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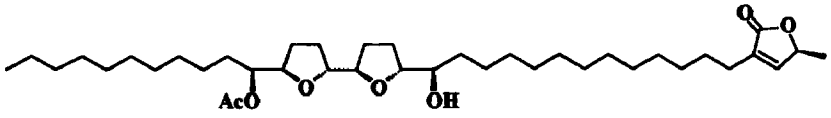
^{1}H NMR Analysis and Conformation of Bis-Tetrahydrofurans Related to Annonaceous Acetogenins

L. Autissier, P. Bertrand, J.-P. Gesson* and B. Renoux

Laboratoire de Chimie 12, Associé au CNRS
40, Avenue du Recteur Pineau, 86022 Poitiers (France)

Abstract: ^{1}H NMR analysis of diastereoisomeric bis-tetrahydrofuran compounds reveals interesting changes in their conformation due to stereoelectronic effect and intramolecular hydrogen bonding. This is particularly demonstrated in one case (7) by anisotropic shielding of a remote anomeric proton by a phenyl group.

Over ninety mono- and bis-tetrahydrofuran acetogenins have been isolated from *Annonaceae* species since the discovery by Cole[1] of Uvaricin **1** in 1982.[2,3] They are characterized by the presence of *cis* or mainly *trans* disubstituted tetrahydrofuran rings bearing α-hydroxyl groups (which could be acetylated as for **1**) on the side chain with a relative configuration between the two oxygenated carbons being either *threo* or *erythro*, and a butyrolactone moiety. Most of these compounds display very promising biological activities (antitumoral, pesticidal, ...) which seem to arise at least in the case of annonin[4] and bullatacin[5] from inhibition of mitochondrial electron transport at site I (involving NADH-ubiquinone oxido-reductase). Although their structures and conformations are not easily determined by NMR due to the presence of several similar functionalities (X-Ray analyses have only been reported for two derivatives[6,7] because of their waxy properties), extensive ^{1}H and ^{13}C NMR studies by Hoye have pointed out useful chemical shift variations to their relative[8,12] and absolute[9] configurations.



1 Uvaricin

As part of a study[10,11] on the enantiospecific synthesis of such acetogenins (and analogs) from carbohydrates we have prepared several related bis-tetrahydrofuran diastereoisomeric intermediates which may be of interest for conformational analysis under different conditions (solvent, added metal salts) because key protons are easily observed. The preliminary observations are reported below.

We have recently published the synthesis of compounds **4** (*threo-trans-threo*) and **5** (*threo-cis-threo*) from aldehyde **2**, easily derived from diacetone-D-glucose, through epoxidation-cyclization of **3**-*Z*.

Based on the same strategy and starting from **3**-*E*, **6** (*erythro-trans-threo*), oil, $[\alpha]_D$ -8 (c 1.1, CH_2Cl_2) and **7** (*erythro-cis-threo*), oil, $[\alpha]_D$ -9 (c 0.5, CH_2Cl_2) have now been obtained. These compounds all have in common a *threo* configuration between C-4 and C-5 (carbohydrate numbering) because the 5*S* alcohol is the major product of the condensation of a Grignard reagent with **2**. However **10** (*threo-trans-erythro*), oil, $[\alpha]_D$ +2 (c 1.1, CCl_4) and **11** (*threo-cis-erythro*) oil, $[\alpha]_D$ +3 (c 1, CCl_4) derived from the minor 5*R* alcohol have been prepared in the *Z* series.

