

cis-2-Amino-3,3-dimethyl-1-indanol: Synthesis, Resolution, and Application as a Highly Efficient Chiral Auxiliary

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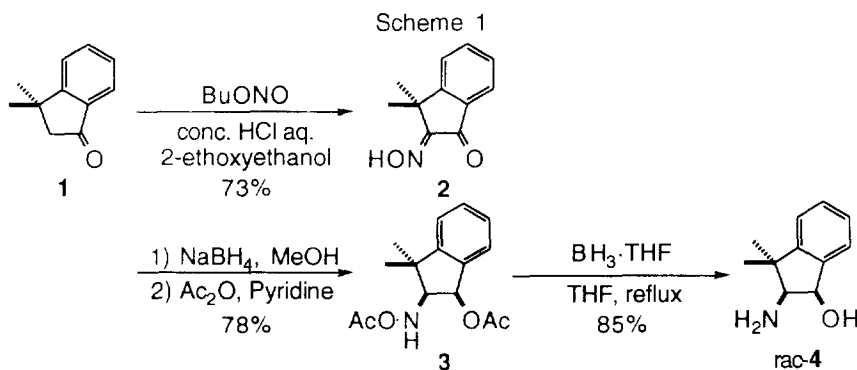
Abstract: The chiral amino alcohol, *cis*-2-amino-3,3-dimethyl-1-indanol was synthesized and resolved. Its oxazolidinone derivative was found to be a highly efficient chiral auxiliary in an asymmetric alkylation reaction.

In the rapid progress of asymmetric synthesis, the development of more efficient chiral auxiliaries and reagents has been a matter of utmost importance. Until now, most of chiral auxiliaries and reagents were derived from naturally occurring homochiral compounds and their derivatives, but limitations in their structural modification are sometimes an obstacle in improvement of the selectivity of asymmetric reactions. Therefore, the development of artificial chiral compounds, which can be suitably designed for each asymmetric process, has recently been drawing considerable attention, and in fact some successful examples have been recently reported.¹

In our study concerning resolutions and asymmetric syntheses, several chiral amino alcohols, which were suitably designed, could be successfully resolved and applied to asymmetric syntheses.² Here we wish to report the synthesis and resolution of the new chiral amino alcohol, *cis*-2-amino-3,3-dimethyl-1-indanol, and its application to an asymmetric alkylation reaction.

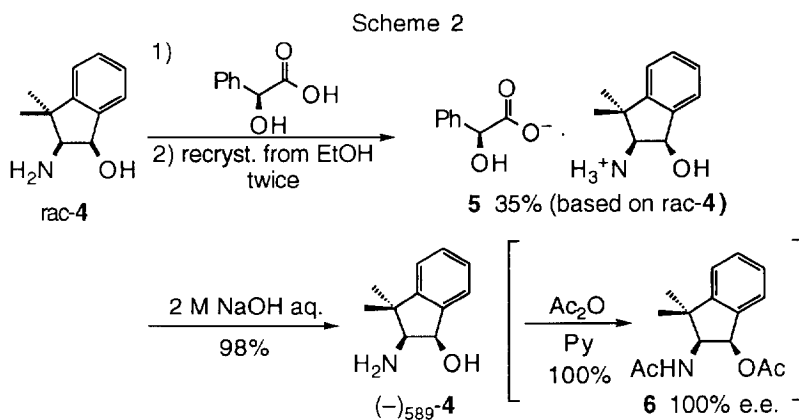
cis-2-Amino-3,3-dimethyl-1-indanol was designed so as to have following structural characteristics:

- 1) The orientation of the amino and hydroxyl groups is fixed.
- 2) The bulkyness of two methyl substituents strongly influences the chiral environment near to the stereogenic center adjacent to the nitrogen atom.



Racemic *cis*-2-amino-3,3-dimethyl-1-indanol (*rac*-**4**) was easily synthesized from 3,3-dimethyl-1-indanone³ (**1**) as shown in Scheme 1. α -Oximation of **1** by butyl nitrite gave **2**,⁴ and reduction of **2** by NaBH₄, followed by acetylation, selectively gave *cis*-diacetate **3**, which was readily reduced by BH₃·THF to give *rac*-**4**. Thus, *rac*-**4** could be easily and inexpensively obtained in large quantities.

We next examined the resolution of *rac*-**4** via diastereomeric salts with several kinds of chiral acids, such as camphorsulfonic acid, tartaric acid, and mandelic acid. Among the resolving agents examined, (*S*)-mandelic acid was the most effective; by recrystallization once from ethanol with seeding, salt **5** was obtained in 40% yield with 96% d.e. The e.e. value of **4** and d.e. value of **5** were determined by the chiral HPLC analysis (Dical Chiralcel OD) of *N,O*-diacetylated product **6**, which was obtained by treatment of **4** or **5** with acetic anhydride and pyridine. One additional recrystallization gave diastereomerically pure **5** in 35% overall yield (Scheme 2). The treatment of **5** with an alkaline solution gave enantiomerically pure (*-*)₅₈₉-**4** quantitatively.



The absolute configuration of (*-*)₅₈₉-**4** was determined by a single-crystal X-ray structural analysis of the salt **5** (Fig. 1).⁵ On the basis of the absolute configuration of (*S*)-mandelic acid, the absolute configuration of (*-*)₅₈₉-**4** was determined to be 1*R*,2*S*.

