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On the Mechanism of the Formation of Tetrahydrofurans from 1,4-Diols Mediated by Triphenylphosphine and N-Bromosuccinimide

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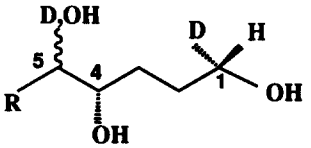
Key words: 1,4-diols; tetrahydrofurans; stereochemistry

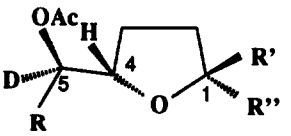
Abstract: *The conversion of yeast generated (1S) [1,5-$^2H_2$] **1** into tetrahydrofuran mediated by triphenylphosphine and N-bromosuccinimide occurs with inversion at position 1, as indicated by NMR studies on* **2**.

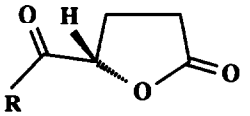
We recently reported on the direct conversion into tetrahydrofurans of 1,4-diols treated with NBS/Ph_3P in dichloromethane. Under identical conditions 1,5-diols afforded the 1-bromo-5-hydroxy derivatives, from which cyclic ethers were accessible upon basic treatment.[1] The isolation of tetrahydrofurans observed in the former instance could be the consequence of a two steps process in which in the intermediate 1-bromo-4-hydroxy derivative formed by the action of Ph_3P/NBS onto the primary alcohol[2] the 4-hydroxyl group displaces the bromide at position 1 or of a single process in which the phosphine-activated oxygen function becomes the leaving group at position 1, thus resembling the "oxidative-reductive"[3,4] ring closure of diols mediated by Ph_3P and diethylazodicarboxylate. Information on the reaction pathway should be accessible from the determination of the stereochemical changes occurring at position 1 of 1,4-diols during the ring closure. Indeed, in the first instance it is expected to observe retention of configuration, as result of two inversions,[4,5] and in the second instance inversion of configuration. We report now on ring closure experiments of a polyol asymmetrically deuterated in position 1, prepared by baker's yeast mediated reduction of the corresponding aldehyde, which support the second hypothesis.

As substrate for the stereochemical study we chose the 1,4,5-triol **1**, asymmetrically deuterated in position 1, because preliminary NMR studies onto the derived tetrahydrofuran **2** indicated the presence in the spectrum of sufficiently distinct signals relative to the methylene protons α to the ring oxygen, thus allowing the determination of the stereochemical changes occurring at that position in the ring closure. The synthesis of **1** proceeded from *L*-glutamic acid through the (*S*)-keto lactone **3**,[6] converted (i: $LiAlD_4/Et_2O$; ii: $(Me)_2C(OMe)_2$/TsOH; iii: pyridinum chlorochromate) into the [1,5-$^2H_2$] aldehyde **4a** (4,5-*syn*/*anti*,

6:4). The latter aldehyde was readily reduced in fermenting baker's yeast to the carbinol **4b** showing a 4,5-*syn/anti* ratio as in the precursor. This carbinol resulted enantiomerically pure at C-1 from the comparison of the NMR spectra of its ester **4c** with (+) α-methoxy-α-trifluoromethylphenylacetic acid (MTPA)[7] and of the same derivative prepared from the diastereoisomeric mixture obtained by $NaBH_4$ reduction of **4a**.[8]



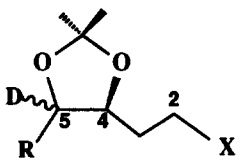


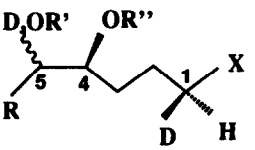


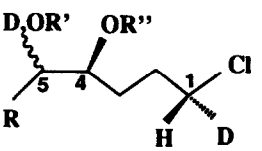
R = CH_2CH_2Ph

1 **2a R'= D, R''= H** **3**
2b R'= H, R''= D
2c R'= D, R''= H

This material was assigned the (1*S*) configuration depicted in **5**, at the light of the NMR studies on the optically active deuterated cyclic products **2** (see below). The observed stereochemistry is in agreement with the known behaviour of baker's yeast.[9] Subsequent acid-catalysed hydrolysis of the dioxolane protecting group afforded the required material **1**. The mode of cyclization of **1** to tetrahydrofuran was compared with that of **7** and **9**, determining in each case the stereochemical changes by NMR studies on **2**.







