Electronic Supplementary Material (ESI) for Chemical Communications

Supporting information

for

Cu(I)-Catalyzed Atom Transfer Radical Cyclization of Trichloroacetamides Tethered to Electron-deficient, -neutral, and -rich Alkenes: Synthesis of 2-Azabicyclo[3.3.1]nonanes

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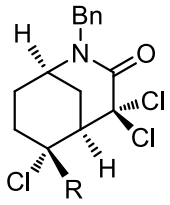
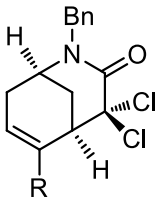
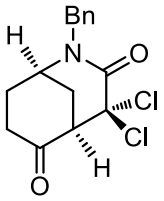
Table 1. ^{13}C NMR chemical shifts of 2-azabicyclo[3.3.1]nonanes **6**,**7**, **9**-**11, 14**[a]



R = CN **6**
CO_2Me **9**
H **10**



R = CN **7**
CO_2Me **14**



11

	6	**7**	**9**	**10**	**11**	**14**
C-1	49.6	48.6	50.3	51.5	51.1	49.3
C-3	163.3	162.9	163.7	164.2	163.9	162.9
C-4	83.0	83.6	84.4	85.4	81.2	85.0
C-5	53.4	45.8	53.0	51.8	63.0	43.1
C-6	59.5	113.4	69.8	57.6	203.5	137.0
C-7	29.7	144.7	26.1	24.4	35.0	131.2
C-8	23.6	31.7	24.2	22.5	30.2	31.2
C-9	26.0	25.9	26.7	24.5	31.1	26.3
Other	118.7	118.4	52.9	-	-	52.3
	(CN)	(CN)	(CH_3)	-	-	(CH_3)
	-	-	170.0	-	-	166.8
	-	-	(CO)	-	-	(CO)
CH_2Ar	49.6	49.7	49.5	49.3	49.7	49.6
Ar(C)	127.9	127.7	127.8	127.8	127.9	127.7
	128.2	128.1	128.0	127.9	128.2	127.9
	129.1	129.0	128.9	128.9	129.1	128.9
	135.6	135.7	136.0	136.1	135.9	136.1

[a] Values were assigned on the basis of gCOSY and gHSQC spectra in $CDCl_3$ (100 MHz).

General. ^{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. All NMR data assignments are supported by COSY and HSQC experiments. 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 or a 1% $KMnO_4$ aqueous solution. Chromatography refers to flash chromatography and was carried out on SiO_2 (silica gel 60, SDS, 230–400 mesh). CuCl (99.99%) was purchased from Sigma-Aldrich and was used as received. All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents and under anhydrous conditions. The reactions were heated using a dry-syn single position heating block and the temperature indicated refers to external temperature. Drying of the organic extracts during reaction work-up was performed over anhydrous Na_2SO_4. Compounds **1**-**5** were synthesized according to our previous published procedures.[1]

General procedures for Atom Transfer Radical Cyclization of trichloroacetamides 1-5.

a) Representative procedure for the $Tp^{x}Cu$ complex radical cyclization. A solution of trichloroacetamide **2** (100 mg, 0.282 mmol), and the corresponding $Tp^{tBu}Cu(NCMe)$ complex (1.25 mg from 0.5 mL of a stock solution,[2] $2.82x10^{-3}$ mmol from a stock solution, 0.01 equiv) and AIBN (4.2 mg, 0.1 equiv) were dissolved in toluene (0.75 mL, 1.25 mL as total volume of solvent). The flask was sealed with a Teflon screw cap and removed from the globe box. The reaction mixture was stirred at 60 ºC for 14 h, worked up, and purified by chromatography (hexane/CH_2Cl_2) to give **9** (80 mg, 80%).

b) Representative procedure for the CuCl radical cyclization in DCE. To a suspension of CuCl (20 mg, 0.2 mmol) in 1,2-dichloroethane (6.5 mL) were successively added TPMA (58 mg, 0.2 mmol) and nitrile **1** (240 mg, 0.67 mmol), and the mixture was heated at 80 °C for 4 h in a sealed tube. The solution was then allowed to reach rt, concentrated and purified by chromatography (hexane/CH_2Cl_2 1:9 to CH_2Cl_2) to yield morphan **6** as a white solid (200 mg, 83%).

c) Representative procedure for the CuCl radical cyclization in DCE and in the presence of AIBN. To a suspension of CuCl (13.3 mg, 0.13 mmol 10%) in 1,2-dichloroethane (8 mL) were successively added TPMA (38.7 mg, 0.13 mmol), nitrile **1**

[1] a) Quirante, J.; Escolano, C.; Massot, M.; Bonjoch, J. *Tetrahedron* **1997**, *53*, 1391-1402. (b) Quirante, J.; Escolano, C.; Diaba, F.; Bonjoch, J. *Heterocycles* **1999**, *50*, 731-738. (c) Quirante, J.; Escolano, C.; Diaba, F.; Bonjoch, J. *J. Chem. Soc. Perkin Trans 1* **1999**, 1157-1162.

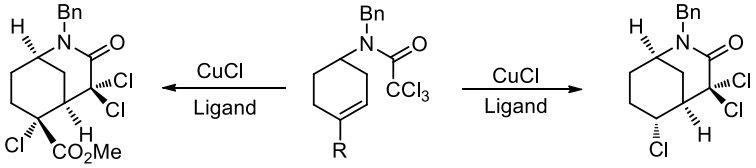
[2] Stock solution was prepared from 5.0 mg of $Tp^{tBu}Cu(NCMe)$ in 2 mL of toluene. (a) Muñoz-Molina, J.M.; Caballero, A.; Díaz-Requejo, M.M.; Trofimenko, S.; Belderraín, T. R.; Pérez, P. J. *Inorg. Chem.* **2007**, *46*, 7725-7730. (b) Muñoz-Molina, J. M.; Belderrain, T. R.; Pérez, P. J. *Inorg. Chem.* **2010**, *49*, 642 –645.

(475 mg, 1.33 mmol), AIBN (109 mg, 0.66 mmol 50%) and the mixture was heated at 60 °C for 2 days in a sealed tube. The solution was then allowed to reach rt, concentrated and purified by chromatography (hexane/CH_2Cl_2 1:9 to CH_2Cl_2) to yield morphan **6** (385 mg, 81%).

d) Representative procedure for the CuCl radical cyclization in DMF. A mixture of CuCl (84 mg, 0.85 mmol, 30%) and nitrile **1** (1 g, 2.80 mmol) in DMF (10 mL) was heated at 80 °C overnight in a sealed tube. The solution was then allowed to reach rt, and water (30 mL), 10 % HCl aqueous solution (10 mL) and AcOEt (50 mL) were successively added. The layers were separated and the aqueous layer was extracted with AcOEt. The combined organic layers were washed with brine, dried and concentrated. After chromatography (hexane/CH_2Cl_2 1:9 to CH_2Cl_2) morphan **6** was isolated (705 mg, 71%).

e) Representative procedure for the CuCl radical cyclization in DMF and in the presence of TPMA. A mixture of CuCl (43 mg, 0.43 mmol, 30%), nitrile **1** (0.5 g, 1.40 mmol) and TPMA (119.3 mg, 0.41 mmol, 30%) in DMF (5 mL) was heated at 80 °C overnight in a sealed tube. The solution was then allowed to reach rt, and water (30 mL), 10 % HCl aqueous solution (10 mL) and AcOEt (50 mL) were successively added. The layers were separated and the aqueous layer was extracted with AcOEt. The combined organic layers were washed with brine dried and concentrated. After chromatography (hexane/CH_2Cl_2 1:9 to CH_2Cl_2) morphan **7** was isolated (270 mg, 60%).

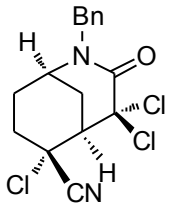
Table 2. Cu(I)-Catalyzed Cyclization of **2** and **3**



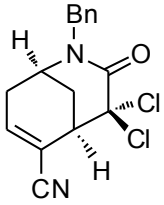
9 **2**, R = CO_2Me; **3**, R = H **10**

Entry Compd	Ligand (equiv)	Additive (equiv)	Solvent (time, Temp)	Products (%)[a]
From **2**				
1	$Tp^{t\,Bu}CuCl$ (0.01)	AIBN (0.1)	Toluene (14 h, 60 ºC)	**9** (70)
2	[$Tp^{tBu}Cu$(NCMe)] (0.01)	AIBN (0.1)	Toluene (14 h, 60 ºC)	**9** (80)
3	CuCl (0.3) TPMA (0.3)	----	DCE (4 h, 80 ºC)	**9** (74)
4	CuCl (0.1) TPMA (0.1)	AIBN (0.5)	DCE (16 h, 60ºC)	**9** (81) **2** (15)
5	CuCl (0.3)	-----	DMF (22 h, 80 ºC)	**9** (67)
6	CuCl (0.3) TPMA (0.3)		DMF (22 h, 80 ºC)	**9** (46) **14**[b] (21)
From **3**				
7	$Tp^{tBu}CuCl$ (0.01)	AIBN (0.1)	Toluene (14 h, 60 ºC)	**10** (60)[c]
8	[$Tp^{tBu}Cu$(NCMe)] (0.1)	AIBN (0.2)	Toluene (24 h, 60 ºC)	**10** (66)
9	CuCl (0.003) TPMA (0.003)	AIBN (0.2)	Toluene (18 h, 60 ºC)	**10** (90)[d]
10	CuCl (0.3) TPMA (0.3)	-----	DCE (4 h, 80 ºC)	**10** (70)
11	CuCl (0.1) TPMA (0.1)	AIBN (0.5)	DCE (48 h 60ºC)	**10** (85)[e]
12	CuCl (0.3)	-------	DMF (16 h, 80 ºC)	**10** (57)

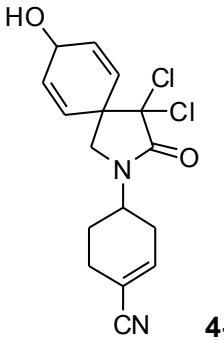
[a]Yields refer to pure isolated products. Unless noted otherwise, reactions were on a 100 mg scale.[b] See S9 of this ESI for the structure of **14.**[c] 200 mg scale.[d] 33 mg scale.[e] 1 g scale.



(1*RS*,5*RS*,6*RS*)-2-Benzyl-4,4,6-trichloro-3-oxo-2-azabicyclo[3.3.1]nonane-6-carbonitrile (6): White solid, mp 139-141 °C; IR (NaCl, neat): 3055, 3034, 2996, 2975, 2949, 2248, 1682, 1492, 1450, 1427, 1366, 1249, 1202, 1188, 1095, 946, 827, 737, 702, 687, 626, 596, 575, 520 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.86 (dm, 1H, *J* = 14.8 Hz, H-8eq), 2.00 (dddd, 1H, *J* = 14.8, 12, 4.8, 2.4 Hz, H-8ax), 2.22 (ddd, 1H, *J* = 15.6, 11.2, 4.4 Hz, H-7ax), 2.29 (dm, 1H, *J* = 15.6 Hz, H-7eq), 2.60 (m, 2H, CH_2-9), 3.38 (m, 1H, H-5), 3.54 (m, 1H, H-1), 4.00 (d, 1H, *J* = 14.8 Hz, CH_2Ar), 5.26 (d, 1H, *J* = 14.8 Hz, CH_2Ar), 7.24-7.40 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 23.6 (C-8), 26.0 (C-9), 29.7 (C-7), 49.6 (C-1 and CH_2Ar), 53.4 (C-5), 59.5 (C-6), 83.0 (C-4), 118.7 (CN), 127.9, 128.2, 129.1 (Ar-CH), 135.6 (*ipso*-C), 163.3 (C-3). HRMS (ESI-TOF): Calcd for $C_{16}H_{16}Cl_3N_2O$ 357.0323 (M^++1). Found 357.0330.



