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The use of J-coupling as a sole criterion to assign the total absolute stereochemistry of new pyrrolidinone class synthetic analogs, derived from *S*-pyroglutamic acid

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ABSTRACT

During the synthesis of new pyrrolidinone analogs possessing biological activity it is intriguing to assign their absolute stereochemistry as it is well known that drug potency is influenced by the stereochemistry. The combination of J-coupling information with theoretical results was used in order to establish their total stereochemistry when the chiral center of the starting material has known absolute stereochemistry. The J-coupling can be used as a sole criterion for novel synthetic analogs to identify the right stereochemistry. This approach is extremely useful especially in the case of analogs whose 2D NOESY spectra cannot provide this information. Few synthetic examples are given to prove the significance of this approach.

1. Introduction

Derivatives of 2-pyrrolidinone have shown significant biological and pharmacological activities. Some of them are well known medicines, eg., 2-oxo-1-pyrrolidine acetamide (piracetam) for patients with seizures, Alzheimer's and senile dementia, concussion and other neurological problems [1], 1-ethyl-4-(2-morpholin-4-ylethyl)-3,3-diphenyl-pyrrolidine-2-one (doxapram) for patiens with respiratory failure [2], etc. Moreover, the pyrrolidinone template, considered as an essential pharmacophore group, is incorporated in more complicated chemical structures, e.g. in Ceruletide [3], which stimulates gastric, biliary and pangreatic secretion, in Gonadorelin (GnRH) [4], responsible for the release of follicle stimulating hormone and luteinizing hormone from the anterior pituitary and many others.

We have developed some pyrrolidinone analogs that are proved to exert anti-inflammatory activity [5–7]. In the first steps of the synthesis of some of these pyrrolidinone analogs, it is intriguing to assign the absolute stereochemistry of the intermediate products. Searching in the literature the topic of stereochemistry of pyrrolidinone analogs, it was observed that information on this aspect was either inadequate or obscured. Some representative examples from the literature are given below (see Fig. 1).

Compound **1** was structurally elucidated based on NMR and MS spectra but no information is given about the assignment of its stereochemistry. For the pyrrolidine analog **1** the proton H3 appears as a doublet with J value of 10 Hz and resonates at $\delta = 4.74$ ppm [8].

Compounds **2** and **3** were structurally elucidated using NMR and MS results. The absolute stereochemistry of the compounds was assigned based on 1D NOE experiments. The J-couplings $^3J_{ab}$ and $^3J_{ac}$ were found to be 9.5 and 1.1 Hz correspondingly for **2** and 8.4 and 7.00 Hz for **3**. Interestingly, only **3** analog shows strong NOE

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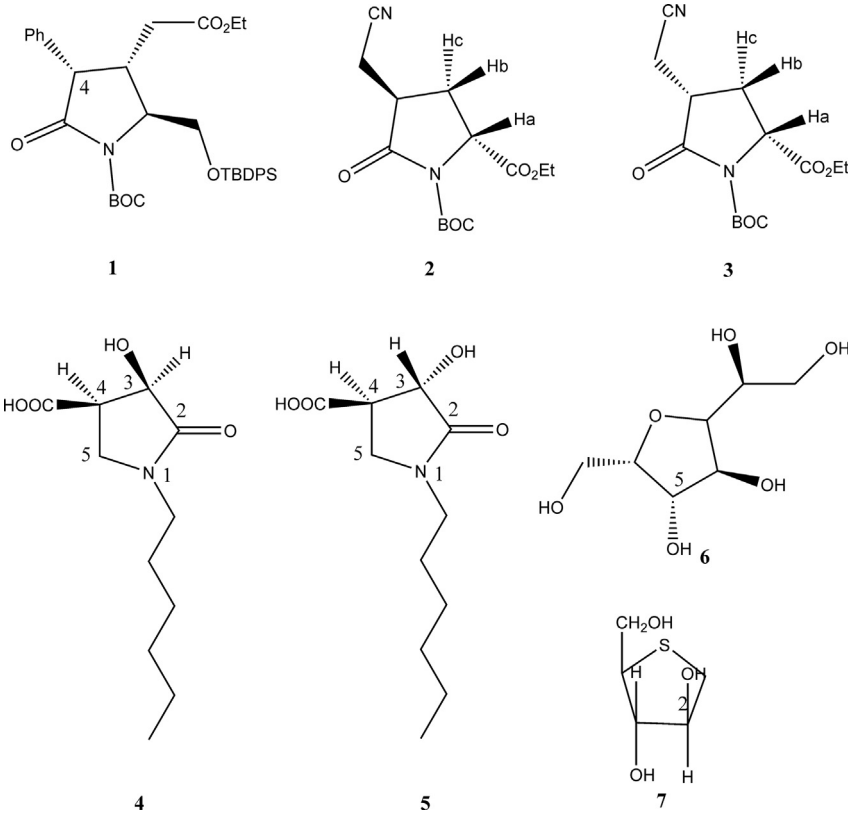


