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ASYMMETRIC SYNTHESIS OF 3-ALKYLSUCCINALDEHYDIC ACID METHYL ESTERS

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

The highly stereoselective Michael addition was achieved by treating an aminal, prepared from (S)-2-(anilinomethyl)pyrrolidine and fumaraldehydic acid methyl ester, with the Grignard reagents. 3-Alkylsuccinaldehydic acid methyl esters were obtained with high enantiomeric excesses by the hydrolysis of the resulting aminals.

Recently several methods have been devised for the synthesis of chiral aldehydes by employing chiral enamines,[1] chiral imines[2] or chiral hydrazone.[3] However, a little is known about an asymmetric synthesis of chiral aldehyde having a functional group in the same molecule. In the preceding paper,[4] we reported a highly stereoselective synthesis of α-hydroxy aldehydes by treating a keto aminal, prepared from (S)-2-(anilinomethyl)pyrrolidine and phenylglyoxal, with Grignard reagents. Thus, it became apparent that the chiral aminal provides an efficient chiral environment.

Now we wish to report the highly stereoselective Michael addition of the Grignard reagent to an α,β-unsaturated ester possessing the aminal function. The aminal (1)[5] was easily prepared by the reaction of (S)-2-(anilinomethyl)pyrrolidine (2) and fumaraldehydic acid methyl ester (3)[6] in THF in the presence of molecular sieves. The treatment of the aminal 1 with the Grignard reagents in the presence of a catalytic amount of CuI, followed by the hydrolysis of the resulting aminals (4a-f) afforded 3-alkylsuccinaldehydic acid methyl esters (5a-f)[7] with high enantiomeric excesses as summarised in a Table.

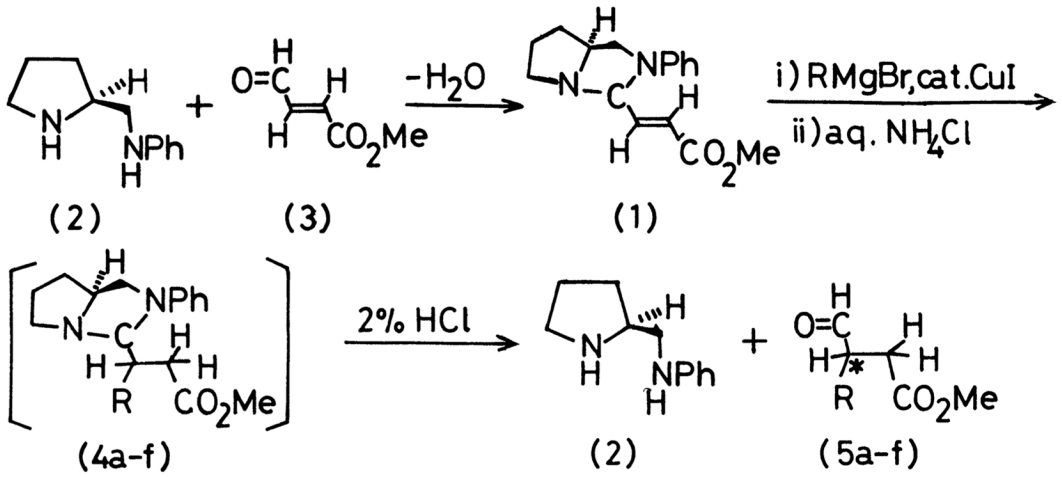

Table. Asymmetric Synthesis of 3-Alkylsuccinaldehydic Acid Methyl Esters

	R	Yield(%)[a]	$[\alpha]_D$ (c, ether)	e.e.(%)[b]
a	Et	73	+ 72.6° (5.03)	93
b	n-Pr	75	+ 74.8° (5.07)	89
c	i-Pr	73	+114.0° (5.22)	85
d	n-Bu	83	+ 71.3° (4.95)	93
e	n-C_5H_{11}	65	+ 68.5° (3.11)	92
f	$C_6H_5CH_2$[c]	38	+ 12.6° (5.07)	35

a) Isolated yields.

b) Enantiomeric excesses were estimated by 60 MHz ^{1}H NMR by using tris-[3-(heptafluoropropylhydroxymethylene)-d-camphorato]europium (III) as shift reagent.

c) The reaction was carried out at -20°C for 2 h.