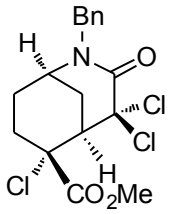
(1*RS*,5*RS*)-2-Benzyl-4,4-dichloro-3oxo-2-azabicyclo[3.3.1]non-6-ene-6-carbonitrile (7): White solid, mp 168-170 °C; IR (NaCl, neat): 3036, 2978, 2953, 2928, 2219, 1658, 1493, 1452, 1435, 1415, 1365, 1323, 1261, 1226, 1203, 1066, 1029, 981, 953, 877, 841, 832, 747, 702, 690, 670, 614, 578 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.95 (ddd, 1H, *J* = 14, 4, 2 Hz, H-9), 2.41 (dddd, 1H, *J* = 20.4, 4.4, 2.8, 1.6 Hz, H-8ax), 2.57 (dd, 1H, *J* = 20.4, 4.4 Hz, H-8eq), 2.80 (dm, 1H, *J* = 14 Hz, H-9), 3.48 (m, 1H, H-5), 3.75 (m, 1H, H-1), 3.92 (d, 1H, *J* = 14.8 Hz, CH_2Ar), 5.35 (d, 1H, *J* = 14.8 Hz, CH_2Ar), 6.75 (ddd, 1H, *J* = 4.4, 2.8, 1.2 Hz, H-7), 7.22-7.39 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 25.9 (C-9), 31.7 (C-8), 45.8 (C-5), 48.6 (C-1), 49.7 (CH_2Ar), 83.6 (C-4), 113.4 (C-6), 118.4 (CN), 127.7, 128.1, 129.0 (Ar-CH), 135.7 (*ipso*-C), 144.7 (C-7), 162.9 (C-3). HRMS (ESI-TOF): Calcd for $C_{16}H_{15}Cl_2N_2O$ 321.0556 (M^++1). Found 321.0552.



4-(4,4-Dichloro-8-hydroxy-3-oxo-2-azaspiro[4.5]deca-6,9-dien-2-yl) cyclohex-1-ene-1-carbonitrile (8): A mixture of CuCl (21 mg, 0.21 mmol, 30%) and nitrile **1** (250 mg, 0.7 mmol) in acetonitrile (5 mL) was heated at 80 °C overnight in a sealed tube. The solution was allowed to reach rt, and water (10 mL), 10 % HCl aqueous solution (3 mL) and AcOEt (30 mL) were successively added. The layers were separated and the aqueous layer was extracted with AcOEt. The combined organic layers were washed with brine, dried and concentrated. After chromatography (hexane/CH_2Cl_2 1:9 to CH_2Cl_2), besides morphan **6** (121 mg, 48%) **8** was isolated as a mixture of two epimers (23 mg, 10%), which were separated by chromatography (CH_2Cl_2/ AcOEt 8:2).

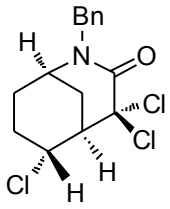
The less polar isomer: IR (NaCl, neat): 3458, 3044, 2930, 2854, 2215, 1722, 1670, 1634, 1477, 1433, 1421, 1307, 1245, 1189, 1027, 858, 735, 681 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.77 (m, 1H), 1.92 (m, 1H), 2.27 (m, 1H), 2.46 (m, 3H), 3.23 (d, 1H, *J* = 10 Hz), 3.27 (d, 1H, *J* = 10 Hz), 4.25 (m, 1H), 4.53 (brs, 1H), 5.94 (m, 2H), 6.26 (m, 2H), 6.58 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 25.0 (CH_2), 26.5 (CH_2), 28.1 (CH_2), 47.2 (CH), 49.4 (C), 50.9 (CH_2), 62.0 (CH), 88.4 (C), 112.6 (C), 118.4 (CN), 126.2 (2 CH), 132.9 (CH), 133.0 (CH), 141.6 (CH), 165.7 (CO). HRMS (ESI-TOF): Calcd for $C_{16}H_{17}Cl_2N_2O_2$ 339.0662 (M^++1). Found 339.0648.

The more polar isomer: IR (NaCl, neat): 3429, 3041, 2938, 2851, 2215, 1715, 1643, 1477, 1433, 1418, 1306, 1244, 1188, 1023, 887, 861, 826, 736, 796 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.78 (m, 1H), 1.93 (m, 1H), 2.28 (m, 1H), 2.46 (m, 3H), 3.28 (d, 1H, *J* = 10 Hz), 3.31 (d, 1H, *J* = 10 Hz), 4.26 (m, 1H), 4.67 (brs, 1H), 5.85 (m, 2H), 6.25 (m, 2H), 6.58 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 25.0 (CH_2), 26.5 (CH_2), 28.2 (CH_2), 47.2 (CH), 49.8 (C), 50.4 (CH_2), 62.3 (CH), 89.2 (C), 112.6 (C), 118.5 (CN), 125.3 (2 CH), 133.8 (2 CH), 141.7 (CH), 165.6 (CO). HRMS (ESI-TOF): Calcd for $C_{16}H_{17}Cl_2N_2O_2$ 339.0662 (M^++1). Found 339.0665.



(1*RS*,5*RS*,6*RS*) Methyl 2-Benzyl-4,4,6-trichloro-3-oxo-2-azabicyclo [3.3.1]nonane-6-carboxylate (9): To a suspension of CuCl (2.5 mg, 0.025 mmol 10%) in 1,2-dichloroethane (2.7 mL) were successively added TPMA (7.4 mg, 0.025 mmol), **2** (100 mg, 0.25 mmol), and AIBN (20.9 mg, 0.125 mmol 50%), and the mixture was heated at 60 °C for 16 h in a sealed tube. The solution was then allowed to reach rt, concentrated and purified by chromatography (CH_2Cl_2) yielding morphan **9** (81 mg, 81%) and **2** (15 mg, 15%).

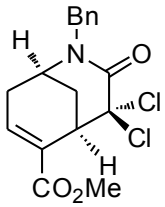
White solid, mp 130-131 °C; IR (NaCl, neat): 3086, 3062, 3030, 2950, 2861, 1745, 1678, 1447, 1360, 1289, 1244, 1203, 1187, 1066, 915, 824, 731, 700, 683 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.72-2.24 (m, 3H, CH_2-8 and H-7ax), 2.17 (m, 1H, H-7eq), 2.44 (brd, 1H, *J* = 14.4 Hz, H-9), 2.57 (brd, 1H, *J* = 14.4 Hz, H-9), 3.46 (m, 1H, H-1), 3.59 (brs, 1H, H-5), 3.78 (s, 3H, CH_3), 3.92 (d, 1H, *J* = 14.8 Hz, CH_2Ar), 5.18 (d, 1H, *J* = 14.8 Hz, CH_2Ar), 7.18-7.32 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 24.2 (C-8), 26.1 (C-7), 26.7 (C-9), 49.5 (CH_2Ar), 50.3 (C-1), 52.9 (CH_3), 53.0 (C-5), 69.8 (C-6), 84.4 (C-4), 127.8, 128.0, 128.9 (Ar-CH), 136.0 (*ipso*-C), 163.7 (C-3), 170.0 (CO). HRMS (ESI-TOF): Calcd for $C_{17}H_{19}Cl_3NO_3$ 390.0425 (M^++1). Found 390.0426.



(1*RS*,5*RS*,6*RS*)-2-Benzyl-4,4,6-trichloro-2-azabicyclo[3.3.1]nonan-3-one (10): To a suspension of CuCl (30 mg, 0.3 mmol 10%) in 1,2-dichloroethane (15 mL) were successively added TPMA (87.2 mg, 0.3 mmol), **3** (1 g, 3 mmol), and AIBN (246 mg, 1.50 mmol 50%), and the mixture was heated at 60 °C for 2 days in a sealed tube. The solution was then allowed to reach rt, concentrated and purified by chromatography (hexane/CH_2Cl_2 1:9 to CH_2Cl_2) to yield morphan **10** (850 mg, 85%).

White solid, mp 116-118 °C; IR (NaCl, neat): 3109, 3089, 3063, 3032, 2960, 2946, 2933, 2859 1659, 1496, 1452, 1423, 1348, 1306, 1241, 1213, 1185, 1149, 1078, 1045, 999, 948, 867, 825, 808, 741, 699, 671, 613, 565 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.70 (m, 1H, H-8eq), 1.84-1.97 (m, 3H,CH_2-7 and H-8ax), 2.41 (m, 2H, CH_2-9), 3.04 (brd, 1H, *J* = 3.2 Hz, H-5), 3.54 (brd, 1H, H-1), 3.91 (d, 1H, *J* = 15.2 Hz, CH_2Ar), 4.96 (brs, 1H, H-6), 5.31 (d, 1H, *J* = 15.2 Hz, CH_2Ar), 7.24-7.40 (m, 5H, ArH); ^{13}C NMR

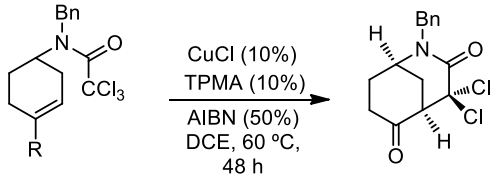
($CDCl_3$, 100 MHz): δ 22.5 (C-8), 24.4 (C-7), 24.5 (C-9), 49.3 (CH_2Ar), 51.5 (C-1), 51.8 (C-5), 57.6 (C-6), 85.4 (C-4), 127.8, 127.9, 128.9 (Ar-CH), 136.1 (*ipso*-C), 164.2 (C-3). HRMS (ESI-TOF): Calcd for $C_{15}H_{17}Cl_3NO$ 332.0370 (M^++1). Found 332.0371.



Methyl 2-Benzyl-4,4,6-trichloro-3-oxo-2-azabicyclo[3.3.1]non-6-ene-6-carboxylate (14): A mixture of CuCl (6.7 mg, 0.07 mmol, 30%) and nitrile **2** (80 mg, 0.22 mmol) in DMF (0.8 mL) was heated at 80 °C overnight in a sealed tube. The solution was then allowed to reach rt, concentrated and purified by chromatography (hexane/CH_2Cl_2 1:9 to CH_2Cl_2) to yield **9** (36.5 mg, 46%) and **14** (16.5 mg, 21%).

