

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

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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 diastereoselective alkylation, acylation, bromination, and hydroxylation reactions.

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Introduction:

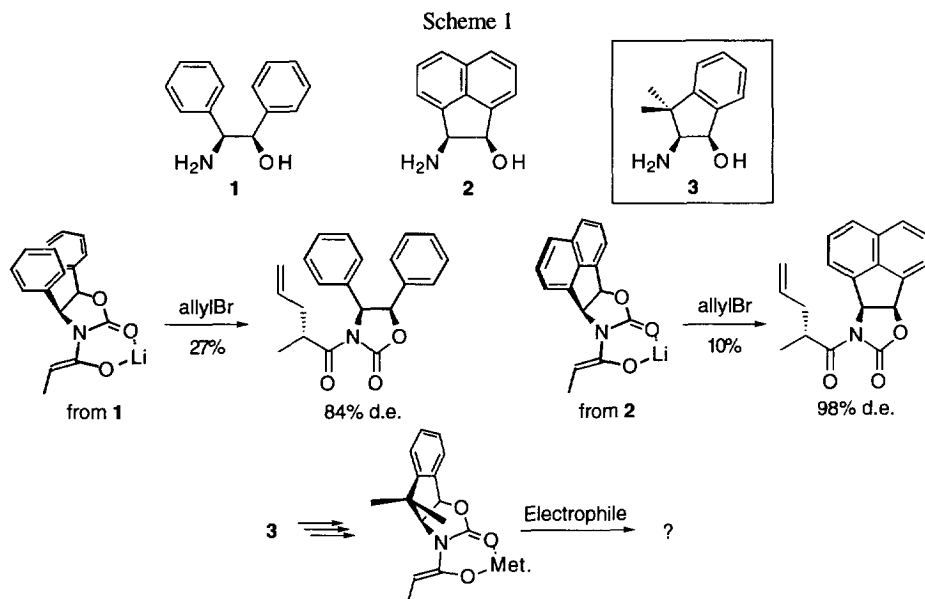
To date, various kinds of chiral auxiliaries and reagents have been developed, enabling the achievement of high stereoselectivities.¹ In general, appropriate chiral auxiliaries selected from the pool of natural chiral compounds have been developed for each asymmetric reaction. However, as long as a natural chiral compound is used as the starting material for the chiral auxiliary, there are some problems in developing more efficient asymmetric reactions in future: *i.e.* 1) Limitations to the possible or available structural modifications of the natural chiral compound are sometimes an obstacle in designing a chiral auxiliary with further improved stereoselectivity. 2) The availability of both enantiomers is not always guaranteed. Therefore, the utilization of non-natural chiral compounds is drawing considerable attention as a cogent solution to the problems.²

In order to obtain both enantiomers of a non-natural chiral auxiliary, resolution should be preferable to asymmetric synthesis from the viewpoint of simplicity and ease of large-scale operation. However, much trial-and-error is sometimes required in order to achieve resolutions, and there are only a few successful reports on the resolutions of a non-natural auxiliary on a large scale by a simple operation. Taking into account these present circumstances, we have been carrying out systematic studies on the design, synthesis, resolution, and application of non-natural chiral auxiliaries. During our investigation on chiral recognition mechanisms for the resolutions of racemates,³ we were able to resolve successfully some chiral amines and amino alcohols, and apply them as non-natural chiral auxiliaries.⁴⁻⁷ In particular, we focused our attention on the development of new chiral amino alcohols, because they would be valuable precursors of various chiral auxiliaries and reagents;⁸ Evans and his co-workers have developed chiral oxazolidinones derived from amino alcohols of natural origin, which are quite efficient in various kinds of asymmetric reaction.⁹⁻¹⁴

In this paper, we describe the design, synthesis, and resolution of a new non-natural chiral amino alcohol, *cis*-2-amino-3,3-dimethyl-1-indanol, and its applications to the asymmetric alkylation reaction and related asymmetric processes.

Results and Discussion:

Recently we achieved resolution and application to asymmetric synthesis of *erythro*-2-amino-1,2-diphenylethanol **1**⁵ and *cis*-2-amino-1-acenaphthenol **2**.⁶ On the basis of these results, we next examined the diastereoselective alkylation of the corresponding imide enolates derived from the amino alcohols (Scheme 1).

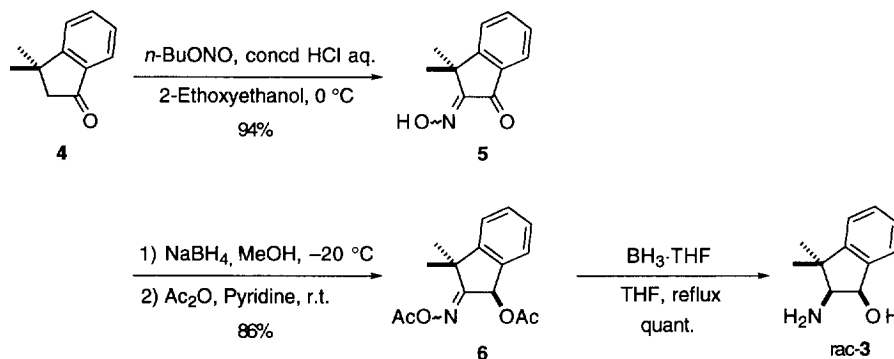


When the lithium enolate of the *N*-propionyloxazolidinone derived from **1** was allowed to react with allyl bromide, the diastereoselectivity was somewhat low (84% d.e.). This low diastereoselectivity was considered to arise from insufficient shielding of one side of the molecule by the phenyl ring attached to the carbon atom adjacent to the nitrogen atom, this arising because the two phenyl groups are obliged to be parallel to each other to avoid serious steric repulsion between their *ortho* hydrogens. We then looked at **2**, in which the two phenyl groups of **1** are replaced by a naphthalene ring, with the expectation that the naphthalene ring would protrude in a direction favorable for efficient shielding of one diastereoface of the enolate. When the lithium enolate of the *N*-propionyloxazolidinone derived from **2** was allowed to react with allyl bromide, the diastereoselectivity was indeed excellent, as predicted. However, the yield of the allylated product was quite low, and the parent oxazolidinone was mainly recovered. Similar phenomena, were also observed in the case of the reaction of the **1**-derived oxazolidinone, indicating these lithium enolates had low stability. Although the reason for this instability is not clear at present, we concluded that *N*-acyloxazolidinones derived from amino alcohols having a benzylamine skeleton, are not favorable for use in reactions via their lithium enolates. Thus, we next designed an amino alcohol, *cis*-2-amino-3,3-dimethyl-1-indanol **3**, which does not contain a "benzylamine" but has a rigid skeleton, with the expectation that the two methyl groups attached to the indane ring would give sufficiently powerful diastereofacial bias, and that the aromatic ring would contribute to the crystallizability of the amino alcohol and its derivatives. Although the synthesis of racemic 2-amino-3,3-dimethyl-1-indanol has already been reported,¹⁵ the stereochemistry of the product (*cis* or *trans*) and the reaction selectivity were unknown. Moreover, optically active **3** has not yet been reported. Thus we first

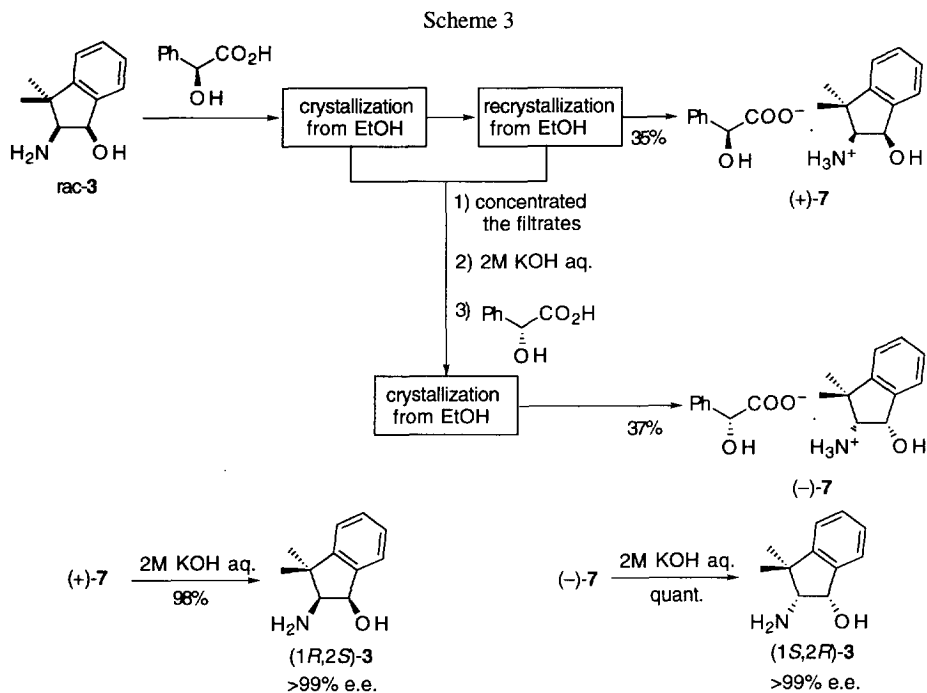
sought to develop an alternative method for the *cis*-selective synthesis of **3**, and to carry out its optical resolution.

