Tetrahedron Letters, Vol.30, No.4, pp 407-410, 1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

# USE OF $^1J_{C1,\ H1}$ VALUES FOR THE STEREOCHEMICAL DETERMINATION OF C-GLYCOSIDES: A SIMPLE TWO DIMENSIONAL NMR PROTOCOL

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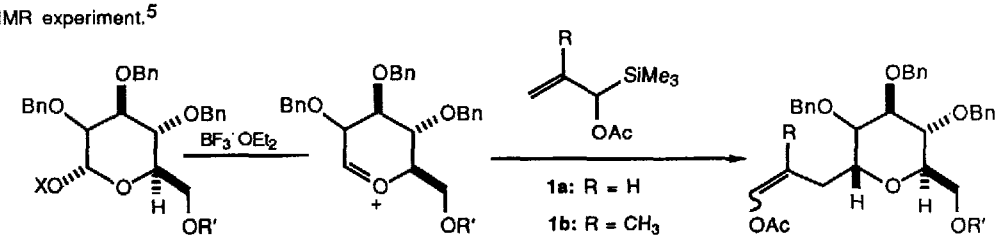
***Abstract.*** A combination of three two-dimensional homo- and heteronuclear correlation methods [COSY, HETCOR, and HETERONUCLEAR-2DJ] have been used to determine the stereochemistry of C-glycosides derived from the reaction of 1-acetyloxy allylic silanes with pyranoside oxonium ions. Of particular significance were the $^1J_{C1,H1}$ values which were used to assign the stereochemistry at the C1 carbon.

We are currently engaged in studies directed toward the chemical synthesis of glycopeptide-based immunomodulating agents and polyoxygenated natural products. A key step in our overall strategy for the synthesis of these potential agents was based on the development of the synthetic utility of C1-oxygenated allylic silanes **1a** and **1b**, as homoenolate equivalents for the stereoselective C-glycosidation of pyranoside derivatives (Equation 1).[1] We had anticipated that these reagents could serve as three-carbon alcohol, two-carbon aldehyde and 2-propanone equivalents in Lewis acid catalyzed C-glycosidation reactions with pyranoside derivatives and thus provide a highly stereoselective entry to a wide range of functionalized C-glycosides.[2] Our successful efforts on the Lewis acid catalyzed C-glycosidations had prompted us to develop a simple nuclear magnetic resonance protocol, one which would allow the direct determination of the stereochemistry at the C1-position of the pyran ring without the need for exchange of the benzyl ether protecting groups. Clearly this would be particularly useful where overlapping resonances obscure the direct measurement of the three-bond coupling of the pyran ring protons. A lack of documented spectroscopic information pertaining to C-glycosides justifies the need for a simple procedure to carry out this task.[3] In addition, it would be of general interest to compare chemical shift and one-bond coupling constant data for the C1-carbon center of C-glycosides to those values of the parent O-glycosides.[4] In this Letter we would like to describe a simple and reliable protocol which utilizes a combination of two-dimensional homo- and heteronuclear correlation experiments to determine the stereochemistry of the C-glycosidation products. Essential to the success of this study was the evaluation of the $^1J_{C1,\ H1}$ values through the examination of the heteronuclear two-dimensional spin-resolved NMR experiment.[5]

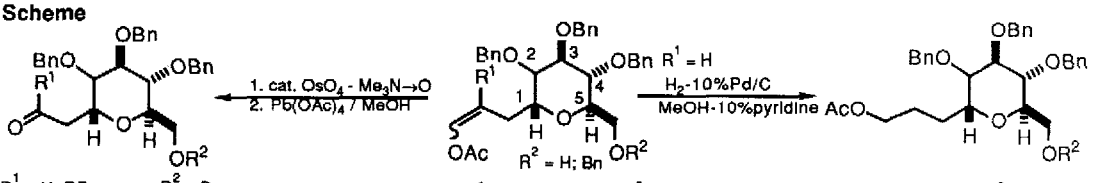



Eq.1

The C-glycosides **2** - **7**, obtained by reaction of **1a** or **1b** with the pyranoside oxonium ions were isolated as mixtures of E/Z stereoisomeric enol acetates. Two different synthetic pathways were utilized to establish the synthon equivalency and simultaneously remove the complication of E/Z stereoisomerism, thus simplifying the spectroscopic analysis. The catalytic hydrogenation of compounds **2** and **3** in the presence of pyridine gave the primary acetates **8** and **9**. Alternatively, a two-step oxidative cleavage sequence of compounds **2** and **3** gave the corresponding aldehydes

**10** and **11**,[6] and the C-glycosides **4 - 6** afforded the methyl ketones **12 - 14**. The processes described above provided the substrates used in the spectroscopic analysis for determination of stereochemistry and measurement of the α:β stereoisomeric ratios (Scheme and Table).

