JOC Article

Development of Highly Stereoselective Asymmetric 6π-Azaelectrocyclization of Conformationally Flexible Linear 1-Azatrienes. From Determination of Multifunctional Chiral Amines, 7-Alkyl *cis*-1-Amino-2-indanols, to Application as a New Synthetic Strategy: Formal Synthesis of 20-Epiuleine

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Received April 13, 2004

The highly stereoselective asymmetric 6π-azaelectrocyclization was achieved as a general synthetic method based on the reaction between the (*E*)-3-carbonyl-2,4,6-trienal compounds and the (−)-7-alkyl-*cis*-1-amino-2-indanol derivatives which are effective chiral amines. The 7-alkyl-substituted 2-indanol moiety of the cyclized products was efficiently removed by the novel manganese dioxide oxidation under remarkably mild conditions, and the method was successfully applied to the formal synthesis of optically active 20-epiuleine.

Introduction

The thermal cyclization of 1-azatrienes into 1,2-dihydropyridines,[1] which is the so-called 6π-azaelectrocyclization, is one of the well-known concerted pericyclic reactions,[2−4] which proceed in a disrotatory mode.[5] Although a number of examples of the 6π-azaelectrocyclization have been reported,[1,6,7] the process required a high temperature and a long reaction time, and therefore, the application of this reaction toward natural products synthesis is very limited in the literature. The recent pioneering work of Okamura and co-workers determined that the introduction of either an electron donor or an acceptor group at the 1-azatriene terminus moderately accelerated the rate of the electrocyclization.[5,8] Quite recently, we independently succeeded in significantly accelerating the azaelectrocyclization, based on the remarkable orbital interaction between the HOMO and LUMO of the 1-azatrienes by the combination of substituent effects, that is, the C4-carbonyl and the C6-alkenyl or phenyl substituents of the 1-azatrienes (Scheme 1).[9,10]

Thus, we quantitatively obtained the corresponding dihydropyridine derivatives within 5 min at room temperature by the reaction of (*E*)-3-carbonyl-2,4,6-trienals with primary amines. Furthermore, as a synthetic application of this established smooth azaelectrocyclization, we realized the novel one-pot synthesis of substituted pyridines, and the method was successfully applied to the synthesis of the ocular age pigment, A2E.[10,11] As a next step to develop our very fast 6π-azaelectrocyclization, we succeeded in demonstrating a general asymmetric azaelectrocyclization using chiral amines as the primary amines. Herein, we report in detail[12] the novel highly stereoselective asymmetric 6π-azaelectrocyclization of the conformationally flexible linear 1-azatriene based on the reactions between the (*E*)-3-carbonyl-2,4,6-trienal compounds and the new 7-alkyl substituted chiral *cis*-1-amino-2-indanol derivatives by a remarkably simple operation under quite mild conditions. The 2-indanol chiral moiety of the cyclized products was successfully removed by treatment with manganese dioxide under remarkably mild conditions. The detailed mechanistic

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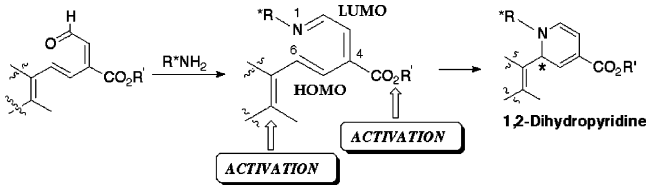
10.1021/jo049381f CCC: $27.50
Published on Web 08/04/2004

SCHEME 1



investigation of this novel phenomenon is also described. In addition, the scale-up synthetic procedure of these enantiomerically pure (−)-7-methyl- and isopropyl-*cis*-aminoindanols is also described. Finally, the developed method was applied toward the formal synthesis of the indole alkaloid, 20-epiuleine.

