Pergamon

Tetrahedron Letters, Vol. 35, No. 48, pp. 9095-9098, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01942-8

Stereochemistry of Reduction of a Heterocyclic α-Hydroxy-Ketone: The Structure, Conformation and Preparation of the *syn* and *anti*- 3,3,6,6 -Tetramethylthiepan-4,5-diols

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Abstract: Reduction of 5-hydroxy-3,3,6,6-tetramethylthiepan-4-one, now readily available by an improved synthesis, with chelating and non-chelating reducing agents allows the preparation of the two diastereoisomers of the title compounds whose structures and conformations are determined by X-ray crystal structure analysis.

The thiepanolone **4** is readily available by an intramolecular acyloin reaction[1] on the diester **3** and has been used as a starting material for the synthesis of a rare seven-membered cyclic alkyne.[2] We have improved the yield of **2** in the first step in this sequence from 50 to 89% simply by using a 2:1 ratio of **1** to Na_2S. We have studied the reduction of the hydroxy ketone **4** with various reducing agents to give the *syn* and *anti* diols **5** and have determined their structures and conformations by X-ray crystal structure analysis.

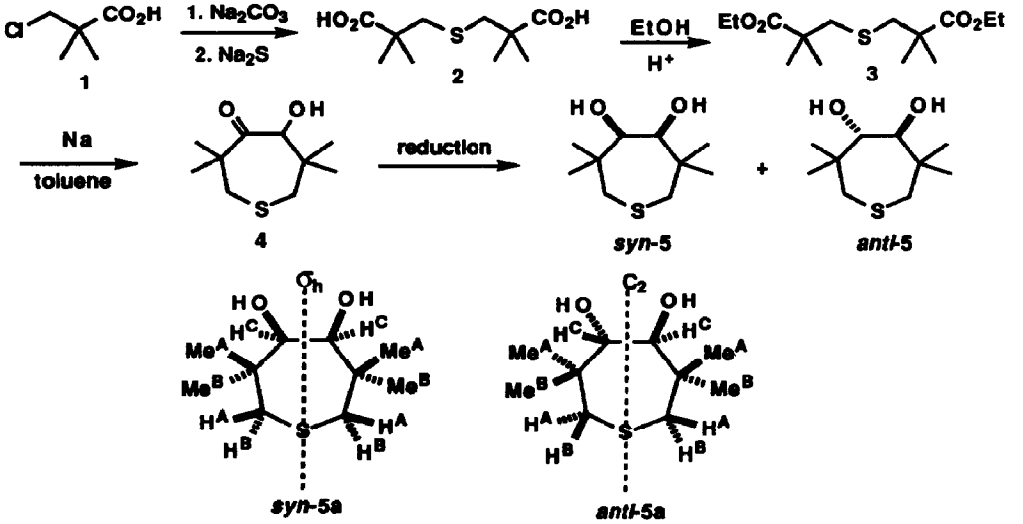


Table 1: 250 MHz NMR ^1H spectra ($CDCl_3$ solution) of *syn* and *anti* diols **5**.

δ OH (ppm)		δ Me^A (ppm)		δ Me^B (ppm)		δ H^A (ppm)		δ H^B (ppm)		J_{AB} (Hz)		δ H^C (ppm)	
syn **5**	*anti* **5**	*syn* **5**	*anti* **5**	*syn* **5**	*anti* **5**	*syn* **5**	*anti* **5**	*syn* **5**	*anti* **5**	*syn* **5**	*anti* **5**	*syn* **5**	*anti* **5**
1.78	2.76	1.08	1.09	1.07	0.95	2.83	2.52	2.28	2.28	14.4	14.7	3.73	3.57