Typical experimental procedure is as follows: The ethereal mixture (15 ml) of the aminal 1 (272 mg, 1 mmol) and CuI (9.5 mg, 0.05 mmol) was added an ethereal solution of isopropylmagnesium bromide (2.5 ml, 2 mmol) at -78°C under an argon atmosphere. The reaction mixture was stirred at -78°C for 4 h, then quenched with saturated aqueous ammonium chloride solution. The aqueous layer was neutralized with sodium hydrogen carbonate solution, followed by extraction with ether and the combined ethereal solution was hydrolyzed with 10 ml of 2% HCl at a room temperature for 2 h. The ethereal layer was dried over Na_2SO_4 and the solvent was evaporated. The resulting oily substance was purified by silica gel column chromatography to give

3-isopropylsuccinaldehydic acid methyl ester 5d (115 mg, 73%). It was purified by distilling in Büchi Kugelrohr apparatus, and 106 mg (120-125°C/2.1 mmHg) of 5d was obtained, $[\alpha]_D^{18}$+114° (c 5.22, ether).

The present asymmetric reaction consists of two stereoselective steps, namely, i) a selective formation of the aminal 1, ii) a selective addition of the Grignard reagent to the aminal 1. As for the step one, only the aminal 1 would be formed because its diastereomer 1' is very crowded by cis-fused bicyclic ring as is supported by molecular model consideration (Figure 1). Based on the results that (R)-aldehydes were obtained in excess,[8] the stereochemical course of the addition of the Grignard reagent to the aminal 1 is reasonably explained by assuming the following path. The most favorable rotational conformation of the C^3-C^4 bond in the aminal 1 in the transition state is such that the double bond is flanked by the two least bulky groups attached to C^4, that is, the hydrogen and the nitrogen (N^2) on the pyrrolidine ring (Figure 2). Then the magnesium of the Grignard reagent preferentially complexes with the nitrogen (N^2) on the pyrrolidine ring, which can presumably more strongly complex with the magnesium than the nitrogen (N^1) substituted by phenyl group. The alkyl group of the Grignard reagent migrates to the double bond to give the aminal 4, which is in turn hydrolyzed to (R)-aldehyde (Figure 2).

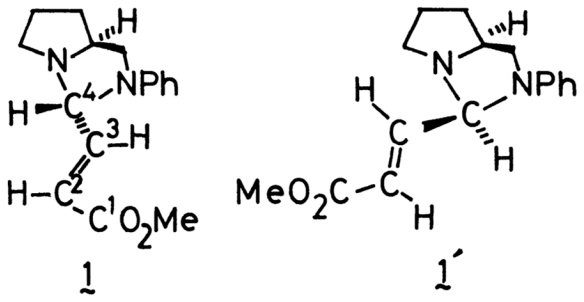

Fig.1

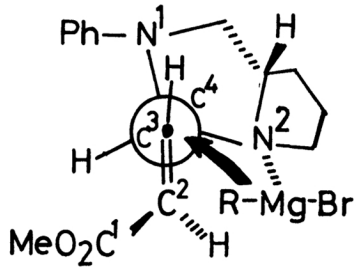

Fig.2

It is noted that, in the present asymmetric synthesis, the aminal group served for the following two significant roles. One of them is the protection of the aldehyde group of fumaraldehydic acid methyl ester and the other is the production of the effective chiral environment for the Michael addition of the Grignard reagent to α,β-unsaturated ester.

Thus, various chiral aldehydes possessing an ester group in the same molecule were obtained in good yields with high enantiomeric excesses. In addition, the procedures for the introduction and the removal of the chiral auxiliary can be performed quite easily with high degrees of recovery.

References and Notes

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b) T. Sone, S. Terashima and S. Yamada, ibid., 24, 1288 (1976).

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c) S. Hashimoto, N. Komeshima, S. Yamada and K. Koga, Tetrahedron Lett., 1977, 2907.

3) D. Enders and H. Eichennauer, Tetrahedron Lett., 1977, 191.

4) T. Mukaiyama, Y. Sakito and M. Asami, Chem. Lett., 1978, 1253.

5) The aminal 1 was recrystallized from cyclohexane (80%): mp 85-86°C; $[\alpha]_D^{16}$-59.0° (c 1.03, EtOH); IR (KBr) 1711 and 1653cm^{-1}; NMR ($CDCl_3$) δ=1.40-4.35 (9H, m), 3.62 (3H, s), 4.89 (1H, d), 5.96 (1H, d) and 6.26-7.62 (6H, m); Found: C, 70.80; H,7.61; N, 10.32%; Calcd for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.29%.

6) F. Bohlmann and E. Inhoffen, Ber., 89, 1276 (1956).

7) All compounds were fully characterized by IR and NMR data.

8) Configuration was estimated by deriving 3-alkylsuccinaldehydic acid methyl esters to the corresponding alkylsuccinic acids.

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