CHEMISTRY LETTERS, pp. 455-458, 1980.

AN ASYMMETRIC SYNTHESIS OF β-FORMYL β-HYDROXY ESTERS

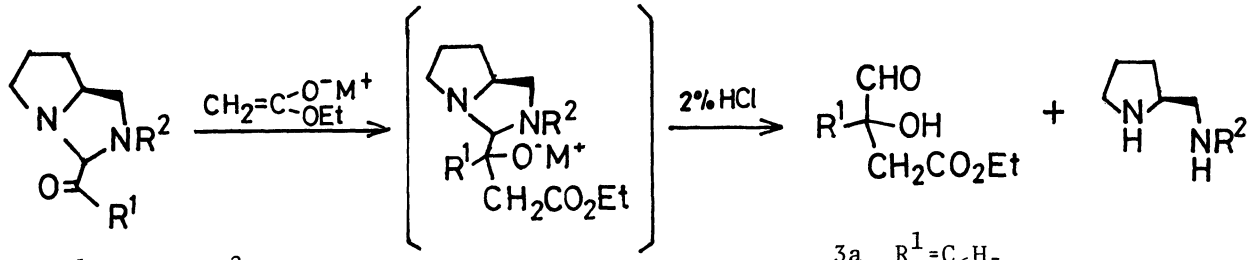
Yoji SAKITO, Masatoshi ASAMI and Teruaki MUKAIYAMA
Department of Chemistry, Faculty of Science
The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113

Optically active β-formyl β-hydroxy esters are prepared in high enantiomeric excess by treating 2-acyl-1,3-diazabicyclo[3.3.0]-octane derivatives, prepared from (S)-2-(substituted aminomethyl)-pyrrolidine and phenylglyoxal monohydrate or methyl hydroxymethoxy-acetate, with metal enolates of ethyl acetate.

We have recently reported asymmetric syntheses of highly optically active α-hydroxy aldehydes, succinaldehydic acid methyl esters and hydroxy oxaindanes by employing the 1,3-diazabicyclo[3.3.0]octane skeleton(aminal) as a chiral moiety[1]. These asymmetric syntheses were carried out by treating the aminals with the Grignard reagents or by generating chiral aryllithium, and it is considered that the coordination of the metals to the nitrogen of the aminal plays an important role in the asymmetric induction.

In this communication we wish to report an asymmetric synthesis of β-formyl β-hydroxy esters by the reaction of 2-acyl-1,3-diazabicyclo[3.3.0]octane derivatives (keto aminals) with metal enolates.

There are two types of easily available metal enolates of ethyl acetate, i) zinc enolates from zinc and esters of haloacetic acids (the Reformatsky reaction), and ii) lithium enolate derived from lithium amide derivatives and esters of acetic acid. i) The reaction of keto aminal 1a[1a] with zinc and ethyl bromoacetate in refluxing benzene, followed by hydrolysis with 2% hydrochloric acid afforded ethyl 3-formyl-3-hydroxy-3-phenylpropionate 3a[2] in 58% yield and 88% e.e. with S-configuration. It is interesting that the ester 3a was obtained in such a high optical yield under the condition of refluxing benzene.



1a $R^1=C_6H_5$ $R^2=C_6H_5$
b $R^1=C_6H_5$ $R^2=o\text{-}MeOC_6H_4$
c $R^1=Me$ $R^2=o\text{-}MeOC_6H_4$
d $R^1=Et$ $R^2=o\text{-}MeOC_6H_4$
e $R^1=Me_2CH$ $R^2=o\text{-}MeOC_6H_4$

2a-e

3a $R^1=C_6H_5$
b $R^1=Me$
c $R^1=Et$
d $R^1=Me_2CH$

ii) The lithium enolate was generated from lithium diisopropylamide and ethyl acetate in tetrahydrofuran, and the reaction with the keto aminal 1a at -78°C, followed by hydrolysis afforded the ester 3a in 85% yield and 62% e.e. with the R-configuration. It is interesting that the opposite enantiomer was obtained by changing the central metal of the enolate from zinc to lithium. In the above reaction, the optical yield was lower probably because of the weakened coordination of lithium to the nitrogen. Therefore we made a design to introduce methoxyl group at the ortho position of the phenyl group of the chiral auxiliary to produce a strong coordination to lithium. Thus, treatment of keto aminal 1b, prepared from (S)-2-(o-anisidinomethyl)pyrrolidine[3] and phenylglyoxal monohydrate, with lithium enolate of ethyl acetate in toluene at -78°C and hydrolysis of the resulting aminal 2b afforded the ester 3a in 85% yield and 84% e.e. with the S-configuration. The optical yield was improved as expected and also chemical yield was higher in comparison with that obtained by the Reformatsky reaction. According to the present procedure, various β-formyl β-hydroxy esters[2] were obtained and the results are summarized in the Table.

