



Facile synthesis of amino bicyclo[2.2.1]heptyl alcohol and its application for enantioselective additions of diethylzinc to aldehydes

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Abstract

Enantioselective additions of diethylzinc to aldehydes were demonstrated, and good to moderate enantioselectivities (54 to 95% enantiomeric excess) were obtained. The ligand **4** was prepared from camphor and acetic acid in a facile process of four steps, and the chiral source was only inexpensive (+)-camphor. © 2000 Elsevier Science Ltd. All rights reserved.

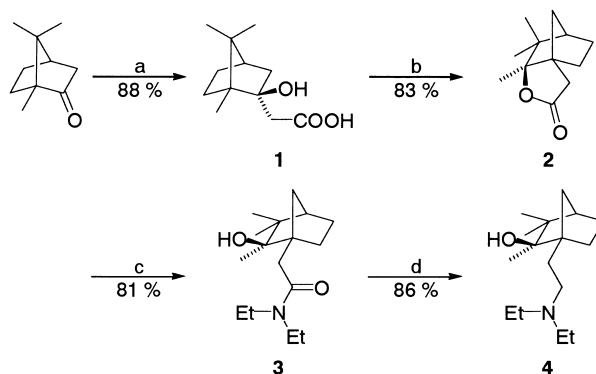
The catalytic enantioselective alkylation of aldehydes is a potentially useful method for preparing chiral secondary alcohols.¹ This structural feature is part of many natural products or precursors as an important synthetic intermediate for various other functionalities. The addition of dialkylzinc to aldehydes in the presence of chiral ligand is one of the most important methods in this area, and many chiral ligands have been reported.² In recent years, a wide variety of amino-alcohols, β -³ or occasionally γ -aminoalcohols,⁴ have been reported as chiral ligands. However, δ -aminoalcohols⁵ have rarely been reported and we could not find efficient δ -aminoalcohols for an asymmetric addition reaction (highest 89% ee^{5b}).

We have been investigating the lactonization of 3-hydroxy acid, which is prepared from a carbonyl compound and carboxylic acid.⁶ When an optically active compound such as (+)-camphor was used as the carbonyl compound in this reaction, chiral lactone was synthesized. Here, we report easily available and efficient δ -aminoalcohol **4** for the asymmetric addition of diethylzinc to aldehydes.

The synthesis method for δ -aminoalcohol **4** is described in Scheme 1. 3-Hydroxy acid **1** was prepared stereoselectively from (+)-camphor and acetic acid by using lithium naphthalenide.⁶ Acetic acid dianion was selectively attacked from the *endo*-side of camphor, and no *exo*-adduct

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was observed. Compound **1** was easily converted to lactone **2** by using acidic materials. On the other hand, Kim⁷ reported that the reaction of steric hindered 4,5-unsaturated acids with a catalytic amount of iodine and led to uniodinated lactones. We employed this protocol with **1**; namely, **1** was placed with 0.2 equivalents of iodine in acetonitrile at room temperature for 3 hours, and lactone **2** was synthesized stereoselectively in good yield.⁸ The configuration of **2** was determined by the NMR technique; specifically, the NOEs were observed between proton a and methyl a proton but not between proton b and methyl a proton. Accordingly, we deduced the 5*S*-configuration (Fig. 1).



Scheme 1. (a) Li-Nap., CH₃COOH in THF; (b) I₂ (0.2 equiv.) in MeCN; (c) Et₂NH, AlCl₃ in THF; (d) LAH in THF

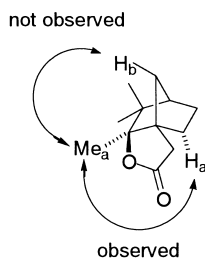
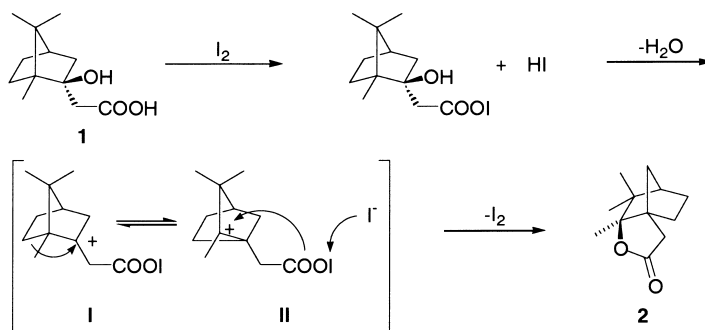


Figure 1.

This mechanism is illustrated in Scheme 2, based on the report by Kim.⁷ Hydrogen iodide was initially formed by the interaction of iodine with free carboxylic acid, and it reacted as Lewis acid. After dehydration, intermediate cation **I** underwent a Wagner–Meerwein-type rearrangement⁹ to intermediate **II**. Finally, the attack of the carbonyl oxygen on the cation formed lactone **2**, and iodine was reproduced. The reaction of **2** with diethylamine in the presence of aluminum chloride¹⁰ led to hydroxyamide **3** in 81% yield.¹¹ Compound **3** could be easily reduced by lithium aluminum hydride to δ -aminoalcohol **4**.¹² It is noteworthy that: (1) the chiral source of **4** was inexpensive (+)-camphor; (2) the reactions proceeded completely stereoselectively during the addition of acetic acid and lactonization (first step and second step in Scheme 1); (3) racemization did not occur in the amidation and reduction (third step and last step in Scheme 1).

