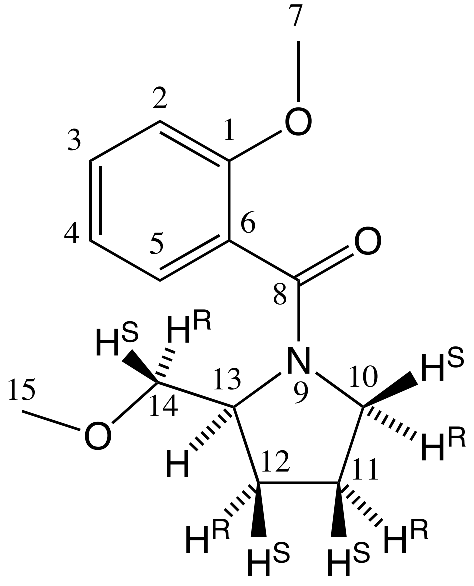
Jeewoo Lim
Brett VanVeller Compound 96 03/23/07



$C_{14}H_{19}NO_3$

Table 1: Assignment of Compound 96 (major conformer)

Label	^{1}H shift (ppm)	^{1}H integration*	^{13}C Shift (ppm)	^{13}C intensity
1			155.2	w
2	6.85	1.37	111.1	s
3	7.28	1.48	130.3	s
4	6.91	1.52	120.7	s
5	7.18	1.29	127.7	s
6			127.1	w
7	3.78	'3'	55.6	s
8			168.0	w
9				
10R	3.17	1.88	48.4	s
10S				
11R	1.87	'1'	24.2	s
11S	1.70	1.04		
12R	1.97	'2'	27.8	s
12S				
13	4.36	1.03	56.2	s
14R	3.69	'1'	72.3	s
14S	3.49	'1'		
15	3.36	3.00	59.1	s

* Integration values in quotes ('') could not be determined because of overlapping signals. Value entered is supposed actual value.

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Entry points:

- MF from MS data gave 249.134 = $C_{14}H_{19}NO_3$
- IHD = 14 - 19/2 + ½ + 1 = 6 (possible benzene ring and carbonyl and one other unsaturation)
- IR spectrum indicated C=O and C-N, possible amide
- 4 aromatic protons with splitting that indicates 1,2 disubstituted benzene (ie: does not resemble 1,4 or 1,3 splitting patterns)
- Two methyl groups (singlets at 3.78 and 3.36) likely bonded to oxygen.
- HSQC and ^1H integrations indicate 2 methyls, 4 methylenes, 1 methine

Assignment of major conformer:

H2-H5

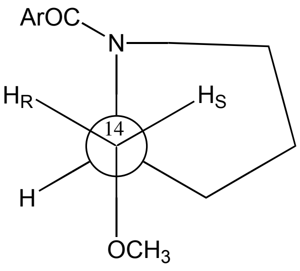
- gCOSY shows coupling of H7 to aromatic proton likely H2.
- gCOSY shows weak cross peak of H2 to signal at 7.18. Also doublet splitting therefore H5 para to H2.
- H4 more shielded by resonance from methoxy leaving H3 as the remaining upfield aromatic signal

H10-H15

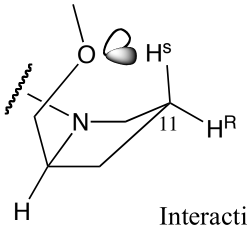
- H13 shows strong coupling to H14's in gCOSY
- H14's adjacent to O due to downfield shift
- H13 also coupled to H12 methylene
- H10 methylene adjacent to nitrogen because of downfield shift
- H10 couple to H11, H11 each couple to H12
- All assignments confirmed by gHMBC

Differentiating proR and pro S of H14 and H11

- Assuming this is a single enantiomer of compound 96 derived from more abundant (S)-Proline and the most stable conformation is the Newman projection shown, H14 proS should be the upfield signal because it resembles an ill-resolved dd due to geminal coupling to H14 proR and trans coupling H13. H14 proR only has strong geminal coupling to H14 proS and thus appears as a doublet (Karplus ^3J) (see 1 below).
- H11 ProS should appear upfield as assigned because of shielding effects of methyl ether through a 6 membered conformation (see 2 below).



