The Conformational Bias of Aryl, Arylsulfonyl Geminally Substituted Tertiary Carbon Centers: Applications in Subtrate-Based Stereocontrol

Jeremy P. Scott,*, † Peter R. Mullens,† Sarah E. Brewer,† Karel M. J. Brands,† Jennifer R. Chilenski,‡ Antony J. Davies,† Andrew D. Gibb,† David R. Lieberman,† Steven F. Oliver† and Ulf-H. Dolling‡

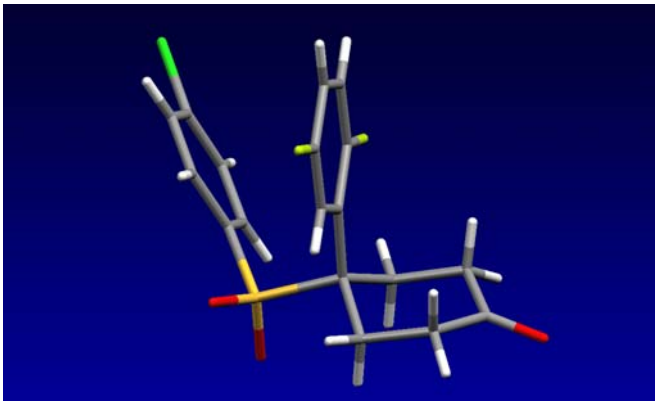
†*Department of Process Research, Merck Sharp & Dohme Research Laboratories, Hertford Road, Hoddesdon, Hertfordshire, EN11 9BU and* ‡*Department of Process Research, Merck Research Laboratories, P.O. BOX 2000, Rahway, New Jersey 07065.*

jeremy_scott@merck.com

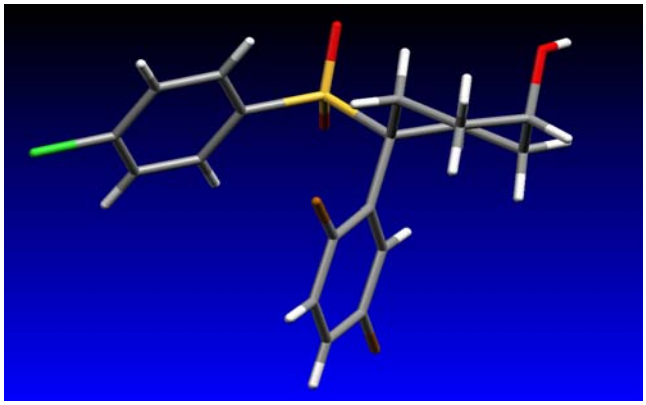
Supporting Information

All reactions were carried out under a nitrogen atmosphere. All solvents and reagents were purchased from commercial sources and were used without further purification. ^{1}H and ^{13}C NMR were recorded on a Bruker 400 MHz instrument with chemical shifts reported relative to residual proton solvent peaks. Melting points (open capillary) were performed on a Stuart Scientific SMP3 apparatus and are uncorrected. Crystallographic data for **2** and **4** have been deposited at the Cambridge Crystallographic Data Centre. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data-request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

Single crystal X-ray structures:



Cyclohexanone **2** (CCDC 236716)



Cis cyclohexanol **4** (CCDC XXXXXX)

Crystal data and structural refinement for cyclohexanone 2. A single crystal was grown from IPAc/heptane (Mpt 449-451 K) was selected for single crystal x-ray data collection on a Bruker Smart Apex system. The crystals were colorless polyhedron with dimensions of 0.44 mm x 0.30 mm x 0.05 mm. The unit cell was collected on 10 second scan rate and manual indexing gave the cell setting to be orthorhombic. The structure was solved in the orthorhombic Pca2(1) space group after a quadrant of data collection using 10 second scan rate.

Identification code	jrc0831n	
Empirical formula	C_{18} H_{15} Cl F_2 O_3 S	
Formula weight	384.81	
Temperature	298(2) K	
Wavelength	0.71073 A	
Crystal system, space group	Orthorhombic,	Pca2(1)
Unit cell dimensions	a = 15.450(10) A	alpha = 90 deg.
	b = 10.490(7) A	beta = 90 deg.
	c = 10.828(7) A	gamma = 90 deg.
Volume	1755(2) A^3	
Z, Calculated density	4,	1.456 Mg/m^3
Absorption coefficient	0.371 mm^{-1}	
F(000)	792	
Crystal size	0.44 x 0.30 x 0.05 mm	
Theta range for data collection	1.94 to 26.47 deg.	
Limiting indices	-19<=h<=19,	
	-12<=k<=13,	
	-12<=l<=13	
Reflections collected / unique	13312 / 3373 [R(int) = 0.1182]	
Completeness to theta = 26.47	99.6 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3373 / 1 / 226	
Goodness-of-fit on F^2	0.957	
Final R indices [I>2sigma(I)]	R1 = 0.0515,	wR2 = 0.1173
R indices (all data)	R1 = 0.0622,	wR2 = 0.1225

