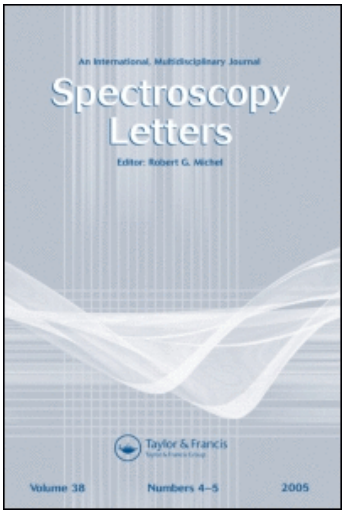

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Nuclear Magnetic Resonance Spectroscopy Study of a Disaccharidic Crown Ether.

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NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY STUDY OF A DISACCHARIDIC CROWN ETHER.

Key words : Disaccharide, Crown Ether, Intramolecular Cyclisation, NMR.

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ABSTRACT

The disaccharidic anhydro derivative 6-*O*-(5,6-anhydro-3-deoxy-1,2-*O*-isopropylidene α-D-glucofuranos-3-yl)-1,2-*O*-isopropylidene-3-*O*-n-dodecyl-α-D-glucofuranose (**1**) led to the disaccharidic crown ether **2** in 40% yield when treated at low concentration with 2.5 eq. of KOH in toluene-Me_2SO. Compound **2** structure was proved through a detailed NMR analysis (^1H, ^{13}C, ^1H-^1H and ^{13}C-^1H 2D correlations). This structural elucidation indicated that compound **2** resulted from the intramolecular attack of the C-5-O^- alkoxide group, generated in the basic medium, on the C-6' carbon of the 5',6'-anhydro group.

INTRODUCTION

Macrocyclic polyethers or crown ethers have attracted considerable attention because of their ability to form stable complexes with a wide variety of guests[1-5] as

covalent compounds and metal ions. In the polysaccharide area, the formation of cycles with 6, 7 or 8 glucose units (α, β and γ cyclodextrins) allows hydrophobic organic compound inclusion in aqueous media[6-11]; moreover, 3,6-peranhydro cyclodextrins with an inversed cavity show an interesting specificity in the selective complexation of ions[12].

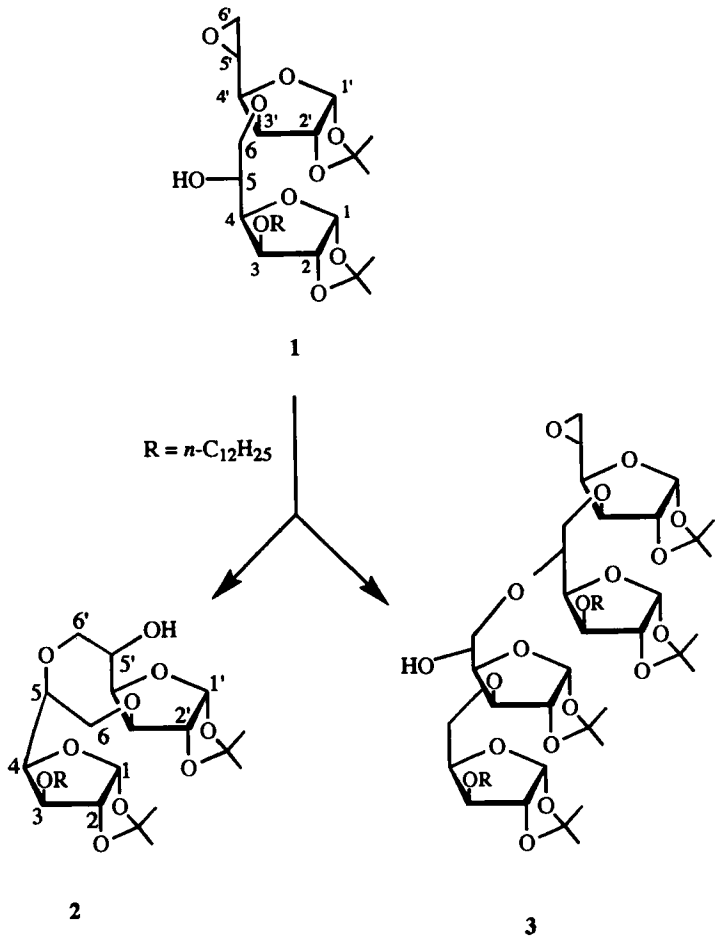
In this study, we described the disaccharidic crown ether **2** synthesis from 6-*O*-(5,6-anhydro-3-deoxy-1,2-*O*-isopropylidene α-D-glucofuranos-3-yl)-1,2-*O*-isopropylidene-3-*O*-n-dodecyl-α-D-glucofuranose[13] (**1**) by an intramolecular process (scheme 1). The structure of the compound **2** was studied through a detailed NMR analysis (^1H, ^{13}C, ^1H-^1H and ^{13}C-^1H 2D correlations). This compound has eight member ring with 2 oxygen atoms allowing eventual complexation. Further functionalization of the C-5'-OH group, as well as alkyl chain length choice at the C-3 position and acetal group deprotection, can be used to modify the inclusion ability.