1

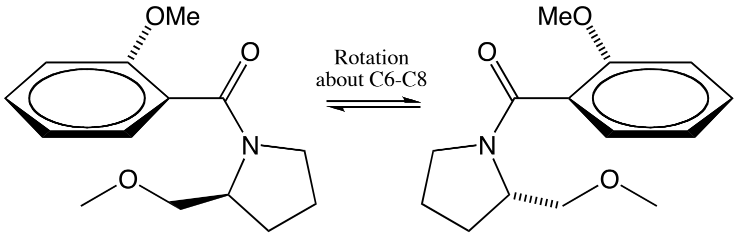


Interaction via 6-membered conformation

2

Assignment of minor conformer:
Other peaks in NMR not due to impurity. GC trace confirms single, pure molecule. Different conformers (a and b) because of rotation about the C8-N9 bond of the amide. Each conformer has a rotamer related by rotation about the C6-C8 bond (amide carbonyl is perpendicular to the benzene to avoid unfavorable steric interactions – confirmed by MM2 calculations)

Minor **a**



Major **b**

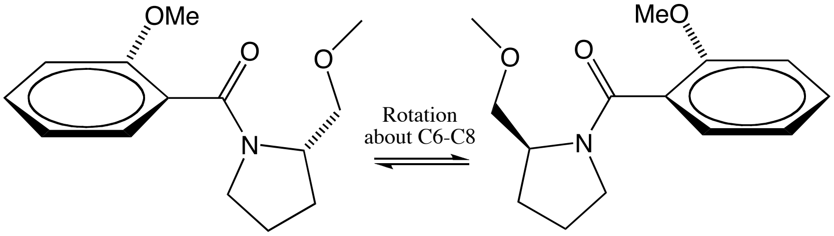


Table 2: Assignment of minor conformer of Compound 96

Label	^{1}H shift (ppm)	^{13}C Shift (ppm)
10R	2.98	73.4
10S		
11R	1.90	22.2
11S		
12R	1.90	28.4
12S		
14R	3.73	45.8
14S	3.54	
15	3.02	58.7

- Conformer b is the major because the downfield H15 signal is more intense (approx 2.5 times by integration) than the downfield H15 signal.
- Differences in methyl (H15) shift arise from π shielding interactions of the benzene ring in conformer a
- Interestingly, H11 and H12 coalesce around 1.90
- Also observe extremely fine changes in the aryl ^{13}C peaks, most notably with C5 (127.574 versus 127.651) because it is most proximal to the pyrrolidine.
- All other shifts (ie: not reported in table 2) appear relatively unaffected
- It is difficult to completely assign the minor conformer because HSQC cross-peaks are often not visible in the 13C 20-30ppm