**Scheme**




**10**: $R^1$ = H; OBn $_{C2}$ = α; $R^2$ = Bn
**11**: $R^1$ = H; OBn $_{C2}$ = β; $R^2$ = Bn
**12**: $R^1$ = $CH_3$; OBn $_{C2}$ = α; $R^2$ = Bn
**13**: $R^1$ = $CH_3$; OBn $_{C2}$ = β; $R^2$ = Bn
**14**: $R^1$ = $CH_3$; OBn $_{C2}$ = β; $R^2$ = H

**2**: $R^1$ = H; OBn $_{C2}$ = α; $R^2$ = Bn
**3**: $R^1$ = H; OBn $_{C2}$ = β; $R^2$ = Bn
**4**: $R^1$ = $CH_3$; OBn $_{C2}$ = α; $R^2$ = Bn
**5**: $R^1$ = $CH_3$; OBn $_{C2}$ = β; $R^2$ = Bn
**6**: $R^1$ = $CH_3$; OBn $_{C2}$ = β; $R^2$ = H

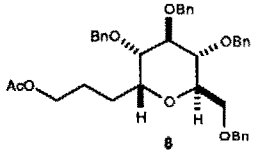
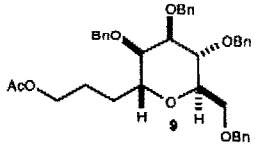
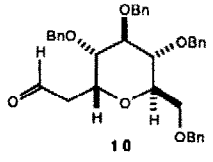
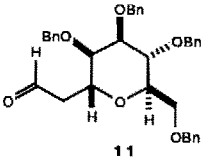
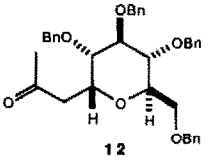
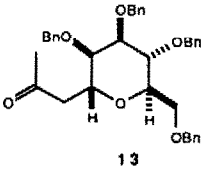
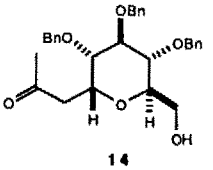
**8**: OBn $_{C2}$ = α; $R^2$ = Bn
**9**: OBn $_{C2}$ = β; $R^2$ = Bn

Assignment of stereochemistry for the C-glycosides **8-14** was accomplished by examination of the one-bond coupling [$^1J_{C1,\ H1}$] of the C1 carbon and three-bond coupling constants [$^3J_{H1,\ H2}$] of the pyran ring protons as shown in the Table. The chemical shifts of the C1 protons were discerned by analysis of a homonuclear correlation experiment (COSY)[7], where the off diagonal elements arising from coupling between the C1 proton and the methylene protons adjacent to the carbonyl functionality clearly indicated the position of the C1 protons. The three-bond coupling constants were then determined via a first order analysis; however, these values for the β-stereoisomers were obscured by resonances from the pyran ring protons of the α isomer and were therefore unmeasurable. Once the chemical shifts of the C1 protons were known, it was a simple matter to assign the C1 carbons using a heteronuclear correlation experiment (HETCOR).[8] A heteronuclear two-dimensional J resolved experiment (HETERO-2DJ)[5] was then performed in order to measure the one-bond coupling constants of the C1 carbons. The α:β ratios for the C-glycoside products **8** and **9** were determined by integration of the carbon resonances using inverse gated decoupling experiments.[9] The ratios of stereoisomers for the methyl ketone C-glycosides **12**, **13**, and **14** were determined by integration of the C1' methylene group (See Figure for representative J resolved spectrum of compound **12**).

The Table summarizes the important $^1H$ NMR and $^{13}C$ NMR data for the C-glycosides. A clear trend was observed for the $^1J_{C1,\ H1}$ values, where for the cases examined *the α stereoisomer has the larger coupling constant by as much as 11 Hz.* The C1 carbon resonances for the α-C-glycosides appear at higher field than the corresponding β stereoisomer. These observations parallel those of the parent O-glycosides, with the expected difference in chemical shift for the C1 carbons being 25 to 35 ppm upfield from those values reported for O-glycosides.[4] Additional support for the stereochemical assignments was provided by the $^3J_{H1,\ H2}$ values. For the α-C-glycosides examined in this study, the three-bond spin-spin coupling constants fall within an acceptable range of 5.1-7.6 Hz, consistent with vicinal coupling constants of pseudo diequatorial and pseudo axial - equatorial hydrogen relationships[2a,d].