Results and Discussion

Establishment of the Stereoselective 6π-Azaelectrocyclization. Our strategy is based on controlling the facial selectivity of the disrotatory azaelectrocyclization, which would be affected by a chiral auxiliary on the nitrogen[13] under the established smooth azaelectrocyclization by the reaction of (*E*)-3-carbonyltrienals with primary amines (Scheme 1). First, we selected the reaction between trienal **1** containing the bulky 2,6,6-trimethylcyclohexene moiety and the various commercially available amines such as those shown in Table 1 and examined the diastereoselectivity of the azaelectrocyclization. For screening of the many chiral amines in a short time, each reaction was directly carried out in an NMR sample tube at 24 °C in $CDCl_3$, and the diastereomeric ratio of the produced 1, 2-dihydropyridine was analyzed by observation of its characteristic ^{1}H NMR signals. The representative results are shown in Table 1, entries 1−6. The reactions with 1-phenylethylamine **i** or 1-aminoindan **iv** provided the corresponding 1,2-dihydropyridine derivatives with a 3:1 diastereoselectivity (entries 1 and 4). A complex mixture of the products was produced by the reaction with 2-phenylglycinol **ii** (entry 2), and cyclization was not observed for the 1-azatriene which was smoothly obtained by the reaction with the bulky 2-amino-1,2-diphenylethanol **iii** (entry 3). Fortunately, a 10:1 diastereoselectivity was obtained by the reactions with **v** and **vi**, which bear an additional methyl or methoxy substituent cis to the amino group of 1-aminoindan **iv** (entries 5 and 6). Unfortunately, these generated chiral dihydropyridines[14,15] were found to be very unstable and were only treated as their solutions, such as in ether or benzene (in $CHCl_3$, they gradually decomposed). Furthermore, several trials to derivatize the dihydropyridines into stabilized compounds such as the corresponding tetrahydropyridines by hydrogenation led to the decomposition of the 1,2-dihydropyridines. Therefore, the stereochemistry at the C-2 position of the dihydropyridines produced from **i** and **iv**−**vi** could not be determined at this stage.

However, we later postulated that their stereochemistry was the same as that of (−)-**1a** (structure shown in Scheme 2), which was yielded by the reaction with *cis*-hydroxy-substituted aminoindanol (−)-**a**. Finally, it was found that the reaction of **1** with (1*S*,2*R*)-(−)-*cis*-1-amino-2-indanol **a**[16] quantitatively produced the pentacyclic piperidine derivative (−)-**1a**, $[\alpha]^{24}_D$ −45.4 (*c* 1.1, $CHCl_3$), as a single stereoisomer (Scheme 2). The relative stereochemistry was assigned based on the observation of the NOE correlation between protons H_a and H_b and unambiguously determined by the X-ray crystallographic analysis of the carboxylic acid, prepared by the treatment of **1a** with a 2 N solution of potassium hydroxide in methanol followed by acidification (Figure 1). The ^{1}H NMR spectrum of the carboxylic acid was very similar to that of **1a** except for the disappearance of the methyl ester protons, and this indicated that no epimerization occurred during the hydrolysis of **1a** (see the Experimental Section). The reaction proceeded by smooth azaelectrocyclization followed by aminoacetal formation between the resulting enamine moiety of dihydropyridine and the hydroxy group of the indanol moiety (Scheme 2).

The acetal formation was so fast in $CDCl_3$ that the presence of the corresponding dihydropyridine was not observed. Since deuterated chloroform contains a small amount of hydrochloric acid as a contaminant, the enamine moiety of the dihydropyridine easily tautomerized into the corresponding imminium ion, and then the nucleophilic attack by the neighboring hydroxy group would be facilitated.[17] Actually, when the reaction was analyzed in pyridine-d_5, the dihydropyridine intermediary and the subsequent slow transformation into the piperidine derivative **1a** was clearly observed. Noteworthy is the fact that the hydroxy group of aminoindanol is protecting the reactive enamine moiety of the chiral dihydropyridine as its aminoacetal and contributing to the significant stabilization of the dihydropyridine. Therefore, this chiral dihydropyridine equivalent **1a** could be

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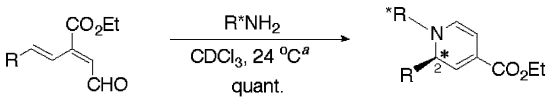
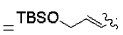
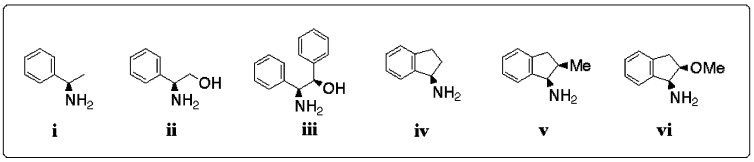
TABLE 1.