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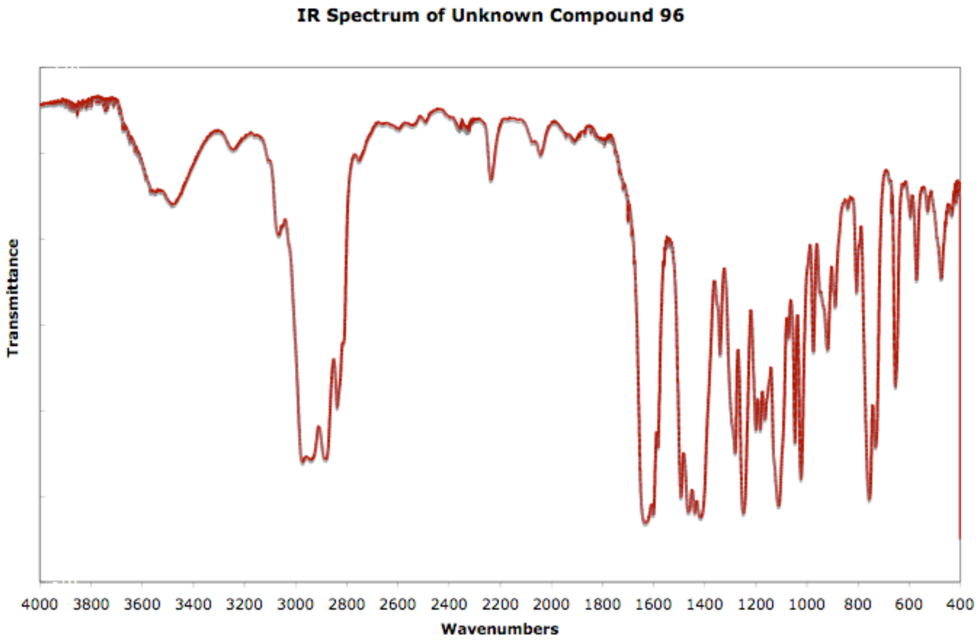
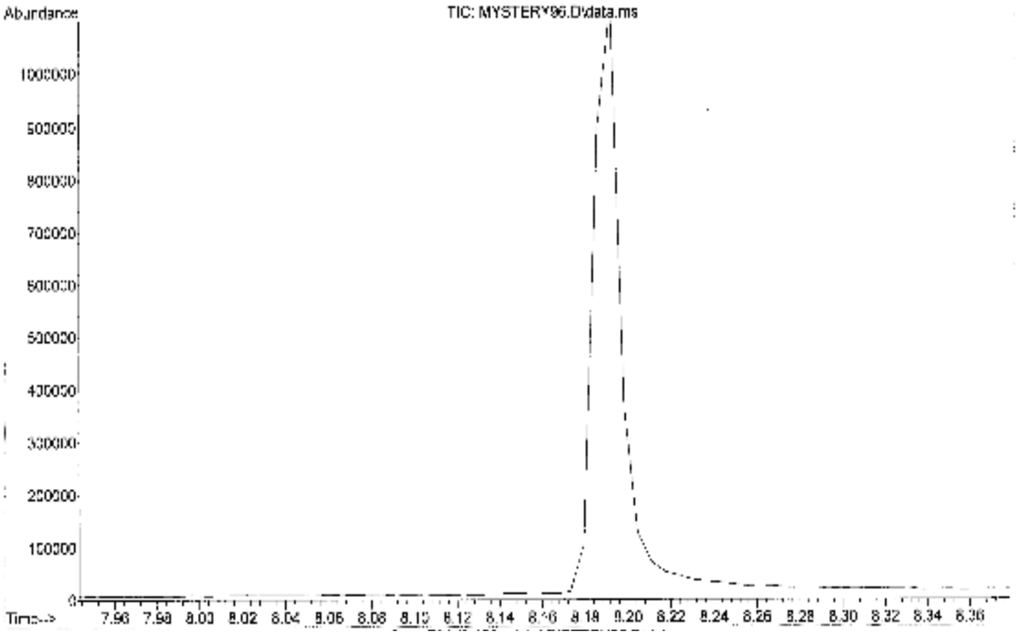
IR Spectrum