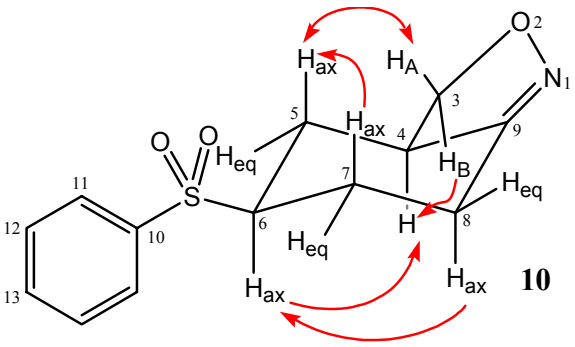
Absolute structure parameter	-0.01(9)
Largest diff. peak and hole	0.303 and -0.172 e.A^{-3}

Crystal data and structure refinement for cis cyclohexananol 4. Crystals were grown by evaporation of an acetonitrile solution of **4**. Mpt 456-457 K. The unit cell dimensions are a=6.932 Å; b=8.4366 Å; c=29.3225 Å; alpha=90°; beta=92.74°; gamma=90° with a unit cell volume of 1706.1 $Å^3$. A single crystal was selected for single crystal x-ray data collection on a Bruker Smart Apex CCD system at low temperature (-50ºC). The crystal was a colorless polyhedron with dimensions of 0.360 mm x 0.225 mm x 0.130 mm. The unit cell was collected on 5 second scan rate and auto indexing gave the cell setting to be monoclinic P. The structure was solved in the monoclinic P $2_1/c$ space group after a quadrant data collection using 5 second scan rate.

Identification code	jrc2573n	
Empirical formula	C_{18} H_{17} Cl F_2 O_3 S	
Formula weight	386.83	
Temperature	223(2) K	
Wavelength	0.71073 A	
Crystal system, space group	Monoclinic,	P $2_1/c$
Unit cell dimensions	a = 6.9274(5) A	alpha = 90 deg.
	b = 8.4158(6) A	beta = 92.7430(10) deg.
	c = 29.301(2) A	gamma = 90 deg.
Volume	1706.3(2) A^3	
Z, Calculated density	4,	1.506 Mg/m^3
Absorption coefficient	0.382 mm^{-1}	
F(000)	800	
Crystal size	0.36 x 0.225 x 0.13 mm	
Theta range for data collection	1.39 to 26.41 deg.	
Limiting indices	-8<=h<=8,	
	-10<=k<=10,	
	-36<=l<=36	
Reflections collected / unique	17593 / 3513 [R(int) = 0.0271]	
Completeness to theta = 26.41	99.8 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	

Data / restraints / parameters	3513 / 0 / 227	
Goodness-of-fit on F^2	1.041	
Final R indices [I>2sigma(I)]	R1 = 0.0401,	wR2 = 0.1009
R indices (all data)	R1 = 0.0472,	wR2 = 0.1054
Largest diff. peak and hole	0.413 and -0.208 e.A^{-3}	

Major diastereomer: *Cis*-5-(Phenylsulfonyl)-3,3a,4,5,6,7-hexahydro-2,1-benzisoxazole (**9**). ^{1}H NMR (400 MHz, C_6D_6) δ 7.72-7.68 (m, 2 x ArH), 7.03-6.93 (m, 3 x ArH), 3.89 (dd, *J* = 8.3, 10.4 Hz, 3-H_A), 3.22 (dd, 1H, *J* = 8.3, 10.3 Hz, 3-H_B), 2.51 (m, H_6), 2.43-2.36 (m, 8-H_{eq}), 2.22-2.11 (m, 4-H). 2.05-1.98 (m, 1H, 5-H_{eq}), 1.91-1.84 (m, 7-H_{eq}), 1.35 (ddt, *J* = 1.2, 5.2, 13.4 Hz, 8-H_{ax}), 1.32-1.17 (m, 7-H_{ax}), 1.16-1.06 (m, 5-H^{ax}). ^{13}C NMR (100 MHz, C_6D_6) δ 156.1 (C_9), 137.8 (C_{10}), 133.5 (C_{13}), 129.2 (C_{11}), 129.1 (C_{12}), 73.0 (C_3), 61.2 (C_6), 46.7 (C_4), 30.9 (C_5), 25.8 (C_7), 22.9 (C_8). Red arrows indicate nOe contacts which confirm *cis* relative stereochemistry of major diastereomer.