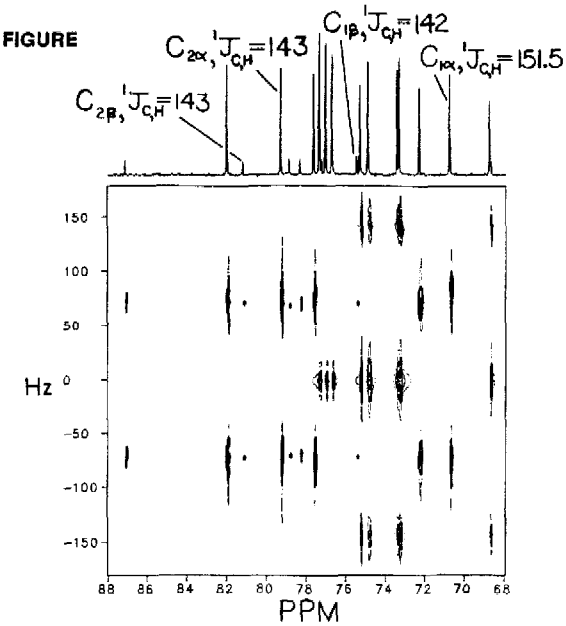
In summary, the combined use of the three two-dimensional homo- and heteronuclear correlation methods described herein has provided a reliable protocol for the determination of stereochemistry of C-glycosides. The evaluation of the $^1J_{C1,\ H1}$ values should be particularly useful for the stereochemical evaluation of a variety of C-glycosides where the vicinal proton coupling constants are unmeasurable due to resonance overlap.

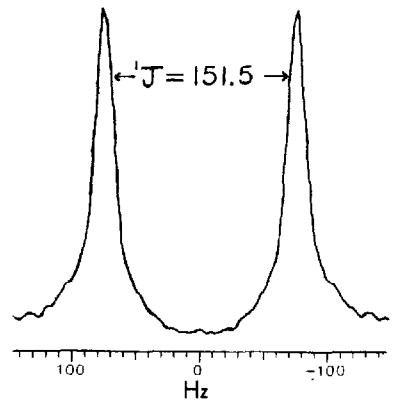
**Table** $^{1}H$ NMR and $^{13}C$ NMR Data of C-Glycosides[a]

| Major Stereoisomer | Yield%[b, c] | α:β ratio | $^{1}J_{C1, H1}$ (δ) | $^{3}J_{H1, H2}$ (δ) |
|---|---|---|---|---|
|  **8** | 85 | 10 :1[d] | α = 146.6 Hz (73.72) | α = 5.1 Hz (4.03) |
|  **9** | 85 | 10 :1[d] | α = 143.9 Hz (71.97) | α = 5.4 Hz (3.92) |
|  **10** | 54 | 10 :1 | α = 150.0 Hz (69.64)<br>β = 145.7 Hz (74.31) | α = 5.8 Hz (4.70) |
|  **11** | 54 | 10 :1 | α = 145.0 Hz (66.07)<br>β = 143.6 Hz (73.23) | α = 7.6 Hz (4.41) |
|  **12** | 54 | 7 :1[e] | α = 151.5 Hz (70.64)<br>β = 142.0 Hz (75.34) | α = 5.7 Hz (4.72) |
|  **13** | 56 | 5:1[e] | α = 148.2 Hz (67.54)<br>β = 145.1 Hz (73.99) | α = 6.6 Hz (4.50) |
|  **14** | 65 | 6 :1[e,f] | α = 155.2 Hz (70.58)<br>β = 142.8 Hz (75.65) | α = 5.6 Hz (4.78) |

a. All spectra were recorded on a Varian XL400 (93.84 KG) in $CDCl_3$ (23 °C) unless otherwise indicated. b. Yields refer to chromatographically pure material. c. All compounds gave satisfactory IR, MS,$^{1}H$ and $^{13}C$ NMR data. d. Ratio determined by integration of the carbon resonances using inverse gated decoupling experiments. e. Ratio determined by integration of the C1' methylene protons. f. $^{1}H$ NMR and $^{13}C$ NMR were recorded in benzene-$d_6$.

FIGURE




This one-dimensional slice taken from the HETERO-2DJ (left) illustrates the measurement of the one bond coupling constant for C1 of **12**. ($^1J_{C1, H1}$ = 151.5 Hz, δ = 70.64)

**Acknowledgment.** Financial support for this work provided by Boston University, American Cancer Society (through the auspices of the Hubert H. Humphrey Cancer Research Center; Boston University Medical School) Grant No. IN-97K and the National Institutes of Health - NCI (CA47249) is gratefully acknowledged. We would also like to thank Professor John Snyder and the members of his research group for many helpful discussions.

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6. In the cases of **8** and **9**, we were unable to unequivocally assign the chemical shift of the C1 proton for the β stereoisomer from the COSY spectra. Hence the chemical shift of the C1 carbon and the corresponding one-bond coupling constant could not be reported. In order to establish the C1 stereochemistry of the glycosidation products as well as to demonstrate the synthon equivalency, **2** and **3** were subjected to the oxidative cleavage sequence to yield the aldehydes **10** and **11**. With the methylene protons adjacent to the carbonyl of the aldehyde, the task of assigning the chemical shifts of the C1 proton and carbon, as well as measurement of the one-bond coupling constant, was straightforward.
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(Received in USA 13 October 1988)