MATERIALS AND METHODS

The reaction was monitored by HPLC (Waters 721) using the reverse phase column RP-18 (Merck). Specific rotation was determined with a JASCO-DIP 970 polarimeter (Prolabo). NMR spectra and 2D correlation experiments were recorded using a Bruker WB 300 spectrometer. In the 2D, long range, heteronuclear-shift-correlation technique, the delay D_2 (0.1 s) was chosen for a coupling constant of 5Hz.

The disaccharidic crown ether **2** was obtained following scheme 1.

Very low initial reagent concentrations were chosen to favour the intramolecular attack of C-5-O^- alkoxide group, generated in the basic medium, on the C-6' carbon of the 5',6'-anhydro group leading to compound **2**. So, 2.5 g (4.5 mmol) of anhydro precursor **1**, described in a previous work[13] and 0.63 g (11.3 mmol) of powdered KOH were stirred in 500 mL toluene-Me_2SO 1:1 (v/v) at 40°C. After 24 h, compound **1** disappeared and the mixture was filtered and neutralized with saturated aqueous solution of NH_4Cl. The aqueous phase was extracted with toluene and the solvent concentrated under diminished pressure to give 2.3 g of syrupous residue in which two compounds A and B were detected by HPLC in the



Scheme 1. Disaccharidic crown ether **2** synthesis.

(A) / (B) ratio 4:1. Silica gel column elution of this residue with hexane-acetone 23:2 (v/v) gave :

- 0.99 g (40%) of pure A compound identified as the disaccharidic crown ether **2** : liquid; $[\alpha]_D^{25}$ = -32.6° (c = 1.1, $CHCl_3$); NMR analysis see below; Anal. Calcd for $C_{30}H_{52}O_{10}$: C, 62.91; H, 9.16. Found : C, 62.66; H, 9.19;

- 0.24 g (10%) of compound B and 0.8 g of an unidentified fraction. Compound B could be the tetrasaccharide derivative **3** resulting from the intermolecular condensation of two molecules of the precursor **1** (C-5-O^- alkoxide attack on the 5',6'-anhydro group of another molecule) because ^{13}C NMR spectra indicated the presence of one 5,6-anhydro group (δC-5 = 47.8 ppm; δC-6 = 46.5 ppm).

RESULTS AND DISCUSSION

Compound **2** ^{13}C NMR spectrum shows that the signals at 47.9 and 46.6 ppm which characterize the 5',6'-anhydro group in the precursor **1**, are absent. The peaks at 105.3 and 103.9 ppm (Table 1) correspond to the anomeric carbons of two furanosic cycles. The presence of two isopropylidene groups is confirmed by the resonances near 110 ppm (110.5 and 110.4 ppm) corresponding to iso carbons. The numerous ^{13}C peaks between 20 and 30 ppm indicate the presence of a long alkyl chain. To confirm the supposed cyclisation between C-5-O^- alkoxide group and C-6' carbon, a complete ^1H and ^{13}C assignment using 2D correlation experiments is then necessary.

