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STEREOSELECTIVE PREPARATION OF ACYCLIC *syn*-1,3-AMINO ALCOHOLS FROM β-HYDROXY KETONES

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syn-1,3-Amino alcohols are prepared in good yields by the stereoselective reduction of β-hydroxy ketone-O-benzyloximes derived from acyclic β-hydroxy ketones with lithium aluminium hydride.

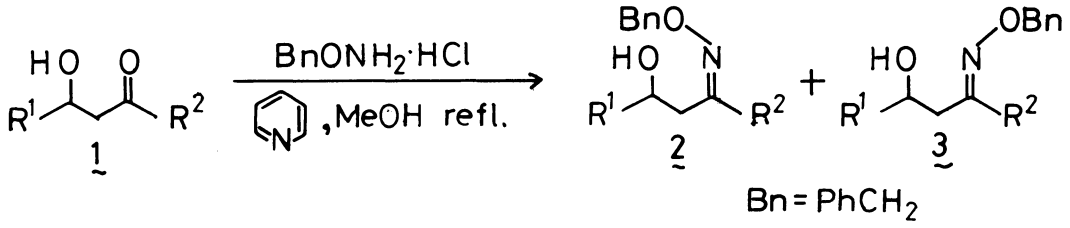
In recent years, many approaches to the asymmetric induction in the reaction of acyclic precursors have been widely studied, and various useful and stereoselective methods have been developed.[1] Concerning with this problem, we have studied on the 1,3-asymmetric induction of acyclic system and have developed a facile method for the synthesis of *syn*-1,3-diols from β-hydroxy ketones via boron chelates.[2] According to the 1,3-asymmetric induction directed by hydroxyl group, we examined the stereoselective synthesis of acyclic 1,3-amino alcohols, and now we report a highly stereoselective method for the preparation of 1,3-amino alcohols from β-hydroxy ketones.

Although acyclic 1,2-amino alcohols are obtained in fairly good selectivity from acyclic compounds such as α-amino ketones and α-hydroxy oximes with nucleophilic reagents such as Grignard reagents, the preparation of 1,3-amino alcohols from acyclic precursors has still remained as a formidable synthetic problem.[3,4] Recently, Jäger and Kozikowski have presented a useful method for the preparation of 1,3-amino alcohols in considerable stereoselectivity from cyclic intermediates, isoxazolines.[5]

In the present study, we have examined the stereoselective transformation of β-hydroxy ketones to 1,3-amino alcohols, and it was found that the lithium aluminium hydride(LAH) reduction of β-hydroxy ketone-O-benzyloximes which were

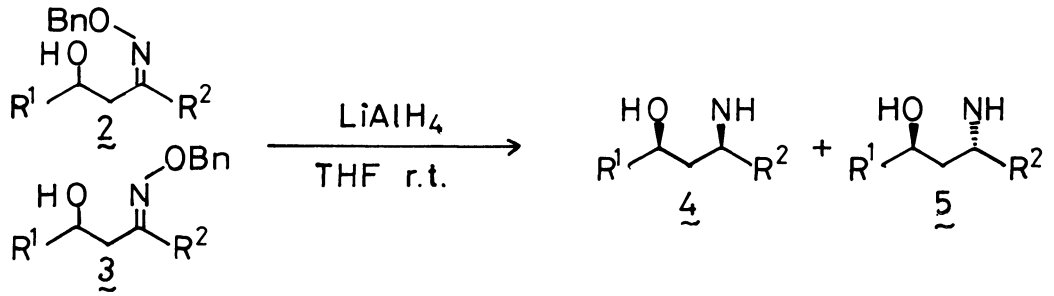
readily prepared from β-hydroxy ketones proceeds stereoselectively to afford *syn*-1,3-amino alcohols.

The conversion of β-hydroxy ketones (1) to the corresponding O-benzyloximes (2, 3) was performed by treatment of 1 with O-benzylhydroxylamine hydrochloride and pyridine in refluxing methanol.[6] The resulting *syn* and *anti* isomers (2, 3) were readily separated by column chromatography on silica gel.[7]



Then the 1,3-asymmetric induction in the reduction of each isomers (2, 3) was investigated using some metal hydrides such as LAH, diborane, etc. And as shown in the table, high stereoselectivity was observed when *syn*-O-beyzyloximes (2) were treated with LAH in tetrahydrofuran(THF) at room temperature, and *syn*[8]-1,3-amino alcohols (4) were obtained in good yields. A representative procedure for the synthesis of 4 is as follows.