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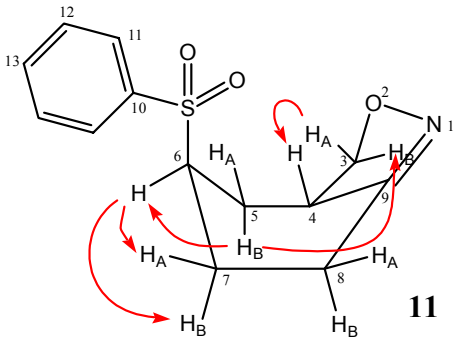
Minor diasteromer: *Trans*-5-(Phenylsulfonyl)-3,3a,4,5,6,7-hexahydro-2,1-benzisoxazole (**10**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95-7.92 (m, 2 x 11-H), 7.74-7.68 (m, 13-H), 7.66-7.58 (m, 2 x 12-H), 4.56 (dd, *J* = 8.0, 10.4 Hz, 3-H_A), 4.03-3.91 (m, 4-H), 3.77 (dd, *J* = 8.0, 9.8 Hz, 3-H_B), 3.35-3.30 (m, 6-H), 2.96 (dt, *J* = 14.0, 5.7 Hz, 8-H_A), 2.79-2.68 (m, 5-H_A and 8-H_B), 2.49-2.41 (m, 7-H_A), 1.87-1.80 (m, 1H, 7-H_B), 1.80-1.70 (m, 5-H_B); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3 (C_9), 137.7 (C_{10}), 134.1 (C_{13}), 129.5 (C_{11}), 128.4 (C_{12}), 73.7 (C_3), 58.4 (C_6), 43.9 (C_4), 30.2 (C_5), 24.9 (C_7), 20.7 (C_8); mp 155-156 °C; HRMS (ES) Calcd. for $C_{13}H_{16}NO_3S$ (M + H) 266.0851. Found 266.0844. Red arrows indicate observed nOe contacts which confirm relative stereochemistry.



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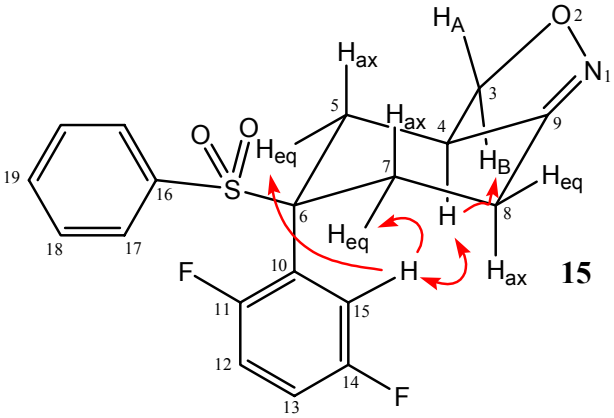
cis-5-Phenyl-5-(2,5-difluorophenylsulfonyl)-3,3a,4,5,6,7-hexahydro-2,1-benzisoxazole (**14**). ^{1}H NMR (600.1 MHz, d_7-DMF, 350K) δ 7.77 (m, 19-H), 7.58 (m, 2 x 18-H), 7.52 (m, 2 x 17-H), 7.35-7.30 (om, 13-H, 15-H), 7.16 (ddd, J = 13.6, 9.1, 4.9 Hz, 12-H), 4.50 (dd, J = 9.8, 7.9 Hz, 3-H_A), 3.87 (dd, J = 10.2, 7.9 Hz, 3-H_B), 3.32-3.22 (om, 4-H, 5-H_{eq}), 3.17 (m, 7-H_{eq}), 2.84 (m, 8-H_{eq}), 2.23-2.15 (om, 7-H_{ax}, 8-H_{ax}), 2.09 (td, J = 12.5, 1.9 Hz, 5-H_{ax}). Red arrows indicate observed nOe contacts.