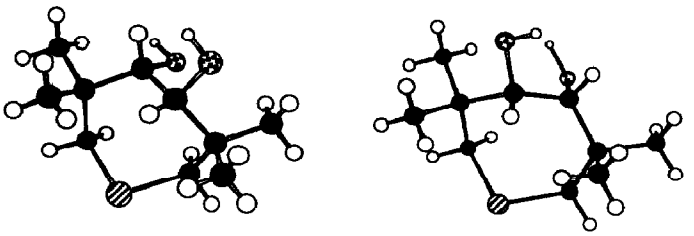
The stereochemistry of the two diols **5** is interesting as the *syn* compound has a plane of symmetry (it is a meso compound) while the *anti* compound has C_2 symmetry: the symmetry axes are shown on structures **5a**. In both diols the CH_2 groups and the CMe_2 groups are diastereotopic but in different ways indicated as H^A, H^B and Me^A, Me^B in *syn* and *anti* **5a**. The compounds can be distinguished by their NMR spectra (table 1) but the stereochemistry cannot be assigned by this means.

The original workers[3] mention reduction by lithium aluminium hydride to "a diol" m.p. 179-180 °C in 64% yield but do not specify which diastereoisomer is formed. They quote "four methylene protons" in the ^1H NMR spectrum at δ 3.01, 2.78, 2.30 and 2.05 (60 MHz): these are presumably two AB systems and the separation of about 0.24 p.p.m. is actually a coupling constant of about 14 Hz. Since J_{AB} is a geminal coupling in both isomers, it is not diagnostic (table 1), but we believe their diol was *syn*-**5a**. P. Y. Johnson and co-workers produced both diols[4] and say[5] that they assigned the stereochemistry by chiral shift reagents. They definitely assigned the stereochemistry of related azepine diols by achiral shift reagents.[6] Though they quote J_{AB} as 12 Hz for the *syn* diol, and there are doubts about their method,[5] their m.p. (183-185 °C) is right for the *syn* diol and we believe their assignments are correct.

Table 2: Diastereoisomeric Ratios in the Reduction of Acyloin **4** to the Diols **5**.

Reagent	Conditions	*syn:anti* ratio	Isolated Yield (%) *syn* or *anti*
$LiAlH_4$	Et_2O, reflux	84:16	-
$NaBH_4$	EtOH, room temp.	100:0	*syn* 92%
$NaBH_4/CeCl_3$	EtOH, –78 °C	100:0	-
$Zn(BH_4)_2$	Et_2O, 0 °C	64:36	*syn* 61%; *anti* 34%
DIBAL	CH_2Cl_2, –78 °C	95:5	-
DIBAL/$ZnCl_2$	THF/Et_2O, room temp.	39:61	*syn* 36%; *anti* 56%

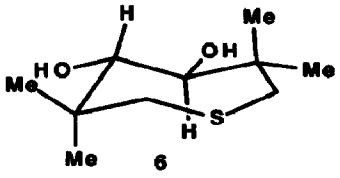
Figure 1: X-Ray structure of the *syn*-diol *syn*-**5** showing the conformation of the two molecules in the unit cell.



We reduced the acyloin **4** with $NaBH_4$/EtOH and got one diol, m.p. 180-182 °C, in high yield: the *syn* product was expected on a Felkin argument.[7,8] The structure of this highly crystalline diol was shown to be *syn*-**5** by an X-ray structure analysis (figure 1). Open chain hydroxy ketones normally give *anti* diols with chelating reducing agents,[7,9] particularly $Zn(BH_4)_2$, and so we also tried the Luche[10] conditions which we have found effective in reversing stereoselectivity in α-Ph_2PO-ketones.[11] In fact the addition of Ce(III) made no difference to the stereoselectivity. Reduction with $LiAlH_4$ gave a similar ratio (table 2) to that observed by Johnson,[4] and only with the most chelating reducing agents, $Zn(BH_4)_2$ or DIBAL with $ZnCl_2$, was any reasonable amount of *anti* diol, m.p. 89-91 °C, produced and it was the major product only with the DIBAL/$ZnCl_2$ combination. The *anti* diol **5** was separated by column chromatography on silica, eluting with

hexane–EtOAc (6:1), and its structure was also proved by X-ray (figure 2). The *syn* diol has two conformations in the crystal (figure 1) differing in the way the ring is puckered. The *anti* diol has only one conformation: a chair-like arrangement **6** with pseudoequatorial OH groups (figure 2).