Fig. 1. Chemical structures of pyrrolidinone analogs (1-5), sugar (6) and thiosugar 1,4-dideoxy-1,4-epithio D-arabinitol (7).

between H_a and H_c protons [9].

Compounds **4** and **5** were synthesized and their absolute stereochemistry was assigned using the 2D NOESY experiments. The proton H3 resonates at 4.21 ppm in **4** and at 4.20 ppm in **5** and appears as a doublet in both cases. The J-coupling for this proton was not provided by the authors [10].

Sugar and thiosugar analogs are well known to be potent inhibitors of glycosidases. For example for compound **6** it has been

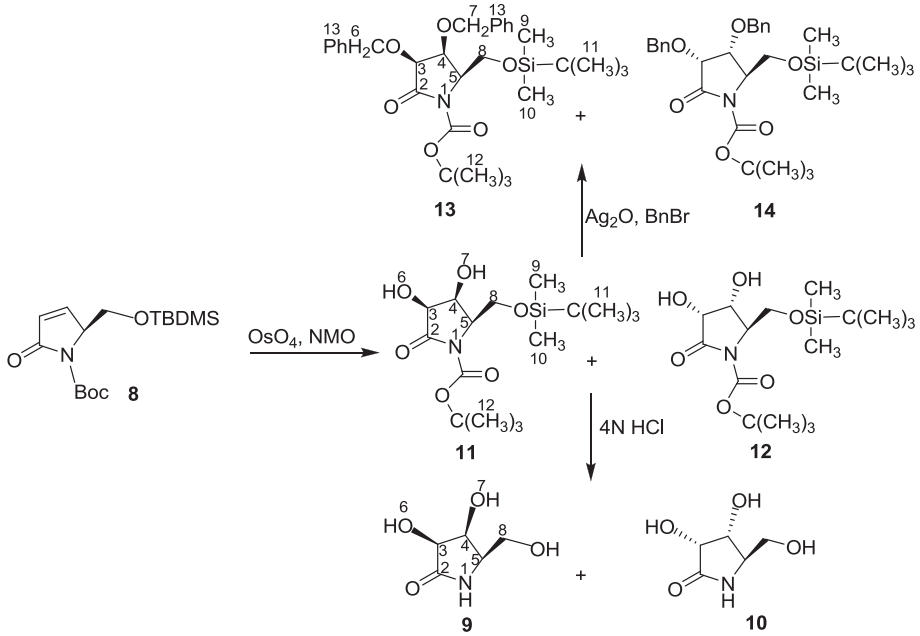


Fig. 2. The reactions used for obtaining possible products **9**–**14**. Under the described experimental conditions only products **10**, **12** and **14** are observed.

reported that proton H4 resonates at 4.70 ppm and it has J-couplings of 5.2 and 3.5 Hz with adjacent protons (*cis* and *trans* relationship) [11]. H3 (Fig. 1) of compound **7** resonates at 4.23 ppm as ddd with J-couplings 6.0, 6.4 and 6.4 Hz and H4 resonates at 3.92 ppm and shows a triplet with J coupling 6.4 Hz [12].