Typical experimental procedure is described for the preparation of ethyl 3-formyl-3-hydroxy-3-phenylpropionate: ethyl acetate (3.57 mmol) was added to a solution of lithium diisopropylamide (3.40 mmol prepared in situ from diisopropylamine and n-butyllithium in n-hexane) in toluene at -78°C. After 30 min, a toluene solution of keto aminal 1b(1.70 mmol) was added dropwise and the reaction mixture was stirred for one hour at -78°C. Hydrochloric acid(2%) was added to the reaction mixture and vigorous stirring was continued for 2 hours at a room

Table Asymmetric synthesis of β-formyl β-hydroxy esters

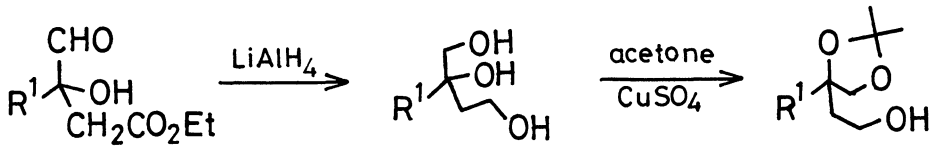
	R^1	R^2	Reaction Conditions	$[\alpha]_D(C_6H_6)$	Yield(%)	ee(%)[d]	config.
1	C_6H_5	C_6H_5	a)	-135°	58	88	S[f]
2	C_6H_5	C_6H_5	b)	+96.3°	85	62	R
3	C_6H_5	o-$MeOC_6H_4$	c)	-128°	85	84	S
4	Me	o-$MeOC_6H_4$[e]	c)	-26.2°	70	92	R[g]
5	Et	o-$MeOC_6H_4$[e]	c)	-17.5°	64	87	h)
6	Me_2CH	o-$MeOC_6H_4$[e]	c)	-25.6°	50	92	h)

a) $Zn/BrCH_2CO_2Et$, benzene, reflux

b) Lithium diisopropylamide/CH_3CO_2Et, THF, -78°C

c) Lithium diisopropylamide/CH_3CO_2Et, toluene, -78°C

d) The enantiomeric excess was determined by integration of one of the methyl groups of the acetonides 5a-d by ^{1}H-NMR using tris[3-(trifluoromethyl-hydroxymethylene)-d-camphorato]praseodymium(III) as a chiral shift reagent. The conversion to the acetonide was carried out by the following reaction sequence.



3a-d 4a-d 5a-d

e) Keto aminals 1c-e were prepared according to the method shown in reference 1c) employing (S)-2-(o-anisidinomethyl)pyrrolidine with the exception that 2 equivalents of magnesium chloride were used.

f) The absolute configuration was determined from the sign of rotation of 2-phenyl-1,2-butandiol[4] derived from the acetonide 5a by the following reaction sequence: 1) NEt_3/mesyl chloride 2) $LiAlH_4$ 3) 10% HCl.

g) The absolute configuration was determined from the sign of rotation of the acetonide 5b reported in reference 5).

h) The absolute configuration was not determined.

temperature. The organic layer was separated and washed with saturated sodium chloride solution. After drying over anhydrous sodium sulfate, the solvent was evaporated under reduced pressure. The crude product was purified by silica gel column chromatography and ethyl 3-formyl-3-hydroxy-3-phenylpropionate was isolated in 85% yield, which gave $[\alpha]_D^{26}$ -128°(c 1.92, benzene) after bulb-to-bulb distillation.

References and Notes

1) a) T. Mukaiyama, Y. Sakito, and M. Asami, Chem. Lett., 1978, 1253. b) M. Asami and T. Mukaiyama, ibid, 1979, 569. c) T. Mukaiyama, Y. Sakito, and M. Asami, ibid, 1979, 705. d) M. Asami and T. Mukaiyama, ibid, 1980, 17.

2) All β-formyl β-hydroxy esters are fully characterized by IR and NMR data.

3) M. Asami, H. Ohno, S. Kobayashi, and T. Mukaiyama, Bull, Chem. Soc. Jpn., 51, 1869(1978).

4) S. Mitsui, S. Imaizumi, Y. Senda, and K. Konno, Chem. Ind., 1964, 233.

5) P. A. Stadler, A. J. Frey, and A. Hofmann, Helv. Chim. Acta, 46, 2300 (1963).

(Received February 16, 1980)