

Structural and Conformational Characterization of a Carbohydrate Based Bicyclic Fused δ -Lactone

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Abstract: Free radical mediated carbocyclization of methyl 2,3-di-O-benzyl-4-O-cinnamoyl-6-deoxy-6-iodo- α -D-glycopyranoside using Bu_3SnH and AIBN in refluxing benzene afforded a fused-ring bicycle δ -lactone. The characterization of its structure and the determination of the configuration of the newly formed stereogenic center were accomplished by analysis of its 1H NMR and ^{13}C NMR spectra and the bidimensional experiments COSY, NOESY, HMQC and HMBC.

Resumo: A reação de carbociclicação radicalar de 2,3-di-O-benzil-4-O-cinamoi-6-desoxi-6-iodo- α -D-glicopyranosídeo de metila utilizando-se Bu_3SnH e AIBN em benzeno a refluxo forneceu uma δ -lactona bicíclica com anéis fundidos. A caracterização de sua estrutura e a determinação da configuração do novo centro estereogênico formado foram efetuadas com base na análise de seus espectros de RMN de 1H e RMN de ^{13}C , juntamente com experimentos bidimensionais de COSY, NOESY, HMQC and HMBC.

Introduction

The radical cyclization reactions are widely used for the formation of carbon-carbon bonds in a regio- and stereoselective fashion. They are of recognized utility in the synthesis of a variety of natural products possessing the δ -lactone moieties.¹ In a program aimed to the synthesis of chiral

δ -lactones from carbohydrates, the radical mediated carbocyclization² of compound 1 was investigated. Thus, treatment of 1 with Bu_3SnH and AIBN in boiling benzene furnished 2 in 20 % yield (Figure 1).

Structural characterization of the lactone 2 was performed by the analysis of its NMR data (Table I).

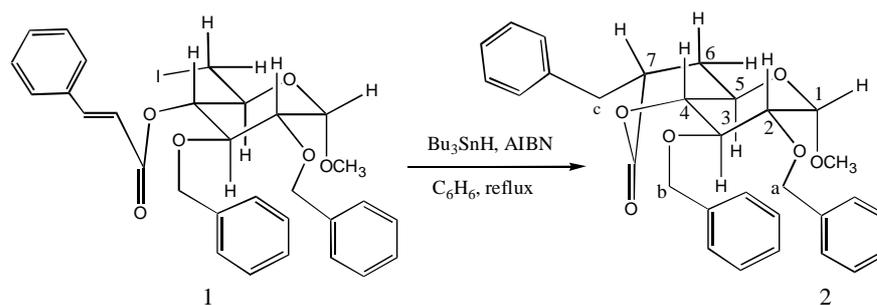


Figure 1 – Reaction conditions for the preparation of δ -lactone 2

Table 1

1H NMR and ^{13}C NMR data of compound 2

	1	2	3	4	5	6a; 6b	7	a	b	c
δ $^1H^{**}$ (M)	4.95 (d)	3.76 (dd)	4.24 (t)	4.42 (t)	3.94 (q)	2.02-1.88 (m)	3.42-3.33 (m)	4.79 (d) 4.84 (d)	5.02 (d) 5.07 (d)	2.82-c (dd) 3.47-c' (dd)
J / Hz*	3.6	9.2	9.2	9.2	9.2	-	-	12.0	11.6	***
δ $^{13}C^{**}$	98.89	79.83	79.04	79.15	64.07	29.63	38.62	73.12	75.20	37.28

- Progressive values for the coupling constants; ** OMe δ_H 3.37, δ_C 55.32; δ aromatic δ_H 7.56-7.24 and δ_C 139.51-126.89; δ CO 173.72; *** 13.8 Hz ($J_{c,c'}$); 9.2 Hz ($J_{c,7}$); 4.8 Hz ($J_{c',7}$)

Experimental

NMR experiments were performed with a solution of **2** (50 mg) in pyridine-d₅ (except for the HMBC experiment that was performed in CDCl₃) with TMS as the internal standard, with a Bruker AVANCE DRX-400 spectrometer equipped with a dual direct probe; chemical shifts are given in the δ -scale and *J*-values are given in Hz. For the proton, carbon and DEPT experiments, the spectra were acquired with the sample spinning at 20 Hz at 300K. The 2D-experiments were acquired in the non-spinning mode. The homonuclear chemical shift correlation was established by COSY with homospoil gradients with the cosygr pulse program [number of scans (transients) = 1, dummy scans = 8, time domain in F2 = 2048, time domain in F1 = 1024].