IR (NaCl, neat): 3082, 3042, 2950, 2926, 2850, 1719, 1670, 1449, 1332, 1258, 1206, 1088, 1060, 759, 732, 698, 672 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.86 (ddd, 1H, *J* = 14, 4, 2.4 Hz, H-9), 2.37 (dddd, 1H, *J* = 20, 3.6, 2.8, 1.6 Hz, H-8ax), 2.55 (dd, 1H, *J* = 20, 4 Hz, H-8eq), 2.77 (dm, 1H, *J* = 14 Hz, H-9), 3.71 (brs, 1H, H-1), 3.81 (s, 3H, CH_3), 3.89 (d, 1H, *J* = 14.8 Hz, CH_2Ar), 4.04 (m, 1H, H-5), 5.84 (d, 1H, *J* = 14.8 Hz, CH_2Ar), 6.92 (t, 1H, *J* = 4, Hz, H-7), 7.24-7.39 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 26.3 (C-9), 31.2 (C-8), 43.1 (C-5), 49.3 (C-1), 49.6 (CH_2Ar), 52.3 (CH_3), 85.0 (C-4), 127.7, 127.9, 128.9 (Ar-CH), 131.2 (C-7), 136.1 (*ipso*-C), 137.0 (C-6), 162.9 (C-3), 166.8 (CO). HRMS (ESI-TOF): Calcd for $C_{17}H_{18}Cl_2NO_3$ 354.0658 (M^++1). Found 354.0655.

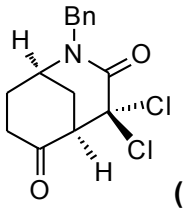
Scheme 1. Cu(I)-Catalyzed Cyclization of **4** and **5**



4, R = OAc
5, R = $OSiMe_3$

11 55% (from 4)[a,b]
22% (from 5)[c]

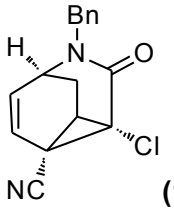
[a] 500 mg scale. [b] No AIBN, and 30 % catalyst and ligand loadings led to **11** in 42% yield from **4**. Using CuCl (30%) in DMF (80 ºC, 16 h), **11** was isolated in 51% yield from **4**, these runs were carried out using 100 mg of starting material. [c] *N*-benzyl-2,2,2-trichloro-*N*-(4-oxocyclohexyl) acetamide (25%) was recovered.



(1*RS*,5*RS*)-2-Benzyl-4,4-dichloro-2-azabicyclo[3.3.1]nonane-3,6-dione (11): To a suspension of CuCl (11 mg, 0.11 mmol 10%) in 1,2-dichloroethane (4 mL) were successively added TPMA (32 mg, 0.11 mmol), **4** (500 mg, 1.1 mmol), AIBN (89 mg, 0.55 mmol 50%) and the mixture was heated at 60 °C for 2 days in a sealed tube. The solution was then allowed to reach rt, concentrated and purified by chromatography (hexane/AcOEt 8:2) to yield morphan **11** (187 mg, 55%).

IR (NaCl, neat): 2924, 2853, 1732, 1668, 1450, 1423, 1275, 1243, 1202, 1108, 1033, 956, 860, 813, 733, 662, 565 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 1.70 (dddd, 1H, *J* = 16, 10.4, 6, 2.4 H-8ax), 2.07 (ddd, 1H, J = 14.4, 3.6. 2.8 Hz, H-9), 2.24 (m, 1H, H-8eq), 2.51 (m, 2H, CH_2-7), 2.77 (dq, 1H, *J* = 14.4, 3.2 Hz, H-9), 3.59 (m, 1H, H-5), 3.70 (brs, 1H, H-1), 4.10 (d, 1H, *J* = 15.4 Hz, CH_2Ar), 5.38 (d, 1H, *J* = 15.4 Hz, CH_2Ar), 7.29-7.41 (m, 5H, ArH); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 30.2 (C-8), 31.1 (C-9), 35.0 (C-7), 49.7 (CH_2Ar), 51.1 (C-1), 63.0 (C-5), 81.2 (C-4), 127.9, 128.2, 129.1 (Ar-CH), 135.9 (*ipso*-C), 163.9 (C-3), 203.5 (C-6). **HRMS** (ESI-TOF): Calcd for $C_{15}H_{16}Cl_2NO_2$ 312.0553 (M^++1). Found 312.0555.

Reaction of 6 with DBU. To a solution of **6** (100 mg, 0.28 mmol) in benzene (4.5 mL) was added DBU (0.083 mL, 0.56 mmol) and the mixture was heated to reflux for 3 h. The mixture was then diluted in ether and washed with 1M HCl solution and brine, dried and concentrated to yield **12** (75 mg, 94%).

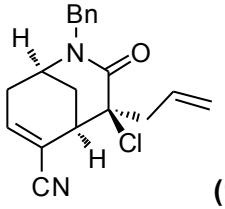


(1*RS*,2*SR*,5*SR*,8*SR*)-4-benzyl-2-chloro-3-oxo-4-azatricyclo[3.3.1.0^{2,8}] non-6-ene-8-carbonitrile (12): Colorless oil; IR (NaCl, neat): 3059, 3033, 2966, 2930, 2243, 1667, 1495, 1450, 1428, 1357, 1333, 1268, 1180, 1106, 1075, 973, 936, 844, 790, 735, 702, 679, 614, 578, 526 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.50 (dt, 1H, *J* = 14, 2.8 Hz, H-9), 2.13 (ddd, 1H, *J* = 14, 3.6, 2.4 Hz, H-9), 2.92 (dt, 1H, *J* =2.8, 1.6 Hz, H-1), 3.82 (m, 1H, H-5), 4.55 (d, 1H, *J* = 14.4 Hz, CH_2Ar), 4.71 (d, 1H, *J* = 14.4 Hz, CH_2Ar), 5.95 (dd, 1H, *J* = 9.2, 6.4 Hz, H-6), 6.11 (dd, 1H, *J* = 9.2, 1.2 Hz, H-7), 7.22-7.38 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.7 (C-9), 26.2 (C-8), 32.6 (C-1), 47.3 (C-5), 50.8 (CH_2Ar), 50.9 (C-2), 117.4 (CN), 122.9 (C-7), 128.2, 128.6, 128.9, 136.5 (*ipso*-C), 136.5 (C-6), 160.4 (C-3). HRMS (ESI-TOF): Calcd for $C_{16}H_{14}ClN_2O$ 285.0789 (M^++1). Found 285.0788.

Allylation of 7

Method A: To a solution of **7** (74 mg, 0.23 mmol) and allylbromide (0.35 mL, 4.66 mmol) in THF (2 mL) was added a 2-methyltetrahydrofuran solution of *i*-PrMgBr (1.52, 1.5 mmol) dropwise at -78 ºC. The mixture was then stirred at this temperature for 1 h and at rt for 3 h. The reaction was quenched with satd. aqueous NH_4Cl solution, extracted with CH_2Cl_2 and the organic layers were dried and concentrated. Flash chromatography (hexane/AcOEt 8:2 to 7:3) afforded **13** as a white solid (46 mg, 60%).

Method B: A solution of **7** (75 mg, 0.23 mmol), allyl tributyltin (0.14 mL, 0.53 mmol) and AIBN (3.8 mg, 0.023 mmol) in benzene (2 mL) was heated to reflux for 4 h then 0.02 mL of allyl tributyltin and 3.8 mg of AIBN were added and the mixture was heated to reflux for 3 h. The reaction mixture was concentrated and the residue purified by chromatography (hexane/AcOEt 8:2 to 7:3) to yield **13** (49 mg, 63%).



(1*RS*,4*SR*,5*RS*)-4-Allyl-2-Benzyl-4-chloro-6-cyano-2-azabicyclo [3.3.1]non-6-en-3-one (13): White solid, mp 136-138 °C; IR (NaCl, neat): 3062, 3031, 2928, 2217, 1652, 1494, 1450, 1415, 1204, 1069, 927, 760, 730, 696 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.83 (ddd, 1H, *J* = 14, 4, 2 Hz, H-9), 2.24 (dm, 1H, *J* = 14 Hz, H-9), 2.37 (dm, 1H, *J* = 20.4, H-8ax), 2.56 (dd, 1H, *J* = 20.4, 4.4 Hz, H-8eq), 2.74 (dd, 1H,

J = 14.8, 8.8 Hz, CH_2C=), 3.08 (brs, 1H, H-5), 3.11 (dd, 1H, *J* = 14.8, 4.8 Hz, CH_2C=), 3.70 (brs, 1H, H-1), 3.90 (d, 1H, *J* = 14.8 Hz, CH_2Ar), 5.28 (m, 2H, =CH_2), 5.35 (d, 1H, *J* = 14.8 Hz, CH_2Ar), 6.06 (m, 1H, =CH), 6.69 (t, 1H, *J* = 3.2 Hz, H-7), 7.20-7.39 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 25.7 (C-9), 31.4 (C-8), 38.1 (C-5), 45.2 (CH_2C=), 48.3 (C-1), 49.3 (CH_2Ar), 71.9 (C-4), 115.8 (C-6), 119.2 (CN), 120.6 (=CH_2), 127.8, 127.9, 128.9 (Ar-CH), 131.4 (=CH), 136.5 (*ipso*-C),142.9 (C-7), 168.0 (C-3). HRMS (ESI-TOF): Calcd for $C_{19}H_{20}ClN_2O$ 327.1259 (M^++1). Found 327.12

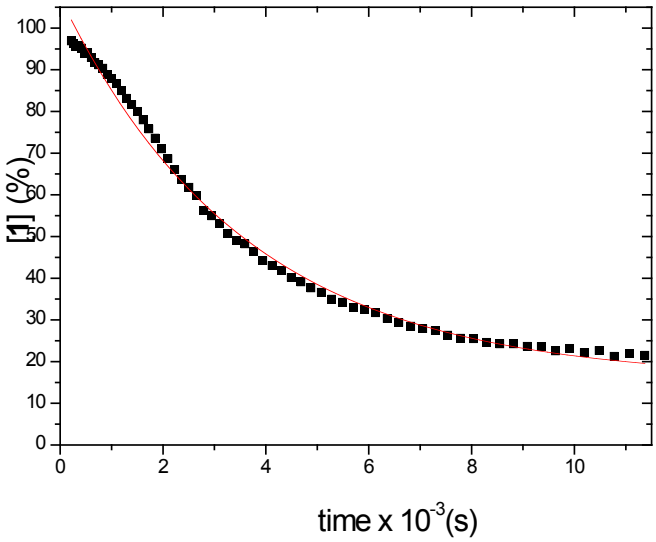


Figure S-1. Kinetic monitoring of **1** consumption (^{1}H NMR, 60 ºC, C_6D_6) in the reaction of the formation of **6,** using Tp^{tBu}CuCl. [Cu]/[AIBN]/[**1**] = 1:2:10. Rate constant, k_{obs} = 2.78x10^{-4} s^{-1}.