2. Materials and methods

2.1. Theoretical calculations

The molecules were built using z-matrix editor in Molden program [13] (freeware, available at http://www.cmbi.ru.nl/molden/molden.html). The coordinates were saved in xyz format and used as the input coordinates for geometry optimization. The molecules were optimized *ab initio* in Gaussian 09 program [14] using B3LYP/6-31G** model chemistry (a hybrid density functional model using a 6-31G** basis set). The program was run to find not only the optimization of the structure but also the J-couplings between H4 and H5 using Gaussian nmr = SpinSpin option.

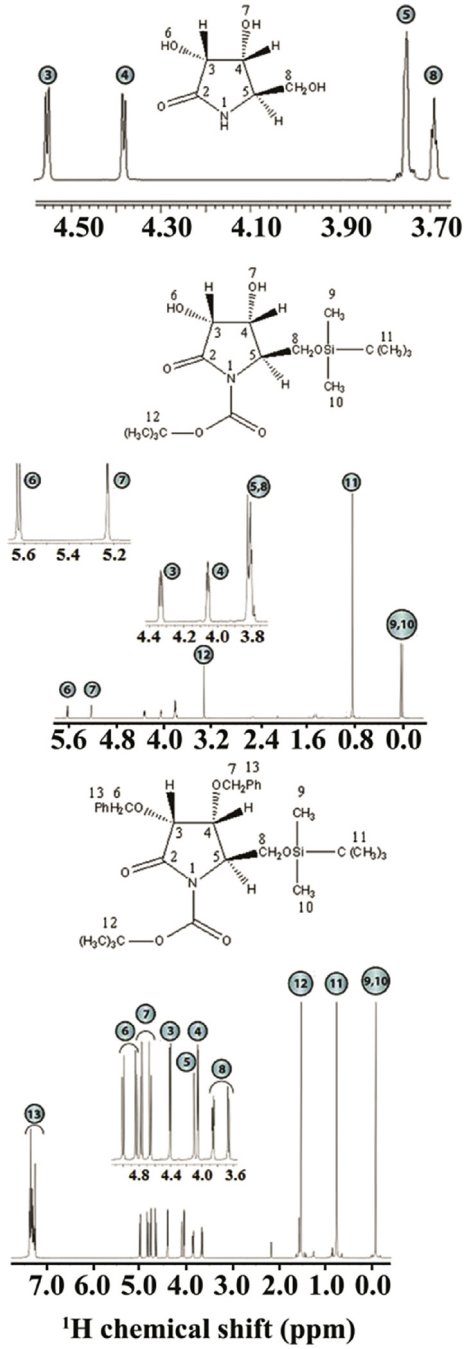


Fig. 3. ^{1}H NMR spectra of **12** (top), **10** (middle) and **14** (bottom).

2.2. NMR spectroscopy and organic synthesis

1D and 2D NMR spectra were obtained using 600 and 800 MHz Varian spectrometers for the structure identification of the compounds. Deuterated solvents (DMSO-d_6, CD_3OD and $CDCl_3$) were obtained from Sigma-Aldrich with purity >99%. Spectra were collected using the pulse sequences in the Varian library of pulse programs. The molecules were synthesized using known procedures reported in the literature [10].

3. Results and discussion

The reaction of *tert*-butyl (2*S*)-2-([[*tert*-butyl(dimethyl)silyl]oxy]methyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (**8**) [15] with OsO_4/NMO followed by acidolysis with 4N HCl in dioxane can lead to two possible isomers (3*S*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)pyrrolidin-2-one (**9**) and (3*R*,4*R*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)pyrrolidin-2-one (**10**) as it is shown in Fig. 2.

However, the experimental data have shown the existence only of the product **10**. CD_3OD is used for obtaining NMR spectra as it dissolves the compound **10** completely but it also avoids any complications caused by the geminal and vicinal couplings of protons with −OH protons. As it can be observed from the ^{1}H NMR spectrum (Fig. 3, top) two resonance doublets at 4.56 and 4.38 ppm are assigned to H3 and H4 protons correspondingly.