GC Trace



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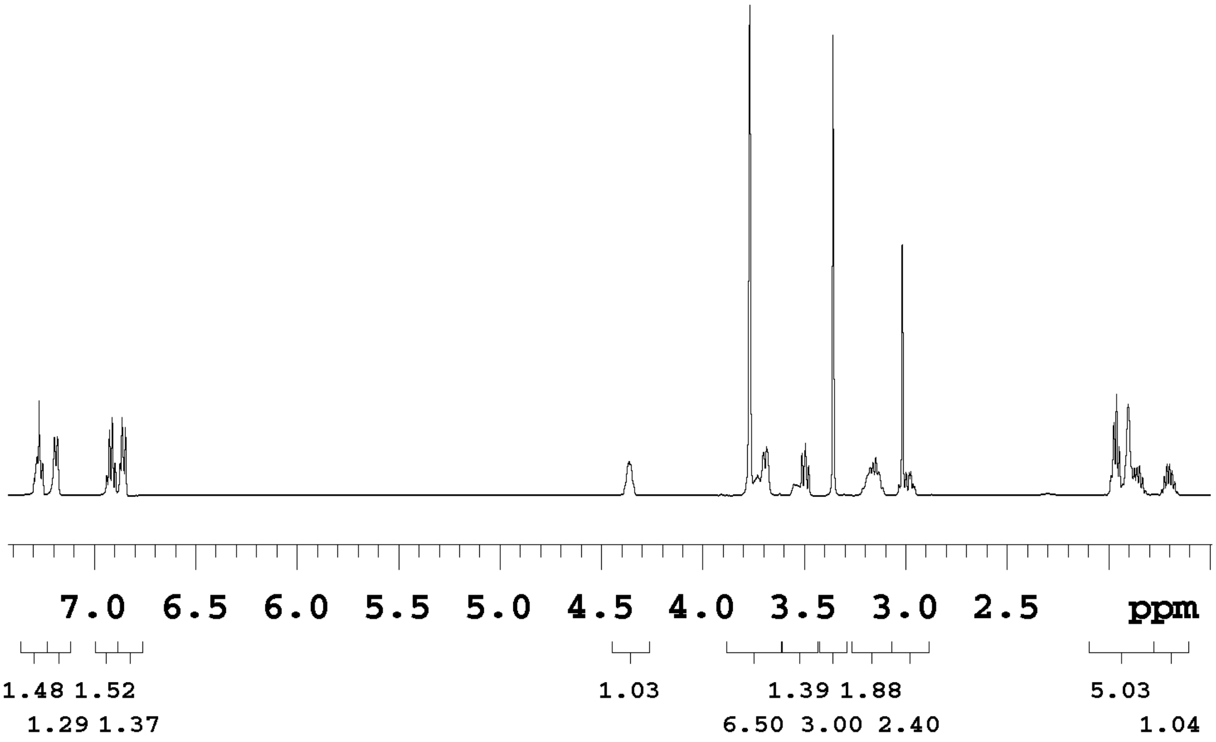
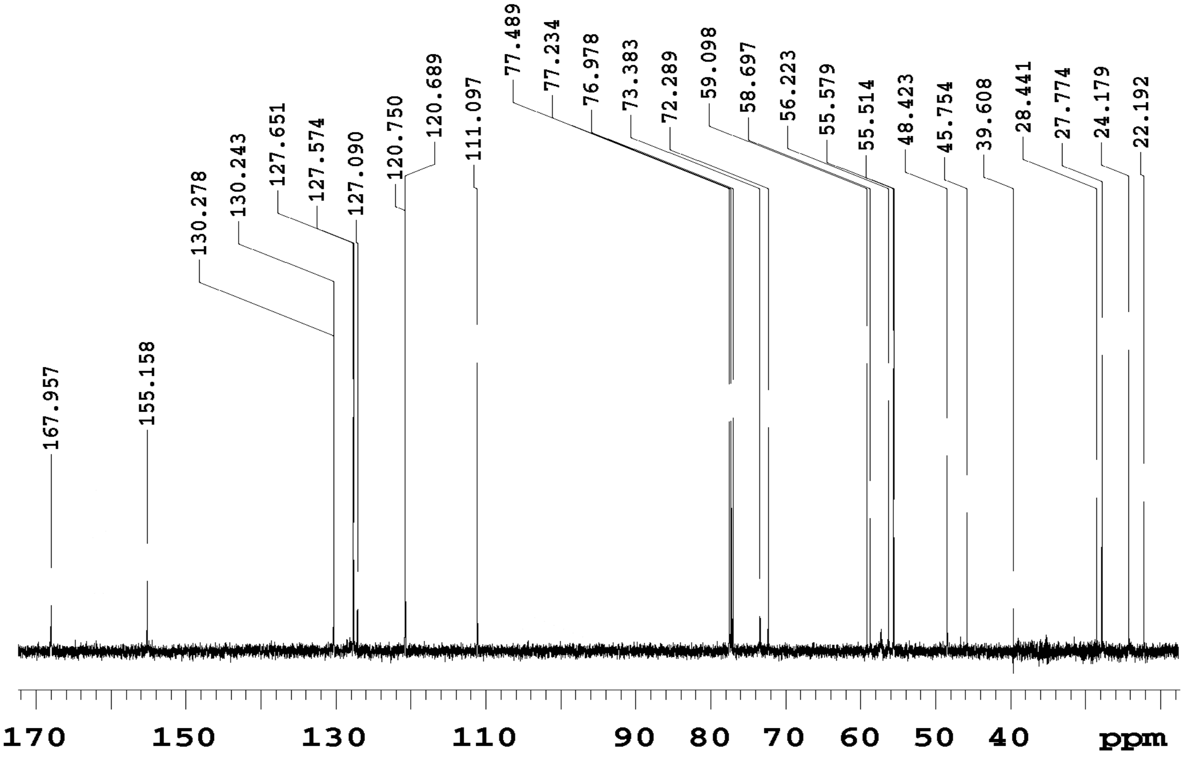
^{1}H NMR 1D