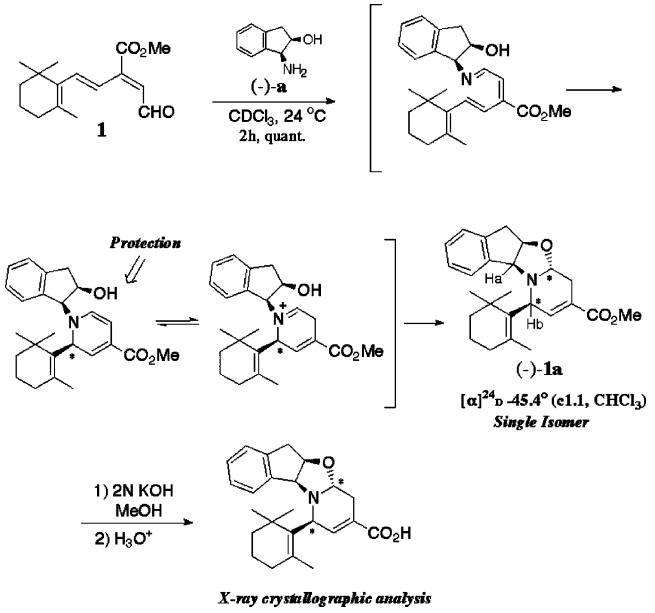
1 : R =  **2** : R =  **3** : R = 

entry	aldehyde	amine	dr (at the 2-position)	entry	aldehyde	amine	dr (at the 2-position)
1	**1**	**i**	3 : 1	10	**2**	**iv**	1 : 1
2	**1**	**ii**	complex mixture	11	**2**	**v**	1 : 1
3	**1**	**iii**	no cyclization	12	**2**	**vi**	1 : 1
4	**1**	**iv**	3 : 1	13	**3**	**i**	1 : 1
5	**1**	**v**	10 : 1	14	**3**	**ii**	2 : 1[b]
6	**1**	**vi**	10 : 1	15	**3**	**iii**	1 : 1[b]
7	**2**	**i**	1 : 1	16	**3**	**iv**	1 : 1
8	**2**	**ii**	1 : 1[b]	17	**3**	**v**	1 : 1
9	**2**	**iii**	no cyclization	18	**3**	**vi**	1 : 1



[a] Compounds **1**−**3** were reacted with 1.1 equiv of chiral amines at 24 °C in $CDCl_3$. Each reaction was directly monitored by ^1H NMR, and the ratio of the produced 1,2-dihydropyridines was analyzed by their characteristic signals in their ^1H NMR. [b] The products were the aminoacetal derivatives of the corresponding dihydropyridines.

SCHEME 2



easily handled for further functional transformations as shown in the following experiments. Thus, by summarizing the results for the reactions of **1** with various amines, it was suggested that the 1-aminoindan structure and its *cis*-substituent with respect to the amino group, especially the *cis*-hydroxy group, would be important for giving good diastereoselectivity through azaelectrocyclization.

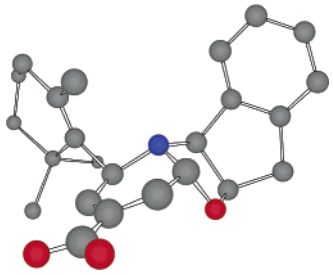
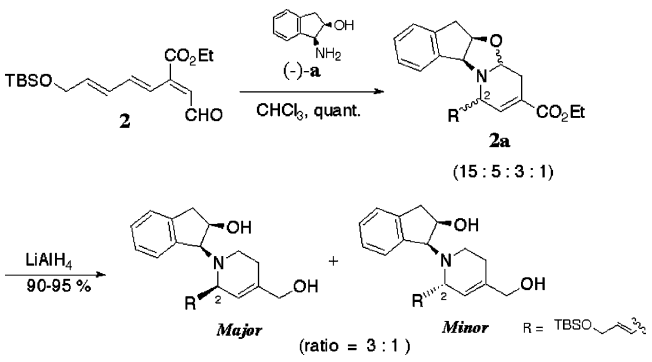


FIGURE 1. Three-dimensional image of X-ray crystallographic analysis.

