-7ax), 2.56 (dd, 1H, *J* = 17.6, 8 Hz, H-7eq), 2.98 (brs, 1H, H-5), 3.01 (dd, 1H, *J* = 14.4, 10.4 Hz, H-3ax), 3.71 (s, 3H, CH$_3$), 4.21 (dd, 1H, *J* = 13.6, 7.6 Hz H-3eq), 4.43 (brs, 1H, H-1), 5.08 (dt, 1H, *J* = 8.8, 7.2 Hz, H-4), 5.92 (s, 1H, CHAr), 7.34-7.46 (m, 5H, ArH); **^{13}C NMR** (CDCl$_3$, 100 MHz): δ 20.5 (CH$_3$), 29.8 (C-8), 30.7 (C-9), 38.6 (C-7), 43.4 (C-3), 44.3 (C-1), 47.2 (C-5), 52.9 (CH$_3$), 69.3 (C-4), 74.3 (CHAr), 127.7, 128.8, 129.3 (CHAr), 133.8 (ipso-C), 155.9 (CO), 167.7 (CO), 169.9 (CO), 207.0 (CO); **HRMS** (ESI-TOF) calcd for $C_{20}H_{23}NO_7Na$ 412.1367 (M$^+$+Na). Found 412.1364.



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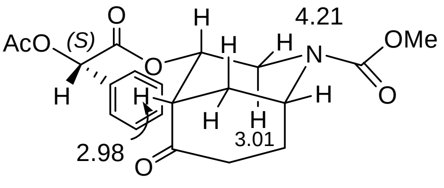
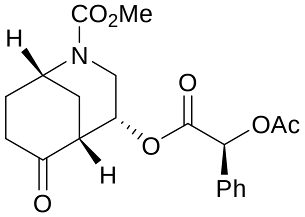
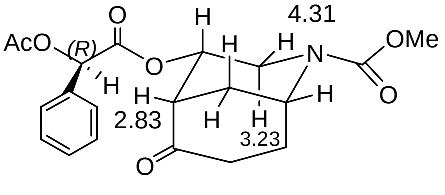


major

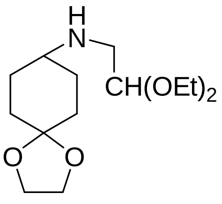


4.AcMA (1*S*,4*R*,5*R*)



ent-minor (the enantiomer was drawn for sake a major clarity)

II) Copies of ^{1}H NMR and ^{13}C NMR spectra of compounds 1-5



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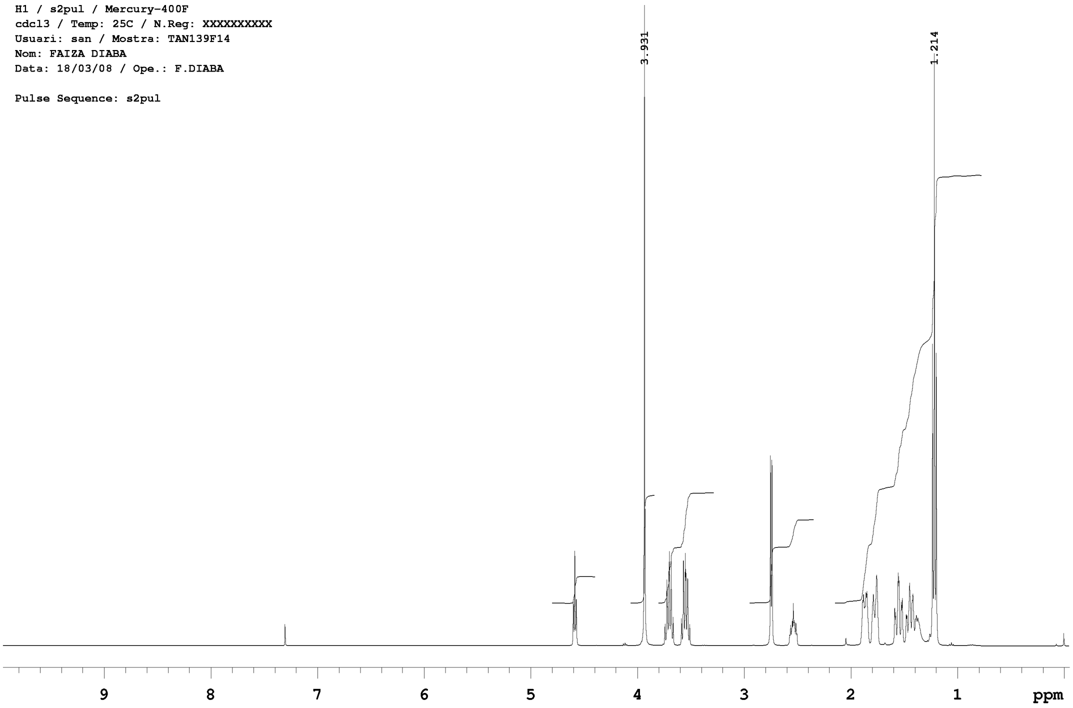