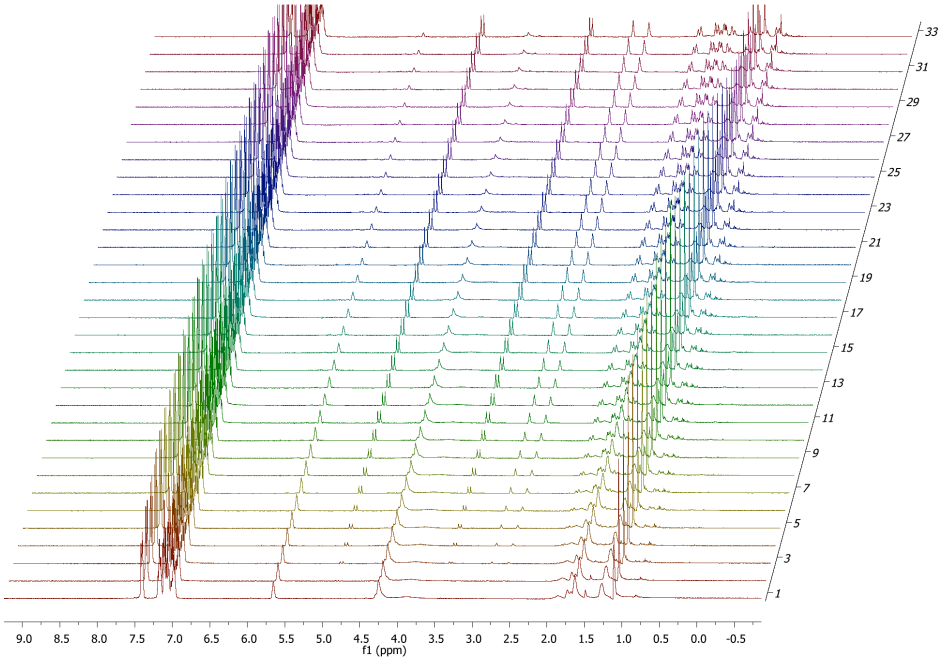
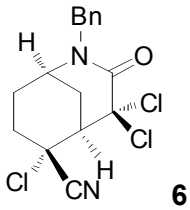
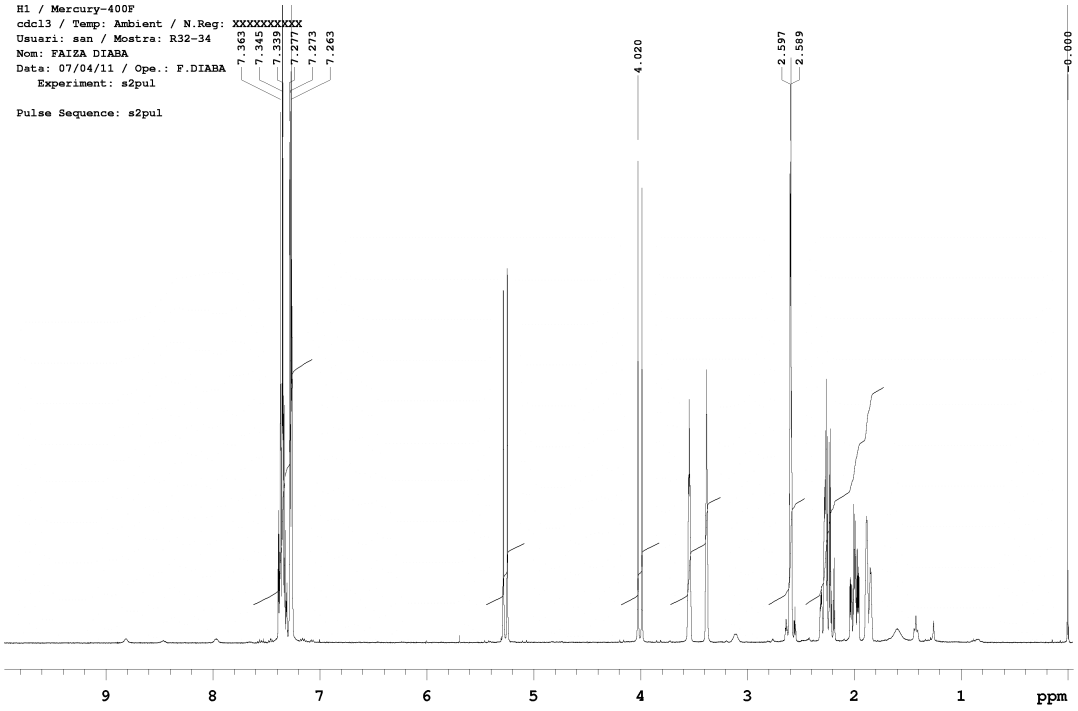
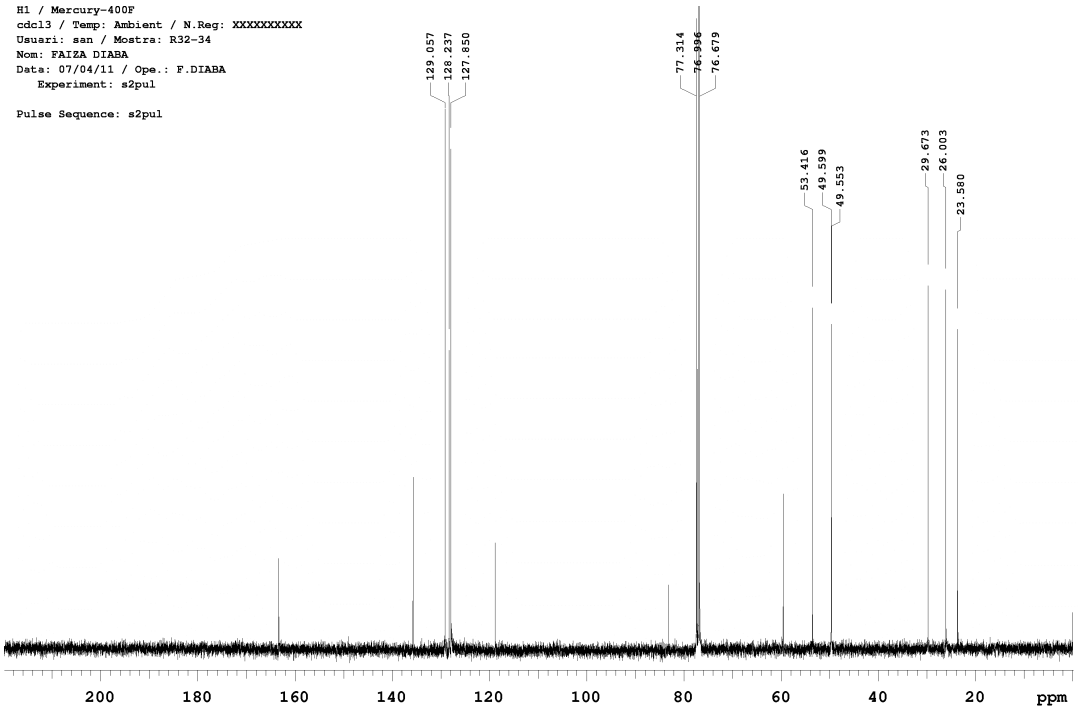


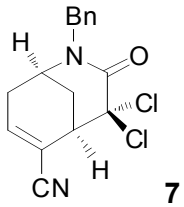
Figure S-2. ^{1}H spectra reaction monitoring of Tp^{tBu}Cu(NCMe):AIBN:**1** (ratio1:20:200) in C_6D_6 at 60ºC. A proton spectrum was registered every 3.6 min.


Bn
H
N
O
Cl
Cl
Cl
CN
H

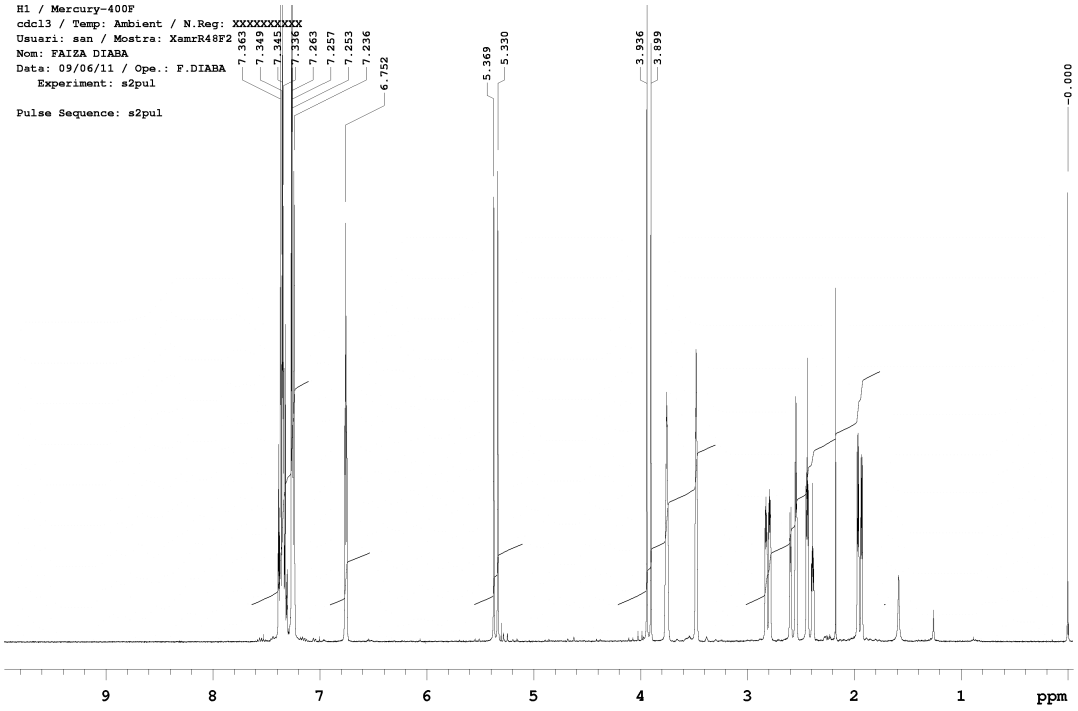
6

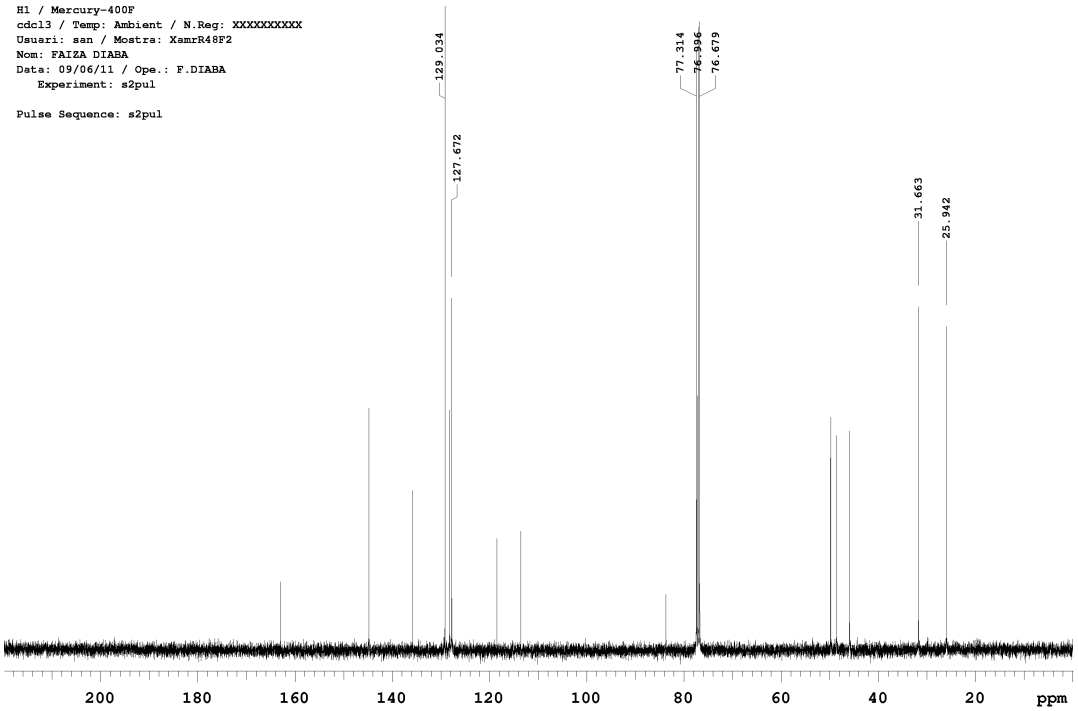

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXX
Usuari: san / Mostra: R32-34
Nom: FAIZA DIABA
Data: 07/04/11 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
7.363
7.345
7.339
7.277
7.273
7.263
4.020
2.597
2.589
0.000
9
8
7
6
5
4
3
2
1
ppm