We next examined the reactions of the chiral amines with more general aldehydes **2** and **3**,[10] which contain linear alkenyl or phenyl substituents, respectively (Table 1, entries 7−18). Disappointedly, almost no diastereoselectivity was observed even by the reactions with amines **v** or **vi**, which showed a 10:1 selectivity by the reaction with **1** (entries 11, 12, 17, and 18). However, it was encouraging to find that the reaction of **2** with *cis*-aminoindanol **a** yielded the corresponding piperidine derivatives **2a** as a mixture of its four inseparable stereoisomers (Scheme 3). The ratio of the four stereoisomers was established to be 15:5:3:1 based on the integration of the characteristic vinyl protons of the

SCHEME 3



piperidine ring in its NMR spectrum. The main isomer of **2a** was suggested to possess the same relative configurations as that of **1a**, by comparing their ^{1}H NMR spectra one another. The stereoselectivity at the 2-position of piperidine **2a** that corresponded to the diastereoselectivity of the azaelectrocyclization, was then elucidated to be 3:1 by treating **2a** with lithium aluminum hydride and analyzing the resulting diols by its ^{1}H NMR. Similarly, the reaction of **3** with **a** gave the corresponding piperidine **3a** in the ratio of 3:1 (see Table 2, entries 1 and 2). Thus, only the *cis*-aminoindanol **a** among the commercially available amines tested exhibited a moderate selectivity by the reactions with **2** and **3**.

Based on these results, we planned to increase the bulkiness of the *cis*-aminoindanol **a** by introducing an alkyl substituent on the benzene ring and tried to improve the selectivity (Table 2). Unfortunately, our first trial upon utilizing the 4-methyl- or isopropyl-substituted *cis*-aminoindanols afforded a 3:1 diastereoselectivity by the reaction with aldehyde **3**, the selectivity of which was similar to that obtained by employing the simple aminoindanol **a** (date not shown).[18] In contrast, the aminoindanol derivatives **b**−**e** having the alkyl substituents at the 7-position of **a** were successfully synthesized (vide infra), and quite fortunately, these derivatives significantly improved the diastereoselectivity of the azaelectrocyclization. Thus, the reactions of **2** and **3** with the methyl-substituted aminoindanol (−)-**b** provided the corresponding piperidines (−)-**2b** and (−)-**3b** in the diastereomeric ratio of 5:1 and 12:1 (entries 3 and 4), respectively. Furthermore, the reactions with the ethyl-substituted aminoindanol **c** gave the corresponding piperidine derivatives in the ratio of 7:1 and 20:1, respectively (entries 5 and 6). The highest selectivity was obtained by utilizing the isopropyl-substituted aminoindanol (−)-**d**, and the corresponding piperidine derivatives (−)-**2d** and (−)-**3d** were produced in the ratio of 10:1 and 24:1 (entries 7 and 8), respectively. Moreover, (−)-**3d** was obtained as an almost single isomer at the lower temperature of 13 °C (entry 9). Unexpectedly, the reactions with the more bulky *tert*-butyl-substituted aminoindanol **e** showed a slightly decreased selectivity (5:1 and 17:1 for **2e** and **3e**, entries 10 and 11, respectively). Thus, the highly stereoselective 6π-azaelectrocyclization of the conformationally flexible linear 1-azatrienes was achieved by utilizing the novel 7-alkyl-substituted *cis*-aminoindanol derivatives. Quite recently, Hsung and co-workers also succeeded in the highly stereoselective azaelectrocyclization of their conformationally restricted 1-azatrienes under thermodynamically equilibrated conditions.[19,20] In our case, the observed diastereoselectivity was not the result of the thermodynamic equibration, because no equiblium between the separated diastereomers could be observed under the reaction conditions of Table 2. To the best of our knowledge, this is the first achievement of the highly stereoselective asymmetric 6π-azaelectrocyclization of linear 1-azatriene derivatives in a kinetically controlled way.