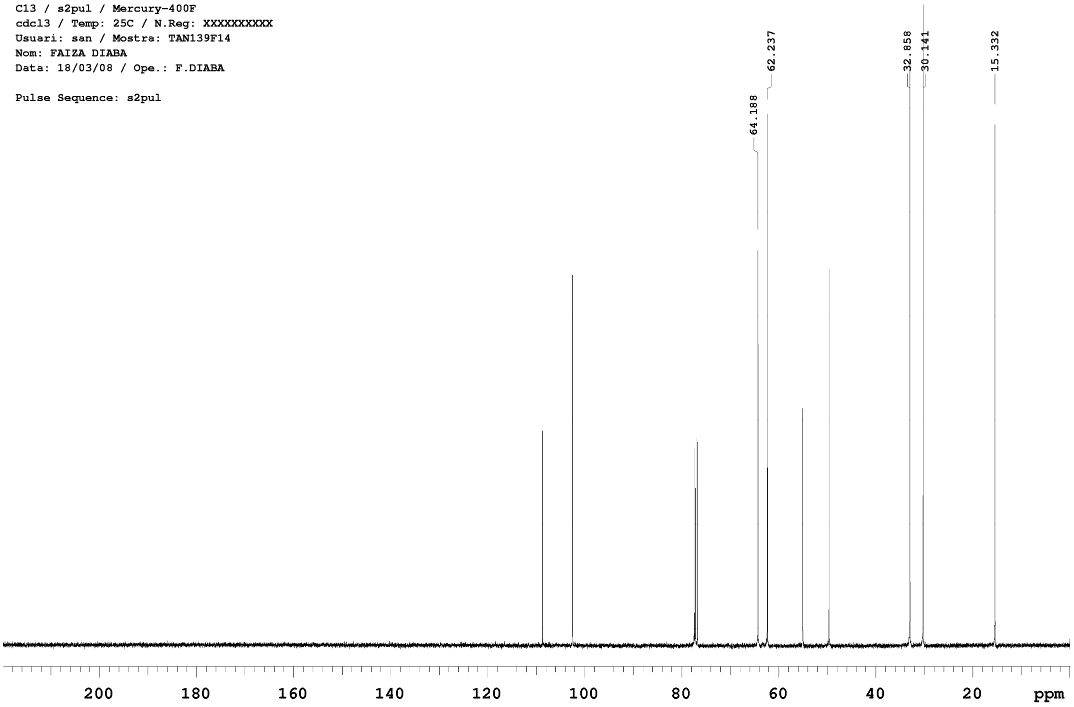

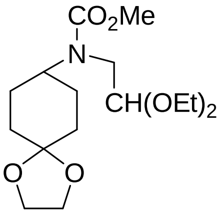

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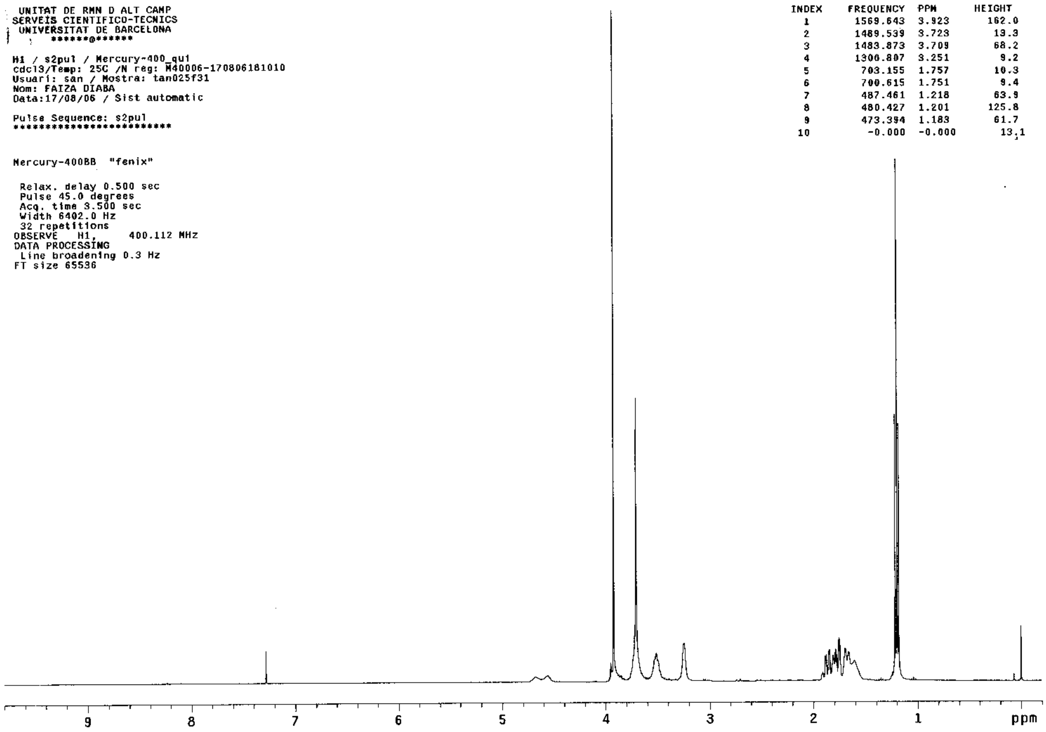