To a THF (3 ml) solution of 5-hydroxy-1,7-diphenyl-3-heptanone-*syn*-O-benzyloxime (2a, 0.56 mmol) was added a solid LAH (2.8 mmol) at 0 °C under an argon atmosphere. The reaction mixture was stirred at room temperature over night and was quenched with aqueous sodium sulfate (0.8 ml). The resulting precipitate was filtered off, and the filtrate was purified by preparative tlc on aluminium oxide to give *syn*-5-amino-3-hydroxy-1,7-diphenylheptane (4a, 77%) along with the *anti*-isomer (5a, 8%).

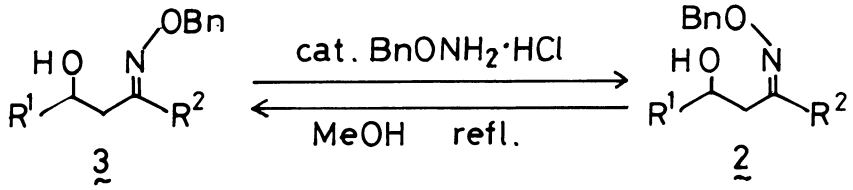


In comparison with the high asymmetric induction in the reduction of *syn*-O-benzyloximes (2), the reduction of *anti*-O-benzyloximes (3) proceeded only in moderate selectivity. Therefore, the isomerization of *anti*-O-benzyloximes (3) to

Table 1. Synthesis of 1,3-amino alcohols (4, 5)

	R^1	4 or 5	R^2	Ratio of 4 : 5 (Total yield) from 2 (*syn*)	from 3 (*anti*)
a	$PhCH_2CH_2$		$PhCH_2CH_2$	91 : 9 (85%)	79 : 21 (96%)
b	n-Bu		n-Bu	95 : 5 (87%)	77 : 23 (96%)
c	i-Bu		i-Bu	95 : 5 (77%)	77 : 23 (83%)
d	$PhCH_2CH_2$		CH_3	88 : 12 (78%)	78 : 22 (85%)
e	Ph		CH_3	88 : 12 (74%)	85 : 15 (82%)

syn-O-benzyloximes (2) was then investigated. It is well known that oximes are susceptible to isomerization by acid and base.[9] On the other hand, O-benzyloximes (2, 3) did not isomerized so easily under the same reaction conditions. Finally, it became apparent that the equilibrium between *syn* and *anti*-O-benzyloximes was attained when 2 or 3 was treated with a catalytic amount of O-benzylhydroxylamine hydrochloride in refluxing methanol for 2 or 3 h,[10] and as described before these isomers were easily separated by chromatography.



3 2

Since β-hydroxy ketones are now readily available by a variety of aldol type reactions,[11] this method provides a simple and useful route for the synthesis of acyclic *syn*-1,3-amino alcohols. Further the stereocontrol directed by hydroxyl group seems to be a useful strategy for the asymmetric induction of acyclic system.

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7) In this report, the isomer (2) whose benzyloxyl group is *syn* to hydroxyl group is presented as *syn*-O-benzyloxime, and the other isomer (3) is called *anti*-O-benzyloxime. β-Hydroxy ketone-O-benzyloximes (2 and 3) were obtained in high yields, and the ratios of isomers were 2a : 3a = 51 : 49, 2b : 3b = 52 : 48, 2c : 3c = 53 : 47, 2d : 3d = 34 : 66, and 2e : 3e = 31 : 69. In nmr spectra, chemical shifts of methylene protones (-CH(OH)-$\underline{CH}_2$-C=N-) of 2 appeared at lower fields than those of 3.[12] The *syn*-isomers (2) were transformed to the corresponding isoxazolines by treatment with methanesulfonyl chloride and triethylamine. However, the *anti*-isomers were not. These facts also assigned the stereochemistry.

8) The relative stereochemistry of 1,3-amino alcohols is presented according to the Masamune's nomenclature using *syn* and *anti* terms; S. Masamune, S. A. Ali, and D. L. Snitman, Angew. Chem. Int. Ed. Engl., 19, 557 (1980). The stereochemistry of 1,3-amino alcohols was determined by ^{13}C nmr spectra in which chemical shifts of -$\underline{C}$H(OH)- were observed at lower fields (about 4-3 ppm).[5b] Further, each of the amino alcohol was converted to the cyclic urethane and the nmr spectra well agreed with the assigned structure.

9) C. G. McCarty, "Chemistry of the Carbon-Nitrogen Double Bond," ed by S. Patai, John Wiley & Sons, Inc., New York (1970), p. 383.

10) The ratios of 2 to 3 at equilibrium were the same as those in the preparation of O-benzyloximes from β-hydroxy ketones.[7]

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