Racemic *cis*-2-amino-3,3-dimethyl-1-indanol **rac-3** was easily synthesized from 3,3-dimethyl-1-indanone **4**¹⁶ as shown in Scheme 2.⁷ Indanone **4** was readily converted into oxime **5** with butyl nitrite under acidic conditions.¹⁷ At this stage, several attempts were made to obtain directly the desired **rac-3** by reduction of **5**. Reduction of **5** with lithium aluminium hydride in refluxing THF gave a mixture of *cis*- and *trans*-amino alcohols (*cis:trans*=ca 1:2), while palladium/charcoal-catalyzed hydrogenation of **5** resulted in the formation of a complex mixture, in which none of the desired amino alcohol was detected. Thus, we next tried a stepwise route combining separate reductions of the keto and imino groups. Reduction of **5** with NaBH₄ in methanol gave the hydroxy oxime, which was then treated with acetic anhydride and pyridine to give diacetate **6**.⁷ Borane-reduction of **6** gave **rac-3** with complete *cis*-selectivity. Thus, **rac-3** could be easily and inexpensively obtained in large quantity.

Scheme 2



We next examined the resolution of **rac-3** via diastereomeric salts with chiral acids, such as camphorsulfonic acid, tartaric acid, and mandelic acid. Of these, mandelic acid was found to be very effective; upon crystallization of the salt of **rac-3** with (*S*)-mandelic acid from ethanol, (*1R,2S*)-**3** was obtained in 40% yield with 96% e.e. as determined by chiral HPLC analysis (Daicel Chiralcel OD) of the *N,O*-diacetylated product **8**, which was obtained by treatment of **3** with acetic anhydride and pyridine. On the basis of this result, we attempted to obtain both enantiomers of **3** by the combined use of commercially available (*S*)- and (*R*)-mandelic acids as shown in Scheme 3. Crystallization and successive recrystallization of a diastereomeric salt mixture of **rac-3** with (*S*)-mandelic acid from ethanol gave diastereomerically pure (+)-**7** in 35% yield. Treatment of (+)-**7** with alkali gave enantiomerically pure (*1R,2S*)-**3** in almost quantitative yield. The combined filtrates of the crystallization and recrystallization were concentrated under reduced pressure to afford a solid mass, which gave (*1S,2R*)-enriched **3** on treatment with alkali. Crystallization of the salt of this (*1S,2R*)-enriched **3** with (*R*)-mandelic acid gave diastereomerically pure (–)-**7** in 37% yield, which gave enantiomerically pure (*1S,2R*)-**3** upon treatment with alkali. From the filtrate, almost racemic **3** was recovered with no chemical deterioration nor significant loss, which could be used in the next resolution. Thus, we were able to develop an efficient route to enantiomerically pure (*1R,2S*)- and (*1S,2R*)-**3**.



The absolute configuration of $(1R,2S)\text{-3}$ was determined by a single-crystal X-ray structural analysis of salt $(+)\text{-7}$, which consisted of $(1R,2S)\text{-3}$ and (S) -mandelic acid (Figure 1). The absolute configuration of $(1R,2S)\text{-3}$ follows from the known absolute configuration of (S) -mandelic acid.

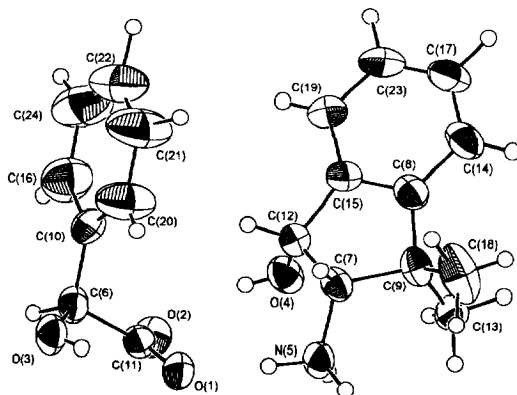
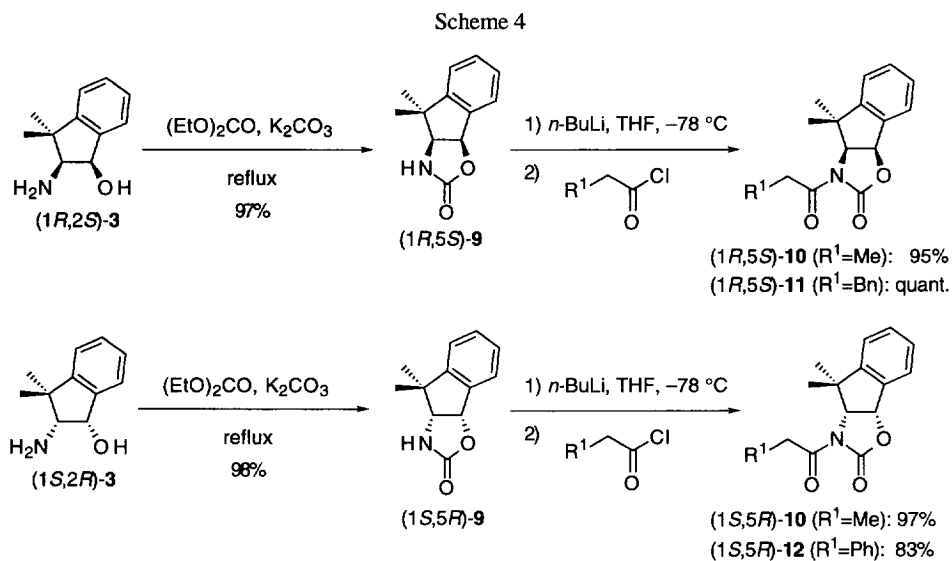


Figure 1. ORTEP Drawing of $(+)\text{-7}$

Next, in order to apply this amino alcohol to asymmetric synthesis, the chiral oxazolidinones $(1R,5S)\text{-9}$ and $(1S,5R)\text{-9}$ were prepared almost quantitatively from the enantiomers of $\mathbf{3}$, $(1R,2S)\text{-3}$ and $(1S,2R)\text{-3}$, by treatment with diethyl carbonate (Scheme 4)¹⁰ and employed as chiral auxiliaries in several diastereoselective

reactions of carboxylic acid derivatives. Substrates (1*R*,5*S*)-**10**, (1*S*,5*R*)-**10**, (1*R*,5*S*)-**11** and (1*S*,5*R*)-**12** were obtained nearly quantitatively by the *N*-acylation of (1*R*,5*S*)- or (1*S*,5*R*)-**9** under standard conditions.¹⁰



First, the alkylation reaction of the corresponding enolates of the *N*-acyloxazolidinones was examined (Scheme 5). Substrate (1*R*,5*S*)-**10** or (1*R*,5*S*)-**11** was treated with LDA in THF, and the resulting lithium enolate was alkylated with alkyl halides (Table 1).

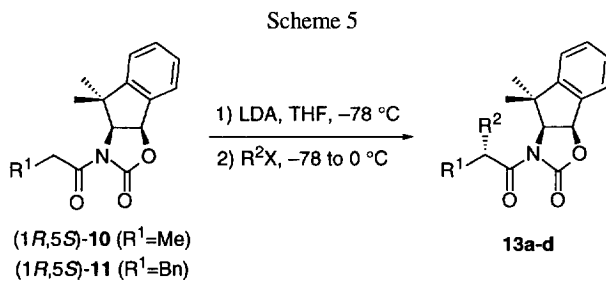
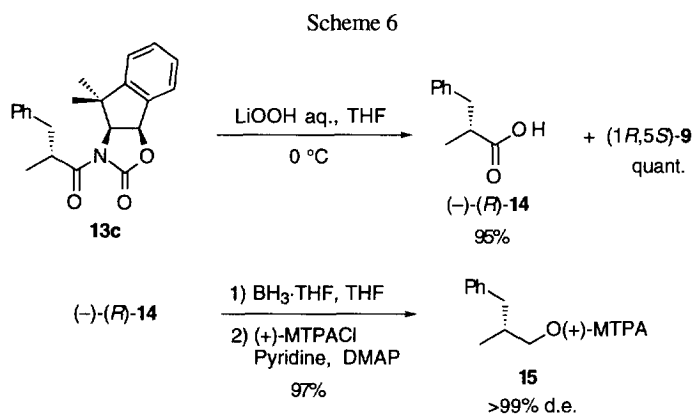


Table 1. Alkylation of *N*-Acylloxazolidinones

entry	R ¹	R ² X	product	yield/% ^a	% d.e. ^b
1	Me	EtI	13a	57	99
2		AllylBr	13b	95	98
3		BnBr	13c	quant.	98
4	Bn	MeI	13d	83	94

^a Isolated yield of major product. ^b Determined by HPLC analyses.

