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AN ASYMMETRIC SYNTHESIS OF α-BENZYLOXY ALDEHYDES HAVING A CHIRAL TERTIARY CENTER —— AN APPLICATION TO THE ASYMMETRIC SYNTHESIS OF exo-(+)-BREVICOMIN ——

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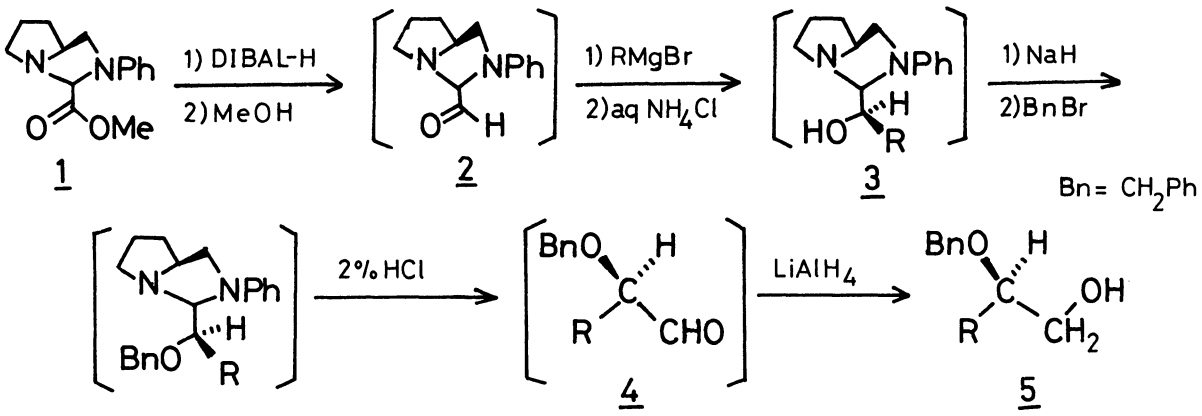
α-Benzyloxy aldehydes having a chiral tertiary center at α-carbon atom are synthesized in high enantiomeric excess by successive treatment of 2-methoxycarbonyl-3-phenyl-1,3-diazabicyclo[3.3.0]octane with diisobutylaluminum hydride (DIBAL-H) and Grignard reagents. The asymmetric reaction is applied to the total synthesis of exo-(+)-brevicomin.

In the previous paper,[1] we reported a highly enantioselective synthesis of α-hydroxy aldehydes having a chiral quarternary center starting from a chiral aminal, 2-methoxycarbonyl-3-phenyl-1,3-diazabicyclo[3.3.0]octane (1). In the above mentioned reaction, both enantiomers of the α-hydroxy aldehydes were obtained by simply changing the order of the addition of two different Grignard reagents, and the reaction has been successfully applied to the total syntheses of natural products, such as (+)- and (-)-frontalin[2] and (+)-malyngolide.[3]

In this communication, we wish to report the efficient method for the synthesis of α-benzyloxy aldehydes having a chiral tertiary center at α-carbon atom starting from the aminal (1). The aminal (1), prepared from (S)-2-(anilinomethyl)-pyrrolidine and methyl hydroxymethoxyacetate,[1] was first converted to an aldehyde (2) with diisobutylaluminum hydride (DIBAL-H). As the aldehyde (2) is unstable to either distillation or chromatography, it was used for following reactions without purification. The reaction of the aldehyde (2) with Grignard reagents afforded the α-benzyloxy aldehydes (4) in high enantiomeric excess after benzylation of the resulting hydroxy compounds and acid hydrolysis. (Scheme 1)

A general experimental procedure is as follows; DIBAL-H (0.4 ml, 2.23 mmol) was added to an ethereal solution of 1 (246 mg, 1 mmol) at -75°C and stirring was continued for 0.5 h. The reaction mixture was quenched with methanol (1 ml) at this temperature and further stirred for 1 h at room temperature. The resulting aluminum complex was removed by filtration and the filtrate was concentrated. An ethereal solution of the resulting oily material was stored over molecular sieves 4A (0.3 g) overnight. Evaporation of the solvent gave almost pure aldehyde (2), which was used for following reactions. The aldehyde (2) in THF (5 ml) was added at -75°C to a THF solution (10 ml) of Grignard reagent, prepared from Mg (88 mg,



Scheme 1

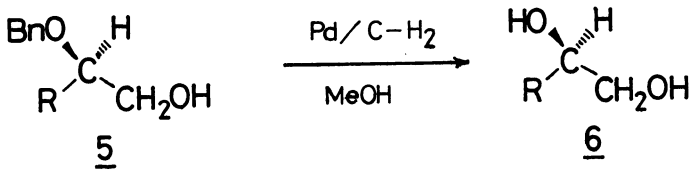
3.33 mmol) and an alkyl bromide (3 mmol), and the reaction mixture was stirred for 3 h at this temperature. After the reaction mixture was gradually warmed to room temperature, saturated ammonium chloride solution was added. The hydroxy aminal (3) thus obtained was treated with sodium hydride (55% mineral oil dispersion) (88 mg, 2 mmol) and benzyl bromide (342 mg, 2 mmol) in DMF (2 ml), and the resulting oily material was hydrolyzed with 2% HCl (10 ml) at 0°C for 4 h to give the crude α-benzyloxy aldehyde (4).[4] Due to the instability of the aldehydes (4) to chromatographic purification, the yields were determined by transforming the aldehydes (4) to the corresponding alcohols (5) with excess lithium aluminum hydride in ether (5 ml) at -75°C. The results are summarized in Table 1.