From the ^1H NMR spectrum, the two doublets at 5.94 and 5.78 ppm have the same coupling constant (J 3.75 Hz). The distinction between the two furanosic cycles is therefore not possible by considering only the coupling constant values. Moreover, in the 1,2-*O*-isopropylidene-glucofuranose cycles, the coupling constant between H-2 and H-3 is practically null and prevents the attribution of H-3 from H-2. This lack of information is illustrated by the homonuclear ^1H-^1H correlation experiment (COSY) which shows a spot between H-2 and H-1 and no spot between H-2 and H-3 (figure 1). This correlation experiment allows also to observe that the most deshielded (H-1' and H-2') protons belong to the same cycle. Hαa and Hαb protons of the lateral chain are located near 3.4 and 3.6 ppm on account of the cross peak with Hβ at 1.65 ppm. The integration curve shows that under each of the two multiplets corresponding to Hαa and Hαb exist an other proton. A detailed ^1H and ^{13}C NMR analysis of 3-*O*-n-dodecyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose in the same solvent ($CDCl_3$) gave the chemical shifts 3.46 and 3.56 ppm for the two protons in α-position on the lateral chain with $J_{H\alpha a,\ H\alpha b}$ 9.2 Hz and $J_{H\alpha,\ H\beta}$ 6.5 Hz[14]. In account of the two above J values, a chemical shift of

TABLE 1: ^{1}H and ^{13}C NMR signals of compounds **1** and **2** ($CDCl_3$)

	Compound **1**	Compound **2**			
	^{13}C	^{13}C	^{1}H		
	δ ppm	δ ppm	δ ppm	J (H_z)	
1	104.9	105.3	5.78	1,2	3.7
2	83.2	81.2	4.45	2,3	0.0
3	82.1	81.8	3.82	3,4	3.2
4	81.0	80.8	3.78	4,5	8.7
5	67.9	76.3	4.43	5,6a	3.0
6	72.3	75.1	3.45(a)	6a,6b	12.8
			4.13(b)	5,6b	2.9
1'	104.7	103.9	5.94	1',2'	3.8
2'	82.2	86.0	4.52	2',3'	0.0
3'	81.8	89.1	4.38	3',4'	3.7
4'	79.2	79.6	4.21	4',5'	3.6
5'	47.9	73.1	4.12	5',6'a	1.5
6'	46.6	71.7	3.77(a)	5',6'b	1.5
			3.98(b)	6'a,6'b	13.3
α	70.3	70.0	3.41(a)		
			3.55(b)		
iso	111.4	110.5			
	111.2	110.4			