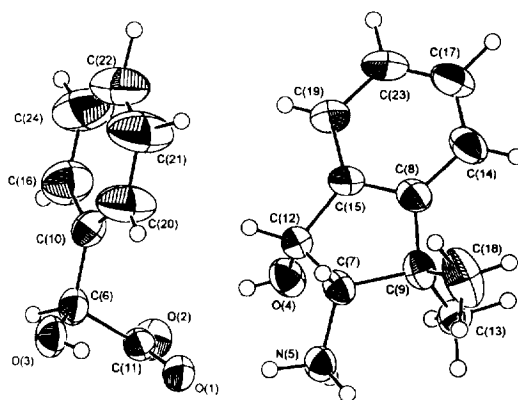


Fig. 1 ORTEP Drawing of **5**

Next we applied this new chiral amino alcohol as a precursor of a chiral auxiliary for asymmetric synthesis. Chiral oxazolidinone (+)₅₈₉-7 was prepared and applied to the alkylation reaction of a carboxylic acid derivative. Substrate (+)₅₈₉-8 was obtained by *N*-acylation of (+)₅₈₉-7 without any problem (Scheme 3) and was alkylated by several alkyl halides via its lithium enolate, formed by LDA (Scheme 4). The results are given in Table. While no optimization was performed in order to improve the yields and selectivities, excellent diastereoselectivities were observed in all cases. These results are superior compared to those obtained by using oxazolidinones derived from natural compounds.⁶ Hydrolysis of **11** with aqueous LiOOH gave (-)₅₈₉-(*R*)-**12**⁷ and oxazolidinone auxiliary (+)₅₈₉-7 almost quantitatively (Scheme 5).

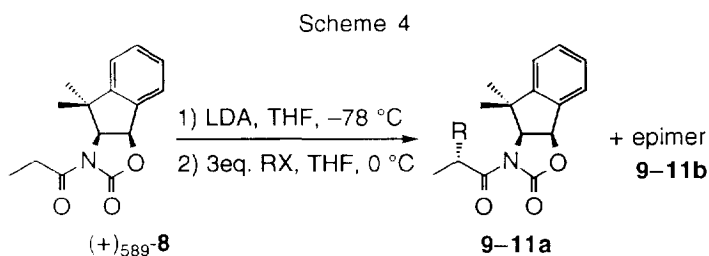
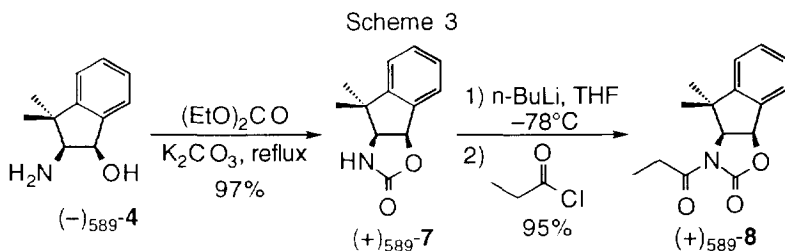
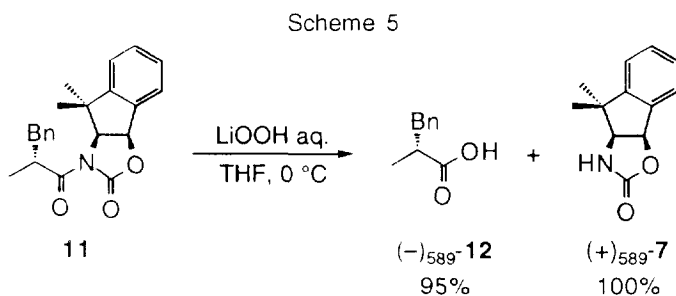


Table. Diastereoselective alkylation of (+)₅₈₉-8

Entry	Product	RX	Yield/%	Ratio (a:b) ^{a)}
1	9	EtI	57	>99:1
2	10	AllylBr	95	>99:1
3	11	BnBr	100	>99:1

a) Determined by HPLC analysis.



A representative procedure for the benzylation reaction of (+)₅₈₉-**8** is as follows. To a stirred solution of diisopropylamine (151.4 mg, 1.496 mmol) in anhydrous THF (3.0 ml) was added butyllithium (0.85 ml, 1.4 mmol; 1.63 M hexane solution) at 0 °C under an argon atmosphere, and the mixture was stirred for 30 min. To this solution was added *N*-propionyloxazolidinone (+)₅₈₉-**8** (302.8 mg, 1.167 mmol) in THF (3.0 ml) at -78 °C, and the solution was stirred for 30 min at the same temperature. To this solution was added benzyl bromide (0.60 g, 3.5 mmol) in THF (3 ml) at -78 °C, and then the temperature was allowed to raise to 0 °C. After stirring for 30 min at 0 °C, saturated aqueous ammonium chloride (5 ml) was added to the reaction mixture. Usual workup gave the corresponding benzylated product **11** (408.0 mg, 1.167 mmol, 100%).

In summary, *cis*-2-amino-3,3-dimethyl-1-indanol has been synthesized and resolved. This new homo-chiral amino alcohol was converted into an oxazolidinone, which was found to be highly effective chiral auxiliary in an asymmetric alkylation reaction.

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References and notes

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5. Crystal data for **5**: C₁₉H₂₃NO₄, *M*=329.40, monoclinic, space group C2, *a*=21.778(2) Å, *b*=5.4726(6) Å, *c*=16.417(3) Å, β=115.252(8)°, *V*=1769.6(3) Å³, *Z*=4, *D*_c=1.20 gcm⁻³, *R*=0.0470, reflections used=2084.
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7. The absolute configuration of 2-methyl-3-phenylpropionic acid (**12**) was determined to be *R* by the measurement of its specific rotation ([α]₅₈₉²⁰-27.3 (*c* 7.66, CHCl₃), lit. [α]₅₈₉-25.4 (neat)).⁶ Acid **12** was quantitatively reduced to 2-methyl-3-phenyl-1-propanol by BH₃-THF, and this alcohol was derived into its MTPA ester which was confirmed to consist of a single diastereomer by the 270 MHz ¹H-NMR analysis.