

Short Note

Determination of the Absolute Configurations of (+)-*N*-((3*S*)-3- $\{[(4\text{-methylphenyl)sulfonyl]amino}\}$ -1-oxaspiro[4.5]deca-6,9-dien-2,8-dion-7-yl) Acetamide and Benzamide

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Received: 18 September 2008 / Accepted: 3 November 2008 / Published: 7 November 2008

Abstract: We recently reported the asymmetric synthesis of the two title compounds without the configurational assignments of the newly formed chiral spirocarbons. We now wish to report that both compounds have a (*R*)-configuration at the spirocarbon based on 1D and 2D nuclear Overhauser enhancement (nOe) experiments.

Keywords: Spiroannulation, stereochemistry, nOe, NMR, absolute configuration.

1. Discussion

For the past few years we have studied the diastereoselective spiroannulation of simple phenols [1-11], and we recently reported the asymmetric synthesis of two new spiro lactones (+)-**1** and (+)-**2** (Figure 1) from optically active (*S*)-3-nitrotyrosine [1]. However, at the time of publication we had yet to determine the absolute configuration of the newly formed spirocentre in (+)-**1** and (+)-**2**. We now wish to report the absolute configuration of these two compounds as determined using one- and two-dimensional nuclear Overhauser enhancement [nOe] NMR methods. In the absence of crystals suitable for X-ray analysis, we felt that nOe techniques would be the best way to determine these

configurations. We believe that such assignments can be made using NMR techniques since the structure of the two spirocompounds is rigid at the spirocarbon and the stereochemistry of carbon 3 of the lactone ring is known to have a (*S*)-configuration.

The two possible diastereomers of (+)-1 and (+)-2 are shown in Figure 1 (structures A and B). Since carbon 3 in the lactone ring has a (*S*)-configuration as shown in Figure 1 [12], irradiation of H₃ should affect only one of H₁₀ (structure A) or H₆ (structure B) assuming that these protons are in close enough proximity to H₃ to be affected. It is normally assumed that ¹H nOe can be observed between protons located within 500 pm (5Å) of each other [13,14]. This is about twice the distance separating 1,3-diaxial protons on the chair form of cyclohexane (~2.6Å) [14]. When comparing models of cyclohexane with either structures A or B, we estimated that the distance between H₃ and either H₁₀ or H₆ falls within the range normally expected to observe nOe [15].

