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HIGHLY ENANTIOSELECTIVE SYNTHESIS OF *ANTI(THREO)*-ALDOLS BY THE ASYMMETRIC ALDOL REACTION UTILIZING A CHIRAL AZAENOLATE

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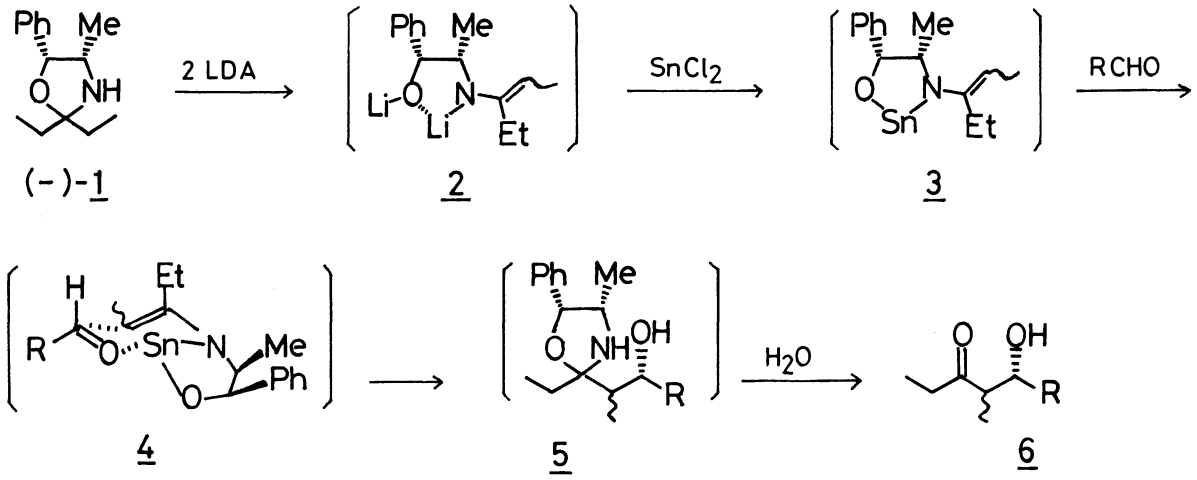
Diastereo- and enantioselective aldol reaction between 3-pentanone and aldehydes is achieved utilizing a chiral oxazolidine derived from 3-pentanone and chiral norephedrine. The reaction of a tin(II) azaenolate generated from the chiral oxazolidine with aldehydes affords predominantly *anti(threo)*-aldols of high enantiomeric purity.

Much effort has been directed toward the development of asymmetric aldol reactions and has resulted in the recent rapid progress in this field.[1] Although several useful methods have been reported for the preparation of optically active *syn(erythro)*-aldols,[2] highly enantioselective synthesis of *anti(threo)*-aldols has still remained as a formidable synthetic problem.[3] Now we wish to report a highly enantioselective systhesis of *anti*-aldols of 3-pentanone with aldehydes.

In the preceding communication, we reported the highly enantioselective aldol reaction of methyl ketones utilizing chiral tin(II) azaenolates.[4] This method was applied to the asymmetric aldol reaction of 3-pentanone based on the following considerations. It was expected that treatment of the chiral oxazolidine 1 with 2 molar amount of LDA would generate the (E) or (Z)-lithium azaenolate 2 stereoselectively as reported for the metallation of acyclic imines.[3,5] By the addition of tin(II) chloride, the lithium azaenolate 2 would be converted into the cyclic tin(II) azaenolate 3, and hence the aldol reaction with an aldehyde should

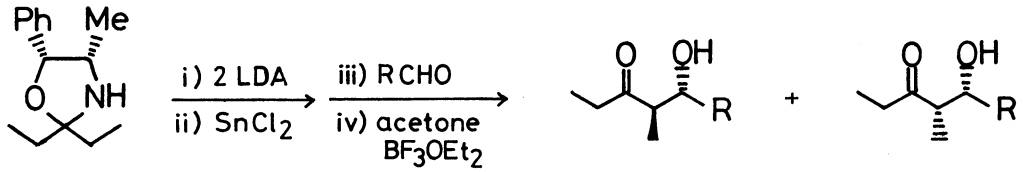


(-)-1 2 3

4 5 6

proceed *via* the bicyclic transition state 4 to give an optically active aldol 6. Based on this assumption, the aldol reaction of the chiral oxazolidine 1 was examined.