The diastereomeric excesses of the products were determined by HPLC analysis. In all cases, the reaction proceeded easily, and excellent diastereoselectivities were observed, superior to those obtained by using oxazolidinones derived from natural compounds.¹¹ Furthermore, removal of the oxazolidinone auxiliary was easily achieved by hydrolysis of the products with aqueous LiOOH;¹⁰ for example, hydrolysis of **13c** gave (-)-(*R*)-**14**¹⁸ and oxazolidinone-auxiliary (1*R*,5*S*)-**9** almost quantitatively (Scheme 6). In order to examine the enantiomeric purity of (-)-(*R*)-**14** thus obtained, it was reduced with borane-THF complex to give the corresponding alcohol, which was converted to the corresponding (+)-MTPA ester **15**. ¹H-NMR analysis of **15** showed that it was diastereomerically pure, indicating that (-)-(*R*)-**14** obtained in the present reaction, was almost enantiomerically pure and that no epimerization occurred under the conditions of hydrolysis. The absolute configuration of **13c** was determined on the basis of the absolute configuration of **14**. The absolute configurations of the other major products of the present reactions were correlated with that of **13c** by comparing their ¹H-NMR spectral and HPLC data.

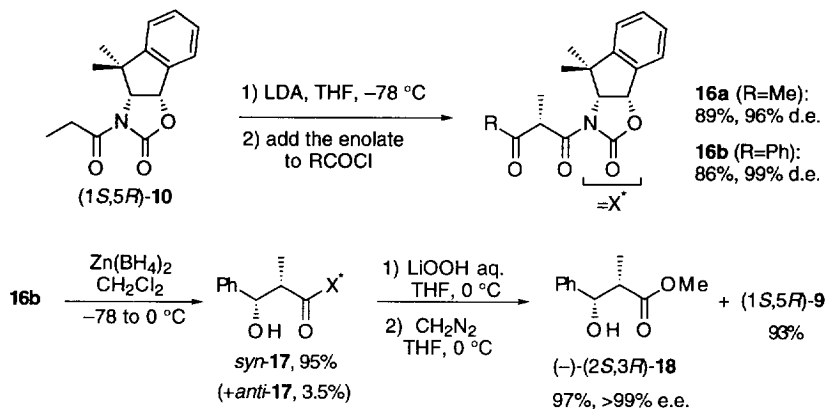


We next applied the chiral enolates to other diastereoselective reactions, such as acylation, hydroxylation, and bromination. These types of reactions have been investigated by Evans and his co-workers using oxazolidinone-type auxiliaries derived from natural chiral compounds.¹²⁻¹⁴ However, in spite of the quite significant synthetic utility of these reactions, no further investigation on improvement of the stereoselectivities by designing new oxazolidinones¹⁹ has been reported.

First, a diastereoselective acylation reaction of the imide enolate was attempted. When the lithium enolate of (1*S*,5*R*)-**10** was added to a THF solution of acetyl chloride or benzoyl chloride, the corresponding β-keto carboximide (**16a** or **16b**) was obtained with excellent diastereoselectivity (Scheme 7); the selectivity is better than that reported by Evans and his co-workers for the acylation of valinol- and norephedrine-derived *N*-propionyloxazolidinones (up to 92% d.e.).¹² The newly created asymmetric centers of these acylated products were not effected during its purification by chromatography or recrystallization, while they were slowly epimerized under basic conditions (1M Et₃N, CH₂Cl₂, room temperature), as was reported.¹² The absolute configuration of **16a** was determined by its single-crystal X-ray structural analysis. In order to determine the absolute configuration of **16b**, diastereomerically pure **16b** was converted to the corresponding β-hydroxy carboximide **17** (*syn:anti*=96:4) by treatment with zinc borohydride in dichloromethane.^{12,20} Diastereomerically pure *syn*-**17**, obtained upon recrystallization, was hydrolyzed with aqueous LiOOH, and the resulting mixture was then treated with CH₂N₂ in ether to give the known β-hydroxy ester (-)-(*2S*,*3R*)-

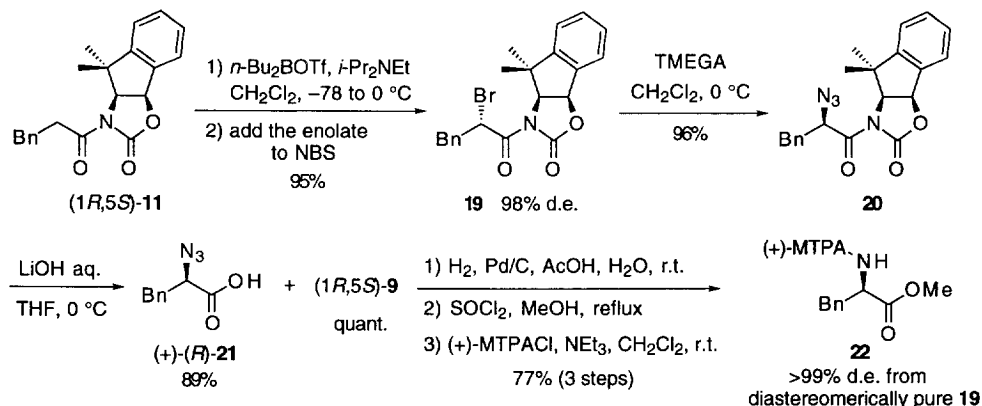
18,¹⁰ and oxazolidinone-auxiliary (1*S*,5*R*)-**9** in good yields. The absolute configurations of **16b** and *syn*-**17** were determined on the basis of the absolute configuration of (–)-(2*S*,3*R*)-**18**. The enantiomeric purity of (–)-(2*S*,3*R*)-**18** was found to be >99% e.e. by a chiral HPLC analysis (Daicel Chiralcel OJ).

Scheme 7



The boron enolate, generated from (1*R*,5*S*)-**11** by the Mukaiyama method,²¹ reacted easily with NBS suspended in CH₂Cl₂ to give the corresponding α-bromo carboximide **19** with very high diastereoselectivity (Scheme 8), also better than that reported for a phenylalaninol-derived oxazolidinone (90% d.e.).¹³ The selectivity was determined by HPLC analysis of the unpurified product. Diastereomerically pure **19**, easily purified by chromatography, was treated with 1,1,3,3-tetramethylguanidinium azide (TMEGA),^{13, 22} to give the corresponding α-azido carboximide **20** (almost complete inversion at the stereogenic center was observed), which was then hydrolyzed with lithium hydroxide to give α-azido acid (+)-(*R*)-**21**¹³ in good yield, along with quantitative recovery of oxazolidinone auxiliary (1*R*,5*S*)-**9**. The absolute configurations of **19** and **20** were determined on the basis of the absolute configuration of (+)-(*R*)-**21**. Hydrogenation of (+)-(*R*)-**21**, followed by esterification, gave the corresponding methyl phenylalaninate hydrochloride, the enantiomeric purity of which was confirmed to be >99% by ¹H-NMR analysis of its (+)-MTPA amide **22**.

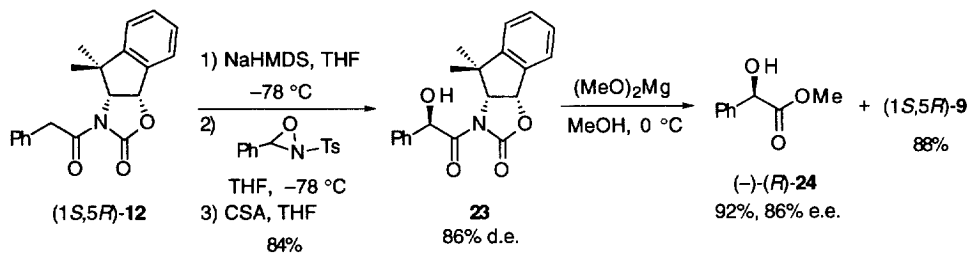
Scheme 8



Finally, a diastereoselective hydroxylation reaction of the imide enolate was examined (Scheme 9). Treatment of the sodium enolate, generated from (1*S*,5*R*)-**12** by the reaction with sodium

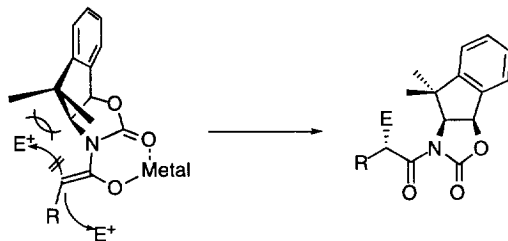
hexamethyldisilazide (NaHMDS), with 2-(*p*-toluenesulfonyl)-3-phenyloxaziridine,²³ followed by quenching with a THF solution of camphorsulfonic acid, gave hydroxylated product **23** with high diastereoselectivity, also better than that reported for a phenylalaninol-derived oxazolidinone (80% d.e.).¹⁴ Hydroxy imide **23** was treated with magnesium methoxide to give (*R*)-methyl mandelate (**24**) and oxazolidinone-auxiliary (**1S,5R**)-**9** in 92 and 88% yields, respectively. The absolute configuration and enantiomeric purity of **24** were determined by chiral HPLC analysis (Daicel Chiralcel OJ). The absolute configuration of **23** was determined on the basis of the absolute configuration of **24**.

Scheme 9



The absolute configurations of the products obtained in the present reactions are in good agreement with those expected from a chelate model shown in Scheme 10. The conformation of the (*Z*)-enolate relative to the oxazolidinone part would be defined by chelation of the metal of the enolate with the carbonyl oxygen of the auxiliary regardless of the kind of metal used. Thus, the reaction of the (*Z*)-enolate with electrophiles occurred at the less hindered diastereotopic face not shielded by the two methyl groups of the auxiliary.