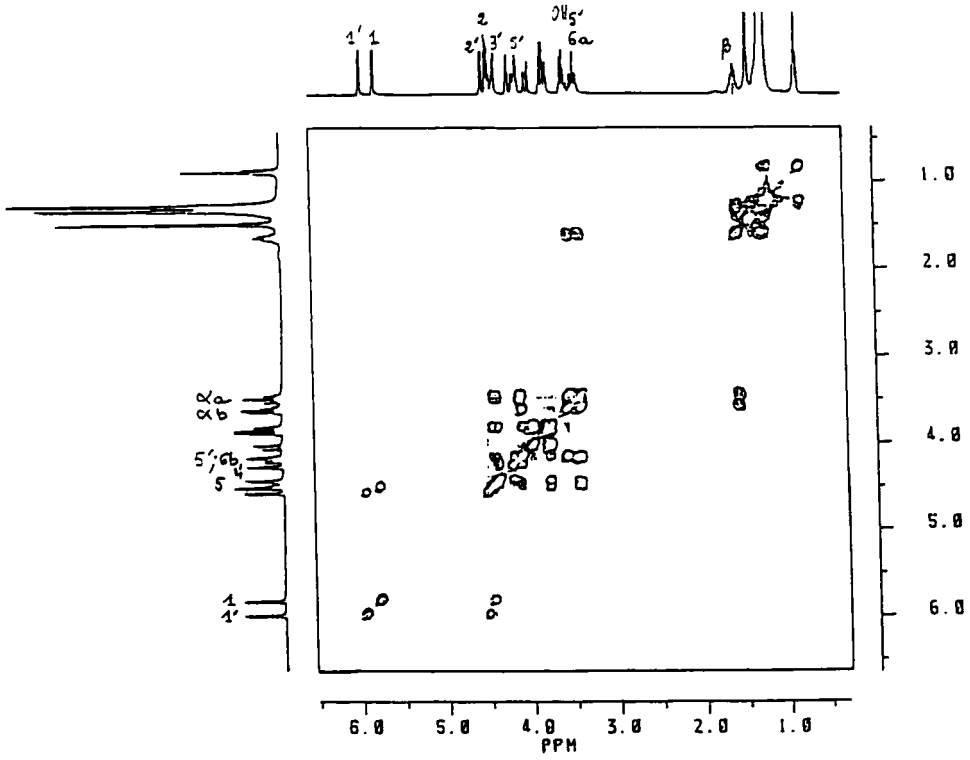


FIG. 1. COSY Experiment for compound **2**.

3.41 ppm is found for Hα in the first multiplet located below 3.5 ppm. An analogous process leads to 3.55 ppm for Hαb ; so these two masked protons appear as two doublets. The most shielded doublet at 3.45 ppm with a coupling constant higher than 12 Hz corresponds to a methylen group (H-6 or H-6'). The other doublet at 3.57 ppm with a coupling constant of 7.5 Hz is attributed to the hydroxylic proton C-5'-OH coupled with H-5'. The assignment of the C-5'-OH proton allows to affirm that the H-5' proton is masked by the multiplet located between 4.1 and 4.2 ppm, which corresponds to two protons from the integration curve. Starting from the diagonal with the resonance for H-5', H-4' can be identified by its cross peak with H-5'. Proceeding in a similar fashion, H-4' and H-3' chemical shifts are found at 4.21 and 4.38 ppm respectively. These results are

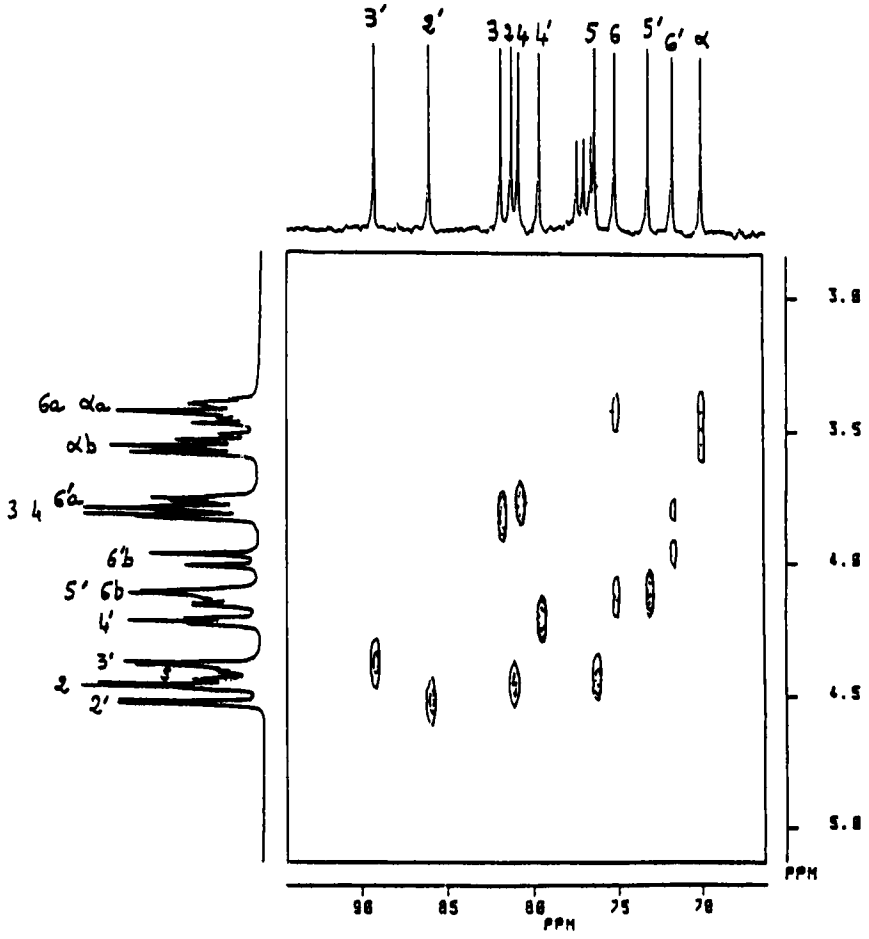


FIG. 2. C-H Correlation for compound **2**.

confirmed by decoupling experiments : the signal at δ 4.12 ppm is ascribed to the H-5' proton ; irradiation at this position simplifies the triplet at 4.21 ppm to a doublet.