The experimental procedure is as follows. The starting material, (4S,5R)-2,2-diethyl-4-methyl-5-phenyl-1,3-oxazolidine (1), was prepared quantitatively by condensing (-)-norephedrine and 3-pentanone azeotropically and purified by distillation.[6] A THF (2 mL) solution of 1 (1 mmol) was added to a THF (2 mL) solution of LDA (2.1 mmol) at 0 °C, and the mixture was stirred for 2 h. Then a THF (3 mL) solution of tin(II) chloride (1.05 mmol) was added at 0 °C and stirred for 30 min. To the resulting mixture was added a THF (2 mL) solution of 3-phenylpropanal (1.2 mmol). After stirring for 20 min at 0 °C, the reaction mixture was quenched with aqueous 4% $NaHCO_3$. Filtration through a Celite pad, extraction of the filtrate with ether and evaporation of the solvent gave an oily residue. To this residue were added acetone (3 mL) and a catalytic amount of



(-)-1 7 8

a R= $Ph(CH_2)_2$
b R= c-C_6H_{11}
c R= t-C_4H_9

RCHO	Yield/%	7 : 8[a]	Optical Purity of 7 /% ee	$[\alpha]_D$ of 7 ($CHCl_3$)
$Ph(CH_2)_2CHO$	77	7 : 1	92[b]	$[\alpha]_D^{18}$ +18.8°(c 2.2)
c-$C_6H_{11}CHO$	75	9 : 1	92[b]	$[\alpha]_D^{19}$ + 6.7°(c 2.1)
t-C_4H_9CHO	56	6 : 1	>95[c]	$[\alpha]_D^{20}$ +11.8°(c 2.4)

a) The relative stereochemistry of each isomer (7a,b and 8a,b) was assigned by the measurement of the coupling constant between the protons on C-4 and C-5.[8] In the case of 7b,c and 8b,c, it was also indentified by the chemical shift of the methyl carbon on C-4.[9]

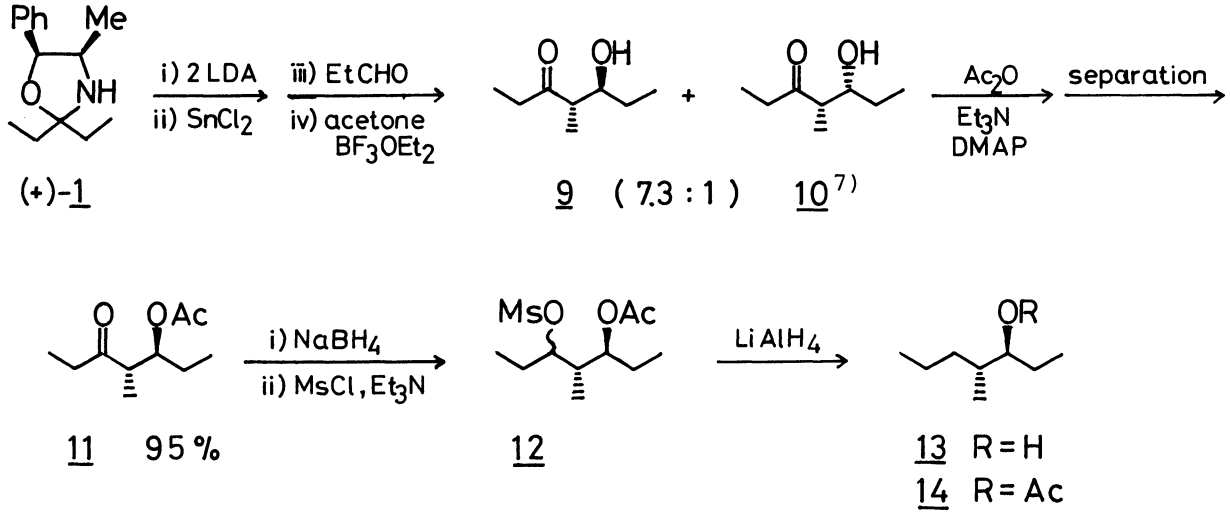
b) Determined by ^1H and ^{19}F NMR measurement of its MTPA ester in the presence of $Eu(fod)_3$.[10]

c) Determined by ^1H NMR measurement in the presence of $Eu(hfc)_3$.

$BF_3 \cdot OEt_2$ and the mixture was stirred overnight to complete the acetal exchange. After the evaporation of acetone, the residue was purified by column chromatography on silica gel to give a mixture of *anti*-5-hydroxy-4-methyl-7-phenyl-3-heptanone (7a) and the *syn*-isomer 8a in total yield of 77%. Each isomer was separated by Chromatotron (silica gel, hexane-ethanol) and the relative stereochemistry of these isomers and the optical purity of the *anti*-isomer 7a were determined.