Scheme 10



Conclusions:

An artificial chiral auxiliary, *cis*-2-amino-3,3-dimethyl-1-indanol was designed, stereoselectively synthesized, resolved, and applied as a precursor of a chiral oxazolidinone, which was quite effective in asymmetric alkylation, acylation, hydroxylation, and bromination reactions via the corresponding chiral imide enolates. This new chiral oxazolidinone has several favorable characteristics: 1) It induces stereoselectivity more effectively than the usually used chiral oxazolidinones derived from naturally occurring compounds. 2) All of the reaction products obtained here were crystalline due to the high crystallizability of the auxiliary moiety. This enables us to obtain compounds in high enantiomeric purity after a single recrystallization of the products, when necessary. 3) Both enantiomers of the oxazolidinone were easily and equally available. We can control asymmetric induction in the desired direction by the proper use of each enantiomer of the auxiliary.

Experimental Section

General. The starting materials and reagents, purchased from commercial suppliers, were used after standard purification. 3,3-Dimethyl-1-indanone,¹⁶ 2-hydroxyimino-3,3-dimethyl-1-indanone,¹⁷ Zn(BH₄)₂ (0.14 M ethereal solution),²⁰ 1,1,3,3-tetramethylguanidinium azide,²² and 2-(*p*-toluenesulfonyl)-3-phenyloxaziridine²³ were prepared according to the literature procedures. All of the solvents were dried over sodium wire or molecular sieves, and were distilled before use. Reaction flasks were flame-dried under a stream of argon. All moisture- and oxygen-sensitive reactions were conducted under an Ar atmosphere. Flash chromatography was carried out using silica-gel 60 (70-230 mesh). Preparative TLC (PTLC) was carried out with Wakogel B-5F. "Usual workup" represents the sequence of drying the combined extracts over Na₂SO₄, filtering off Na₂SO₄, and concentrating the filtrate under reduced pressure.

The melting points are uncorrected. HPLC analyses were performed with detection by UV light. ¹H-NMR (270 MHz) spectra were measured with Me₄Si as an internal standard; the δ and *J* values are given in ppm and Hz, respectively. The unit for the values of IR spectra is cm⁻¹.

2-Acetoxyimino-3,3-dimethyl-1-indanyl acetate 6. To a solution of 2-hydroxyimino-3,3-dimethyl-1-indanone (**2**)¹⁷ (10.0 g, 52.8 mmol) in methanol (250 mL) at -20 °C was added in several portions sodium borohydride (9.00 g, 238 mmol). After evolution of gas had ceased, the solution was stirred at 0 °C for 3 h. The reaction mixture was poured into cold 1 M HCl aq. (300 mL), and the resulting mixture was stirred for 30 min. The mixture was added NaCl to saturate, and extracted with ether (5 × 200 mL). Usual workup gave a colorless solid (2-hydroxyimino-3,3-dimethyl-1-indanol), which was somewhat unstable to air-exposure. Without further purification, this hydroxy oxime was treated with pyridine (200 ml) and acetic anhydride (100 mL), and this mixture was left to stand for 12 h. Then excess pyridine and acetic anhydride were evaporated, and the highly polar by-products were removed by short column chromatography (CH₂Cl₂). Evaporation of the eluent gave a slightly yellow solid, which was recrystallized from hexane (350 mL) to give **6** (12.5 g, 45.4 mmol, 86%) as colorless prisms: mp 114.0-114.5 °C; IR (KBr) 1764, 1738, 1660; ¹H-NMR (CDCl₃) δ 1.63 (3H, s), 1.69 (3H, s), 2.12 (3H, s), 2.33 (3H, s), 6.67 (1H, s), 7.20-7.56 (4H, m). Anal. Calcd for C₁₅H₁₇NO₄: C, 65.44; H, 6.22; N, 5.08. Found: C, 65.30; H, 6.23; N, 5.10.

Racemic cis-2-Amino-3,3-dimethyl-1-indanol rac-3. To a stirred solution of **6** (8.82 g, 32.0 mmol) in THF (50 mL) was added borane-THF complex (130 mL, 130 mmol; 1.0 M THF solution) to 0 °C. Then the reaction mixture was gradually heated and finally refluxed for 3 h. With cooling at 0 °C, 1 M HCl aq. (30 mL) was cautiously added to the mixture. After being stirred for 30 min, the mixture was basified to about pH 14 with 2 M KOH aq. and extracted with CH₂Cl₂ (5 × 200 mL). Usual workup gave rac-**3** (5.69 g, 32.0 mmol, 100%), which was sufficiently pure for further use.

An analytical sample was recrystallized from hexane/benzene (3/1) to give colorless prisms: mp 108.5-109.0 °C; IR (KBr) 3200, 2950, 1580, 995, 770; ¹H-NMR (CDCl₃) δ 1.21 (3H, s), 1.23 (3H, s), 1.80-2.50 (3H, br s), 3.21 (1H, br d), 4.93 (1H, br d), 7.19-7.43 (4H, m). Anal. Calcd for C₁₁H₁₅NO: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.33; H, 8.62; N, 7.90.

Resolution of rac-3.

(1*R*,2*S*)-2-Amino-3,3-dimethyl-1-indanol-(*S*)-mandelic acid salt (+)-7. To a solution of rac-3 (5.28 g, 29.8 mmol) in ethanol (10 mL) was added (*S*)-mandelic acid (4.53 g, 29.8 mmol). To the resulting suspension of the diastereomeric salt mixture was added ethanol (60 mL), and the suspension was refluxed to dissolve the diastereomeric salt mixture completely. The clear solution was allowed to stand at rt for 1 h (from the point when the precipitation started), and then for 1 h at 0 °C. The precipitate was collected by filtration, and washed with cold ethanol (10 mL). Recrystallization of the precipitate from ethanol (70 mL) under similar conditions gave diastereomerically pure (+)-7 (3.40 g, 10.3 mmol, 35% based on rac-3 used) as colorless needles: $[\alpha]_{20}^{20.4}_{\text{D}} +38.3$ (*c* 1.98, MeOH); mp 202.0-202.5 °C; IR (KBr) 3100, 1605, 1568, 1540, 760; ¹H-NMR (DMSO-*d*₆) δ 1.20 (3H, s), 1.29 (3H, s), 3.34 (1H, d, *J*=6.2), 4.64 (1H, s), 5.00 (1H, d, *J*=6.2), 5.20-6.90 (5H, br), 7.15-7.49 (9H, m). Anal. Calcd for C₁₉H₂₃NO₄: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.13; H, 7.10; N, 4.16. X-ray crystallographic details: monoclinic, space group *C*2, *a*=21.778(2)Å, *b*=5.473(6)Å, *c*=16.417(2)Å, *V*=1770(3)Å³, β =115.25(8)°, *R*=0.047, *R*_w=0.051.

To diastereomeric salt (+)-7 (20.0 mg, 0.0607 mmol), dissolved in pyridine (2 mL), was added acetic anhydride (1 mL), and the reaction mixture was allowed to stand for 12 h at rt. Then excess pyridine and acetic anhydride were evaporated, and the residue was purified by PTLC (ethyl acetate) to give (1*R*,2*S*)-2-acetamido-3,3-dimethyl-1-indanyl acetate ((1*R*,2*S*)-8) (15.8 mg, 0.0606 mmol, quant.) Chiral HPLC analysis (Daicel Chiralcel OD, hexane/2-propanol (9/1), α 1.38, shorter retention time for the 1*R*,2*S* isomer) of (1*R*,2*S*)-8 indicated that (+)-7 was diastereomerically pure.

An analytical sample of (1*R*,2*S*)-8 was recrystallized from hexane/benzene (9/1) to give colorless needles: $[\alpha]_{20}^{20.8}_{\text{D}} -170$ (*c* 1.00, CHCl₃); mp 123.0-123.5 °C; IR (KBr) 3320, 1730, 1650; ¹H-NMR (CDCl₃) δ 1.22 (3H, s), 1.37 (3H, s), 2.07 (3H, s), 2.11 (3H, s), 4.66 (1H, dd, *J*=5.9, 9.9), 5.80 (1H, d, *J*=9.9), 6.04 (1H, d, *J*=5.9), 7.21-7.54 (4H, m). Anal. Calcd for C₁₅H₁₉NO₃: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.81; H, 7.39; N, 5.30.

(1*R*,2*S*)-2-Amino-3,3-dimethyl-1-indanol ((1*R*,2*S*)-3). To a stirred suspension of (+)-7 (3.40 g, 10.3 mmol) in CH₂Cl₂ (100 mL) was added 2 M KOH aq. (200 mL). The mixture was separated, and the aqueous layer was extracted with CH₂Cl₂ (3 × 100 mL). Usual workup of the combined organic layer and extracts gave (1*R*,2*S*)-3 (1.79 g, 10.1 mmol, 98%) as a colorless powder: $[\alpha]_{18}^{18.0}_{\text{D}} -16.8$ (*c* 1.00, MeOH); mp 100.5-101.0 °C; IR (KBr) 3400, 2900, 1560, 1195, 758. The ¹H-NMR was identical with that of rac-3. Anal. Calcd for C₁₁H₁₅NO: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.67; H, 8.43; N, 8.20.