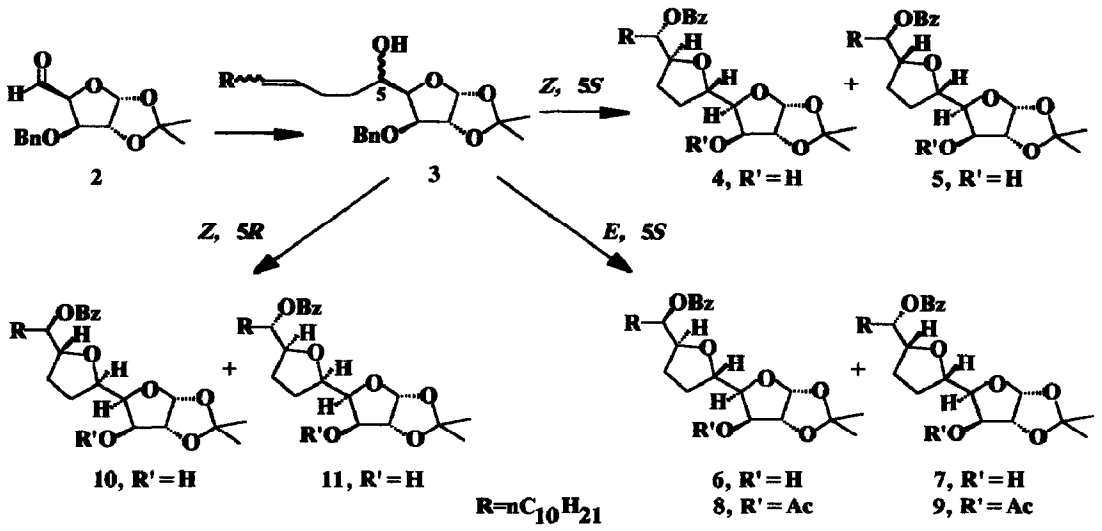


Table 1. Chemical shifts of O-C-H protons for compounds **4-7** and **10-11** ($CDCl_3$, 200MHz).
(th: threo, er: erythro)

	4	**5**	**6**	**7**	**10**	**11**
	(th-trans-th)	*(th-cis-th)*	*(er-trans-th)*	*(er-cis-th)*	*(th-trans-er)*	*(th-cis-er)*
H-1	5.92	5.93	5.93	5.35	6.00	5.96
	Δδ = +0.01		*Δδ = -0.58*		*Δδ = -0.04*	
H-2	4.49	4.49	4.50	4.36	4.57	4.52
	Δδ = 0		*Δδ = -0.14*		*Δδ = -0.05*	
H-3	4.25	4.20	4.22	4.18	4.39	4.13
	Δδ = -0.05		*Δδ = -0.04*		*Δδ = -0.26*	
H-4	4.07	4.06	4.04	4.01	4.08	3.92
	Δδ = -0.01		*Δδ = -0.03*		*Δδ = -0.16*	
H-5	4.52	4.44	4.45	4.38	4.14	4.10
	Δδ = -0.08		*Δδ = -0.07*		*Δδ = -0.04*	
H-8	4.32	4.14	4.28	4.12	4.29	4.10
	Δδ = -0.18		*Δδ = -0.16*		*Δδ = -0.19*	
H-9	5.15	5.25	5.22	5.35	5.21	5.10
	Δδ = +0.10		*Δδ = +0.13*		*Δδ = -0.11*	

The structures of **4** and **5** have been unambiguously determined by degradation to an aldehyde compared to an authentic racemic sample.[10] Representative ^1H NMR data for these bis-tetrahydrofuran compounds are listed in Table 1. A comparison of NMR data of **4/5** and **6/7** allows to identify **6** as the *erythro-trans-threo* isomer and **7** as the *erythro-cis-threo* one based on chemical shifts variations of specific protons as already noticed.[8,12] Particularly the ring methine protons (H-5 and H-8) are expected to be more shielded in the *cis* isomers whatever the other *erythro* or *threo* configurations are. Both pairs of diastereoisomers exist preferentially as rotamer **B** ($J_{H\text{-}4,H\text{-}5}$= 4 Hz) which is favored over rotamer **A** usually observed for bis-tetrahydrofurans with a *threo* relationship between the linking carbons[13] (**C** should be least stable than **B** due to an alkyl-alkyl gauche interaction). Such a situation results obviously from hydrogen bonding betwen OH (C-3) and the oxygen of the second THF ring (Fig. 1).