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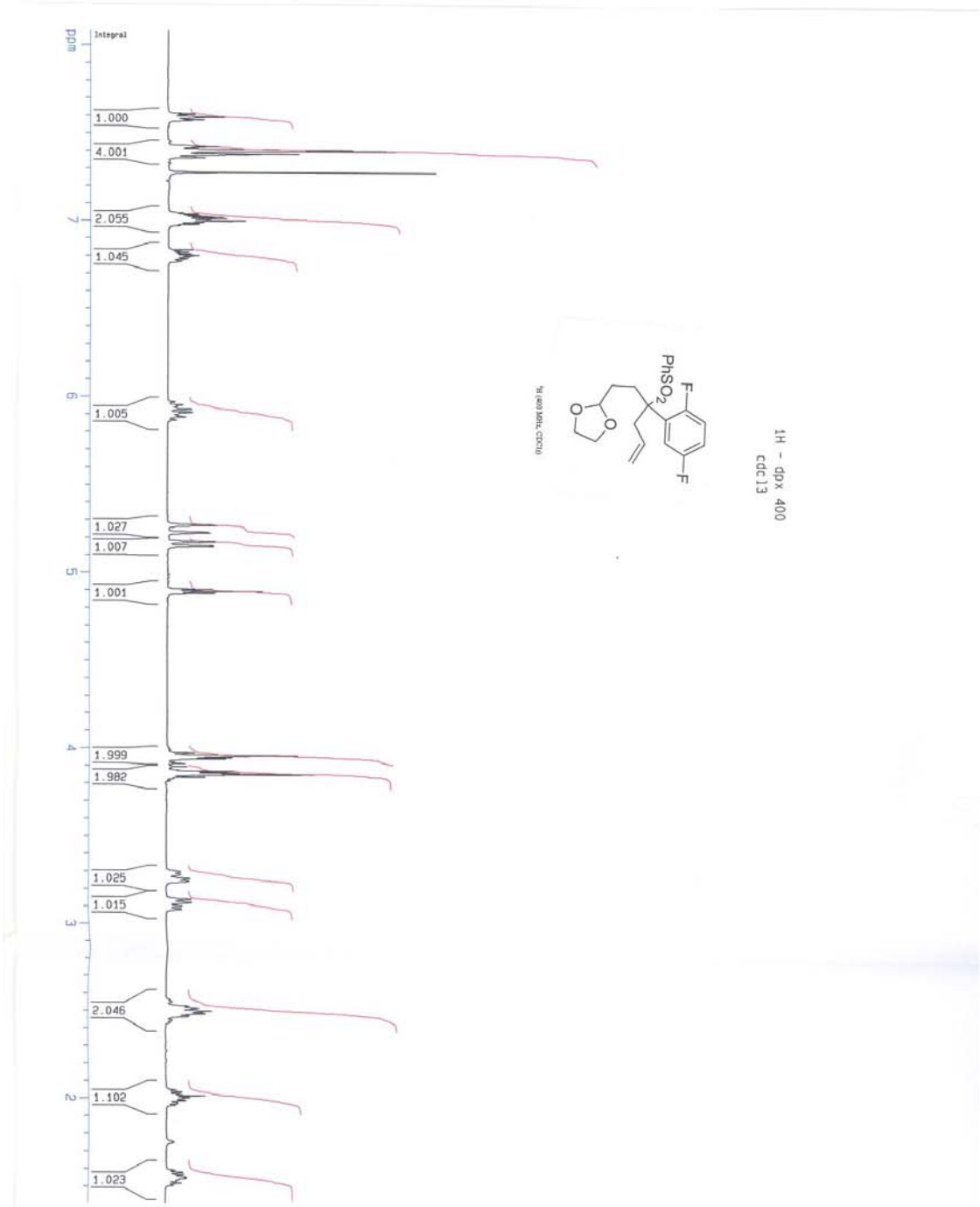