To amino alcohol (1*R*,2*S*)-3 (15.6 mg, 0.0880 mmol), dissolved in pyridine (2 mL), was added acetic anhydride (1 mL), and the reaction mixture was allowed to stand for 12 h at rt. Then excess pyridine and acetic anhydride were evaporated, and the residue was purified by PTLC (ethyl acetate) to give (1*R*,2*S*)-8 (22.9 mg, 0.0876 mmol, quant.) Chiral HPLC analysis of (1*R*,2*S*)-8 indicated that (1*R*,2*S*)-3 was enantiomerically pure.

(1*S*,2*R*)-2-Amino-3,3-dimethyl-1-indanol-(*R*)-mandelic acid salt (-)-7. The combined filtrates of the crystallization and recrystallization performed in order to obtain (1*R*,2*S*)-7, were concentrated under reduced pressure to give a solid mass, which was treated with 2 M KOH aq. (300 mL) and extracted with CH₂Cl₂ (3 × 100 mL). Usual workup of the extracts gave (1*S*,2*R*)-enriched 3 (3.39 g, 19.1 mmol), which was treated with (*R*)-mandelic acid (2.91 g, 19.1 mmol) to give the diastereomeric salt mixture. Crystallization of this salt mixture from ethanol (70 mL) according to the procedure given for the preparation

of (+)-**7** gave diastereomerically pure (–)-**7** (3.63 g, 11.0 mmol, 37%) as colorless needles: $[\alpha]_{20.8}^D -38.9$ (*c* 2.08, MeOH). The other physical data were identical with those of (+)-**7**. Chiral HPLC analysis of (1*S*,2*R*)-**8** ($[\alpha]_{20.8}^D +170$ (*c* 1.00, CHCl₃); the other physical data were identical with those of (1*R*,2*S*)-**8**, derived from (–)-**7** in a similar procedure to the preparation of (1*R*,2*S*)-**8**, indicated that (–)-**7** was diastereomerically pure.

(1*S*,2*R*)-2-Amino-3,3-dimethyl-1-indanol (1*S*,2*R*)-3. According to the procedure given for the preparation of (1*R*,2*S*)-**3**, (1*S*,2*R*)-**3** (963 mg, 5.43 mmol, 100%) was obtained from (–)-**7** (1.79 g, 5.43 mmol) as a colorless powder: $[\alpha]_{18.0}^D +16.7$ (*c* 1.02, MeOH). The other physical data were identical with those of (1*R*,2*S*)-**3**. Chiral HPLC analysis of (1*S*,2*R*)-**8**, derived from (1*S*,2*R*)-**3** by similar procedure to that used in the preparation of (1*R*,2*S*)-**8**, indicated that (1*R*,2*S*)-**3** was enantiomerically pure.

(1*R*,5*S*)-7,8-Benzo-6,6-dimethyl-3-oxo-4-aza-2-oxabicyclo[3.3.0]octane (1*R*,5*S*)-9. A mixture of (1*R*,2*S*)-**3** (542 mg, 3.06 mmol), K₂CO₃ (30 mg) and diethyl carbonate (4 mL) was stirred at reflux for 7 h. After being cooled, the reaction mixture was filtered, and excess diethyl carbonate was evaporated to give an oil. The oil was purified by column chromatography (CH₂Cl₂) to give (1*R*,5*S*)-**9** (603 mg, 2.97 mmol, 97%), which was used for the following reaction without further purification.

An analytical sample was recrystallized from hexane/ethyl acetate (3/1) to give colorless prisms: $[\alpha]_{20.4}^D +179$ (*c* 5.00, CHCl₃); mp 124.5–125.0 °C; IR (KBr) 3280, 1750, 1718; ¹H-NMR (CDCl₃) δ 1.18 (3H, s), 1.34 (3H, s), 4.24 (1H, d, *J*=6.8), 5.96 (1H, d, *J*=6.8), 6.6–6.7 (1H, br s), 7.16–7.49 (4H, m). Anal. Calcd for C₁₂H₁₃NO₂: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.87; H, 6.38; N, 6.73.

(1*S*,5*R*)-7,8-Benzo-6,6-dimethyl-3-oxo-4-aza-2-oxabicyclo[3.3.0]octane (1*S*,5*R*)-9. According to the procedure given for the preparation of (1*R*,5*S*)-**9**, (1*S*,5*R*)-**9** (1.13 g, 5.54 mmol, 98%) was obtained from (1*S*,2*R*)-**3** (1.00 g, 5.64 mmol) as colorless prisms: $[\alpha]_{22.6}^D -180$ (*c* 5.10, CHCl₃). The other physical data were identical with those of (1*R*,5*S*)-**9**.

***N*-Propionyl-(1*R*,5*S*)-7,8-benzo-6,6-dimethyl-3-oxo-4-aza-2-oxabicyclo[3.3.0]octane (1*R*,5*S*)-10**. To a solution of (1*R*,5*S*)-**9** (306 mg, 1.51 mmol) in THF (3.0 mL) was added butyllithium (1.05 mL, 1.77 mmol; 1.69 M hexane solution) at –78 °C, and the mixture was stirred for 10 min at –78 °C. To this solution was added a solution of propionyl chloride (0.17 g, 1.8 mmol) in THF (1 mL) at –78 °C, and the mixture was stirred at –78 °C for 30 min and then at 0 °C for 30 min. The reaction was quenched by adding saturated NH₄Cl aq. (5 mL). The mixture was extracted with ethyl acetate (3 × 10 mL). Usual workup gave a colorless solid, which was purified by column chromatography (hexane/ethyl acetate (9/1)) to give (1*R*,5*S*)-**10** (370 mg, 1.43 mmol, 95%) as colorless crystals, which was used in the following reaction without further purification.

An analytical sample was recrystallized from petroleum ether to give colorless needles: $[\alpha]_{22.4}^D +366$ (*c* 5.00, CHCl₃); mp 98.5–99.0 °C; IR (KBr) 1760, 1700; ¹H-NMR (CDCl₃) δ 1.13 (3H, s), 1.22 (3H, t, *J*=7.9), 1.57 (3H, s), 2.90–3.18 (2H, m), 4.85 (1H, d, *J*=7.8), 5.79 (1H, d, *J*=7.8), 7.20–7.57 (4H, m). Anal. Calcd for C₁₅H₁₇NO₃: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.42; H, 6.55; N, 5.24.

***N*-Propionyl-(1*S*,5*R*)-7,8-benzo-6,6-dimethyl-3-oxo-4-aza-2-oxabicyclo[3.3.0]octane (1*S*,5*R*)-10**. According to the procedure given for the preparation of (1*R*,5*S*)-**10**, (1*S*,5*R*)-**10** (621 mg, 2.40 mmol, 97%) was obtained from (1*S*,5*R*)-**9** (500 mg, 2.46 mmol) as colorless needles: $[\alpha]_{22.4}^D -364$ (*c* 4.05, CHCl₃). The other physical data were identical with those of (1*R*,5*S*)-**10**.

***N*-(3-Phenylpropionyl)-(1*R*,5*S*)-7,8-benzo-6,6-dimethyl-3-oxo-4-aza-2-oxabicyclo[3.3.0]octane (1*R*,5*S*)-11.** According to the procedure given for the preparation of (1*R*,5*S*)-10, from (1*R*,5*S*)-9 (271 mg, 1.33 mmol) and 3-phenylpropionyl chloride (0.27 g, 1.6 mmol), (1*R*,5*S*)-11 (446 mg, 1.33 mmol, 100%) was obtained as a colorless solid.

An analytical sample was recrystallized from hexane/benzene (19/1) to give colorless prisms: $[\alpha]_D^{21.4} +254$ (*c* 3.30, CHCl₃); mp 97.5-98.0 °C; IR (KBr) 1778, 1692; ¹H-NMR (CDCl₃) δ 1.08 (3H, s), 1.55 (3H, s), 2.97-3.07 (2H, m), 3.23-3.39 (2H, m), 4.83 (1H, d, *J*=7.8), 5.76 (1H, d, *J*=7.8), 7.18-7.55 (9H, m). Anal. Calcd for C₂₁H₂₁NO₃: C, 75.20; H, 6.31; N, 4.18. Found: C, 75.04; H, 6.25; N, 3.92.

***N*-Phenylacetyl-(1*S*,5*R*)-7,8-benzo-6,6-dimethyl-3-oxo-4-aza-2-oxabicyclo[3.3.0]octane (1*S*,5*R*)-12.** According to the procedure given for the preparation of (1*R*,5*S*)-10, from (1*S*,5*R*)-9 (500 mg, 2.46 mmol) and phenylacetyl chloride (0.46 g, 2.9 mmol), (1*S*,5*R*)-12 (656 mg, 2.04 mmol, 83%) was obtained as a colorless solid.

An analytical sample was recrystallized from hexane/benzene (19/1) to give colorless prisms: $[\alpha]_D^{22.4} -331$ (*c* 2.11, CHCl₃); mp 117.5-118.0 °C; IR (KBr) 1780, 1700; ¹H-NMR (CDCl₃) δ 1.08 (3H, s), 1.52 (3H, s), 4.36 (2H, dd, *J*=15.8, 17.5), 4.85 (1H, d, *J*=7.9), 5.78 (1H, d, *J*=7.9), 7.20-7.56 (9H, m). Anal. Calcd for C₂₀H₁₉NO₃: C, 74.75; H, 5.96; N, 4.36. Found: C, 74.54; H, 5.88; N, 4.13.