The heteronuclear shift correlation was achieved by the HMQC [number of scans (transients) = 8, dummy scans = 16, time domain in F2 = 1024, time domain in F1 = 1024] and HMBC [number of scans (transients) = 16, dummy scans = 16, delay for evolution of long range couplings = 60 ms, time domain in F2 = 4096, time domain in F1 = 1252] experiments. Nuclear Overhauser effect was detected via NOESY experiment [number of scans (transients) = 8, dummy scans = 16, mixing time = 600 ms, time domain in F2 = 2048, time domain in F1 = 512], and the contour plot was not symmetrized.

Results and Discussion

The bidimensional COSY, HMQC and HMBC experiments supported the assignment of protons and carbons from the respective NMR spectra. The COSY contour plot (Figure 2) allowed the location of H-3 at δ 4.24 and H-4 at δ 4.42, as two triplets with *J* 9.2 Hz. The NOESY contour plot allowed the assignment of the methylene protons a (correlation with H-2) and b (correlation with H-3) which, in turn, allowed the assignment of the corresponding carbon atoms by analysis of the HMQC contour plot (data not shown).

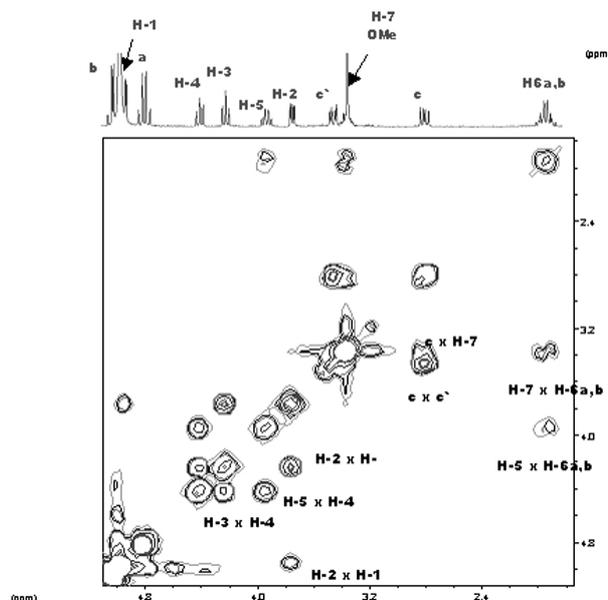


Figure 2 – Expanded section of the COSY contour plot of **2**

The assignment of C-2, C-3 and C-4 was then possible by analysis of the HMQC contour plot (Figure 3).

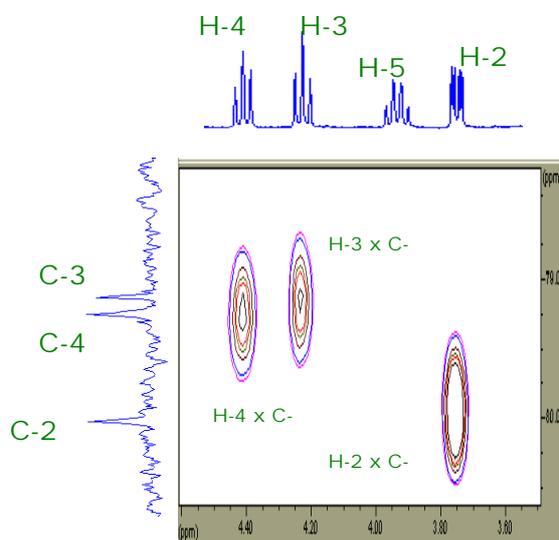


Figure 3 – Expanded section of the HMQC contour plot of **2**

The 6-*exo*-trig cyclization mode, as predicted by the Baldwin rules³, was deduced by the HMBC experiment (in CDCl₃), due to a three-bond correlation between H-6a,b and the carbonyl carbon (Figure 4).