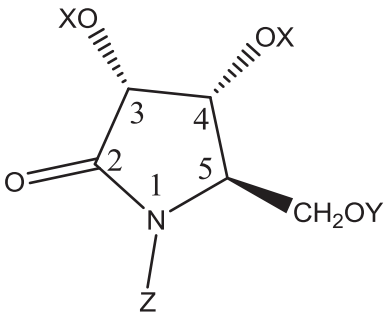
The proton adjacent to NH (labeled as H5) appears as a resonance triplet at 3.74 ppm. Another peak at 3.68 ppm is attributed to the hydroxyl methylene protons (-CH_2OH). The spectrum although very simple, it generates a lot of information. From the spectrum, it appears that vicinal protons attached to the same carbons as the two hydroxyl groups (labeled as H3 and H4, Table 2) are coupled to each other with J coupling of 5.4 Hz (calculated from the distance between the doublet peaks). The ^{1}H NMR spectrum shows that no observable coupling exists between protons H4 and H5 since the resonance of H4 appears only as a doublet (d) and not as a doublet of doublet (dd) (see Table 1).

For the clarification of spectrum appearance of the resulted compound we calculated the J-couplings of the possible products **9** and **10**. Isomers **9** and **10** were minimized in energy using quantum mechanical calculations and the vicinal J-couplings between H4 and H5 ($^3J_{45}$) were calculated. The theoretical results showed that *trans*$^3J_{45}$coupling is almost zero (−0.1 Hz) for isomer **10** (Fig. 4).

The dihedral angles calculated in the optimized structure are also shown in Table 2. The *cis*$^3J_{34}$ coupling for isomer **10** between H3 and H4 protons was found to be 5.1 Hz and is in a close proximity to the experimental value of 5.4 Hz (Table 1). The same procedure was applied for the putative product **9** (Table 1). The theoretical results for this compound showed that the *trans*$^3J_{45}$ coupling is 6.3 Hz, far away from the experimental value. Thus, the complementary results derived from ^{1}H NMR spectrum and J-coupling theoretical calculations show unequivocally the stereochemistry of the compound **10**.

For gaining more applicability to this observation, the compounds **11** and **12**, precursors of **9** and **10** respectively, were also examined [16]. These compounds bear the protecting groups tert-butyloxycarbonyl (BOC) and tert-butyldimethylsilyl (TBDMS). The compounds **13** and **14** protected at the hydroxyl groups by benzyl

Table 1
Theoretical and experimental vicinal J-couplings $^3J_{34}$ and $^3J_{45}$.



Compound	Structure	Exp. $^3J_{34}$	Th. $^3J_{34}$	Exp.$^3J_{45}$	Th.$^3J_{45}$	Solvent
10	X = Y = Z = H	5.4	5.1	–	−0.13	CD_3OD
12	X = H, Y = $Si(CH_3)_2C(CH_3)_3$ Z = $COOC(CH_3)_3$	5.1	5.0	–	0.61	DMSO
14	X = CH_2Ph, Y = $Si(CH_3)_2C(CH_3)_3$ Z = $COOC(CH_3)_3$	5.33	5.6	–	0.35	$CDCl_3$

Table 2
Dihedral angles Φ_{34} and Φ_{45}(four numbers in parenthesis).

Compound	Φ_{34} (H3-C3-C4-H4)	Φ_{45} (H4-C4-C5-H5)
10	−40.4	−94.5
12	−36.8	−92.7
14	−42.4	−86.4

group were also synthesized [17]. The protection of all these compounds **11, 12, 13, 14** cannot affect the configuration of the stereogenic centers, but the substituent might affect the critical dihedral angle Φ_{45} (see Table 2 for its definition) and therefore the $^3J_{45}$ coupling.