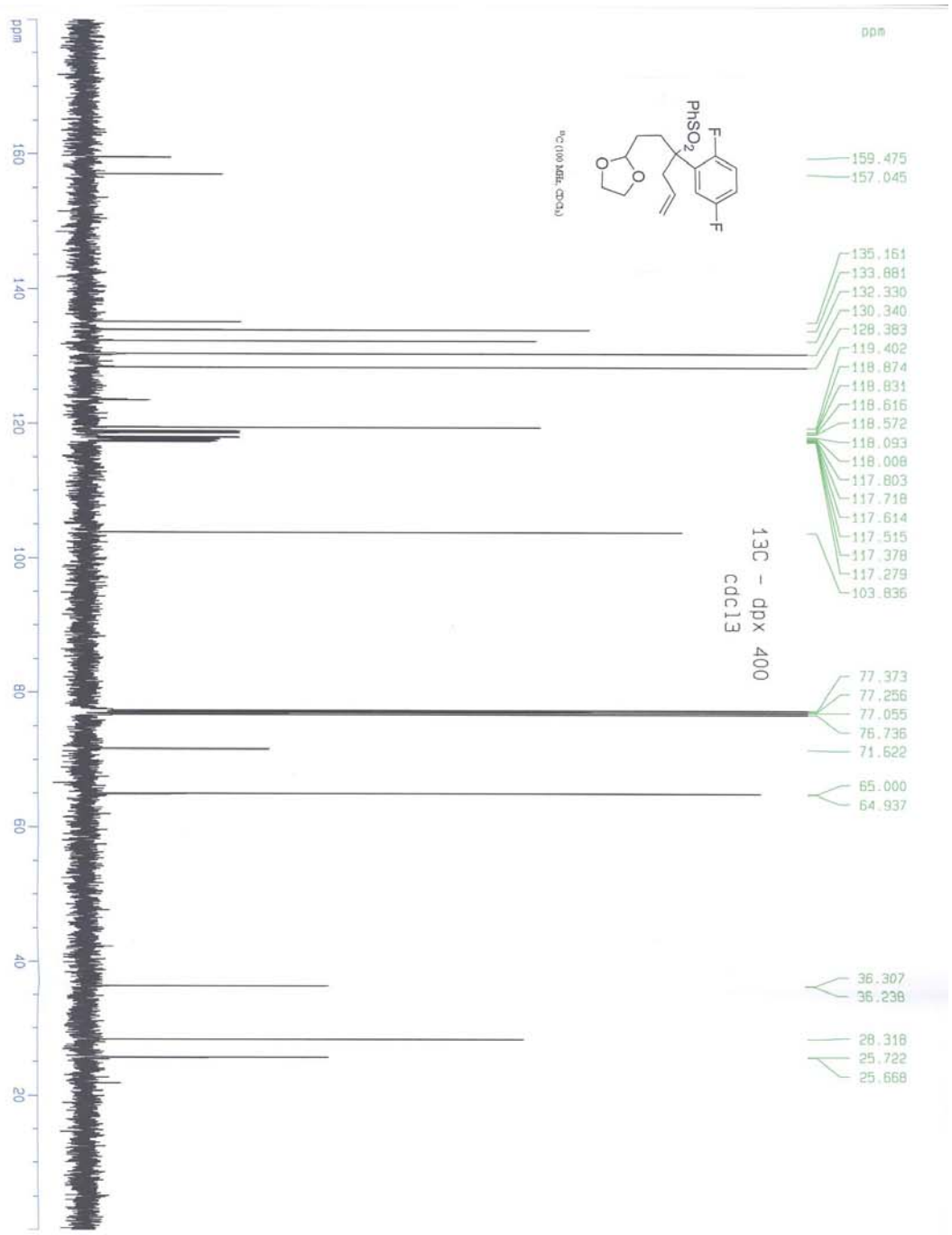
