Pergamon

Tetrahedron: Asymmetry, Vol. 8, No. 12, pp. 1959–1961, 1997

Printed in Great Britain
PII: S0957-4166(97)00207-3
0957-4166/97 $17.00 + 0.00

Stereochemical analysis of D-galacto-sulfoxides using (*S*)-α-methoxyphenylacetic acid

Peter H. Buist,[a,*] Behnaz Behrouzian,[a] Stephanie Cassel,[b] Christelle Lorin,[b] Patrick Rollin,[b] Anne Imberty[c] and Serge Perez[c]

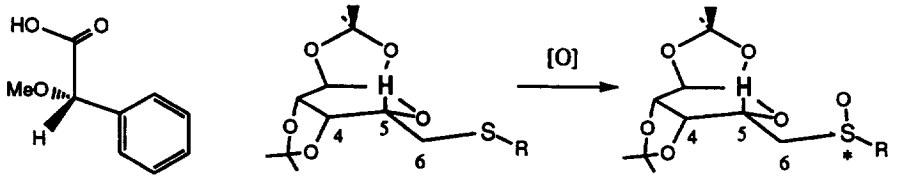
[a] Ottawa–Carleton Chemistry Institute, Department of Chemistry, Carleton University, 1125 Colonel By Drive, Ottawa, Ontario, Canada, K1S 5B6

[b] ICOA, Université d'Orléans, B.P. 6759, F-45067 Orléans, France

[c] CERMAV,[1] CNRS, B.P. 53X, F-38041 Grenoble, France

Abstract: (*S*)-α-Methoxyphenylacetic acid (MPAA) was used as an NMR shift reagent to predict the absolute configuration of some sulfoxide-containing sugars. The correctness of this assignment was confirmed by X-ray crystallography. © 1997 Elsevier Science Ltd

We have recently reported the use of (*S*)-(+)-α-methoxyphenylacetic acid (MPAA) **1** as a chiral NMR shift reagent to determine the enantiomeric purity and absolute configuration of a number of acyclic sulfoxides.[2a] In this paper, we demonstrate that our methodology can be used to analyze the stereochemistry of some epimeric D-galacto-sulfoxides **3a–d** which are available by oxidation[3] of the corresponding sulfides **2a–d**. The determination of the absolute configuration at the sulfinyl center of **3a–d** is of current interest since these compounds are valuable synthetic intermediates whose further elaboration can depend on the stereochemistry of the sulfinyl function.[4]



1 **2a-d** **3a-d**

a: R = CH_3 **c:** R = Ph
b: R = benzothiazol-2-yl **d:** R = 2-pyridyl

We began our stereochemical analysis by recording the ^1H (400 MHz)and ^{13}C (100.6 MHz) NMR spectrum of the two simplest epimeric sulfoxides **3a1**:**3a2** (2:3 mixture) in $CDCl_3$ and examining the effect of adding (*S*)-(+)-MPAA (3 equiv.) on the signals assigned to the α-sulfinyl methyl group. The ^1H resonances (singlets) of both epimers (2.701 ppm, **3a1**; 2.642 ppm, **3a2**) moved downfield due to H-bonding of the carboxyl group to the sulfinyl oxygen but the resonance belonging to **3a2** shifted to a lesser extent (0.017 ppm, **3a1**; 0.012 ppm, **3a2**). The corresponding ^{13}C signals (37.662 ppm, **3a1**; 39.736 ppm, **3a2**) moved upfield as anticipated[2b] but the resonances due to **3a2** were shifted to a greater extent (−1.133ppm, **3a1**; −1.207 ppm, **3a2**). These results can be rationalized in terms of the typical shielding effects predicted by our Pirkle-type binding model[2a] and on this basis one would assign the (*R*)-configuration to **3a1** and the (*S*)-configuration to **3a2** (Figure 1).

Support for these configurational assignments was obtained by examining the effect of (*S*)-MPAA addition on the ^1H resonances due to the α-sulfinyl methylene group of the two epimers, **3a1** and **3a2** in combination with conformational analysis. As shown in Figure 2, addition of (*S*)-MPAA (3 equiv.) caused the upfield half of the C-6 AB quartet (H_B) of **3a2** to shift downfield significantly (0.18 ppm)

* Corresponding author. Email: pbuist@ccs.carleton.ca

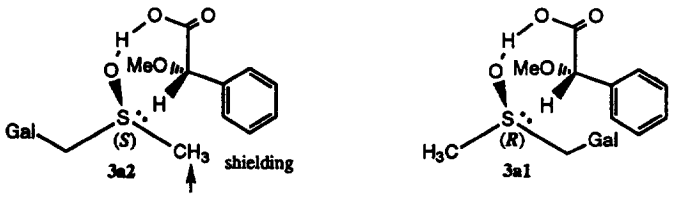


Figure 1. Binding model for the interaction of (*S*)-MPAA with the two epimers of **3a**.