R = CH_2CH_2Ph

4a X = CDO
4b X = CHDOH
4c X = CHDOMTPA

5 R',R''= $C(Me_2)$; X = OH
6 R',R''= $C(Me_2)$; X = OTs
7 R',R''= H; X = OTs

8 R',R''= $C(Me_2)$
9 R',R''= H

The conversion of (1*S*) [1,5-$^2H_2$] triol **1** into the tosylate ester **7** and the (1*R*) 1-chloro derivative **9** was straightforward. **5** gave rise to **6** (TsCl/pyridine, r.t.; 24 h, 100%), transformed, in turn, by mild acid hydrolysis into the desired 4,5-diol **7**. Similarly, the chloro derivative **8** was prepared from **5** in quantitative yield by treatment at reflux with CCl_4/Ph_3P, conditions expected to assure substitution with inversion of configuration.[10] As above, acid hydrolysis of **8** gave rise to **9** in 85% yield. Products **7** and **9**, upon treatment with 1 mol. eq. of MeONa in methanol, afforded in quantitative yield a 6:4 mixture of

4,5-*syn*/*anti* tetrahydrofurans, separated by column chromatography as acetyl derivatives. As expected, the ^2H NMR spectra (Figure) of the minor (4,5-*anti* configuration) diastereoisomers **2a** and **2b**, obtained from **7** and **9**, respectively, indicate that they have opposite stereochemistry of the deuterium atom in the ring methylene.[11] Comparison of the above spectra with that of **2c**, obtained from **1** by treatment with Ph_3P/NBS in dichloromethane, clearly shows that the cyclization took place with inversion of configuration as in the case of the tosylate ester **7**. The stereochemistry of the deuterium atom at C-1 was determined by NOE difference spectroscopy. Thus, irradiation of H-4 produced enhancement of the H-1 signal (ca. 2%) for **2b** and no effect in the case of **2a** and **2c**. The same behaviour showed the major diastereoisomeric tetrahydrofurans having a 4,5-*syn* stereochemistry. Several explanations for the observed partial loss of stereochemical purity in the α-methylene on going from **5** to **2** via **9** and **1** (7% and 10% respectively), could be proposed, all of which require further experiments.