^{13}C NMR 1D



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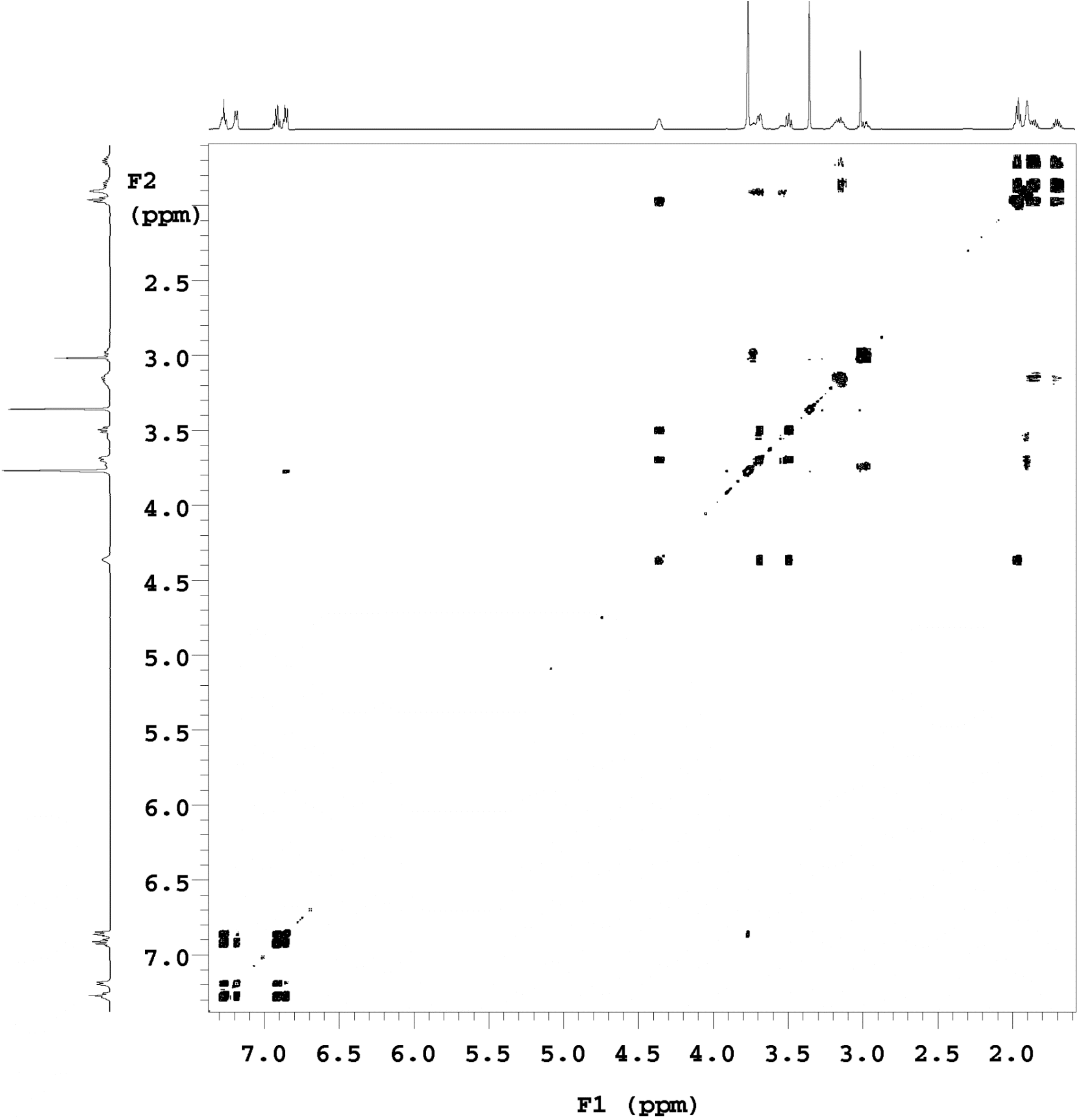
gCOSY