Diastereoselective Alkylation Reaction.

General Procedure. The diastereoselective alkylation reactions were performed on a 0.2-1.2 mmol scale. To a stirred 0.5 M solution of diisopropylamine (1.2 eq.) in THF was added butyllithium (1.1 eq.; 1.63 M solution in hexane) at 0 °C, and the mixture was stirred for 30 min at 0 °C. Then, to this solution was added a 0.3-0.4 M solution of *N*-acyloxazolidinone (1*R*,5*S*)-10 or (1*R*,5*S*)-11 in THF at -78 °C, and the solution was stirred for 30 min at -78 °C. Finally, to this solution was added a 1 M solution of alkylhalide (3 to 6 eq.) in THF at -78 °C, and the reaction mixture was stirred at 0 °C for 0.5-3 h. The reaction was quenched by adding saturated NH₄Cl aq. (5 mL), and the mixture was extracted with CH₂Cl₂ (3 × 10 mL). After the usual workup followed by removal of the highly polar by-products by short column chromatography (hexane/ethyl acetate (1/1)), HPLC analysis of the crude product mixture was performed in order to determine the diastereoselectivity, for which purpose an authentic sample was prepared by reaction of the lithium salt of racemic 9 with the corresponding racemic α-chiral carboxylic acid chloride. Purification by chromatography gave the corresponding α-alkylated carboximide 13a-d as colorless crystals.

***N*-[(2*R*)-2-Methylbutanoyl]-(1*R*,5*S*)-7,8-benzo-6,6-dimethyl-3-oxo-4-aza-2-oxabicyclo[3.3.0]octane 13a.** The reaction of the lithium enolate, derived from (1*R*,5*S*)-10 (80.4 mg, 0.310 mmol), with ethyl iodide (0.30 g, 1.9 mmol) for 3 h at 0 °C, followed by purification by PTLC (hexane/ethyl acetate (4/1)), gave 13a (62.6 mg, 0.179 mmol, 57%) as colorless crystals. The ratio of 13a and its 2*S* isomer was determined to be >99:1 by HPLC analysis (hexane/ethyl acetate (9/1), α 1.44, longer retention time for the 2*R* isomer).

An analytical sample was recrystallized from petroleum ether to give colorless needles: $[\alpha]_D^{22.0} +296$ (*c* 3.61, CHCl₃); mp 149.0-149.5 °C; IR (KBr) 1762, 1695; ¹H-NMR (CDCl₃) δ 0.98 (3H, t, *J*=7.5), 1.14 (3H, s), 1.19 (3H, d, *J*=6.7), 1.45 (1H, m), 1.56 (3H, s), 1.85 (1H, m), 3.70 (1H, m), 4.85 (1H, d,

$J=7.8$), 5.77 (1H, d, $J=7.8$), 7.25-7.53 (4H, m). Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37; N, 4.87. Found: C, 71.03; H, 7.44; N, 4.82.

***N*-[(2*R*)-2-Methylpent-4-enoyl]-(1*R*,5*S*)-7,8-benzo-6,6-dimethyl-3-oxo-4-aza-2-oxabicyclo[3.3.0]octane 13b.** The reaction of the lithium enolate, derived from (1*R*,5*S*)-10 (67.5 mg, 0.249 mmol), with allyl bromide (0.10 g, 0.83 mmol) for 1 h at 0 °C, followed by purification by PTLC (hexane/ethyl acetate (4/1)), gave **13b** (70.0 mg, 0.236 mmol, 95%) as colorless crystals. The ratio of **13b** and its 2*S* isomer was determined to be 99:1 by HPLC analysis (hexane/ethyl acetate (9/1), α 1.71, longer retention time for the 2*R* isomer).

An analytical sample was recrystallized from petroleum ether to give colorless needles: $[\alpha]^{22.0}_D +292$ (*c* 3.78, $CHCl_3$); mp 85.0-85.5 °C; IR (KBr) 1762, 1695; 1H -NMR ($CDCl_3$) δ 1.12 (3H, s), 1.20 (3H, d, $J=6.7$), 1.55 (3H, s), 2.15 (1H, m), 2.60 (1H, m), 3.88 (1H, m), 4.85 (1H, d, $J=7.8$), 5.07 (1H, d, $J=19.3$), 5.09 (1H, d, $J=12.0$), 5.77 (1H, d, $J=7.8$), 5.81(1H, m), 7.25-7.51 (4H, m). Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.07; N, 4.68. Found: C, 72.19; H, 7.10; N, 4.57.

***N*-[(2*R*)-2-Methyl-3-phenylpropionyl]-(1*R*,5*S*)-7,8-benzo-6,6-dimethyl-3-oxo-4-aza-2-oxabicyclo[3.3.0]octane 13c.** The reaction of the lithium enolate, derived from (1*R*,5*S*)-10 (303 mg, 1.17 mmol), with benzyl bromide (0.60 g, 3.5 mmol) for 0.5 h at 0 °C, followed by purification by column chromatography (hexane/ethyl acetate (9/1)), gave **13c** (408 mg, 1.17 mmol, quant.) as colorless crystals. The ratio of **13c** and its 2*S* isomer was determined to be 99:1 by HPLC analysis (hexane/ethyl acetate (9/1), α 1.69, longer retention time for the 2*R* isomer).

An analytical sample was recrystallized from petroleum ether to give colorless prisms: $[\alpha]^{22.0}_D +223$ (*c* 2.24, $CHCl_3$); mp 108.5-109.0 °C; IR (KBr) 1770, 1690; 1H -NMR ($CDCl_3$) δ 0.86 (3H, s), 1.18 (3H, d, $J=6.8$), 1.51 (3H, s), 2.60 (1H, dd, $J=8.3$, 13.0), 3.22 (1H, dd, $J=6.2$, 13.0), 4.18 (1H, m), 4.85 (1H, d, $J=7.9$), 5.77 (1H, d, $J=7.9$), 7.21-7.50 (9H, m). Anal. Calcd for $C_{22}H_{23}NO_3$: C, 75.62; H, 6.63; N, 4.01. Found: C, 75.61; H, 6.69; N, 3.88.

***N*-[(2*S*)-2-Methyl-3-phenylpropionyl]-(1*R*,5*S*)-7,8-benzo-6,6-dimethyl-3-oxo-4-aza-2-oxabicyclo[3.3.0]octane 13d.** The reaction of the lithium enolate, derived from (1*R*,5*S*)-11 (130 mg, 0.387 mmol), with methyl iodide (0.25 g, 1.8 mmol) for 1 h at 0 °C, followed by purification by PTLC (hexane/ethyl acetate (4/1)), gave **13d** (113 mg, 0.322 mmol, 83%) as colorless crystals. The ratio of **13d** and its 2*R* isomer was determined to be 97:3 by HPLC analysis (hexane/ethyl acetate (9/1), α 1.71, shorter retention time for the 2*S* isomer).

An analytical sample was recrystallized from petroleum ether to give colorless needles: $[\alpha]^{22.8}_D +313$ (*c* 5.63, $CHCl_3$); mp 111.0-111.5 °C; IR (KBr) 1770, 1690; 1H -NMR ($CDCl_3$) δ 1.10 (3H, s), 1.28 (3H, d, $J=7.0$), 1.55 (3H, s), 2.74 (1H, dd, $J=6.2$, 13.5), 3.07 (1H, dd, $J=6.2$, 13.5), 4.20 (1H, m), 4.68 (1H, d, $J=7.9$), 5.56 (1H, d, $J=7.9$), 7.12-7.51 (9H, m). Anal. Calcd for $C_{22}H_{23}NO_3$: C, 75.62; H, 6.63; N, 4.01. Found: C, 75.36; H, 6.67; N, 3.89.

Hydrolysis of 13c with Lithium Hydroperoxide. To a solution of **13c** (349 mg, 1.00 mmol) in a mixture of THF (4 mL) and water (1 mL) was added 35% H_2O_2 aq. (0.4 mL, 4 mmol) and $LiOH \cdot H_2O$ (68.3 mg, 1.63 mmol) at 0 °C, and the reaction mixture was stirred for 2.5 h at 0 °C. Then, 1 M Na_2SO_3 aq. (3 mL) was added to the mixture. After the THF was evaporated, 1 M KOH aq. (10 mL) was added to the resulting residue, and the mixture was extracted with CH_2Cl_2 (2 \times 10 mL). The combined CH_2Cl_2 extracts were washed with 1 M KOH aq. (10 mL). Usual workup of the CH_2Cl_2 layer gave oxazolidinone (1*R*,2*S*)-9

(204 mg, 1.00 mmol, quant.). On the other hand, the aqueous layer was cooled to 0 °C, acidified to about pH 1 with 6 M HCl aq., and extracted with ethyl acetate (3 × 10 mL). Usual workup of the extracts gave (*R*)-2-methyl-3-phenylpropanoic acid (**14**) (156 mg, 0.950 mmol, 95 %): $[\alpha]^{19.2}_{\text{D}} -27.3$ (*c* 7.66, CHCl₃) (lit. $[\alpha]_{\text{D}} -25.4$ (neat) for the *R* isomer).¹⁸ The enantiomeric purity of **14** was confirmed as follows: Treatment of **14** (150 mg, 0.911 mmol) with borane-THF complex (1.8 mL, 1.8 mmol: 1.0 M solution in THF) at rt for 1 h gave (*R*)-2-methyl-3-phenylpropanol (137 mg, 0.911 mmol, 100%), whose enantiomeric purity was determined to be >99% by ¹H-NMR analysis of the corresponding (+)-MTPA ester **15**.