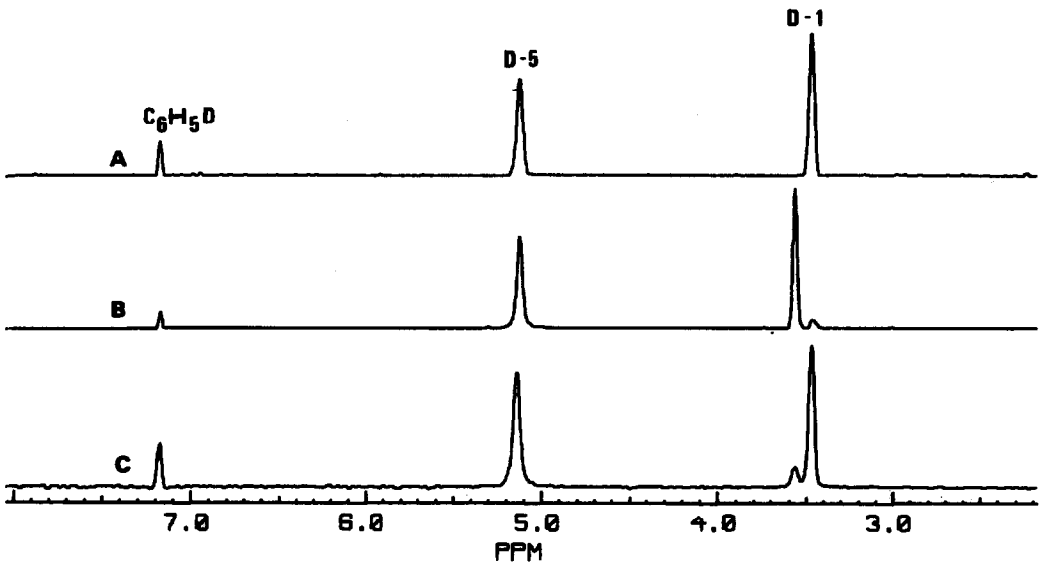


Figure. Deuterium NMR spectra (400 MHz, C_6H_6) of tetrahydrofurans **2a** (A), **2b** (B) and **2c** (C).

However, apart from that, the present results clearly show that the conversion of 1,4-diols treated with Ph_3P/NBS into tetrahydrofurans proceeds predominantly with inversion of configuration although further studies will be needed to elucidate the mechanism.

Finally, the preparation of asymmetrically deuterated **5**, key intermediate for the present mechanistic investigations, through baker's yeast transformation of a non-conventional substrate further expands the use of enzymes in organic synthesis.

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8 ^{1}H NMR (300 MHz, $CDCl_3$): (*4,5-syn/anti mixture* **4c** *obtained by* $NaBH_4$ *reduction of* **4a**): δ 4.35 and 4.31 (two broad triplets, 1 H, H-1, J = 7 Hz), 3.98 (dd, 0.4 H, H-4 of *anti* diastereoisomer, J = 10 and 3.5 Hz), 3.60 (dd, 0.6 H, H-4 of *syn* diastereoisomer, J = 8 and 3.5 Hz), 3.52 (s, 3 H, OCH_3), 2.55-2.90 (m, 2 H, CH_2-7), 1.4-2.0 (m, 6 H, CH_2-2, CH_2-3 and CH_2-6), 1.43, 1.40, 1.38 and 1.33 (s, 6 H, four methyl groups). (*4,5-syn/anti mixture* **4c** *obtained by baker's yeast reduction of* **4a**): δ 4.35 (broad t, 1 H, H-1, J = 7 Hz), all other signals are identical to those reported above.
The major diastereoisomer of the mixture **4c** was assigned the 4,5-*syn* stereochemistry (nuclei H-4 and D-5 on the five membered ring trans oriented) on the basis of the chemical shift of H-4. Cis vicinal protons in 1,2-substituted five membered rings are known to resonate downfield with respect to the corresponding hydrogens of the trans isomer (Anteunis, M.; Danneels, D. *Org. Magn. Reson.* **1975**, *7*, 345).

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11 ^{1}H NMR (400 MHz, C_6D_6): (**2a** and **2c**): δ 3.78 (t, 1 H, H-4, J = 7 Hz), 3.56 (t, 1 H, H-1, J = 7 Hz), 2.65 (m, 2 H, CH_2-6), 1.70 (s, 3 H, $COCH_3$), 1.96 (m, 2 H, CH_2-7), 1.32-1.54 (m, 4 H, CH_2-2 and CH_2-3). (**2b**): δ 3.78 (t, 1 H, H-4, J = 7 Hz), 3.45 (t, 1 H, H-1, J = 7 Hz), 2.65 (m, 2 H, CH_2-6), 1.70 (s, 3 H, $COCH_3$), 1.96 (m, 2 H, CH_2-7), 1.32-1.54 (m, 4 H, CH_2-2 and CH_2-3).
^{2}H NMR (400 MHz, C_6H_6): (**2a** and **2c**): δ 5.12 (D-5), 3.45 (d-1). (**2b**): δ 5.11 (D-5), 3.55 (D-1).

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