Computational Analysis. To rationalize the observed high stereoselectivity of the azaelectrocyclization on the steric/conformational basis, the stable conformation of 1-azatriene **4** derived from compounds **3** and **d** was analyzed by calculation. The stable 2,3-*s*-*cis* and 4,5-*s*-*cis* conformation of **4**, which is the likely conformation just before the disrotatory electrocyclization (as shown in Figure 2), was optimized by a semiempirical method (PM3) using the software packages SPARTAN version 5.0 (Wavefunction, Inc., Irvine CA). The calculation gave the two most stable conformers (*R*)-**4** and (*S*)-**4**, which would provide the experimentally produced major isomer (−)-**3d** and the corresponding minor isomer via disrotatory azaelectrocyclization. In both conformers, the hydroxy group of the indan moiety is expected to participate in the hydrogen bonding with the nitrogen of the 1-azatriene, and stabilizes the conformers. In conformer (*S*)-**4**, there would be the steric interaction between the isopropyl group of the indan moiety and the developing dihydropyridine ring and/or the proton H_a of the azatriene. On the other hand, no such interaction could be observed in conformer (*R*)-**4**, and therefore, the major isomer (−)-**3d** would be preferentially produced through the conformer (*R*)-**4** by the disrotatory azaelectrocyclization. Thus, the above computational analysis strongly supports the observed results that both the *cis*-hydroxy group and an alkyl substituent of the aminoindanol have contributed to improve the stereoselectivity of the azaelectrocyclization. The poorer selectivity using *t*-Bu-aminoindanol derivative **e** is rationalized due to the slightly different conformational arrangement of the 1,2-amino alcohol moiety on the five-membered ring in **e** from those of **a**−**d**. This is indicated by their ^{1}H NMR coupling constants.

Synthesis of 7-Alkyl-Substituted *cis*-1-Amino-2-indanols. To work with this novel azaelectrocyclization

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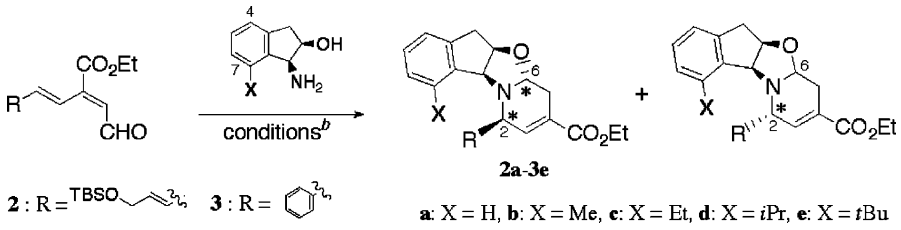
TABLE 2.[a]



entry	aldehyde	amine (X)	product (major isomer)	*T* (°C)	dr (at the 2-position)[c]
1	**2**	(−)-**a**	**2a**	24	3:1[d]
2	**3**	(−)-**a**	(−)-**3a**	24	3:1
3	**2**	(−)-**b**	(−)-**2b**	24	5:1
4	**3**	(−)-**b**	(−)-**3b**	24	12:1
5[e]	**2**	**c**	**2c**	24	7:1
6[f]	**3**	**c**	**3c**	24	20:1
7	**2**	(−)-**d**	(−)-**2d**	24	10:1
8	**3**	(−)-**d**	(−)-**3d**	24	24:1
9	**3**	(−)-**d**	(−)-**3d**	13	>40:1
10[g]	**2**	**e**	**2e**	24	5:1
11[h]	**3**	**e**	**3e**	24	17:1

[a] Unless noted, all the reactions quantitatively provided a diastereomeric mixture of two piperidine derivatives and the stereochemistry as shown. The relative stereochemistry of the products was determined based on their ^{1}H NMR and NOE experiments by comparison with that of **1a**. The stereochemistry of the 6-position of the minor isomers was not determined. [b] $CHCl_3$, 3 h. [c] Determined by ^{1}H NMR (400 MHz). [d] An inseparable mixture of four piperidine derivatives (15:5:3:1) was obtained. The diastereomeric ratio at the 2-position was determined after $LiAlH_4$ reduction of the crude products. [e−h]The racemic **c** and **e** were used to examine the diastereoselectivity of the azaelectrocyclization.