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Data:17/08/06 / Sist automatic

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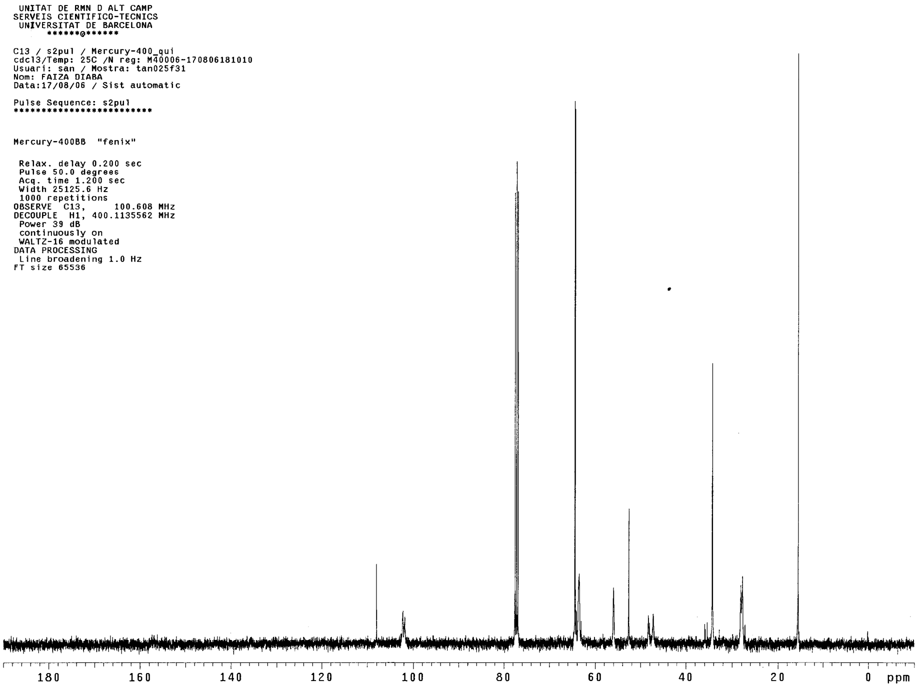