Figure 2: Conformation and X-Ray structure of the *anti*-diol *anti*-**5**



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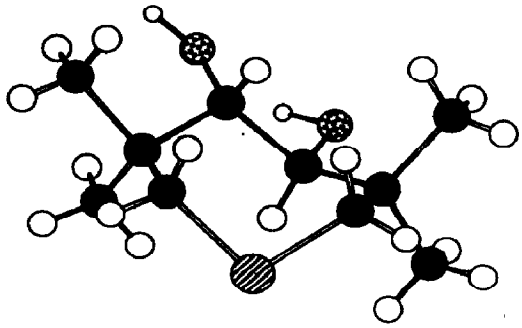
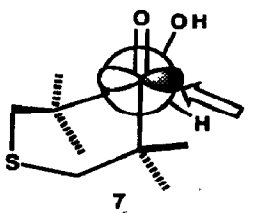


The stereochemistry of the reduction of acyclic α-hydroxyketones can usually be controlled to give either diol since freedom of rotation about the CO-CHOH bond allows the normal Felkin conformation to be changed by chelation into one giving the opposite results. The same freedom of rotation is not available to cyclic compounds and "the influence of polar groups on the stereoselectivity of reduction of cyclic ketones has not been widely studied."[7] *Syn* diol formation in the reduction of the acyloin **4** is probably preferred both because there is no good Felkin conformation for the reactions and because rotation is prevented. Conformations such as **7** have a ring bond rather than the OH group at right angles to the C=O group while the best conformation seems to be the more Cram-like **8** with H eclipsing a ring bond and reduction occurring on the *exo* face of the C=O group. In neither case would complexation of a metal with OH deliver hydride to the opposite face. The X-ray structure of the *anti* diol **6** makes it clear that the hydride must approach from an unfavourable pseudo-axial direction to give this conformation. Coordination with Zn may fix the conformation of **4** by a chelate and allow approach of hydride as in **9** or **10**. Solladié and his co-workers have used chelation of zinc by β-ketosulfoxides to reverse the stereochemistry of reduction by DIBAL both in open chain[12] and in cyclic[13] ketones, though the sulfoxide is always outside the ring.



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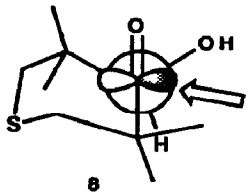

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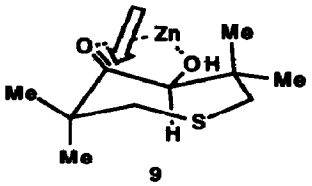

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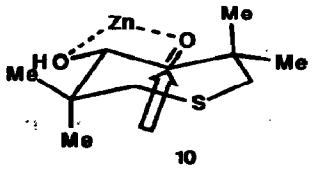

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Acknowledgements: We thank SERC for a grant and Dr W. Jones for the use of CAD4 X-ray equipment.

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5. Note 14 of ref. 4 refers to the *syn* compound: "The stereochemistry of this diol (a meso compound) was determined by using chiral shift reagents.[2c] A complete report of this approach to diol stereochemistry will be forthcoming." Their ref 2c is: Johnson, P. Y.; Jacobs, I.; Kerkman, D. J. *J. Org. Chem.*, in the press. This paper does not seem to have appeared, but it may have become our ref. 6 which describes the assignment of stereochemistry to the related azepine diols. Their method relies on a prochiral substituent on the tetrahedral nitrogen atom and would not apply to the diols **5**. They quote no NMR nor m.p. for the *anti*-diol but imply that they used Applequist's method of making cyclic sulfites to assign its stereochemistry (this would work for both diols), see Applequist, D. E.; Gebauer, P. A.; Gwynn, D. E.; O'Connor, L. H. *J. Am. Chem. Soc.*, **1972**, *94*, 4272-4278.
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(*Received in UK* 12 *September* 1994; *accepted* 30 *September* 1994)