Table 1

	R	Yield of 5[a]	$[\alpha]_D$ (c, C_6H_6)	ee (%)[b]
a	C_2H_5	65	$[\alpha]_D^{21}$ -16.55° (5.07)	96
b	$(CH_3)_2CH$	64	$[\alpha]_D^{22}$ -10.63° (5.04)	97
c	C_4H_9	64	$[\alpha]_D^{20}$ -12.41° (5.07)	94
d	C_5H_{11}	71	$[\alpha]_D^{19.5}$ -10.60° (5.13)	83

a) These alcohols were identified by elemental analysis and nmr and ir spectra.

b) Enantiomeric excess was determined by comparison with the optical rotation values of the diols (6), known from the literature, after the debenzylation of the alcohols (5) by catalytic hydrogenolysis.



5 6

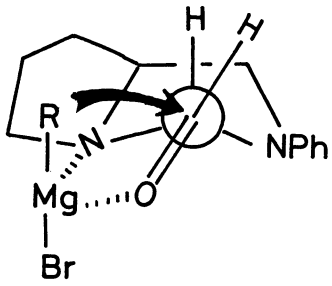
6a, $[\alpha]_D^{20}$ +11.92° (c 2.13, EtOH), 96% ee based on $[\alpha]_D^{21}$ +12.4° (c 2.12, EtOH) reported in reference 5).

6b, $[\alpha]_D^{21}$ -10.61° (c 0.91, $CHCl_3$), 97% ee based on $[\alpha]_D$ -10.95° (c 1, $CHCl_3$) reported in reference 6).

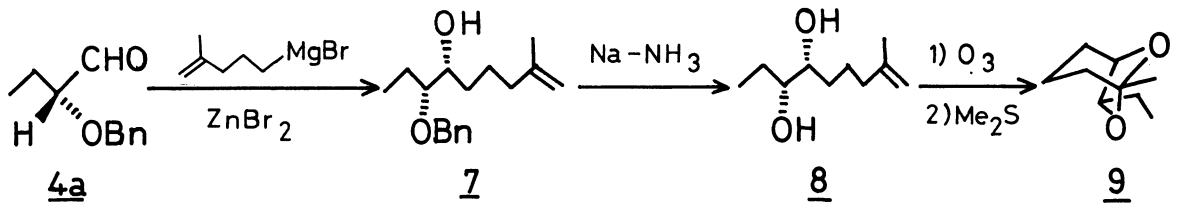
6c, $[\alpha]_D^{20}$ +14.18° (c 12.4, EtOH), 94% ee based on $[\alpha]_D^{22}$ +15.2° (c 13.14, EtOH) reported in reference 7).

6d, $[\alpha]_D^{20}$ +13.82° (c 11.9, EtOH), 83% ee based on $[\alpha]_D^{22}$ -16.6° (c 11.9, EtOH) reported in reference 8).

In the present synthesis of chiral α-benzyloxy aldehydes, the high stereoselectivity is interpreted by assuming the similar mechanistic consideration proposed previously,[1] that is, the initial formation of cis-fused bicyclic ring structure controls the stereoselective addition of the Grignard reagent as rationalized by the Cram's cyclic model.



Next, the asymmetric synthesis of exo-(+)-brevicomin,[9] the principal aggregation pheromone in the frass of the female western pine beetle (Dendroctonus brevicomis), was studied to demonstrate the synthetic utility of the chiral α-benzyloxy aldehydes. The synthetic route is illustrated in Scheme 2.



4a 7 8 9

Scheme 2

The pure aldehyde (4a) was obtained by the above procedure in 71% yield after Kugelrohr distillation. An ethereal solution (0.35 M) of 4-methyl-4-pentenylmagnesium bromide (9 ml, 3.15 mmol) was added to a mixture of the aldehyde (4a) (251 mg, 1.41 mmol) and $ZnBr_2$ (349 mg, 1.55 mmol) in ether (10 ml) at 0°C, and the

reaction mixture was stirred for 1 h. After usual work-up syn-alcohol (7) was obtained in 70% yield ($[\alpha]_D^{23}$ -13.42° (c 5.03, CH_2Cl_2)) with remarkably high stereoselectivity (the diastereomer ratio is 39:1 by HPLC). Interestingly, $ZnBr_2$ plays an important role in this stereoselective addition, while, in the absence of $ZnBr_2$, the selectivity lowers to about 5:1.

The alcohol (7) was separated from the undesired anti-diastereomer by column chromatography and the alcohol (7) was then debenzylated by Na-NH_3 to afford diol (8) in 86% yield ($[\alpha]_D^{20}$ +17.64° (c 2.03, CH_2Cl_2)).[10] Ozonolysis of 8 at -75°C in CH_2Cl_2, followed by reductive work-up with dimethyl sulfide at room temperature afforded (+)-exo-brevicomin (9) in 81% yield after purification by silica-gel column chromatography, which gave identical ir and nmr spectra with those of an authentic sample.[9b] The optical purity of the resulting (+)-exo-brevicomin ($[\alpha]_D^{23}$ +50.3° (c 2.2, ether)) was 60% based on the literature value ($[\alpha]_D^{26}$ +84.1° (c 2.2, ether) reported by Mori.[9b] We tentatively assume that the step of the addition of the Grignard reagent to the aldehyde (4a) causes the partial racemization.

As demonstrated in the synthesis of exo-(+)-brevicomin, optically active α-benzyloxy aldehydes having a chiral tertiary center at α-carbon atom, prepared easily by the present procedure, would be useful synthetic intermediates for the synthesis of optically active natural products. Furthermore, the highly diastereoselective addition of Grignard reagents to α-benzyloxy aldehydes in the presence of $ZnBr_2$ encountered in the synthesis of exo-(+)-brevicomin should also be noted.

References

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