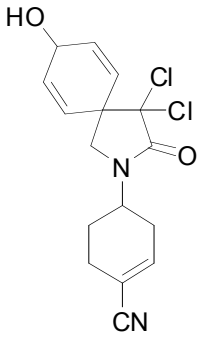

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXX
Usuari: san / Mostra: R32-34
Nom: FAIZA DIABA
Data: 07/04/11 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
129.057
128.237
127.850
77.314
76.996
76.679
53.416
49.599
49.553
29.673
26.003
23.580
200
180
160
140
120
100
80
60
40
20
ppm


Bn
H
N
O
Cl
Cl
H
CN

7

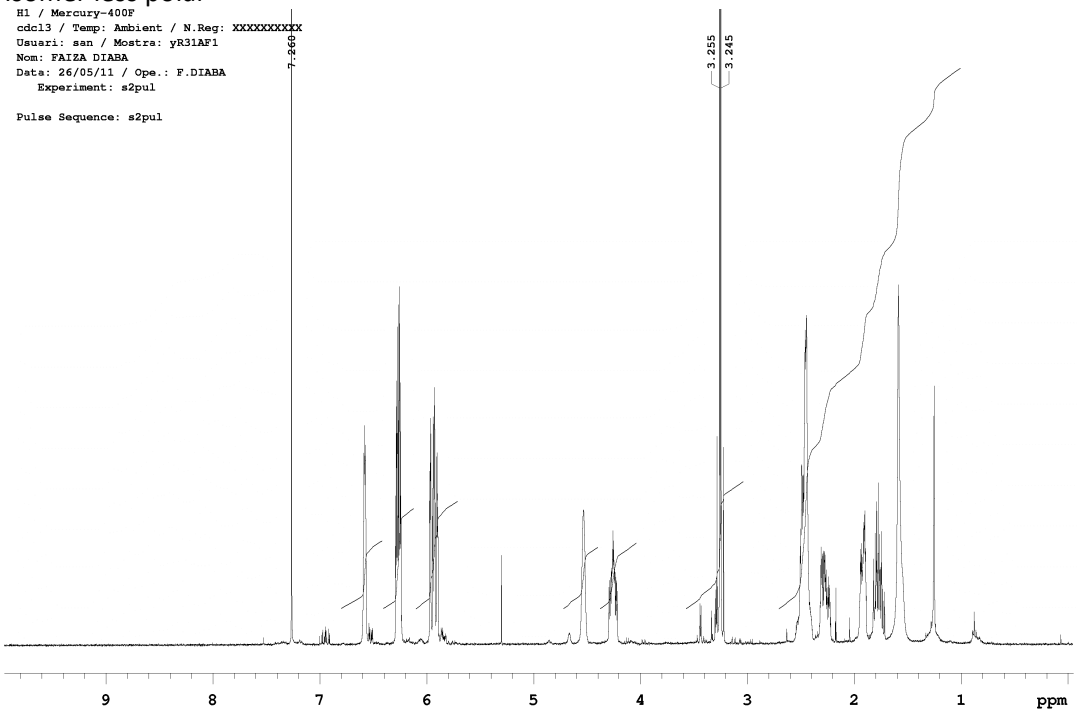

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XamrR48F2
Nom: FAIZA DIABA
Data: 09/06/11 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
7.363
7.349
7.345
7.336
7.263
7.257
7.253
7.236
6.752
5.369
5.330
3.936
3.899
0.000
9
8
7
6
5
4
3
2
1
ppm

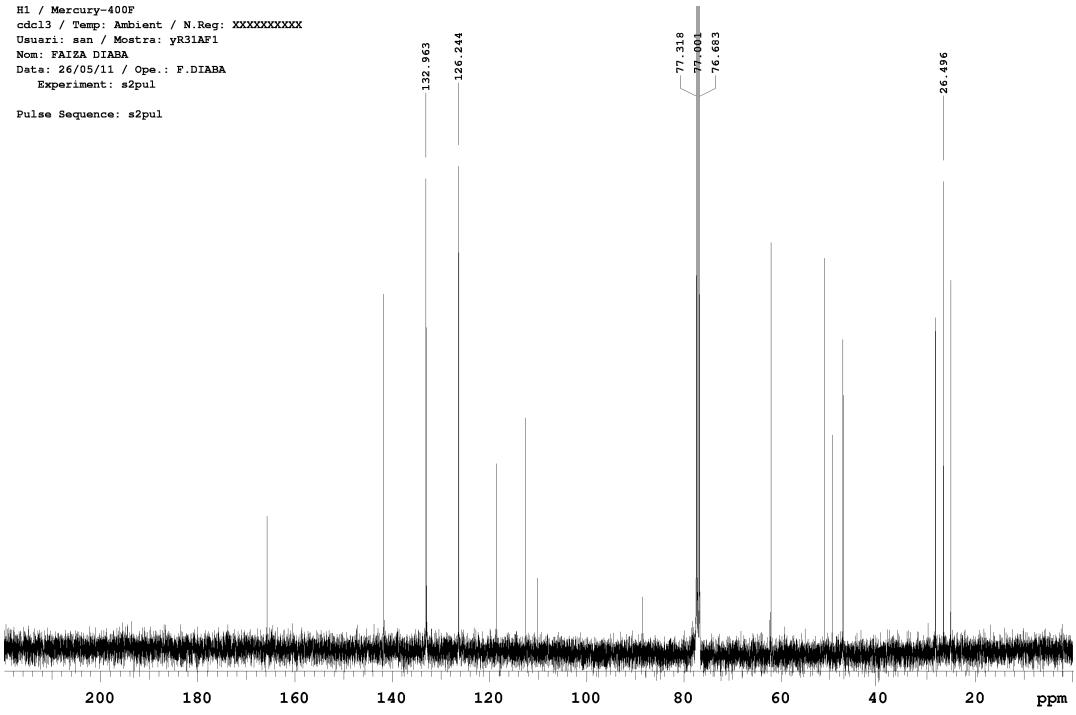

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XamrR48F2
Nom: FAIZA DIABA
Data: 09/06/11 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
129.034
127.672
77.314
76.996
76.679
31.663
25.942
200
180
160
140
120
100
80
60
40
20
ppm

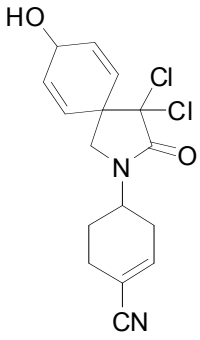


8 (epimer less polar)