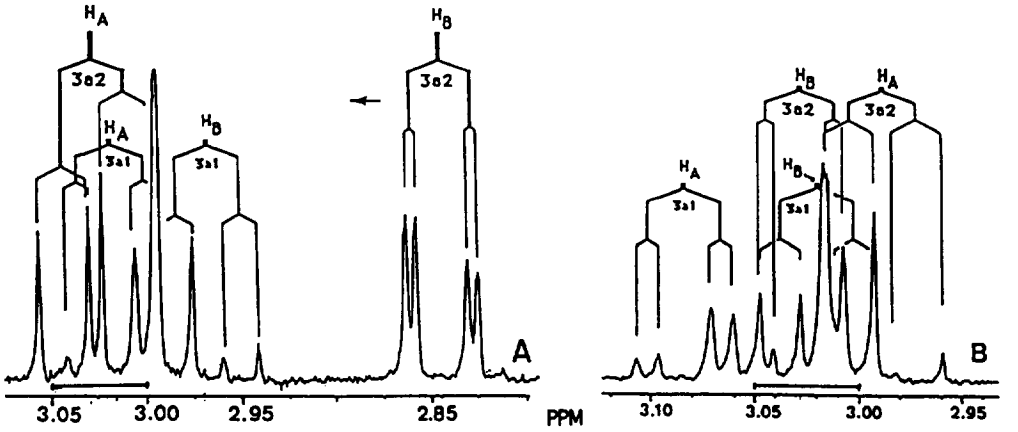


Figure 2. ^{1}H NMR (400 MHz) resonances due to the α-sulfinyl methylene group of **3a1** and **3a2** (A) before and (B) after addition of (*S*)-(+)-MPAA (3 equiv.).

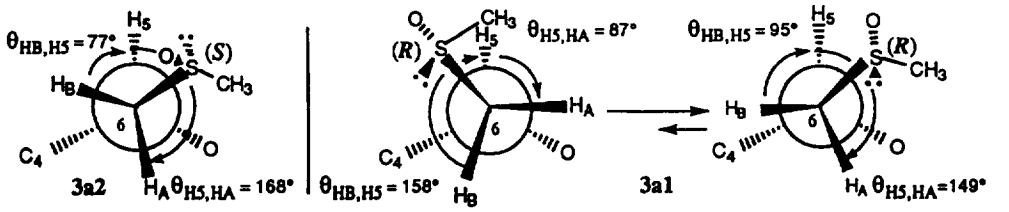


Figure 3. Newman Projections of energy-minimized conformations calculated for **3a1** and **3a2**.

while the corresponding signals due to H_A of **3a2** and the entire AB quartet for **3a1** are only slightly affected.

In order to interpret this data, energy-minimized[5] conformation(s) for the side-chain of each epimer were calculated. As shown in Figure 3, a single preferred conformation was identified for **3a2** while a pair of conformations, separated in energy by 0.6 kcal/mole was found for **3a1**. The calculated[6] values for $^3J_{5,6}$ of each epimer are in qualitative agreement with the observed values for $^3J_{5,6}$ obtained from the ^{1}H NMR spectrum displayed in Figure 2A: (calculated $^3J_{5,6}$ **3a2**: 9.4 Hz (H_A), 0.7 Hz (H_B) and observed $^3J_{5,6}$ **3a2**: 10.6 Hz (H_A), 2.1 Hz (H_B); calculated $^3J_{5,6}$ **3a1**: 5.4 Hz (H_A), 2.6 Hz (H_B) and observed $^3J_{5,6}$ **3a1**: 7.2 Hz (H_A), 4.8 Hz (H_B)).

Assuming that the conformations of the side-chain do not change upon addition of (*S*)-MPAA,[7] the dramatically different effect of this shift reagent on the ^{1}H chemical shifts of the α-sulfinyl methylene hydrogens of each epimer can now be explained. That is, H-bonding of the sulfinyl oxygen in **3a2** strongly deshields[8] the proximal hydrogen, namely H_B. In contrast, the sulfinyl oxygen of **3a1** is pointing away from H_A and H_B in both conformations and thus the ^{1}H signals due to both hydrogens are affected only very slightly and to a similar extent (Figure 2).