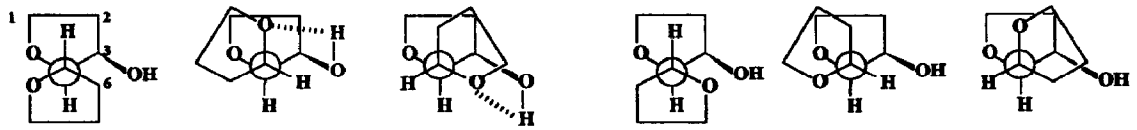


Figure 1. Staggered conformations of 5*S* bis-tetrahydrofurans **4-7** (**A**, **B** and **C**) and of 5*R* bis-tetrahydrofurans **10** and **11** (**A'**, **B'** ans **C'**).

A large shielding is observed in the case of **7** for H-1 ($\Delta\delta$= -0.58 ppm), associated with a smaller one for H-2 ($\Delta\delta$= -0.14 ppm), which may be explained by considering rotamer **E** for the *erythro* configuration between C-8 and C-9. Only in this case can the benzene ring be located above the plane of the carbohydrate moiety and cause anisotropic shielding of H-1 and H-2 (Fig. 2). The preference for rotamer **E** over **D** (**F** being certainly less stable than **E**) has already be pointed out in the case of *erythro* isomers with similar acyloxy substituents (Fig. 3).[14]

In order to verify the major contributions of rotamers **B** and **E** in the case of **7**, acetylation to **9** was carried out (similarly **6** was converted to **8**), but H-4 and H-5 exhibit similar chemical shifts in both series (in $CDCl_3$, CD_3COCD_3 and C_6D_6) and theirs signals are partly hindered by the one of H-8. Furthermore H-1 appears at δ 5.85 ppm both for **8** and **9** and assuming that rotamer **E** is still preferred, this result is consistent with an inversion of stability of rotamers **B** and **A**.

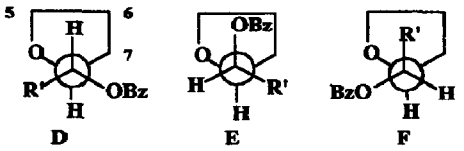


Figure 3. Staggered conformations of *erythro* benzoate **7**.

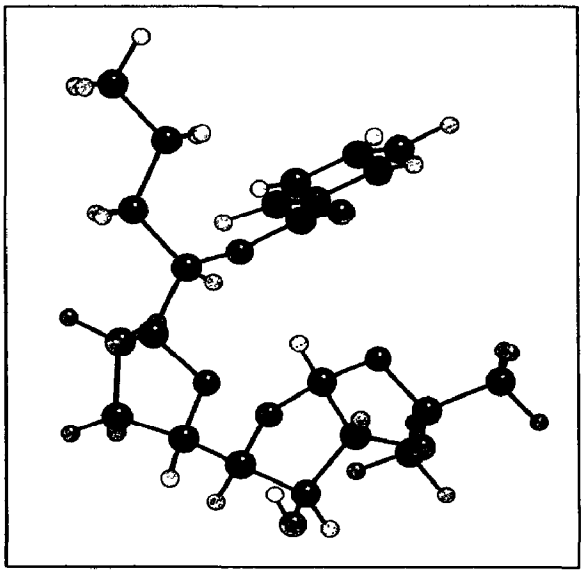


Figure 2. Conformation of **7** (R=C_3H_7) (Nemesis®, Oxford Molecular)

In the 5*R* series, the already mentioned shielding of H-5 and H-8 in the *cis* isomer allows to propose **11** as the *cis* isomer (see Table I). A higher contribution of rotamer A' is expected for such *erythro* bis-tetrahydrofurans[13] but the observed $J_{H\text{-}4,H\text{-}5}$ is higher (7.5 Hz) for **11** than for **10** (4.5 Hz). Such a result may be explained by assuming that rotamer C' (which allows both hydrogen bonding and a stabilizing gauche interaction between the two ring oxygens[15]) is indeed prevailing for **10** but not for **11** due to steric interaction between the *cis* side chain and the furanose ring.