The addition of diethylzinc to a series of aldehydes was carried out under the conditions shown in Table 1, and the results are summarized in Table 1. Despite the reaction of **5g** (entry 8), all



Scheme 2.

reactions proceeded quantitatively. It is noteworthy that when 1 mol% of **4** was used as a ligand, the reaction was quantitative and the enantiomeric excess was still high (97% yield, 91% ee, entry 2). Aromatic aldehydes were ethylated enantioselectively to produce corresponding (*S*)-alcohol **6** in relatively high enantiomeric excesses (entries 1–6), and the best result was obtained by the reaction of 4-methylbenzaldehyde **4d** to yield (*S*)-1-(4'-methylphenyl)-1-propanol in 95% enantiomeric excess. Although in the cases of cinnamaldehyde and 3-phenylpropionaldehyde the yields were still high (98 and 80%, respectively), selectivity was moderate (entries 7 and 8).

Table 1
Enantioselective addition of diethylzinc to aldehydes using chiral ligand **4**

RCHO 5 a: R=Ph b: R=4-MeOPh c: R=2-MeOPh d: R=4-MePh		$\xrightarrow[\text{4 (5 mol\%), toluene, r.t., 24 h.}]{\text{Et}_2\text{Zn (2 equiv.)}}$	$\text{R}-\text{CH}(\text{OH})-\text{CH}_2\text{CH}_3$ (S)-6
Entry	Aldehyde	Yield (%) ^a	ee (%)
1	5a	99	94 ^b
2	5a^c	97	91 ^b
3	5b	98	88 ^b
4	5c	99	73 ^b
5	5d	99	95 ^d
6	5e	96	83 ^d
7	5f	98	60 ^d
8	5g	80	54 ^d

^aDetermined by GC. ^bDetermined by HPLC using a Chiralcel OD column. ^c1 mol% of **4** was used as a ligand. ^dDetermined by HPLC using a Chiralcel OJ column.

In summary, δ -aminoalcohol **4**, which is efficient for asymmetric induction, was easily synthesized in four steps from (+)-camphor. The addition of diethylzinc to aldehydes **5** in the presence of **4** resulted in good yields with high enantiomeric excesses.

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8. Compound **2**: ^1H NMR (δ , ppm): 1.03 (3H, s), 1.07 (3H, s), 1.17 (3H, s), 1.28 (1H, dd, $J=10.2$ and 1.5 Hz), 1.39–1.48 (1H, m), 1.51–1.63 (2H, m), 1.66–1.76 (1H, m), 1.79–1.82 (1H, m), 1.87–1.92 (1H, m), 2.46 (1H, d, $J=17.3$ Hz), 2.59 (1H, d, $J=17.3$ Hz); ^{13}C NMR (δ , ppm): 17.81, 22.37, 23.84, 24.45, 24.73, 34.53, 39.69, 44.88, 48.48, 55.64, 95.21, 176.48; IR: 1765 cm^{-1} ; $[\alpha]_{\text{D}}^{25} -55.6$ (c 1.00, $\text{C}_2\text{H}_5\text{OH}$); m.p. $125\text{--}127^\circ\text{C}$; HRMS (FAB): m/z , calcd: 195.1385 $[\text{M}+\text{H}]^+$; found: 195.1371.
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11. Compound **3**: ^1H NMR (δ , ppm): 0.93 (3H, s), 1.01 (3H, s), 1.07 (3H, s), 1.12 (3H, t, $J=7.1$ Hz), 1.19 (3H, t, $J=7.1$ Hz), 1.08–1.14 (1H, m), 1.34–1.43 (2H, m), 1.50–1.64 (2H, m), 1.66–1.71 (1H, m), 2.13–2.21 (1H, m), 2.45 (1H, d, $J=14.8$ Hz), 2.63 (1H, d, $J=14.8$ Hz), 3.24–3.47 (4H, m), 3.80 (1H, br-s); ^{13}C NMR (δ , ppm): 13.06, 14.42, 19.49, 23.75, 24.73, 25.47, 31.87, 33.96, 38.31, 40.46, 42.81, 45.16, 48.33, 54.36, 80.56, 172.97; IR: 3367, 2964, 1620 cm^{-1} ; $[\alpha]_{\text{D}}^{25} -19.1$ (c 1.00, CH_3CN); m.p. $122\text{--}123^\circ\text{C}$; elemental analysis, calcd: C, 71.86; H, 10.93; N, 5.24; found: C, 71.92; H, 11.08; N, 5.18.
12. Compound **4**: ^1H NMR (δ , ppm): 0.88 (3H, s), 0.99 (3H, s), 1.03 (6H, t, $J=7.2$ Hz), 1.05 (3H, s), 1.01–1.08 (1H, m), 1.12–1.18 (1H, m), 1.23–1.68 (5H, m), 1.87–1.96 (1H, m), 2.10–2.16 (1H, m), 2.24–2.35 (1H, m), 2.37 (1H, dq, $J=7.2$ and 14.4 Hz), 2.51–2.61 (1H, m), 2.68 (2H, dq, $J=7.2$ and 14.4 Hz), 6.52 (1H, br-s); ^{13}C NMR (δ , ppm): 10.63, 19.59, 24.16, 25.58, 25.95, 29.88, 33.70, 37.29, 44.36, 45.74, 48.70, 50.59, 57.04, 78.62; IR: 3195, 3095, 2965 cm^{-1} ; $[\alpha]_{\text{D}}^{25} -11.4$ (c 0.20, CH_3CN); HRMS (FAB): m/z , calcd: 254.2484 $[\text{M}+\text{H}]^+$; found: 254.2472.