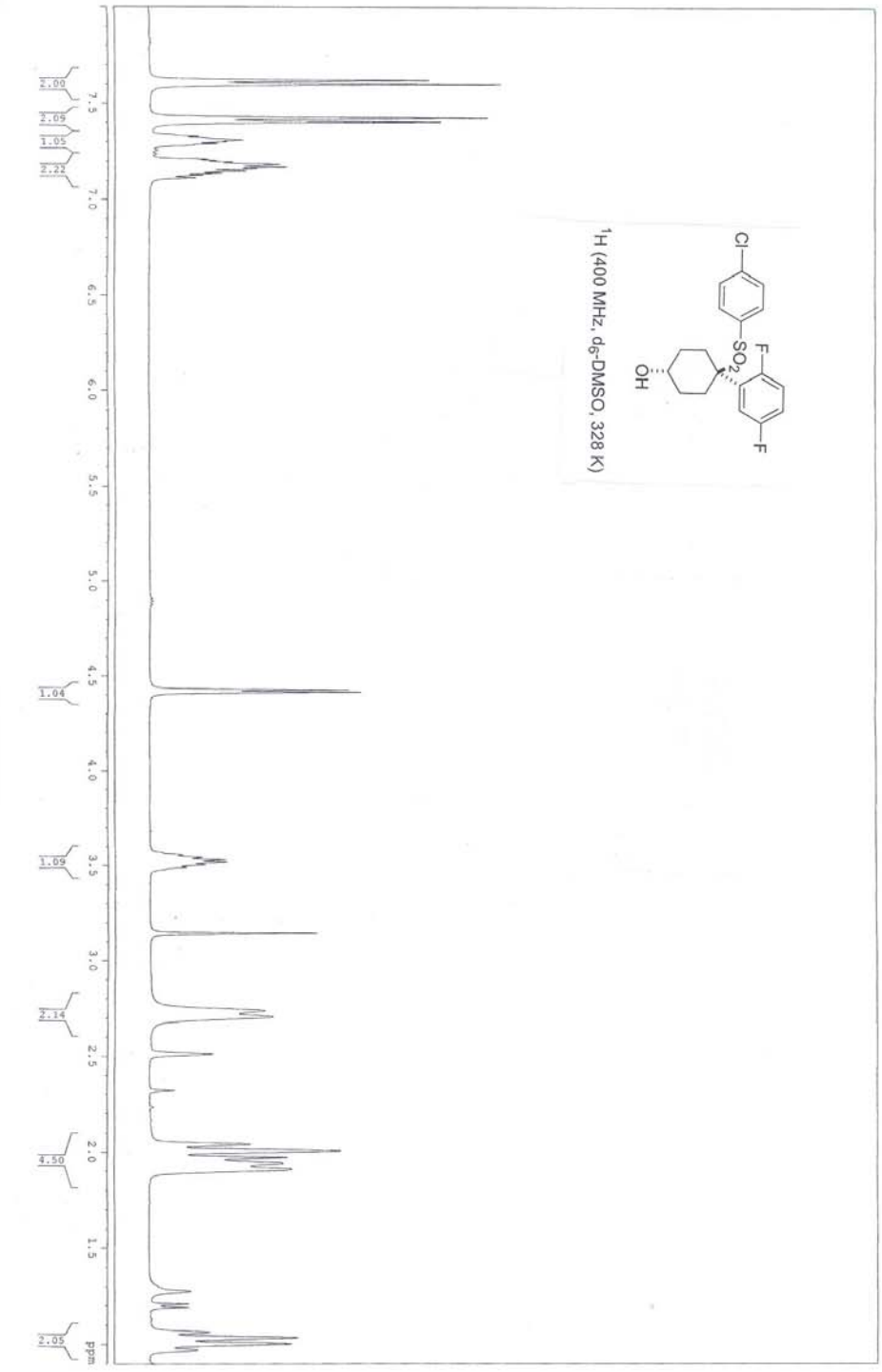
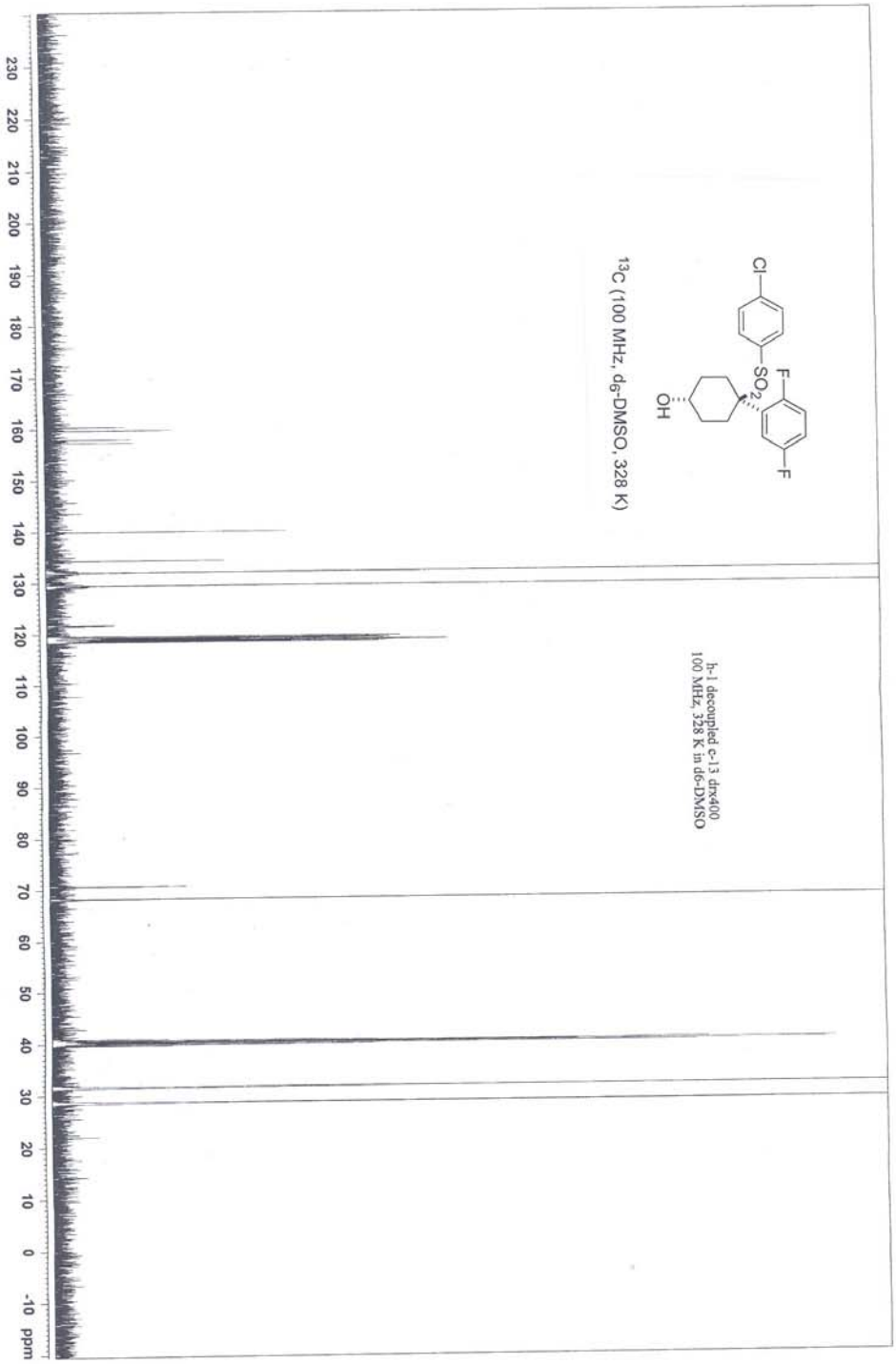