The experimental results showed that the $^3J_{45}$ was not

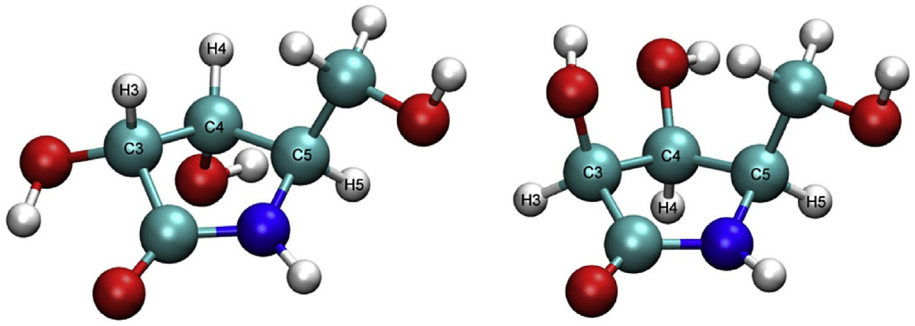


Fig. 4. (Left) Optimized structure of the pyrrolidinone analog **12** using Gaussian 09 program and B3LYP/6-31G** model chemistry. (Right) Optimized structure of the pyrrolidinone analog **11** using Gaussian 09 program and B3LYP/6-31G** model chemistry.

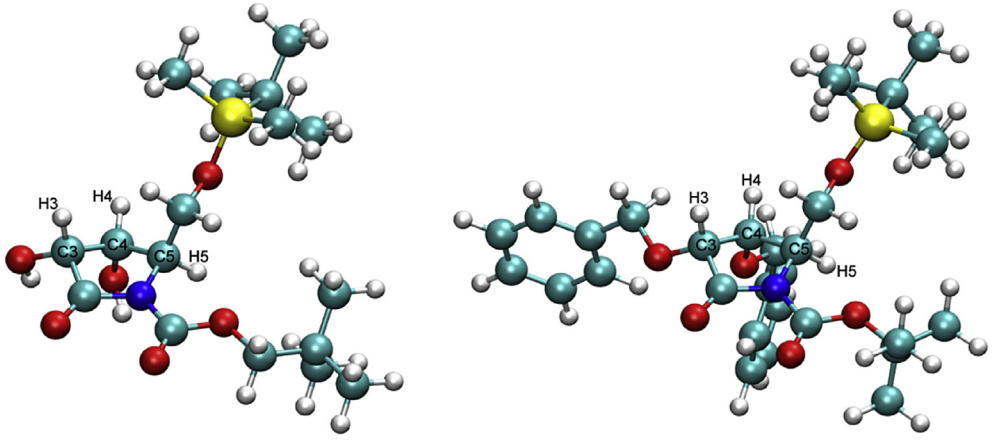


Fig. 5. (Left) Optimized structure of the pyrrolidinone analog **12** using Gaussian 09 program and B3LYP/6-31G** model chemistry. (Right) Optimized structure of the pyrrolidinone analog **14** using Gaussian 09 program and B3LYP/6-31G** model chemistry.

observable for the two precursors and theoretical results confirmed that this is only valid for compounds **12** and **14** as it is expected (see Fig. 5 and Table 1). Compounds **12** and **14** due to their low solubility in methanol were dissolved in solvents $CDCl_3$ and DMSO which appeared to not interfere with the critical dihedral angle Φ_{45} and therefore the $^3J_{45}$ coupling.

4. Conclusions

The described examples are ideal to show how J-coupling as a sole criterion can be utilized to lead to an unambiguous assignment of the stereochemistry for pyrrolidinone analogs. In the light of the importance of these molecules in the rational drug design, this information is valuable in the drug discovery as it can speed up the assignment of the synthesized compounds. Searching to the literature we have found that not a lot of molecules have been synthesized bearing the same stereochemistry in the stereogenic centers as those described.

2D NOESY can be also used to confirm the stereochemistry of the compounds. However, it should be pointed out that obtaining 2D NOESY spectra is time consuming and the critical peaks of interest may suffer from overlapping that hinders such analysis.

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