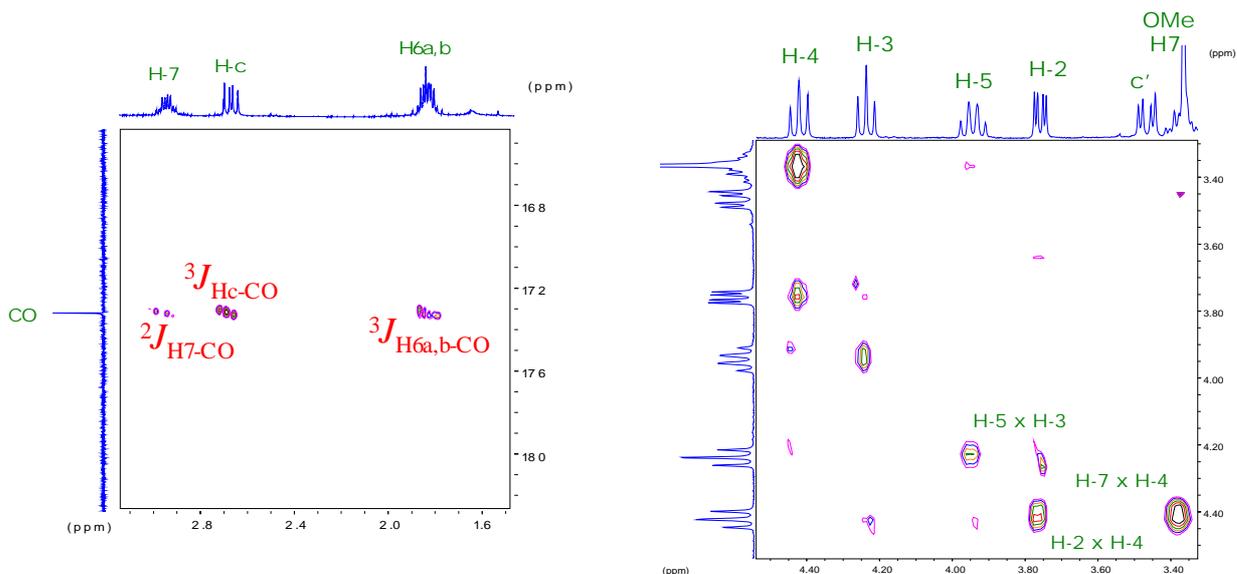


Figure 3 – Expanded section of HMBC contour map (CDCl_3) of **2** showing the correlation between H-6a,b and the carbonyl carbon

A detailed analysis of the proton spectrum shows that the J -values between H-5 and H-6a,b are not related to a chair-like conformation for the lactone ring, as initially expected.

This was concluded from the different multiplicity observed for H-5 (quartet) when compared to the very common triple doublet found in the case of a chair-like conformation.

The NOESY contour map (Figure 4) shows correlation between H-4 and H-7, which is the evidence that these hydrogens are *syn*-orientated. We rationalized this result as being due to the fact that the δ -lactone ring adopts a boat-like conformation. The chair-like conformation would be disfavored by 1,3-diaxial interaction between H-5 and the benzyl group at C-7.

Other examples of δ -lactones prepared by radical mediated carbocyclization adopting boat-like conformations are reported in the literature.⁴

Based on the *syn*-relationship between H-4 and H-7 the absolute configuration of the newly formed stereocenter in the cyclized product was unequivocally determined as **R**.

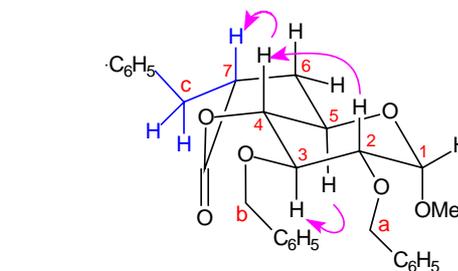


Figure 4 – NOESY contour map and boat-like conformation of **2**

Conclusion

This work highlights the utility of NMR as a powerful tool for the full characterization of organic molecules at the connectivity and conformational levels.

References

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