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 UNIVERSITAT DE BARCELONA
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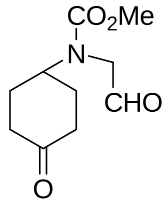
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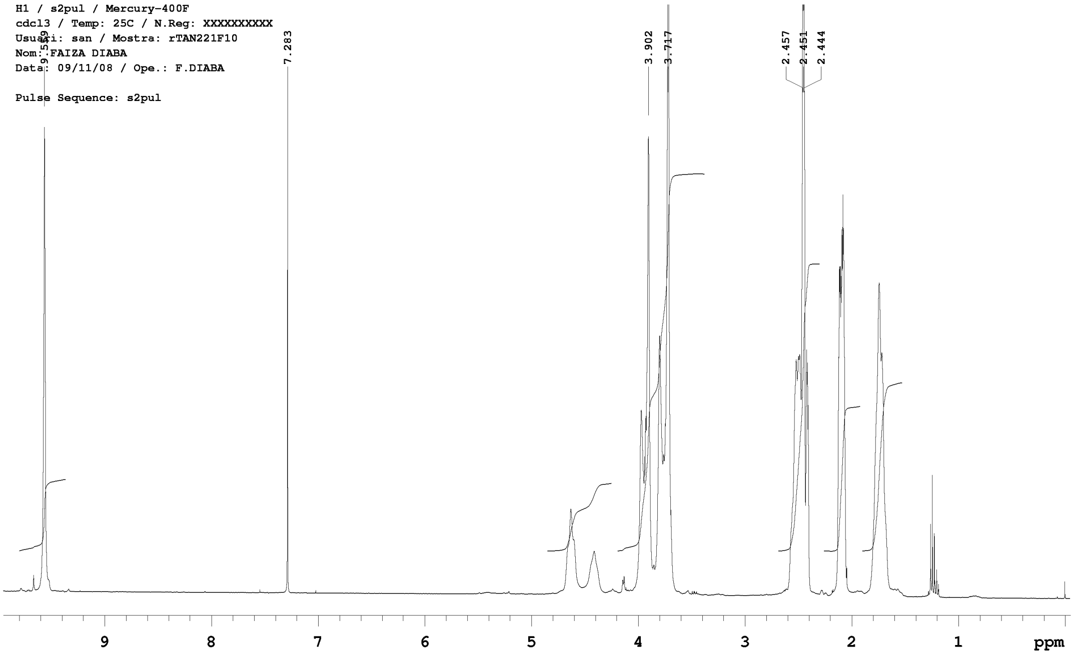