The aldol reaction of 1 with cyclohexanecarbaldehyde or pivalaldehyde was also examined in a similar manner, and the diastereoselectivity of the aldol reaction and the optical purity of *anti*-aldols 7a,b,c are summarized in the Table. In all cases, the *anti*-aldols 7 were obtained predominantly in excellent optical purities.[7)]

In order to determine the absolute stereochemistry of the *anti*-aldol 7 and to demonstrate the usefulness of this asymmetric aldol reaction, an isomer of an insect pheromone, (3S,4R)-4-methylheptan-3-ol 13,[11)] was synthesized from (+)-oxazolidine 1. The reaction of (+)-1 and propanal by the above mentioned procedure gave aldols 9 and 10 in 61% yield (*anti*-9 : *syn*-10 = 7.3 : 1). Separation of the each isomer was carried out after conversion to the corresponding acetate by column chromatography on silica gel. The optical purity of the *anti*-acetate 11 was determined as 95% ee using the chiral shift reagent, $Eu(hfc)_3$. Reduction of 11 with $NaBH_4$ and successive methanesulfonylation gave the sulfonate 12 in 79% yield. The methanesulfonate 12 was reduced with lithium aluminum hydride to give crude (+)-4-methylheptan-3-ol which was purified after conversion to the corresponding acetate 14, and the pure 13 is regenerated by alkali hydrolysis in 31% overall yield from 12. By the comparison of the optical rotation of 13 with that of the literature,[11)] the absolute configuration was determined as (3S,4R) and the optical purity was proved to be over 95% ee.



In summary, the preparation of *anti*-aldols in quite high enatiomeric excess was achieved by the asymmetric aldol reaction between 3-pentanone and aldehydes *via* a chiral Sn(II) azaenolate.

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References

1) C. H. Heathcock, "The Aldol Addition Reaction," in "Asymmetric Synthesis," ed by J. D. Morrison, Academic Press, Inc., Orlando (1984), Vol. 3, p. 111; D. A. Evans, J. V. Nelson, and T. R. Taber, "Stereoselective Aldol Condensations," in "Topics in Stereochemistry," ed by N. L. Allinger, E. L. Eliel, S. H. Wilen, Wiley-Interscience, New York (1982), Vol. 13, p. 1; N. Iwasawa and T. Mukaiyama, Chem. Lett., 1983, 297; M. Braun and R. Devant, Angew. Chem., Int. Ed. Engl., 22, 788 (1983); S. H. Mashraqui and R. M. Kellogg, J. Org. Chem., 49, 2513 (1984).

2) D. A. Evans, J. Bartroli, and T. L. Shih, J. Am. Chem. Soc., 103, 2127 (1981); S. Masamune, W. Choy, F. A. Kerdesky, and B. Imperiali, ibid., 103, 1566 (1981); N. Iwasawa and T. Mukaiyama, Chem. Lett., 1982, 1441.

3) High *anti* stereoselection and satisfactory optical yield have been achieved in the enantioselective aldol reaction between a chiral boron azaenolate and aldehydes; A. I. Meyers and Y. Yamamoto, J. Am. Chem. Soc., 103, 4278 (1981).

4) K. Narasaka, T. Miwa, H. Hayashi, and M. Ohta, Chem. Lett., 1984, 1399.

5) R. Knorr, A. Weiss, P. Low, and E. Rapple, Chem. Ber., 113, 2462 (1980); J. Y. Lee, T. J. Lynch, D. T. Mao, D. E. Bergbreiter, and M. Newcomb, J. Am. Chem. Soc., 103, 6215 (1981); A. I. Meyers, D. R. Williams, S. White, and G. W. Erickson, ibid., 103, 3088 (1981).

6) (4S,5R)-2,2-Diethyl-4-methyl-5-phenyl-1,3-oxazolidine: 95-100 °C (bath temp) / 67 Pa; $[\alpha]_D^{20}$ -60.0°(c 2.3, $CHCl_3$); ^{1}HNMR ($CDCl_3$) δ=0.55 (3H,d,J=7 Hz), 0.95, (6H,t,J=8 Hz), 1.47 (1H,d,J=6 Hz), 1.75 (4H,q,J=8 Hz), 3.4-3.9 (1H,m), 4.86 (1H,d,J=8 Hz), 7.10 (5H,br s); IR (neat) 3300, 2970, 1455, 1020 cm^{-1}.

7) In contrast to the high enantiomeric purity of *anti*-aldols 7, a very low chiral induction was observed in the corresponding *syn*-aldols 8. The absolute configuration of *syn*-aldols 8 and 10 were not determined.

8) M. Stiles, R. Winkler, Y. Chang, and L. Traynor, J. Am. Chem. Soc., 86, 3337 (1964); H. O. House, D. S. Crumrine, A. Y. Teranishi, and H. D. Olmstead, ibid., 95, 3310 (1973); 7a, 6.8 Hz, 8a, 2.2 Hz; 7b, 7.8 Hz, 8b, 2.9 Hz.

9) C. H. Heathcock, M. C. Pirrung, and J. E. Sohn, J. Org. Chem., 44, 4294 (1979). 7b, δ=14.7; 8b, δ=9.51: 7c, δ=18.1; 8c, δ=11.9.

10) J. A. Dale, D. L. Dull, and H. S. Mosher, J. Org. Chem., 34, 2543 (1969).

11) K. Mori, Tetrahedron, 33, 289 (1977).

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