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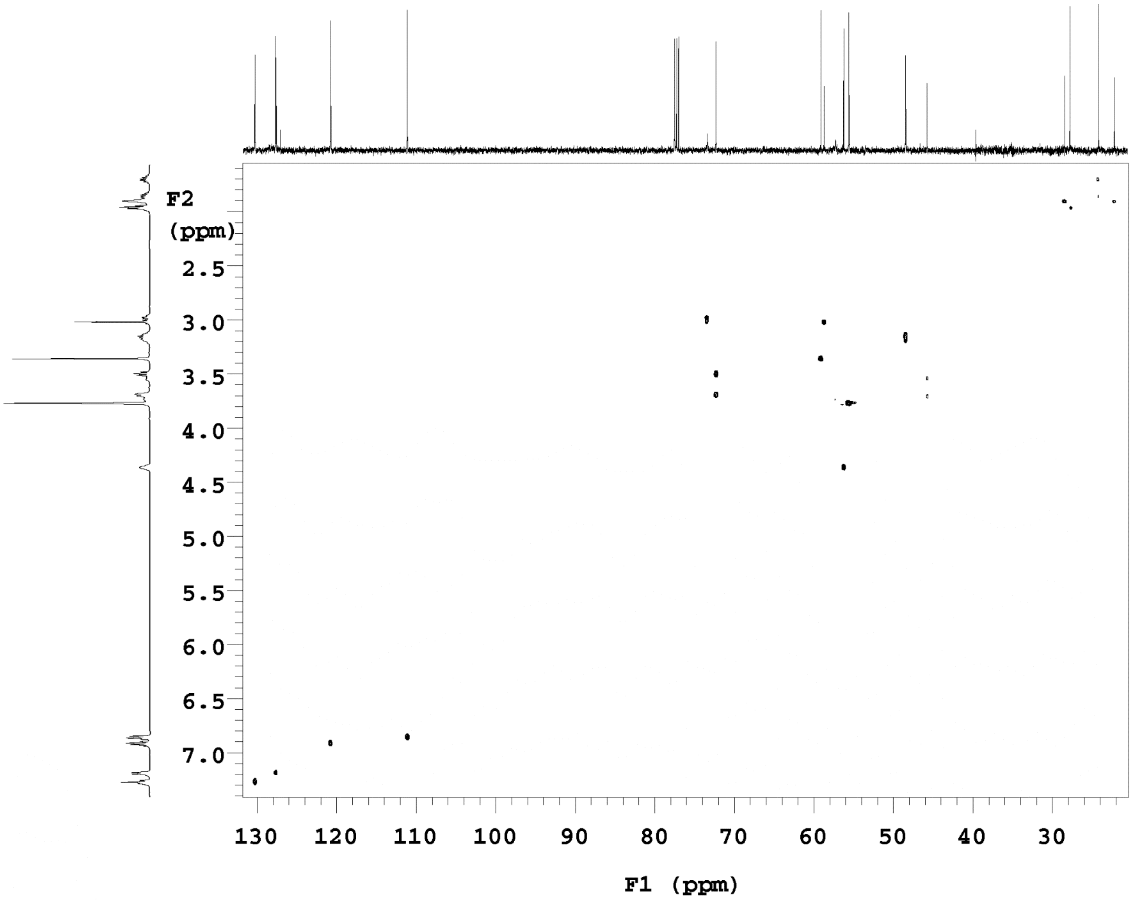
HSQC



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gHMBC