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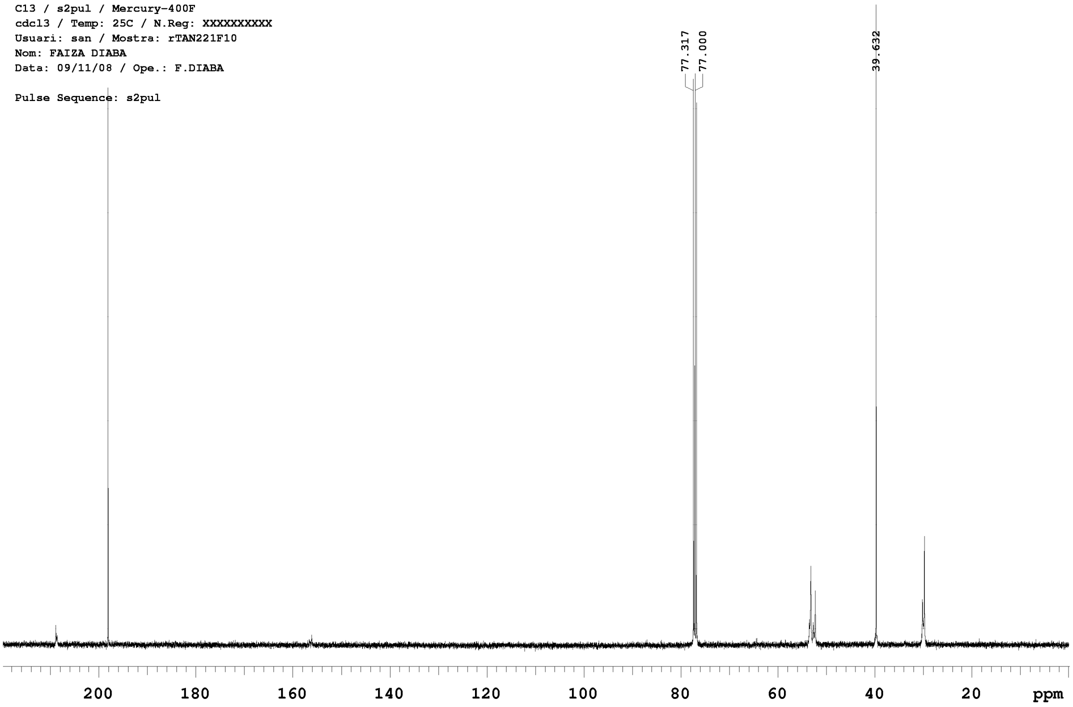
ppm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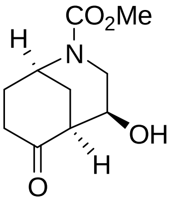
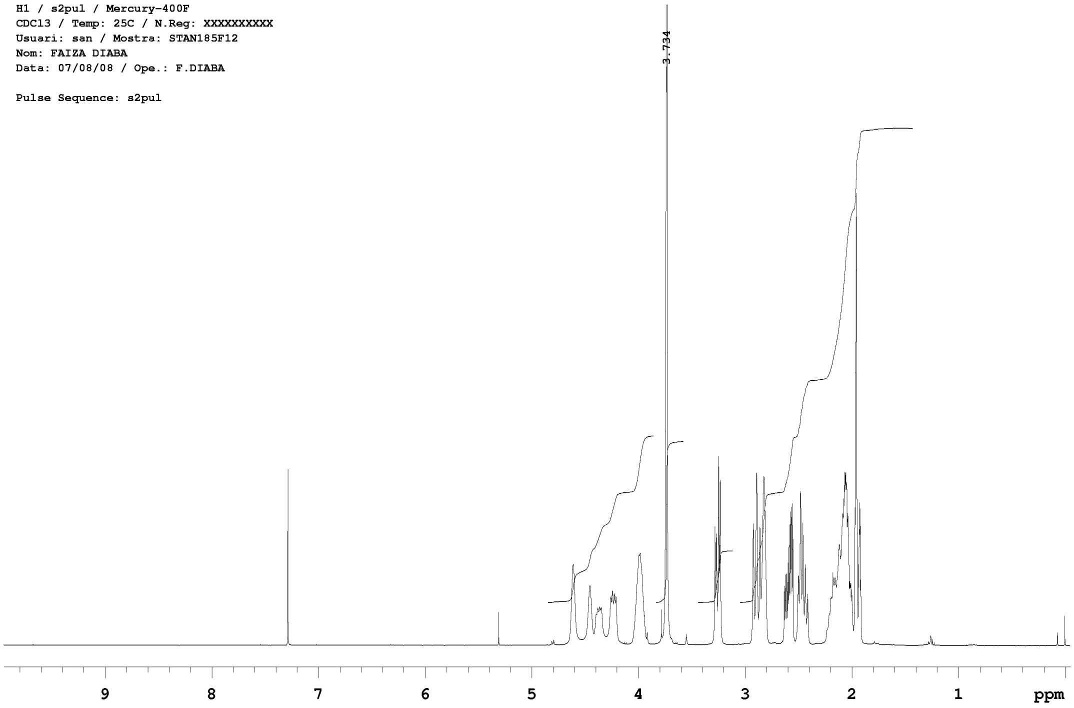
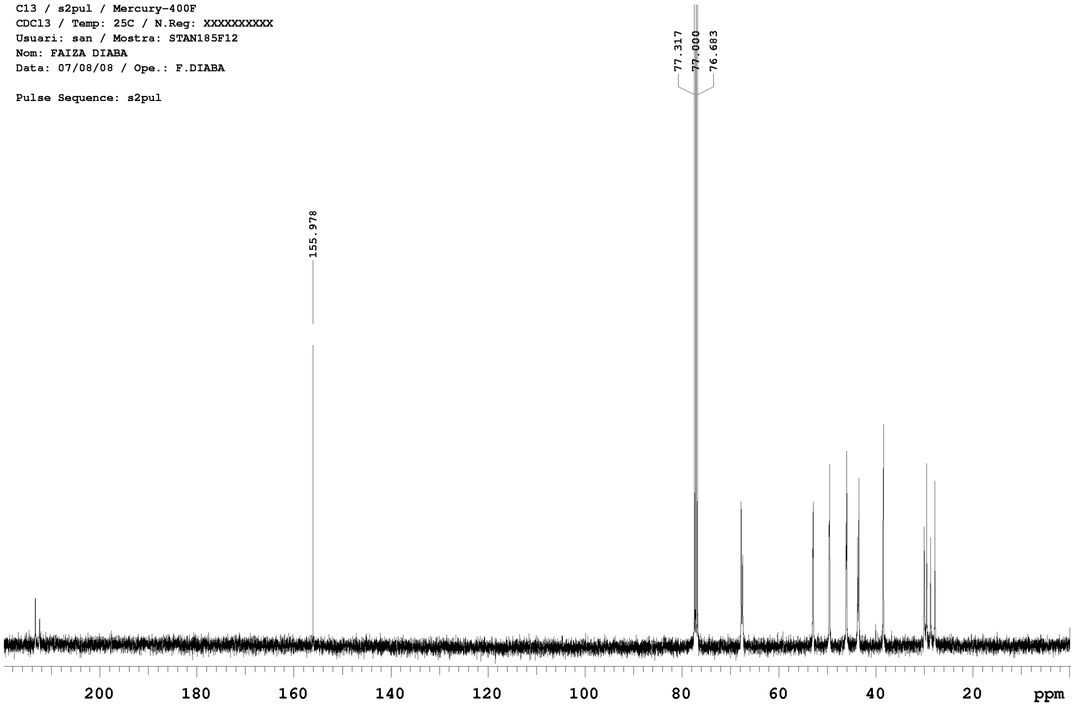
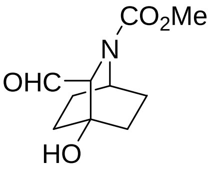
20
ppm