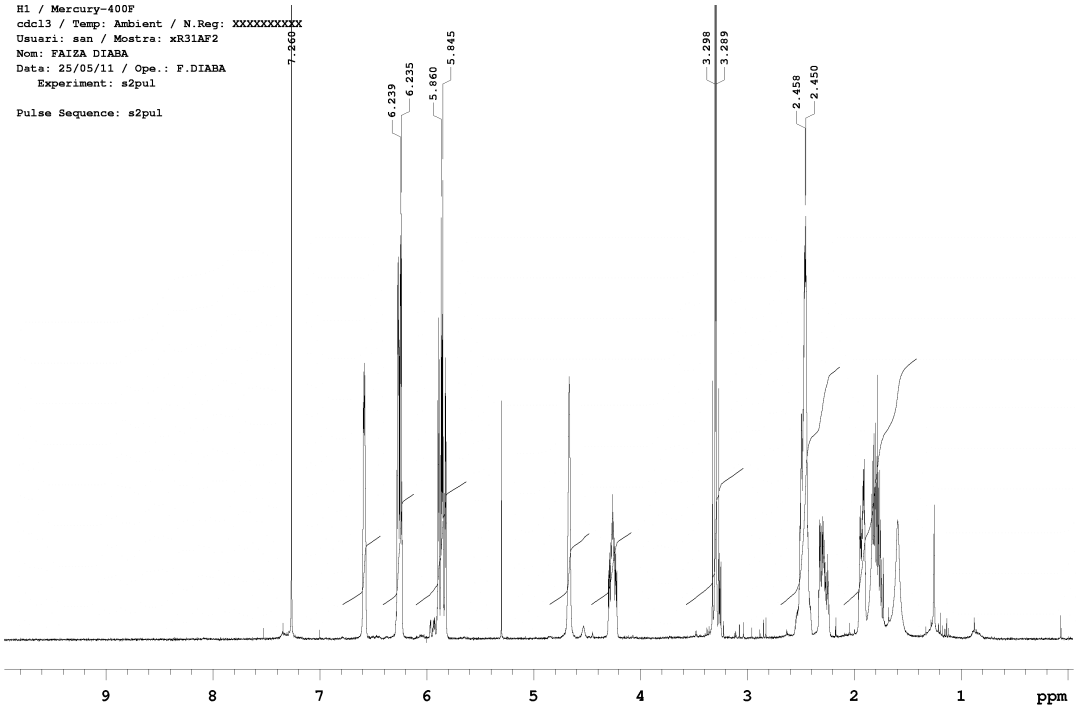
Isomer less polar

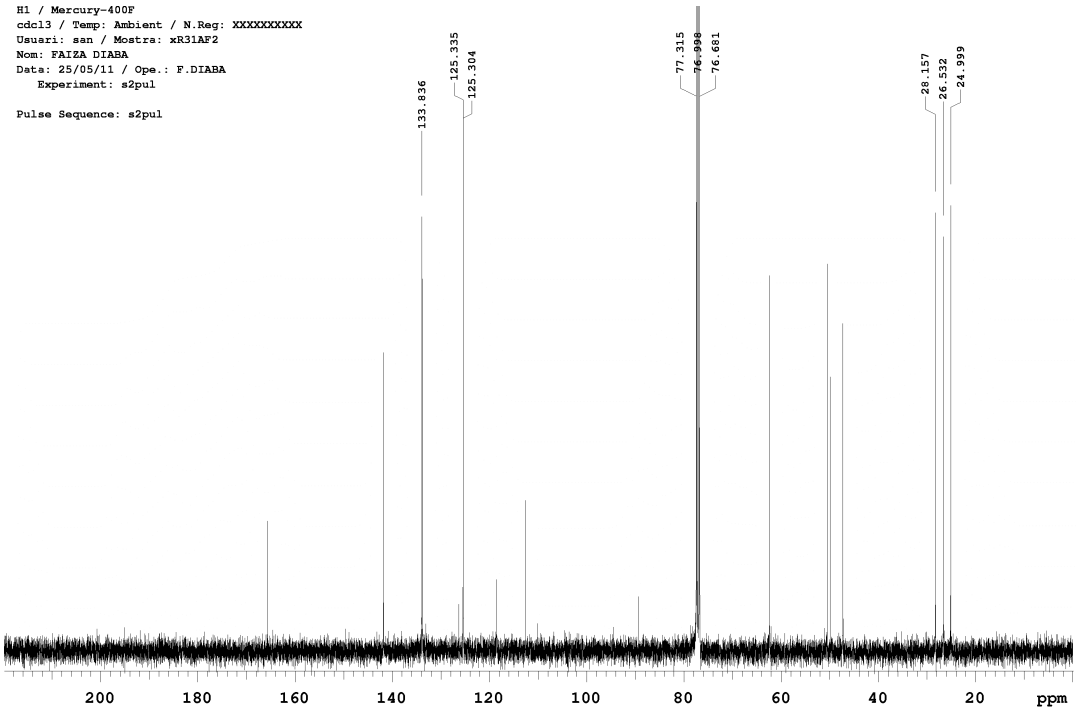


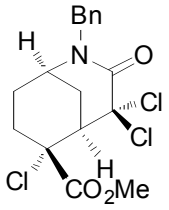




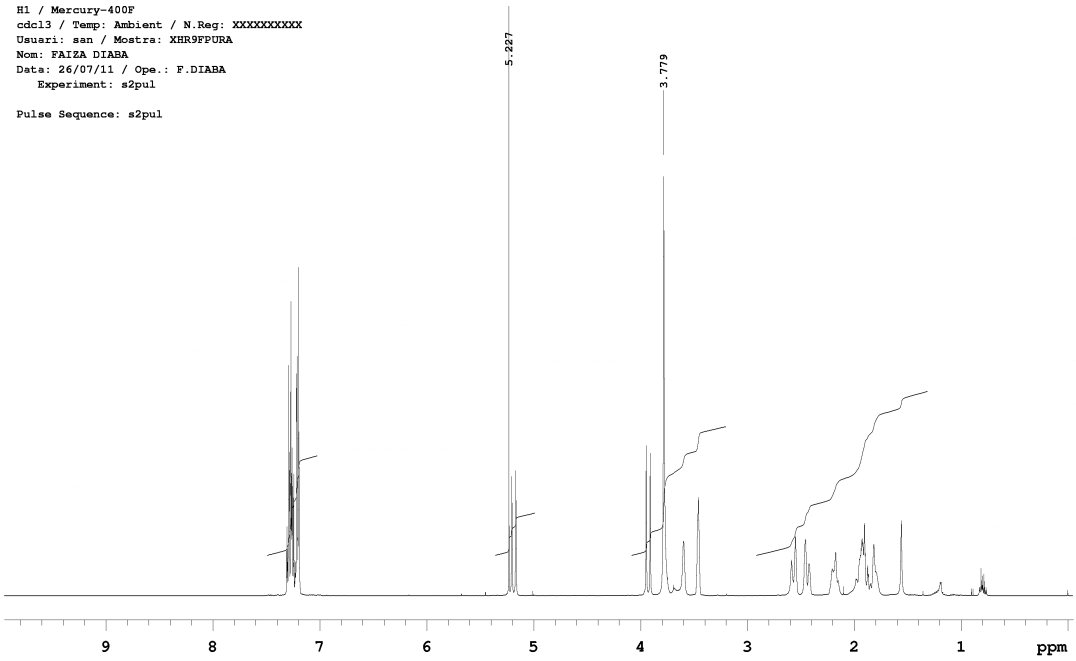
8 (epimer more polar)

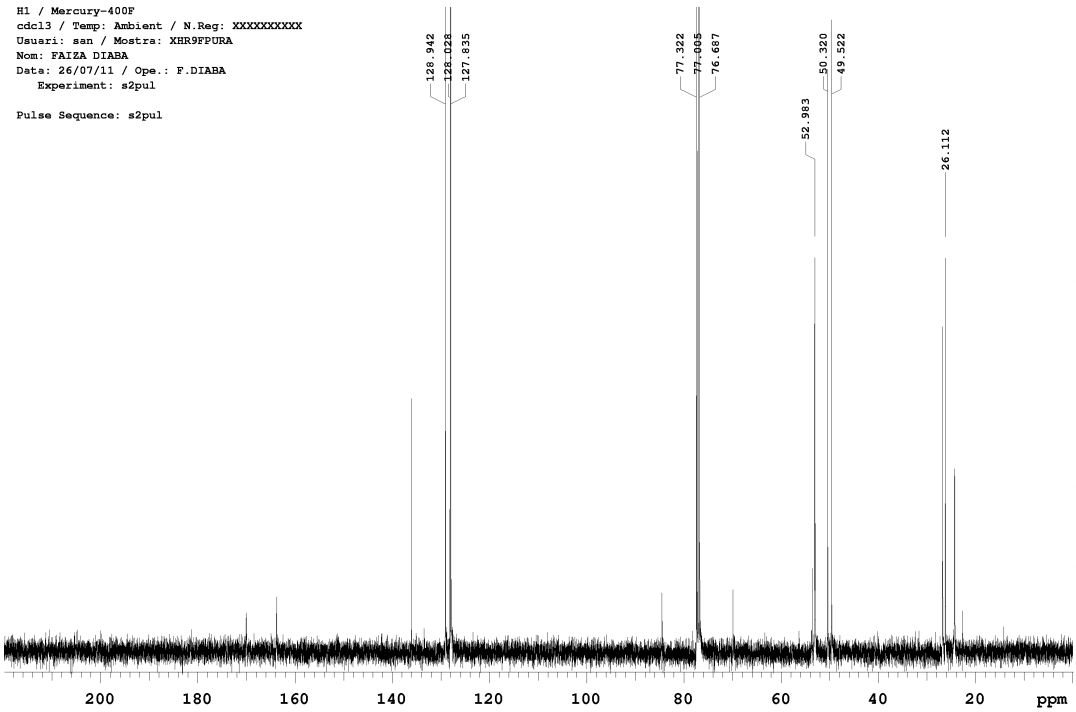


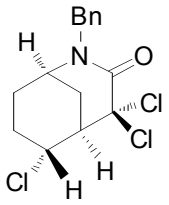



Bn
H
N
O
Cl
Cl
Cl
H
CO2Me

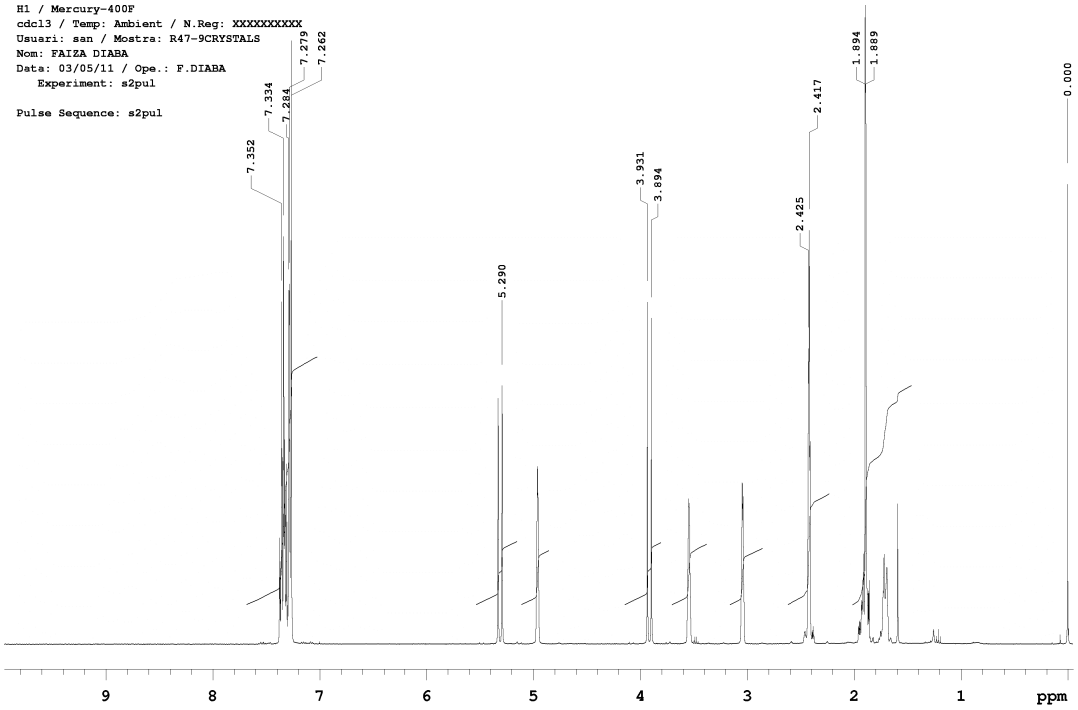
9

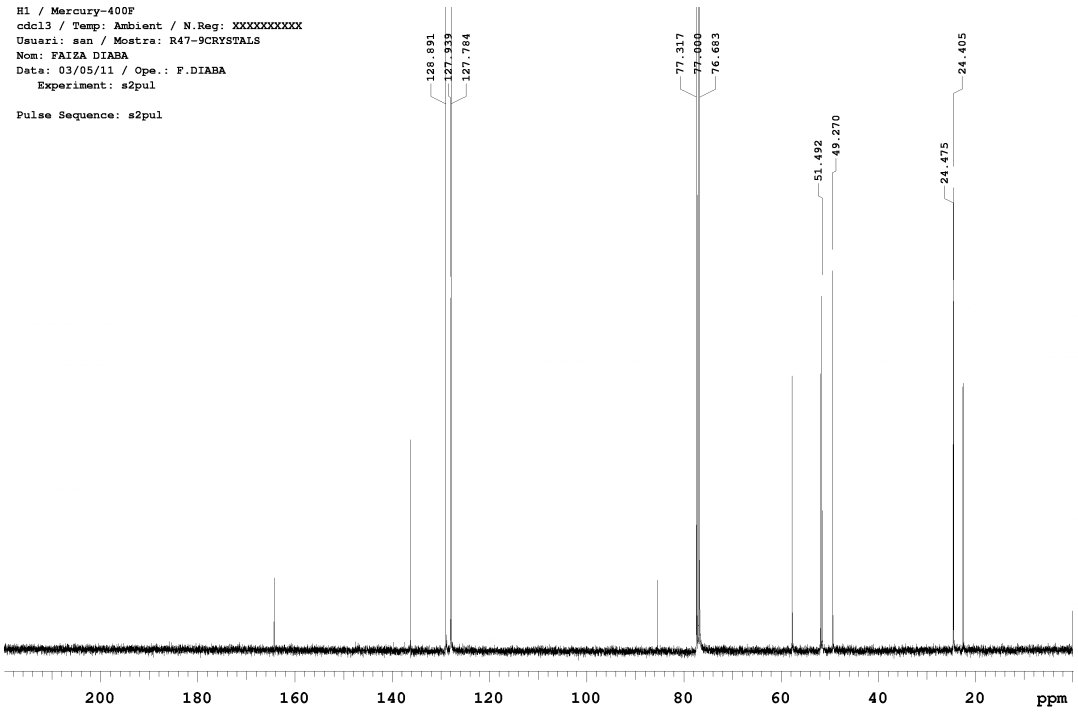

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XHR9FPURA
Nom: FAIZA DIABA
Data: 26/07/11 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
5.227
3.779
9
8
7
6
5
4
3
2
1
ppm

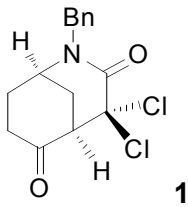

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XHR9FPURA
Nom: FAIZA DIABA
Data: 26/07/11 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
128.942
128.028
127.835
77.322
77.005
76.687
52.983
50.320
49.522
26.112
200
180
160
140
120
100
80
60
40
20
ppm