In conclusion, ^1H NMR analysis of these intermediates demonstrates interesting variations of conformation depending on their relative configurations and eventually on intramolecular hydrogen bonding, the major contribution of rotamers having two oxygens in gauche interaction being worthy of note.

References

1 Jolad, S.D.; Hoffmann, J.J.; Schram, K.H.; Cole, J.R.; Tempesta, M.S.; Kriek, G.R.; Bates, R.B. *J. Org. Chem.* **1982**, *47*, 3151-3153.

2 Rupprecht, J.K.; Liu, Y.H.; McLaughlin, J.L. *J. Nat. Prod.* **1990**, *53*, 237-278.

Fang, X.; Rieser, M.J.; Gu, Z.M.; Zhao, G.; McLaughlin, J.L. *Phytochem. Anal.* **1993**, *4*, 27-67.

3 Cavé, A.; Cortes, D.; Figadère, B.; Hocquemiller, R.; Laprévote, O.; Laurens, A.; Leboeuf, M. *Phytochemical Potential of Tropical Plants, Recent Advances in Phytochemistry*, 27, Downum, K.R.; Romeo, J.; Stafford, H.A. Eds.; Plenum Press: New-York, 1993; pp. 167-202.

4 Londershausen M.; Leicht, W.; Lieb, F.; Moeschler, H.; Weiss, H. *Pestic. Sci.* **1991**, *33*, 427-438.

5 Ahammadsahib, K.L.; Hollingworth, R.M.; McGovren, J.P.; Hui, Y.; J. L. McLaughlin, J.L. *Life Sciences*, **1993**, *53*, 1113-1120.

6 Born, L.; Lieb, F.; Lorentzen, J.P.; Moeschler, H.; Nonfon, M.; Sölner, R.; Wendisch, D.; *Planta Medica*, **1990**, *56*, 312-316.

7 Pettit, G.R.; Cragg, G.M.; Polonski, J.; Herald, D.L.; Goswami, A.; Smith, C. R.; Moretti, C.; Schmidt, J.M.; Weisleder, D. *Can. J. Chem.* **1987**, *65*, 1433-1435.

8 a) Hoye, T.R.; Zhuang, Z.P. *J. Org. Chem.* **1988**, *53*, 5578-5580.
b) Harmange, J.C.; Figadère, B.; Cavé, A. *Tetrahedron Lett.* **1992**, *33*, 5749-5752.

9 Rieser, M.R.; Hui, Y.; Rupprecht, J.K.; Kozlowski, J.F.; Wood, K.V.; McLaughlin, J.L.; Hanson, P.R.; Zuang, Z.; Hoye, T.R. *J. Am. Chem. Soc.* **1992**, *114*, 10203-10213.

10 Bertrand, P.; Gesson, J.-P. *Tetrahedron Lett.* **1992**, *33*, 5177-5180.

11 Bertrand, P.; Gesson, J.-P. *Synlett*, **1992**, 889-890.

12 Gale, J.B.; Yu, J.-G.; Khare, A.; Hu, X.E.; Ho, D.K.; Cassady, J.M. *Tetrahedron Lett.* **1993**, *34*, 5851-5854.

13 Schultz, W.J.; Etter, M.C.; Pocius, A.V.; Smith, S. *J. Am. Chem. Soc.* **1980**, *102*, 7981-7982.

14 Eliel, E.L.; Kaloustian, M.K. *J. Chem. Soc. Chem. Comm.* **1970**, 290.

15 This may be due to the minimal interaction of the individual dipole moments of the two C-O bonds like in the electrostatic theory of the anomeric effect (See: Perrin, C.L.; Armstrong, K.B.; Fabian, M.A. *J. Am. Chem. Soc.* **1994**, *116*, 715-722 and references cited therein).

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