2(*S*),5(*S*)-BIS(HYDROXYMETHYL)-3(*R*),4(*R*)-DIHYDROXYPYRROLIDINE. *OBTENTION, SYMMETRY AND LIQUID STATE CONFORMATION*

Marie-Thérèse Martin and Christophe Morin*

Laboratoire de Chimie Appliquée aux Corps Organisés
Muséum National d'Histoire Naturelle
63, rue de Buffon, 75231 Paris Cedex 05, France

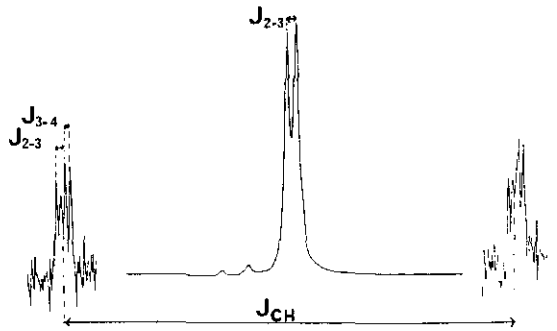
Abstract - A chiral polyhydroxylated pyrrolidine bearing a C_2-axis of symmetry has been obtained. Full ^1H nmr assignments could be made allowing determination of ^4_3T as the liquid state conformation.

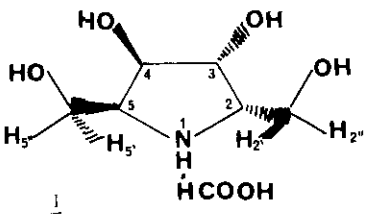
Optically active hydroxylated pyrrolidines are of current interest as chiral inducers[1,2] or glycosidase inhibitors[3-9]. The recent announcement by two teams[10,11] of the synthesis of an isomer of the title compound promts us to disclose hereby our results in that area.

It had been shown earlier that a tricyclic pyrrolidine could be obtained in four steps[12] from a bis-acetal of D-glucitol[13]. It was then realized that removal (formic acid-90°C-150 min) of both acetals would lead to a symmetry-bearing chiral *polyhydroxylated pyrrolidine, namely* 1, *which was* isolated in 97% yield as its formate salt: m.p.114°C (softens), 145°C (fully melts); $[\alpha]_D = -10.1°$ (c = 0.64, H_2O).

Although the synthetic design from D-glucosamine[12,13] secures a built-in symmetry, a detailed nmr work was undertaken to shed light in particular on the conformational features of 1. A C_2-axis of symmetry (on the time-averaged nmr scale) was quickly revealed by the off-resonance 20 MHz ^{13}C spectrum which showed only three types of carbon [D_2O, δ ppm: 74.9 (C_3,C_4), 65.0 (C_2,C_5), 57.5 (CH_2OD)]. The symmetry was confirmed by observation of a single resonance for H_3 and H_4, and a single coupling (with neighbouring H_2 and H_5) in the ^1H nmr spectrum. So as to get the lacking J_{3-4}, an analysis of ^{13}C satellites was carried out: the $H_3-^{12}C-^{13}C-H_4$ array leads to non-equivalence of H_3 and H_4 which allows direct observation (Fig.1) of J_{3-4}. Thus a complete set of values (δ, *J*) for all protons of 1 was obtained (see Table 1), using PANIC (Program for Iterative Simulation, Bruker Software) to solve the ABCX system.

Table 1	δ ppm H_2 & H_5: 3.94 ; H_3 & H_4: 4.32 ; $H_{2'}$ & $H_{5'}$: 3.87 ; $H_{2''}$ & $H_{5''}$: 3.97
J Hz	$J_{2-2'} = J_{5-5'} = 8.8$; $J_{2-2''} = J_{5-5''} = 5.0$; $J_{2-3} = J_{4-5} = 2.9$; $J_{2'-2''} = J_{5'-5''} = -12.4$; $J_{3-4} = 1.7$