Diastereoselective Acylation Reaction.

***N*-[(2*S*)-2-Methyl-3-oxobutanoyl]-(1*S*,5*R*)-7,8-benzo-6,6-dimethyl-3-oxo-4-aza-2-oxabicyclo[3.3.0]octane 16a.** To a solution of diisopropylamine (105 mg, 1.03 mmol) in THF (1.5 mL) was added butyllithium (0.58 mL, 0.93 mmol; 1.60 M solution in hexane) at 0 °C, and the mixture was stirred for 30 min at 0 °C. To this solution was added a solution of (1*S*,5*R*)-**10** (214 mg, 0.824 mmol) in THF (1.5 mL) at -78 °C, and the solution was stirred for 30 min at -78 °C. Then the resulting solution of the lithium enolate in THF was added to a solution of acetyl chloride (0.15 g, 1.9 mmol) in THF (1.5 mL) via a cannular at -78 °C (cannulation time: 3 min). The reaction was immediately quenched by adding saturated NH₄Cl aq. (5 mL). Then the mixture was allowed to warm to rt and extracted with ether (3 × 15 mL). After usual workup of the extracts, the highly polar by-products were removed by short column chromatography (ether). The ratio of **16a** to its 2*R* isomer was determined to be 98:2 by HPLC analysis of the crude product mixture (hexane/ethyl acetate (5/1), α 1.86, longer retention time for the 2*S* isomer), for which purpose an authentic sample was prepared by epimerization of purified **16a** with a 1M solution of about 10 eq. triethylamine in dichloromethane for 12 h at room temperature. Purification by column chromatography (hexane/ether (4/1)) gave **16a** as colorless crystals (222 mg, 0.737 mmol, 89%).

An analytical sample was recrystallized from petroleum ether/benzene (19/1) to give colorless prisms: $[\alpha]^{22.4}_{\text{D}} -218$ (*c* 4.86, CHCl₃); mp 138.0-138.5 °C; IR (KBr) 1765, 1720, 1700; ¹H-NMR (CDCl₃) 1.25 (3H, s), 1.44 (3H, d, *J*=7.3), 1.59 (3H, s), 2.33 (3H, s), 4.55 (1H, q, *J*=7.33), 4.82 (1H, d, *J*=7.6), 5.79 (1H, d, *J*=7.6), 7.23-7.51 (4H, m). Anal. Calcd for C₁₇H₁₉NO₄: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.67; H, 6.37; N, 4.54. X-ray crystallographic details: monoclinic, space group *P*2₁, *a*=15.080(2)Å, *b*=9.126(2)Å, *c*=12.588(1)Å, *V*=1598(3)Å³, β =112.73(8)°, *R*=0.056, *R*_w=0.064.

***N*-[(2*S*)-2-methyl-3-oxo-3-phenylpropionyl]-(1*S*,5*R*)-7,8-Benzo-6,6-dimethyl-3-oxo-4-aza-2-oxabicyclo[3.3.0]octane 16b.** A solution of the lithium enolate, derived from (1*S*,5*R*)-**10** (112 mg, 0.432 mmol), in THF (1.5 mL) was added to a solution of benzoyl chloride (0.10 g, 0.71 mmol) in THF (1.5 mL). The reaction was immediately quenched by adding saturated NH₄Cl aq. (5 mL). According to the procedure given for the preparation of **16a**, the ratio of the titled compound and its 2*R* isomer was determined to be >99:1 by HPLC analysis (hexane/ethyl acetate (4/1), α 2.49, longer retention time for the 2*S* isomer). Purification of the crude products by column chromatography gave **16b** (146 mg, 0.400 mmol, 86%) as colorless crystals.

An analytical sample was recrystallized from petroleum ether/benzene (19/1) to give colorless prisms: $[\alpha]^{22.4}_{\text{D}} -113$ (*c* 1.29, CHCl₃); mp 152.5-153.0 °C; IR (KBr) 1770, 1710, 1685; ¹H-NMR (CDCl₃) 1.27 (3H, s), 1.51 (3H, d, *J*=7.3), 1.59 (3H, s), 4.87 (1H, d, *J*=7.9), 5.45 (1H, q, *J*=7.3), 5.81 (1H, d, *J*=7.9),

7.21-8.01 (9H, m). Anal. Calcd for C₂₂H₂₁NO₄: C, 72.71; H, 5.82; N, 3.85. Found: C, 72.45; H, 5.88; N, 3.86.

***N*-[(2*S*,3*R*)-3-Hydroxy-2-methyl-3-phenylpropionyl]-(1*S*,5*R*)-7,8-benzo-6,6-dimethyl-3-oxo-4-aza-2-oxabicyclo[3.3.0]octane *syn*-17.** To a solution of **16b** (129 mg, 0.356 mmol) in CH₂Cl₂ (20 mL) was added zinc borohydride (7.6 mL, 1.1 mmol; 0.14 M ethereal solution) at -78 °C, and the mixture was stirred for 1 h at 0 °C. After adding water (10 mL) to the mixture, filtration through celite pad was performed in order to remove the insoluble materials, and the filtrate was extracted with CH₂Cl₂ (3 × 10 mL). Usual workup of the extracts, followed by purification by PTLC (CHCl₃), gave *syn*-**17** (124 mg, 0.338 mmol, 95%) and its 2*S*,3*S* isomer, *anti*-**17** (4.6 mg, 3.5%). The relative stereochemistry of *anti*-**17** was established by a comparison of its ¹H-NMR spectrum with those of several kinds of known aldol adducts, obtained by the reactions of chiral *N*-propionyloxazolidinones with benzaldehyde.²⁴

An analytical sample of *syn*-**17** was recrystallized from hexane/benzene (19/1) to give colorless prisms: [α]_D^{22.0} -261 (*c* 1.07, CHCl₃); mp 135.5-136.0 °C; IR (KBr) 3425, 1780, 1762, 1695; ¹H-NMR (CDCl₃) 0.98 (3H, s), 1.17 (3H, d, *J*=6.9), 1.54 (3H, s), 2.83 (1H, d, *J*=3.0), 4.25 (1H, dq, *J*=3.3, 6.9), 4.86 (1H, d, *J*=7.6), 5.22 (1H, dd, *J*=3.0, 3.3), 5.80 (1H, d, *J*=7.6), 7.21-7.52 (9H, m). Anal. Calcd for C₂₂H₂₃NO₄: C, 72.31; H, 6.34; N, 3.83. Found: C, 72.09; H, 6.41; N, 3.71.

Hydrolysis of *syn*-17 with Lithium Hydroperoxide. To a solution of *syn*-**17** (98.6 mg, 0.270 mmol) in a mixture of THF (1.2 mL) and water (0.3 mL) was added 35% H₂O₂ aq. (0.15 mL, 1.5 mmol) and LiOH·H₂O (23.0 mg, 0.55 mmol) at 0 °C. After the solution was stirred for 3 h at 0 °C, Na₂SO₃ (0.2 g) in water (1 mL) and 1 M HCl aq. (10 mL) were added in turn to the solution, and the resulting mixture was extracted with ethyl acetate (4 × 10 mL). Usual workup of the extracts gave the crude product mixture, which was treated with excess CH₂N₂ in THF. After quenching the reaction by adding acetic acid, followed by concentration of the mixture under reduced pressure, the resulting crude product were purified by PTLC (hexane/ethyl acetate (2/1)) to give oxazolidinone (1*S*,5*R*)-**9** (51.3 mg, 0.252 mmol, 93%) and methyl (2*S*,3*R*)-3-hydroxy-2-methyl-3-phenylpropionate (**18**) (50.7 mg, 0.261 mmol, 97%): [α]_D^{22.0} -22.3 (*c* 2.31, CHCl₃) (lit. [α]_D²⁵ -23.1 (*c* 3.2, CHCl₃) for the 2*S*,3*R* isomer).¹⁰ The enantiomeric purity of **18** was confirmed to be >99% by chiral HPLC analysis (Daicel Chiralcel OJ, hexane/2-propanol (15/1), α 1.12, shorter retention time for the 2*S*,3*R* isomer).

Diastereoselective Bromination.