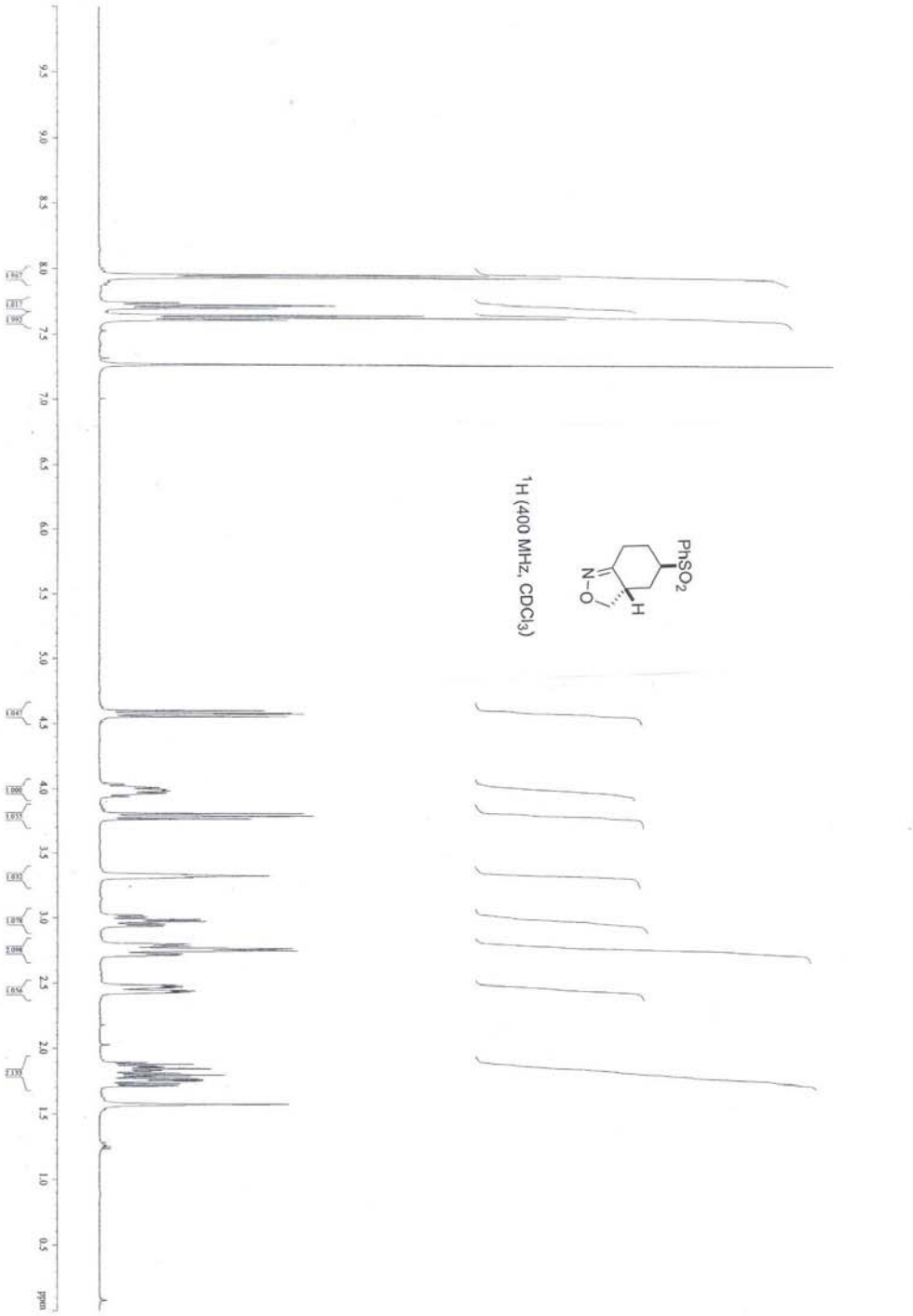
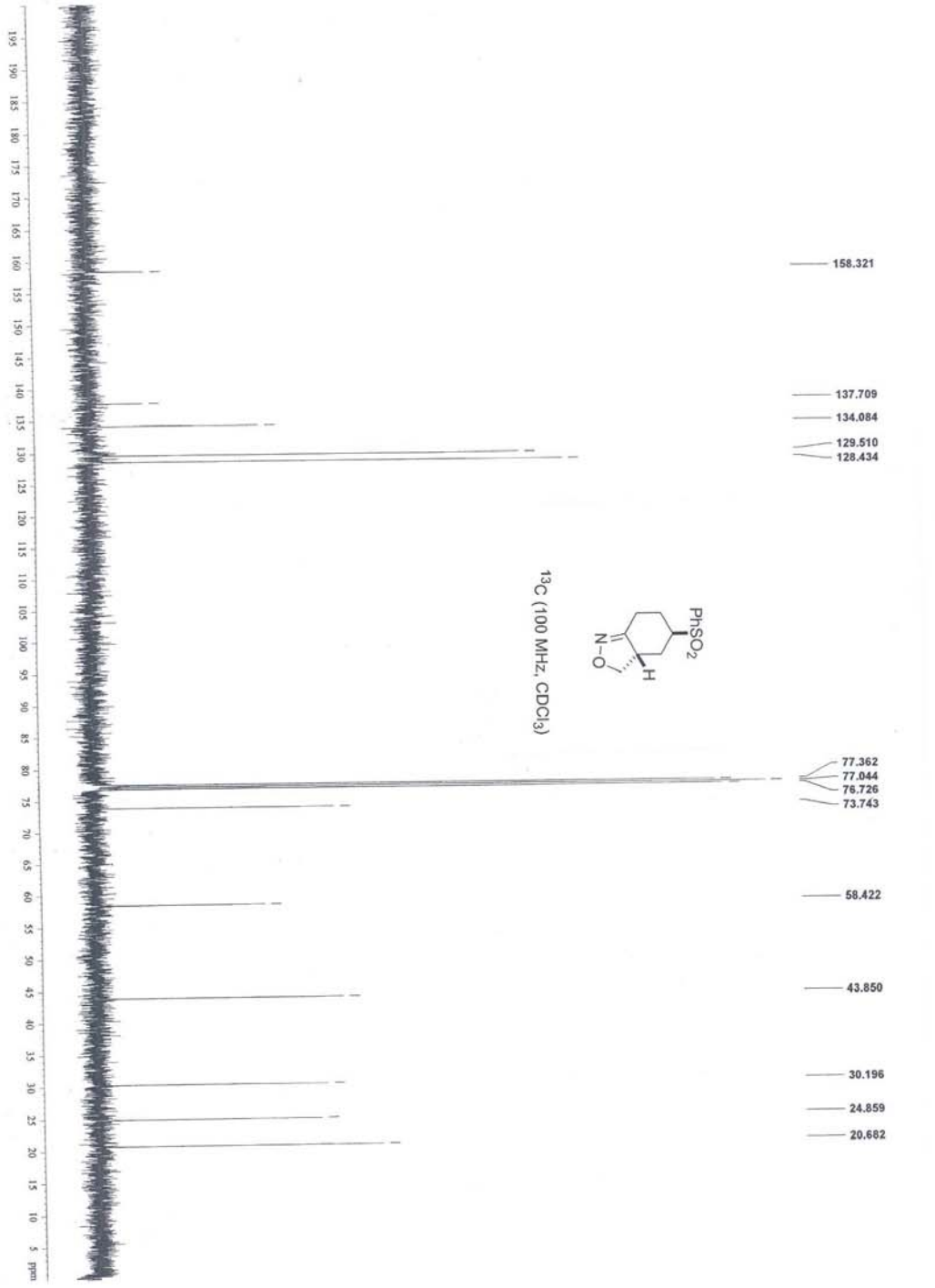