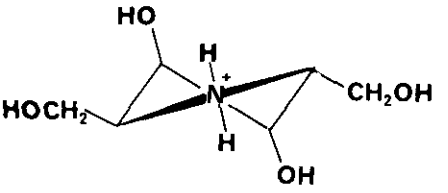


1

Figure 1 - ^{13}C satellite bands observed for H_3 and H_4

There is a key point of interest: when compared with literature values[3,4], J_{3-4} is unexpectedly low. This discrepancy has to be explained as this might reflect a conformational effect. In fact, theoretical calculations in proline series clearly demonstrated that substituent effects on the coupling constants were mainly due to their action on conformation[15]. This was exemplified in 4-hydroxyproline and furthermore with cyclo-$(Pro)_3$ in which differing geometries for each pyrrolidine ring were reduced thus yielding two ranges (1-3 and 8-11 Hz) for J_{3-4} coupling constants[16-18]; these ranges were thus reflective of individual ring geometries.

Now if calculations, using the cyclo-$(Pro)_3$-tailored Karplus equation[16], are made for 1 a 85±7.5° value is found for the $H_3C_3-C_4H_4$ dihedral angle. Among all existing 5-membered ring conformations obtained with the pseudorotation concept[18], only four of them incorporate the desired symmetry: ${}^{N}_{E}$ and ${}^{4}_{3}T$ (and their mirror images). The former is excluded as this would yield a much higher coupling constant[3,4]. Therefore, ${}^{4}_{3}T$ (or ${}^{3}_{4}T$, its mirror image) is retained as the solution conformer for 1.



${}^{4}_{3}T$ conformation of 1

Full assay of the biological activity should allow to know whether this is of significance[8,14].

ACKNOWLEDGMENTS

Drs O.Convert and D.Davoust (Université P.et M. Curie) are thanked for 500 MHz experiments.

REFERENCES AND NOTES

1. J.K.Whitesell and S.W.Felman, J.Org.Chem., 1977, 42, 1663.
2. Y.Ito, T.Katsuki, and M.Yamaguchi, Tetrahedron Lett., 1985, 26, 4643.
3. A.Welter, J.Jadot, G.Dardenne, M.Marlier, and J.Casimir, Phytochemistry, 1976, 15, 747.
4. R.Nash, E.A.Bell, G.W.J.Fleet, R.H.Jones, and J.M.Williams, J.Chem.Soc.,Chem.Commun., 1985,738.
5. D.W.Jones, R.J.Nash, E.A.Bell, and J.M.Williams, Tetrahedron Lett., 1985, 26, 3125.
6. P.DeShong,D.R.Sidler, D.A.Kell, and N.N.Aronson Jr., Tetrahedron Lett., 1985, 26, 3747.
7. G.W.J.Fleet, S.J.Nicholas, P.W.Smith, S.V.Evans, L.E.Fellows, and R.J.Nash, Tetrahedron Lett., 1985, 26, 3127.
8. G.W.J.Fleet, Tetrahedron Lett., 1985, 26, 5073.
9. C.J.Rule, B.A.Wurzburg, and G.Ganem, Tetrahedron Lett., 1985, 26, 5379.
10. P.J.Card and D.W.Hitz, J.Org.Chem., 1985, 50, 891.
11. G.W.J.Fleet and P.W.Smith, Tetrahedron Lett., 1985, 26, 1469.
12. C.Morin, Tetrahedron Lett., 1984, 25, 3205.
13. C.Morin, Carbohydr.Res., 1984, 128, 345.
14. Preliminary results (M.Baran-Marszak and R.Labia) indicated that 1 was inhibitor of Jack bean α-mannosidase (50% inhibition at $6.7.10^{-6}$M).
15. F.A.A.M. de Leeuw, A.A.Van Beuzekom, and C.Altona, J.Comput.Chem., 1983,4, 438.
16. H.Kessler, A.Friedrich, and W.E.Hull, J.Org.Chem., 1981, 46, 3892.
17. H.Kessler, W.Bermel, A.Friedrich, G.Krack, and W.E.Hull., J.Am.Chem.Soc., 1982, 104, 6297.
18. C.Altona and M.Sundaralingam, J.Am.Chem.Soc., 1972, 94, 8205.

Received, 2nd December, 1985