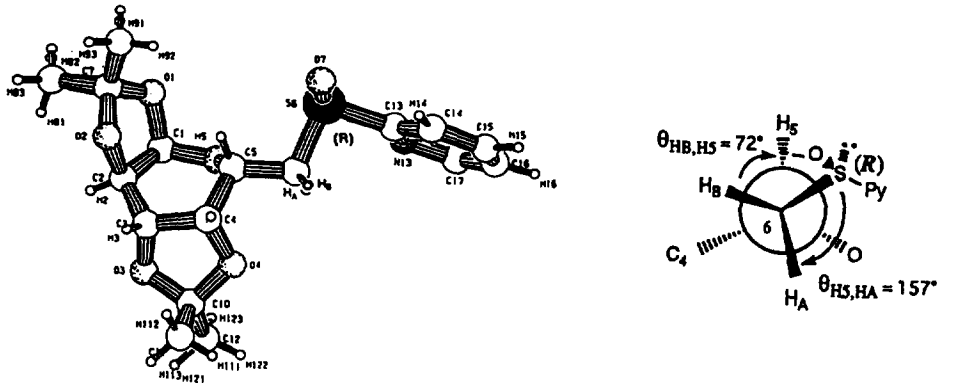


Figure 4. X-ray structure of the more polar epimer of **3d** and a Newman projection along the C-5,6 bond.

A similar dichotomy in sulfinyl side-chain conformations was detected for the two epimeric 2-pyridyl sulfoxides, **3d**. These compounds could be separated by silica gel column chromatography and were examined separately by ^{1}H NMR with the aid of (*S*)-MPAA. The more polar epimer of **3d** possesses disparate $^3J_{5,6}$ values (10.5 Hz (H_A), 2.5 Hz (H_B)=*anti* conformation) and upon addition of the chiral shift reagent, a substantial downfield shift of 0.12 ppm was observed for the upfield half of the C-6 AB quartet (H_B) while the downfield half (H_A) was essentially unaffected. In contrast, the less polar epimer of **3d** exhibits more similar $^3J_{5,6}$ values (4.6 Hz, 7.8 Hz), and both halves of the C-6 AB quartet move downfield very slightly (ca. 0.02 ppm) upon complexation as anticipated. These phenomena clearly link the two sets of epimers, **3a** and **3d**, and on this basis one would assign the (*R*)-configuration (priority change) to the sulfinyl group of the more polar epimer of **3d** and the (*S*)-configuration to its diastereomer. The former compound was subsequently crystallized and our configurational assignments were validated by X-ray crystallography (Figure 4). (Full details of the X-ray work will be published elsewhere (*Journal of Carbohydrate Chemistry*).) It is interesting to note that the conformation of the pendant chain shown in this X-ray structure is similar to that calculated for **3a2** as shown in Figure 3.

Stereochemical analyses of other related compounds in this series are planned.

Acknowledgements

We wish to thank NSERC for financial support of this work and Dr Pierre Genix (Rhone Poulenc Agrochimie, Lyon) for performing the energy-minimization calculations. The ^{1}H and ^{13}C NMR spectra were obtained by Mr. Keith Bourque at Carleton University. Helpful discussions with Prof. G. W. Buchanan (Carleton University) are gratefully acknowledged.

References

1. Associated with the Université Joseph Fourier, Grenoble.
2. (a) Buist, P.H.; Marcecak, D.M.; Holland, H.L.; Brown, F.M. *Tetrahedron: Asymmetry* **1995**, *6*, 7. (b) Buist, P.H.; Marecak, D.M. *J. Am. Chem. Soc.* **1992**, *114*, 5073.
3. Cassel, S.; Chaimbault, P.; Lafosse, M.; Lorin, C.; Rollin, P. *Sulfur Lett.* **1996**, *20*, 63.
4. Carreno, M.C. *Chem. Rev.* **1995**, *95*, 1717.
5. Semi-empirical, gas phase, calculations (MOPAC/AM1) were carried out using a Silicon Graphics workstation and Chem-X software (Chemical Design Ltd., Chipping Norton, UK).
6. Karplus, M. *J. Chem. Phys.* **1959**, *30*, 11. To calculate $^3J_{5,6}$ for **3a1**, we assumed a 73:27 mixture of conformers.
7. This is a reasonable assumption given that values for $^3J_{5,6}$ do not change substantially upon complexation.
8. Fraser, R.R.; Durst, T.; McClory, M.R.; Viau, R.; Wigfield, Y.Y. *Int. J. Sulfur Chem., A* **1971**,*1*, 133.

(Received in USA 8 April 1997)