***N*-[(2*S*)-2-Bromo-3-phenylpropionyl]-(1*R*,5*S*)-7,8-benzo-6,6-dimethyl-3-oxo-4-aza-2-oxabicyclo[3.3.0]octane **19**.** To a solution of (1*R*,5*S*)-**11** (141 mg, 0.420 mmol) in CH₂Cl₂ (1.5 mL) were successively added dibutylboryl triflate (0.46 mL, 0.46 mmol; 1.0 M CH₂Cl₂ solution) and a solution of diisopropylethylamine (68.0 mg, 0.526 mmol) in CH₂Cl₂ (1.5 mL) at -78 °C, and the resulting solution was stirred at 0 °C for 1 h. Then the solution of the boron enolate in CH₂Cl₂ was added to a suspension of NBS (0.90 g, 0.51 mmol) in CH₂Cl₂ (1 mL) via a cannular at -78 °C (cannulation time: 3 min), and the resulting mixture was stirred for 1.5 h at -78 °C. The reaction was quenched by adding 0.5 M NaHSO₄ (5 mL) at -78 °C, and the mixture was allowed to warm to rt and then extracted with ether (3 × 10 mL). After usual workup of the extracts, the highly polar by-products were removed by short column chromatography (ether). The ratio of **19** to its 2*R* isomer was determined to be 99:1 by HPLC analysis (hexane/ethyl acetate (9/1), α 2.71, longer retention time for the 2*S* isomer), for which purpose an authentic

sample was prepared by epimerization of purified **19** with lithium bromide in refluxing THF. Purification by column chromatography (hexane/ether (9/1)) gave **19** (165 mg, 0.398 mmol, 95%) as a colorless solid mass: $[\alpha]^{22.8}_{\text{D}} +200$ (*c* 3.11, CHCl₃); mp 63.0-64.5 °C; IR (KBr) 1770, 1705, 510; ¹H-NMR (CDCl₃) 1.24 (3H, s), 1.57 (3H, s), 3.34 (1H, dd, *J*=6.6, 13.9), 3.59 (1H, dd, *J*=8.9, 13.9), 4.75 (1H, d, *J*=7.7), 5.66 (1H, d, *J*=7.7), 5.95 (1H, dd, *J*=6.6, 8.9), 7.21-7.50 (9H, m); HRMS(EI) calcd for C₂₁H₂₀BrNO₃ 415.0606, found 415.0620.

***N*-[(2*R*)-2-Azido-3-phenylpropionyl]-(1*R*,5*S*)-7,8-benzo-6,6-dimethyl-3-oxo-4-aza-2-oxabicyclo[3.3.0]octane **20**.** To a solution of diastereomerically pure **19** (120 mg, 0.290 mmol) in CH₂Cl₂ (2 mL) was added 1,1,3,3-tetramethylguanidinium azide (0.23 g, 1.5 mmol) in one portion at 0 °C, and the solution was stirred for 1 h at 0 °C. After adding saturated aqueous NaHCO₃ (5 mL), the mixture was extracted with ether (3 × 10 mL). Usual workup of the extracts gave a pale yellow viscous oil, which was purified by PTLC (hexane/ethyl acetate (5/1)) to give pure **20** (105 mg, 0.279 mmol, 96%) as colorless crystals.

An analytical sample was recrystallized from hexane/benzene (19/1) to give colorless prisms: $[\alpha]^{22.4}_{\text{D}} +292$ (*c* 1.08, CHCl₃); mp 109.0-109.5 °C; IR (KBr) 2120, 1765, 1700, 1360, 1200; ¹H-NMR (CDCl₃) 1.06 (3H, s), 1.58 (3H, s), 2.97 (1H, dd, *J*=10.2, 13.5), 3.37 (1H, dd, *J*=4.0, 13.5), 4.91 (1H, d, *J*=7.7), 5.26 (1H, dd, *J*=4.0, 10.2), 5.90 (1H, d, *J*=7.7), 7.21-7.56 (9H, m). Anal. Calcd for C₂₁H₂₀N₄O₃: C, 67.01; H, 5.36; N, 14.88. Found: C, 67.09; H, 5.54; N, 14.71.

Hydrolysis of **20 with Lithium Hydroxide.** To a solution of **20** (105 mg, 0.279 mmol) in THF (2 mL) was added a solution of LiOH·H₂O (50 mg) in water (4 mL) at 0 °C and the mixture was stirred for 2 h at 0 °C. After adding 1 M KOH aq. (10 mL), the mixture was extracted with CH₂Cl₂ (3 × 10 mL). Usual workup of the combined extracts gave oxazolidinone (1*R*,5*S*)-**9** (0.287 mmol, quant.). On the other hand, the aqueous layer was cooled to 0 °C, acidified to pH 1 with 6 M HCl aq., and extracted with ether (4 × 10 mL). Usual workup of the combined extracts gave (*R*)-2-azido-3-phenylpropionic acid (**21**) (47.6 mg, 0.249, 89%): $[\alpha]^{21.6}_{\text{D}} +66.2$ (*c* 2.00, CHCl₃) (lit. $[\alpha]^{21.6}_{\text{D}} +68.6$ (*c* 1.40, CHCl₃) for the *R* isomer).¹³ The enantiomeric purity of **21** was determined as follows: A solution of α-azido acid **21** (37.0 mg, 0.194 mmol) in a mixture of acetic acid (3 mL) and water (1 mL) was treated with 5% Pd/C (30 mg) under a H₂ atmosphere for 7 h. Then the reaction mixture was filtered through a celite pad, and the filtrate was concentrated under reduced pressure to give a colorless solid. To a suspension of the product in methanol (5 mL) was added thionyl chloride (1 mL) drop by drop at 0 °C, and the reaction mixture was refluxed for 2 h. The volatiles were removed under reduced pressure to yield crude methyl (*R*)-phenylalaninate hydrochloride as a slightly brown solid. A suspension of this crude product in CH₂Cl₂ (4 mL) was treated with triethylamine (0.5 mL) and (+)-MTPA chloride (0.10 g, 0.40 mmol), and the mixture was stirred for 2 h at rt. Concentration of the mixture under reduced pressure, followed by purification by PTLC (hexane/ethyl acetate (9/1)), gave the corresponding *N*-(+)-MTPA amino acid methyl ester **22**, whose diastereomeric purity was determined to be >99% by ¹H-NMR analysis.

Diastereoselective Hydroxylation.

***N*-[(2*R*)-2-Hydroxy-2-phenylacetyl]-(1*S*,5*R*)-7,8-benzo-6,6-dimethyl-3-oxo-4-aza-2-oxabicyclo[3.3.0]octane **23**.** To sodium hexamethyldisilazide (1.2 mL, 0.6 mmol; 0.5 M THF solution) was added a solution of (1*S*,5*R*)-**12** (155 mg, 0.482 mmol) in THF (1.2 mL) at -78 °C, and the resulting

solution was stirred for 0.5 h at $-78\text{ }^{\circ}\text{C}$. Then, to the solution was added a solution of 2-(*p*-toluenesulfonyl)-3-phenyloxaziridine (0.20 g, 0.73 mmol) in THF (1.5 mL) drop by drop over a period of 5 min at $-78\text{ }^{\circ}\text{C}$, and the reaction mixture was stirred for 10 min at $-78\text{ }^{\circ}\text{C}$. The reaction was quenched by adding a solution of camphorsulfonic acid (0.56 g, 2.4 mmol) in THF (5.0 mL). The mixture was allowed to warm to rt and then passed through a short silica gel pad (eluent: CH_2Cl_2). Evaporation of the filtrate, followed by purification by PTLC (hexane/ethyl acetate (1/1)), gave 137 mg (0.406 mmol, 84%) of a mixture of **23** and its 2*S* isomer as an oil. The diastereomer ratio was determined to be 93:7 by $^1\text{H-NMR}$ analysis of the diastereomeric mixture. Removal of the isomeric impurity could be performed by recrystallization of the product from petroleum ether/ CH_2Cl_2 (2/1) to give colorless needles: $[\alpha]^{22.4}_{\text{D}} -361$ (*c* 1.00, CHCl_3); mp 124.0-125.0 $^{\circ}\text{C}$; IR (KBr) 3450, 1780, 1700; $^1\text{H-NMR}$ (CDCl_3) 1.19 (3H, s), 1.61 (3H, s), 4.08 (1H, d, $J=8.3$), 4.73 (1H, d, $J=7.6$), 5.66 (1H, d, $J=7.6$), 6.28 (1H, d, $J=8.3$), 7.21-7.50 (9H, m). Anal. Calcd for $\text{C}_{20}\text{H}_{19}\text{NO}_4$: C, 71.20; H, 5.68; N, 4.15. Found: C, 71.08; H, 5.64; N, 4.13.

Methanolysis of 23 with Magnesium Methoxide. A mixture of **23** and its 2*S* isomer (56.5 mg, 0.167 mmol, 2*R*:2*S*=93:7) was treated with magnesium methoxide (7.5 mL, 0.83 mmol; 0.11 M solution in methanol) at $0\text{ }^{\circ}\text{C}$, and the mixture was stirred for 0.5 h at $0\text{ }^{\circ}\text{C}$. The reaction was quenched by adding saturated NH_4Cl aq. (10 mL). The resulting mixture was diluted with water (10 mL) and extracted with CH_2Cl_2 ($3 \times 10\text{ mL}$). Usual workup of the extracts, followed by purification by PTLC (hexane/ethyl acetate (2/1)), gave (1*S*,5*R*)-**9** (30.0 mg, 0.148 mmol, 88%) and methyl mandelate (**24**) (25.4 mg, 0.153 mmol, 92%). The enantiomer ratio for **24** was determined to be *R*:*S*=93:7 by chiral HPLC analysis (Daicel Chiralcel OJ, hexane/2-propanol (9/1), α 1.33, longer retention time for the *R* isomer), for which purpose authentic samples of methyl (*R*)- and (*S*)-mandelate were prepared by treatment of respectively commercially available (*R*)- and (*S*)-mandelic acid with excess CH_2N_2 .

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