The assignment of C-3', C-4' and C-5' carbons is achieved by the use of ^{13}C-^{1}H shift correlation experiment (figure 2), which gives C-3' at 89.15 ppm, C-4' at 79.6 ppm and C-5' at 73.15 ppm.

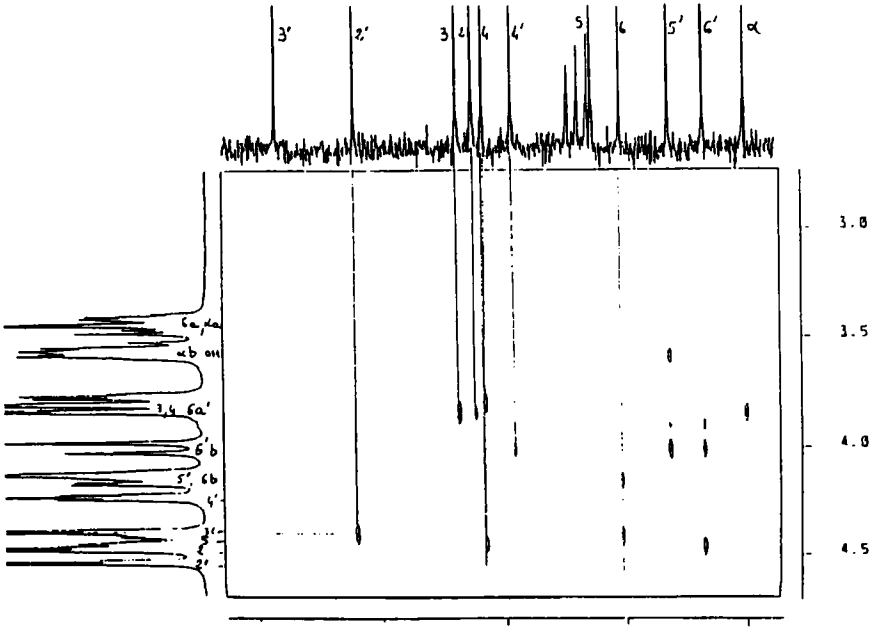


FIG. 3. Long-range, 2D, heteronuclear chemical shift correlation - spectrum of compound **2**.

Advantage is taken of the 2D, long-range, heteronuclear-shift-correlation technique (COLOC experiment) to confirm the location of H-2'. Figure 3 shows that H-3' gives cross peaks with two carbons with chemical shifts at 85.95 and 75.15 ppm; these values correspond neither to C-3' (89.15 ppm) nor to C-4' (79.6 ppm). The ^{13}C peak at 75.15 ppm is assigned to the C-6 methylen carbon from the DEPT experiment; then, the peak at 85.95 ppm can only be attributed only to C-2'. This result is important because it allows to obtain the connectivity between H-2' and H-3' or C-2' and C-3' ($J_{H\text{-}2',\,H\text{-}3'}$ near 0). COLOC experiment allows also to observe the connectivities across an oxygen atom : between H-3' and C-6 and between H-5 and C-6'. The last observation confirms the transformation of the compound **1** to the compound **2** with an eight member ring.

X-H experiment allows to find H-2' at 4.52 ppm from the chemical shift of C-2' and then the chemical shift of H-1' and C-1'.

Table 1 data show also that the cyclisation between C-5 and C-6' carbons by an ether linkage, results in an expected deshielding effect on C-5 (+ 8,4 ppm) and that the deshielding of C-5' and C-6' ($\Delta\delta$ = 25,2 and 25,1 ppm respectively) proves the disappearance of the epoxide group.

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