Bn
H
N
O
Cl
Cl
Cl
H
H

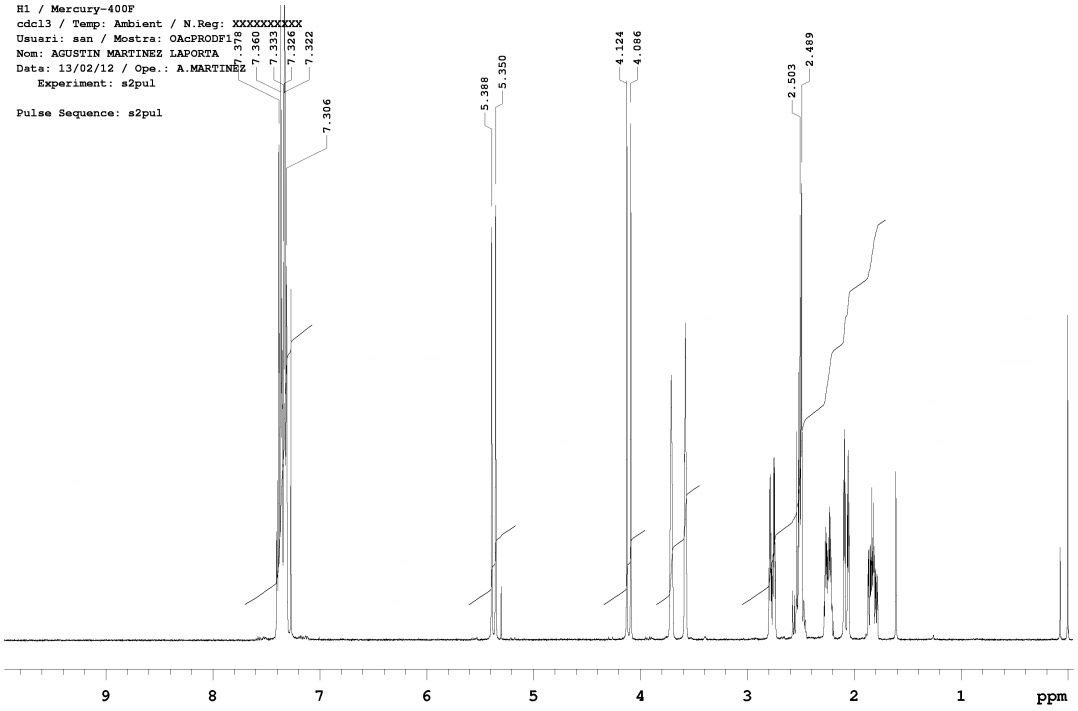
10

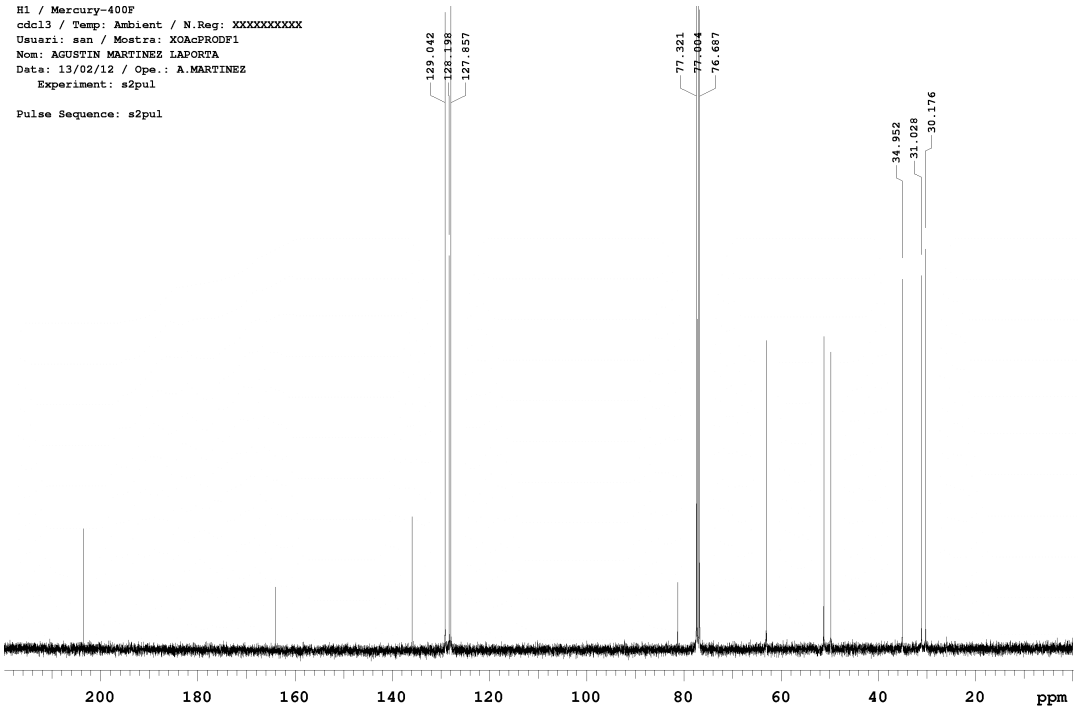

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: R47-9CRYSTALS
Nom: FAIZA DIABA
Data: 03/05/11 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
7.352
7.334
7.284
7.279
7.262
5.290
3.931
3.894
2.425
2.417
1.894
1.889
0.000
9
8
7
6
5
4
3
2
1
ppm

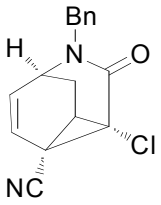

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: R47-9CRYSTALS
Nom: FAIZA DIABA
Data: 03/05/11 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
128.891
127.939
127.784
77.317
77.000
76.683
51.492
49.270
24.475
24.405
200
180
160
140
120
100
80
60
40
20
ppm


Bn
H
N
O
Cl
Cl
H
O

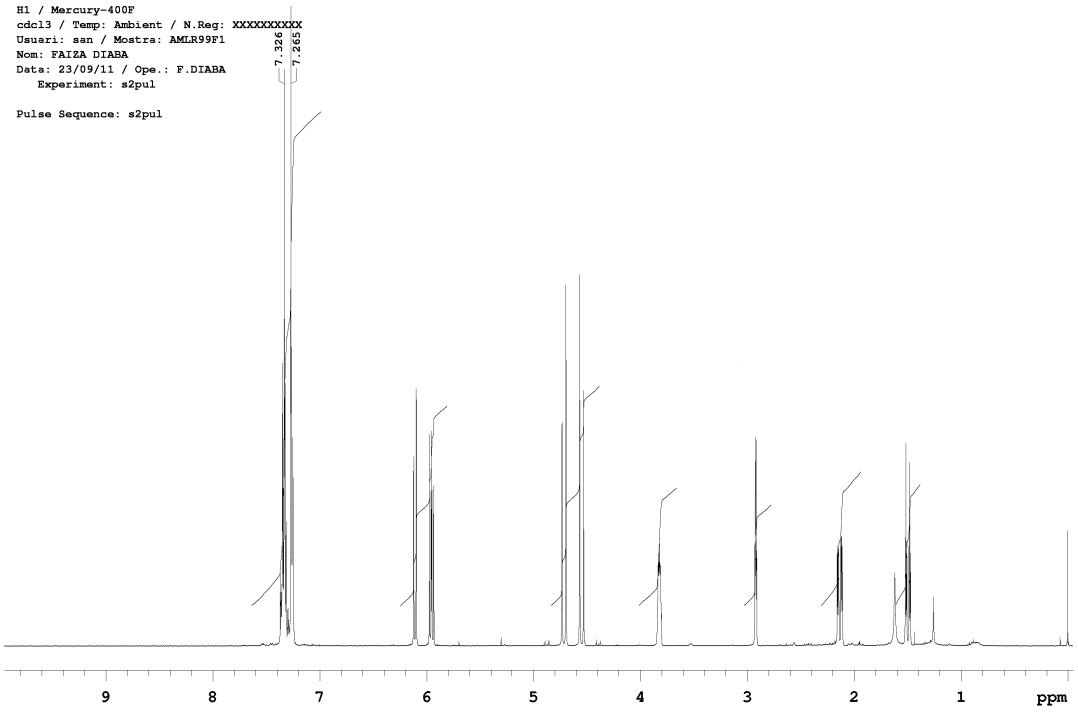
11

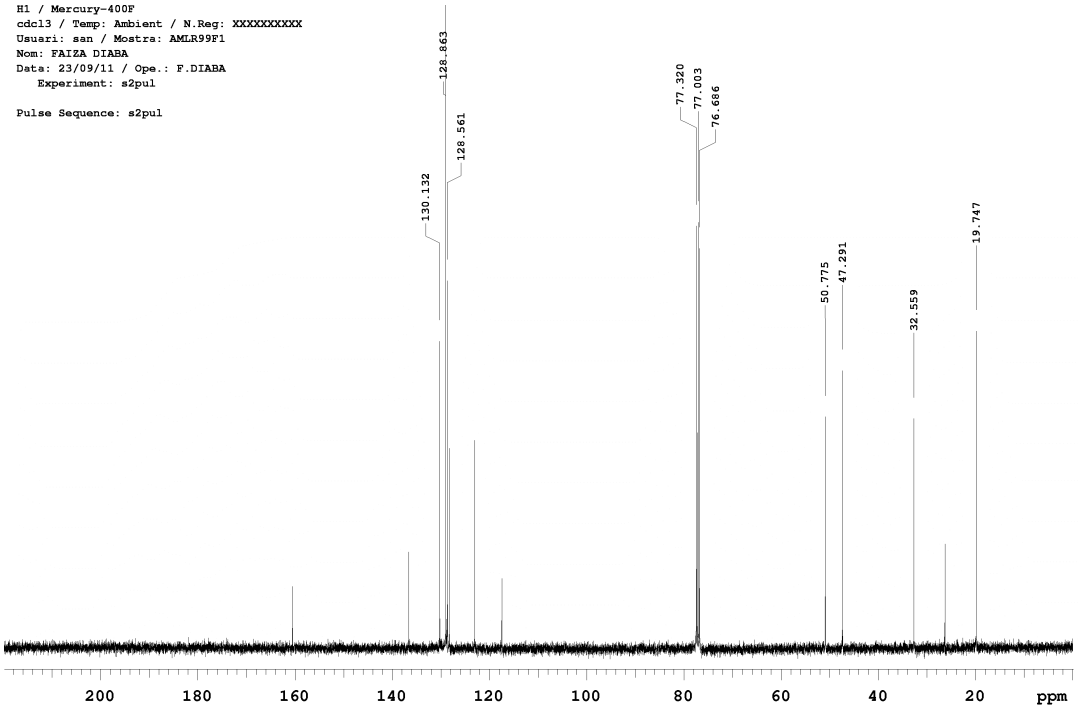

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: OAcPRODF1
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 13/02/12 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
7.378
7.360
7.333
7.326
7.322
7.306
5.388
5.350
4.124
4.086
2.503
2.489
9
8
7
6
5
4
3
2
1
ppm

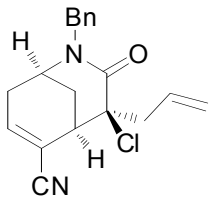

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XOAcPRODF1
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 13/02/12 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
129.042
128.198
127.857
77.321
77.004
76.687
34.952
31.028
30.176
200
180
160
140
120
100
80
60
40
20
ppm