ppm
Integral
1.000
4.001
2.055
1.045
1.005
1.027
1.007
1.001
1.999
1.982
1.025
1.015
2.046
1.102
1.023
PhSO2
F
F
1H - dpx 400
cdc13


ppm
159.475
157.045
135.161
133.881
132.330
130.340
128.383
119.402
118.874
118.831
118.616
118.572
118.093
118.008
117.803
117.718
117.614
117.515
117.378
117.279
103.836
77.373
77.256
77.055
76.736
71.622
65.000
64.937
36.307
36.238
28.318
25.722
25.668
13C - dpx 400
cdcl3
F
PhSO2
F


^{1}H (400 MHz, d_6-DMSO, 328 K)
Cl
F
SO2
OH
F
2.00
2.09
1.05
2.22
1.04
1.09
2.14
4.50
2.05
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm


Cl
F
SO2
OH
F
13C (100 MHz, d6-DMSO, 328 K)
h-1 decoupled c-13 dnx400
100 MHz, 328 K in d6-DMSO
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 ppm


^{1}H (400 MHz, CDCl$_3$)
PhSO$_2$
N–O
H
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


158.321
137.709
134.084
129.510
128.434
77.362
77.044
76.726
73.743
58.422
43.850
30.196
24.859
20.682
^{13}C (100 MHz, CDCl$_3$)
PhSO$_2$
N–O
H
ppm