Figure 1. Possible Configurations for (+)-1 and (+)-2

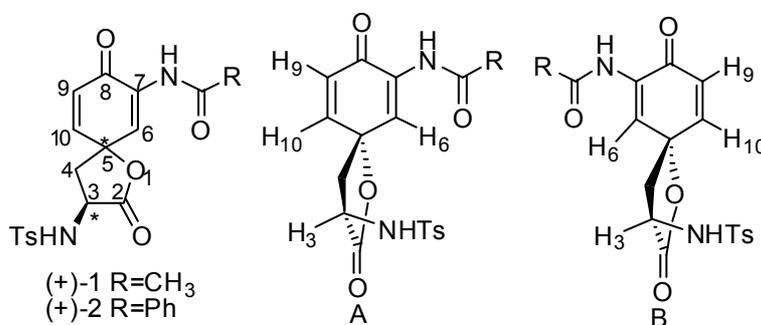


Figure 2. Portion of the Original ¹H-NMR spectrum of (+)-2 in CDCl₃

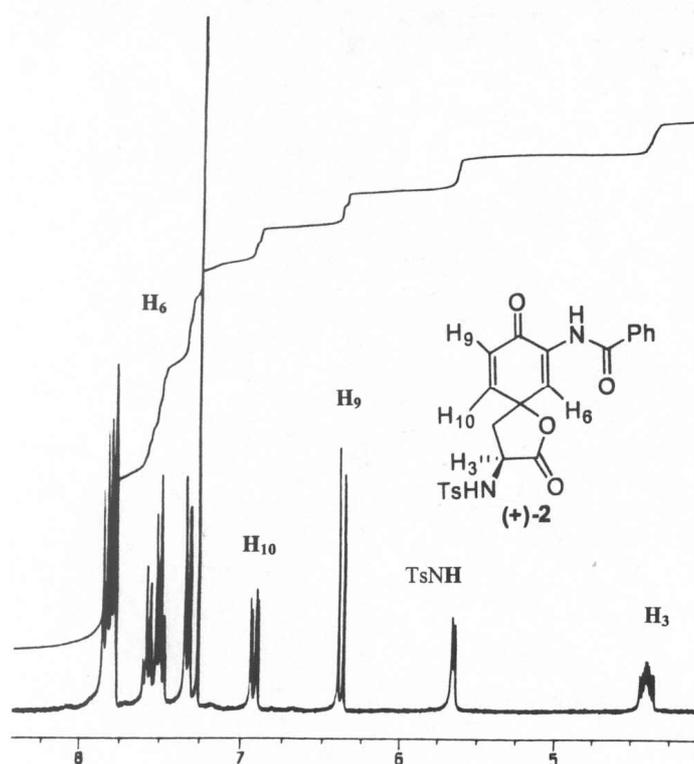


Figure 2 shows a portion of the original ^1H -NMR spectrum of (+)-**2** while nOe results are summarized in Table 1. Irradiation was carried out on all three protons (H_3 , H_6 and H_{10}) with a 2s presaturation time for each experiment. 1D nOe studies of (+)-**1** showed that irradiation of H_3 produced enhancement of the signal of H_{10} (7%) while no nOe effect was observed for H_6 . The reverse experiment, *i.e.* irradiation of H_{10} , showed nOe effect on H_3 (6%) as well as enhancement of the signal of H_9 (5%). No effect was observed between H_3 and H_6 when either H_3 or H_6 were irradiated. This data suggests that the correct configuration for the spirocarbon of (+)-**1** is as shown in structure A found in Figure 1, in other words the spirocarbon has a (*R*)-configuration. A similar analysis can be performed for (+)-**2**.

Table 1. Data from nOe Experiments and Chemical Shifts of Key Protons^a.

Compound	Irradiation	Integration			
		H_{10}	H_9	H_6	H_3
(+)- 1	H_{10} (7.06ppm)	1.00	0.05	n/a	0.06
	H_6 (7.52ppm)	n/a	n/a	1.00	n/a
	H_3 (4.54ppm)	0.07	n/a	n/a	1.00
(+)- 2	H_{10} (6.92ppm)	1.00	0.04	n/a	0.05
	H_6 (7.54ppm)	n/a	n/a	1.00	n/a
	H_3 (4.40ppm)	0.04	n/a	n/a	1.00

^aChemical shifts listed are reported from ref. 1. n/a: no signal visible in nOe difference spectrum

Two dimensional nOe experiments (NOESY and ROESY) were also performed for (+)-**1** and (+)-**2**, and confirmed our results obtained by 1D difference nOe studies. In these experiments, correlation between H_{10} and H_3 for both compounds was observed while correlation between H_3 and H_6 was absent, confirming that structure A is the correct structure for both (+)-**1** and (+)-**2**.

Based on these studies, we can conclude that the chiral spirocarbons in both (+)-**1** and (+)-**2** have a (*R*)-configuration as depicted by structure A in Figure 1. We are still attempting to obtain crystals of the target compounds suitable for X-ray analysis in order to unambiguously assign the configurations of these two compounds.

2. Experimental

1- and 2-dimensional nOe experiments were carried out on a Bruker 300AMX spectrometer at a frequency of 300.13 MHz. Samples were dissolved in CDCl_3 and the spectra were referenced to the residual solvent signal (CHCl_3) at 7.26 ppm. Samples were only slightly soluble in CDCl_3 but stable. Samples were not degassed prior to data accumulation. 1D experiments were performed with a 2s presaturation time, 1024 scans were recorded. Mixing times for the ROESY and NOESY experiments were 200ms and 300ms respectively.

Acknowledgement

We acknowledge the financial contribution of the University of Northern British Columbia in support of this work.

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12. The configuration of the chiral centre at carbon 3 in (+)-**1** and (+)-**2** should be the same as the original chiral centre in (*S*)-3-nitrotyrosine under the reactions conditions used in the synthesis reported [(a) 1) TsCl, THF, 1M NaOH 2) 1M KOH, EtOH, 80-85 °C; (b) H₂, 10% Pd/C, THF; (c) CH₃COCl or PhCOCl, THF, rt; (d) PIFA, acetone, 0°C] (reference 1). Therefore, it is assumed that this centre remained in the (*S*)-configuration.
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15. The distance between H₃ and H₁₀/H₆ is estimated to be between 2.6 Å and 5 Å. The actual distance between these protons in a solution will depend on molecular movement and steric factors found in the molecule. This distance has not been calculated.