CO2Me
H
N
OH
H
O

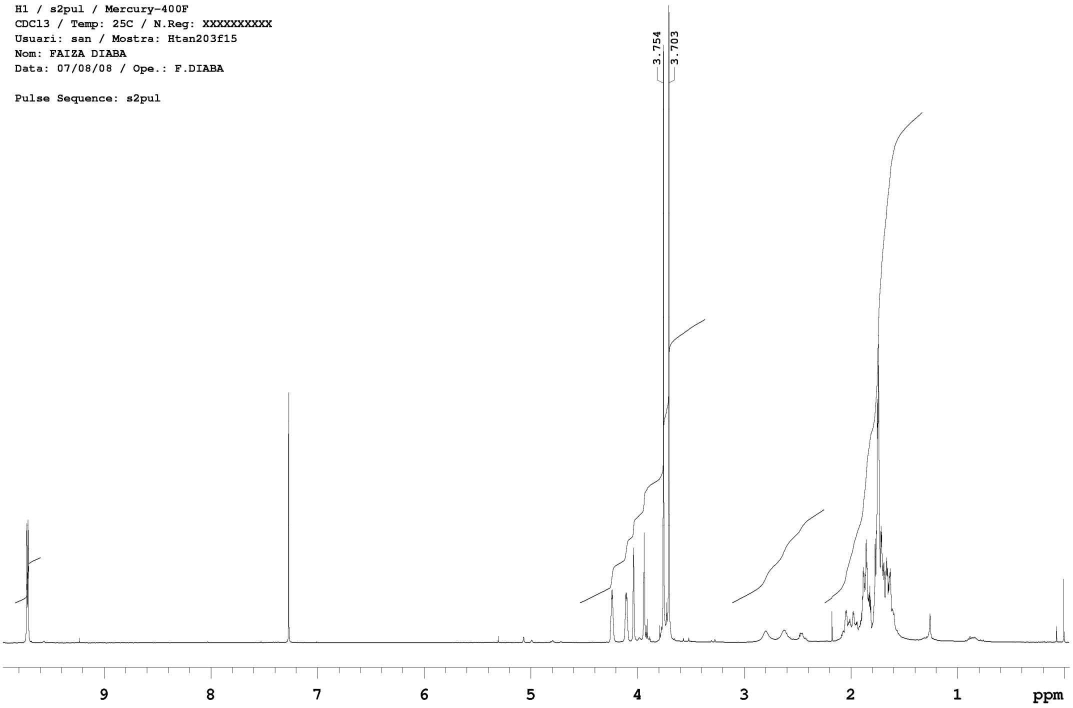
4

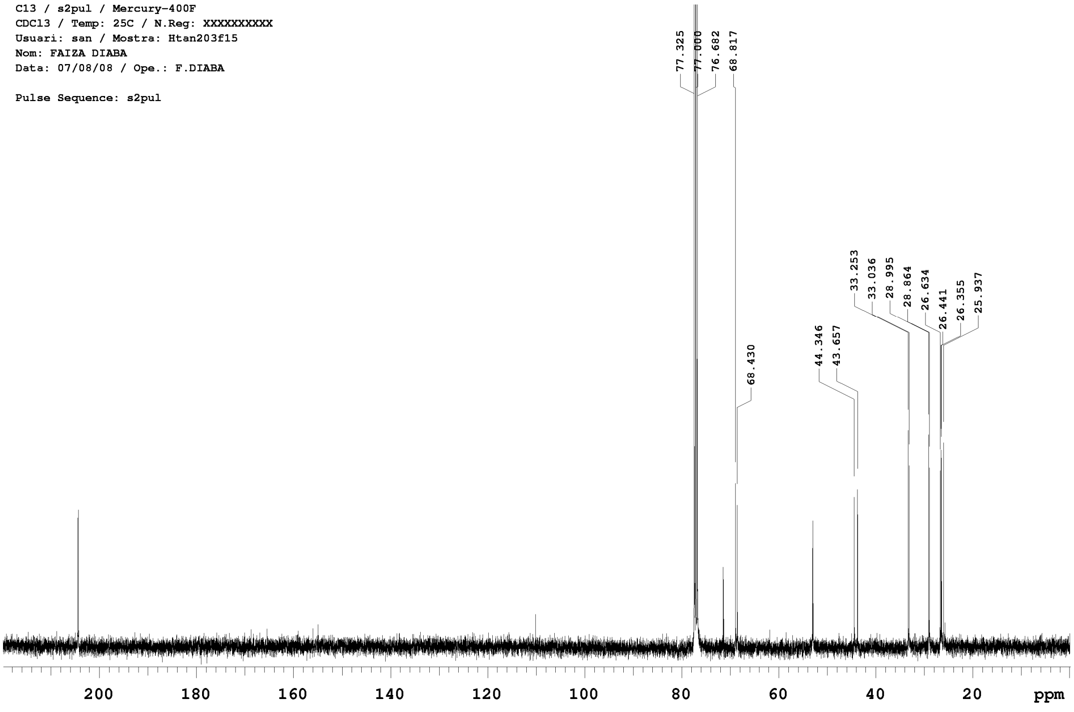

H1 / s2pul / Mercury-400F
CDCl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: STAN185F12
Nom: FAIZA DIABA
Data: 07/08/08 / Ope.: F.DIABA
Pulse Sequence: s2pul
3.734
9
8
7
6
5
4
3
2
1
ppm


C13 / s2pul / Mercury-400F
CDCl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: STAN185F12
Nom: FAIZA DIABA
Data: 07/08/08 / Ope.: F.DIABA
Pulse Sequence: s2pul
155.978
77.317
77.000
76.683
200
180
160
140
120
100
80
60
40
20
ppm


CO2Me
N
OHC
HO

***rac*-5**


H1 / s2pul / Mercury-400F
CDCl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: Htan203f15
Nom: FAIZA DIABA
Data: 07/08/08 / Ope.: F.DIABA
Pulse Sequence: s2pul
3.754
3.703
9
8
7
6
5
4
3
2
1
ppm


C13 / s2pul / Mercury-400F
CDCl3 / Temp: 25C / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: Htan203f15
Nom: FAIZA DIABA
Data: 07/08/08 / Ope.: F.DIABA
Pulse Sequence: s2pul
77.325
77.000
76.682
68.817
68.430
44.346
43.657
33.253
33.036
28.995
28.864
26.634
26.441
26.355
25.937
200
180
160
140
120
100
80
60
40
20
ppm