Bn
H
N
O
Cl
NC

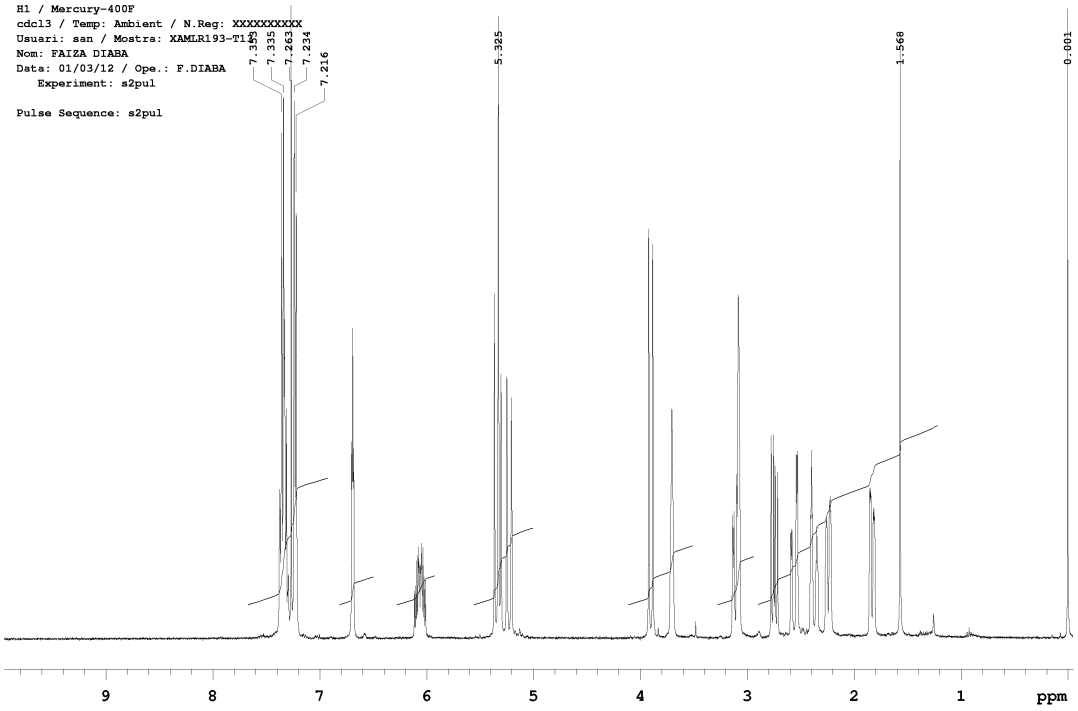
12

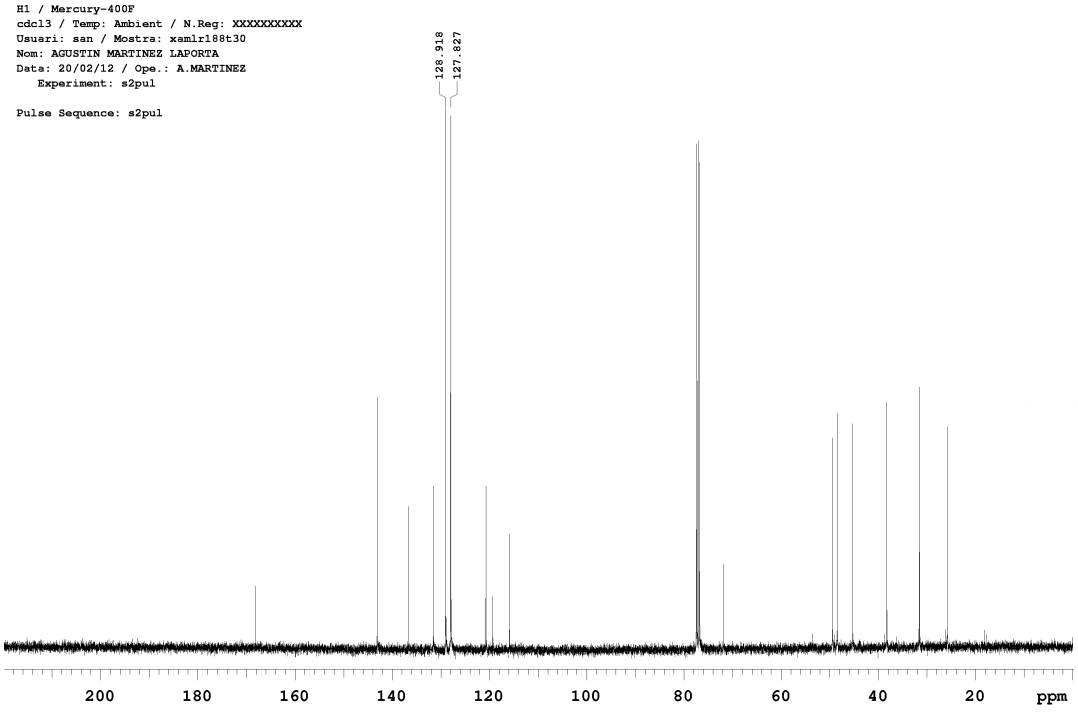

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AMLR99F1
Nom: FAIZA DIABA
Data: 23/09/11 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
7.326
7.265
9
8
7
6
5
4
3
2
1
ppm

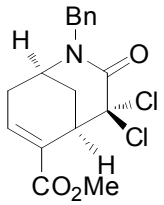

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: AMLR99F1
Nom: FAIZA DIABA
Data: 23/09/11 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
128.863
128.561
130.132
77.320
77.003
76.686
50.775
47.291
32.559
19.747
200
180
160
140
120
100
80
60
40
20
ppm


Bn
H
N
O
Cl
H
CN

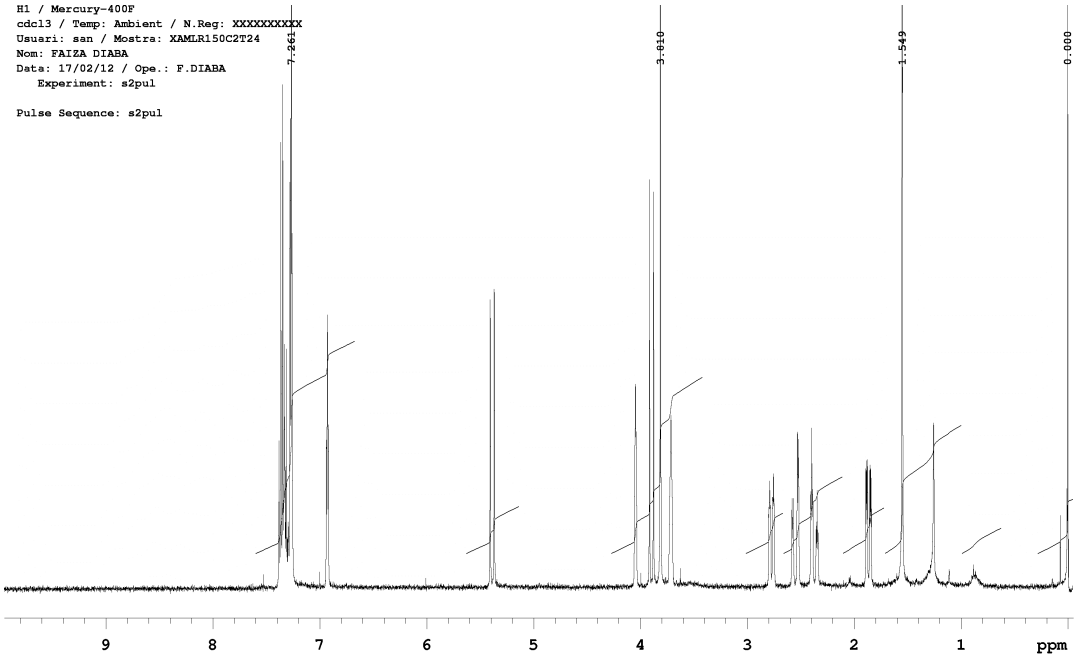
13

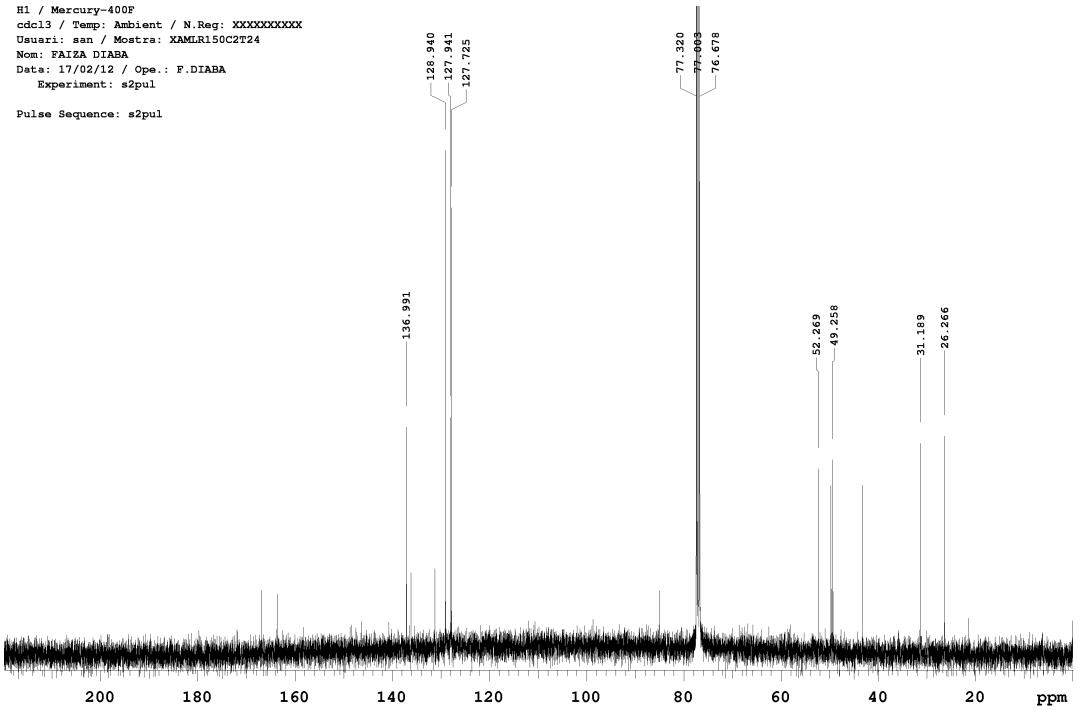

H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XAMLR193-T13
Nom: FAIZA DIABA
Data: 01/03/12 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
7.355
7.335
7.263
7.234
7.216
5.325
1.568
0.001
9
8
7
6
5
4
3
2
1
ppm


H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: xamlr188t30
Nom: AGUSTIN MARTINEZ LAPORTA
Data: 20/02/12 / Ope.: A.MARTINEZ
Experiment: s2pul
Pulse Sequence: s2pul
128.918
127.827
200
180
160
140
120
100
80
60
40
20
ppm


Bn
H
N
O
Cl
Cl
H
CO2Me

14


H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XAMLR150C2T24
Nom: FAIZA DIABA
Data: 17/02/12 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
7.261
3.810
1.549
0.000
9
8
7
6
5
4
3
2
1
ppm


H1 / Mercury-400F
cdcl3 / Temp: Ambient / N.Reg: XXXXXXXXXX
Usuari: san / Mostra: XAMLR150C2T24
Nom: FAIZA DIABA
Data: 17/02/12 / Ope.: F.DIABA
Experiment: s2pul
Pulse Sequence: s2pul
128.940
127.941
127.725
77.320
77.003
76.678
136.991
52.269
49.258
31.189
26.266
200
180
160
140
120
100
80
60
40
20
ppm