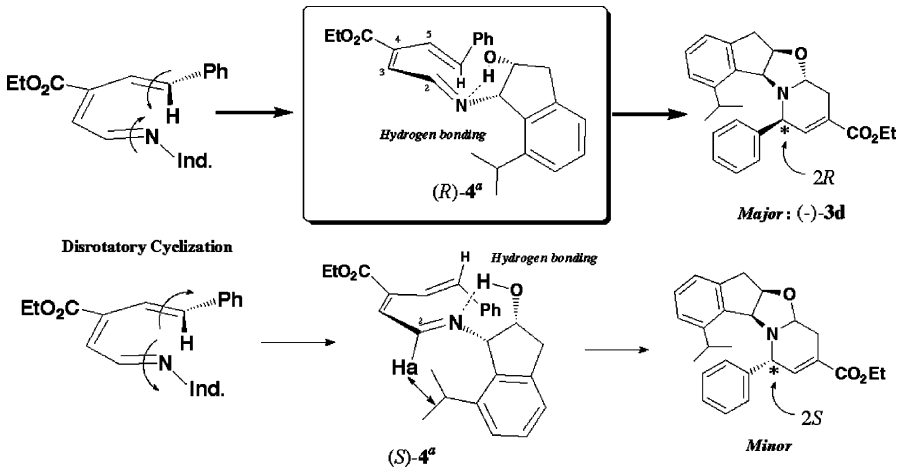


FIGURE 2. Stable 2,3-*s*-*cis*, 4,5-*s*-*cis* conformation of **4**, optimized by a semiempirical method (PM3) using the software package SPARTAN version 5.0 (Wavefunction, Inc., Irvine CA).

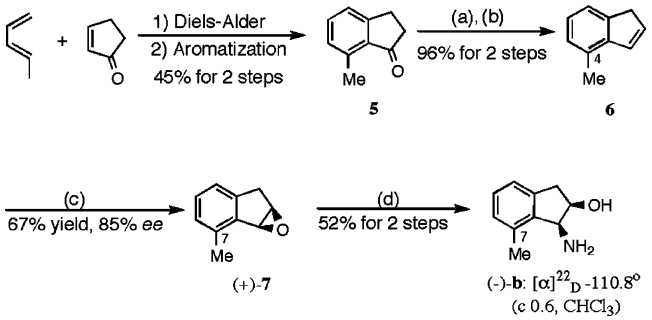
reaction as a general method for chiral piperidine synthesis, it was necessary to develop an efficient scale-up method for the preparation of the chiral 7-substituted *cis*-aminoindanol derivatives.[18] The synthesis of the chiral 7-substituted *cis*-1-amino-2-indanols (−)-**b** and (−)-**d** was followed by the procedure of commercially available (−)-**a** developed by Merck's group.[21] The main feature of this procedure is the Diels−Alder reaction of 1-substituted dienes with cyclopentenone followed by the asymmetric epoxidation of the resulting indene derivatives and then the Ritter reaction.

Thus, 4-methylindene **6** was prepared on a 50-g scale starting from the Diels−Alder reaction between 1,3-pentadiene and cyclopentenone according to the method of House and co-worker.[22] Aromatization of the D−A adduct by treatment with Pd/C at 200 °C produced 7-methylindanone **5** in 45% yield for two steps, which was reduced by $LiAlH_4$ and then dehydrated by treatment with a catalytic amount of *p*-toluenesulfonic acid at 80 °C to give the desired **6** in 96% yield for two steps. The indene **6** was treated with sodium hypochlorite solution in the presence of (*S*,*S*)-(+)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminomanganese(III) chloride and 4-phenylpyridine *N*-oxide at 0 °C for 7 h[21b] to provide the desired indene oxide **7** in 67% yield and 85% ee after rapid chromatography on alumina. Quite fortu-

(21) (a) Senanayake, C. H.; Roberts, F. E.; DiMichele, L. M.; Ryan, K. M.; Liu, J.; Fredenburg, L. E.; Foster, B. S.; Douglas, A. W.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *Tetrahedron Lett.* **1995**, *36*, 3993. (b) Larrow, J. F.; Roberts, E.; Verhoeven, T. R.; Ryan, K. M.; Senanayake, C. H.; Reider, P. J.; Jacobsen, E. N. *Organic Synth.* **1999**, *76*, 46. (c) Muckensturm, B.; Diyani, F. *J. Chem. Res., Synop.* **1995**, 442.

(22) House, H. O.; Rasmusson, C. H. *J. Org. Chem.* **1963**, *28*, 27.

SCHEME 4[a]



[a] Reagents and conditions: (a) $LiAlH_4$, ether; (b) *p*-TsOH (0.1 equiv), benzene, gradually heated to 80 °C; (c) 1.8 M NaClO aq (4.0 equiv), (*S*,*S*)-(+)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminomanganese(III) chloride (1.2 mol %), 4-phenylpyridine *N*-oxide (6 mol %), CH_2Cl_2, rt; (d) fuming H_2SO_4, CH_3CN, rt, 30 min, then H_2O, 100 °C, 2 h.

nately, the compound **7** was recrystallized from a mixture of ether and hexane to give the enantiomerically pure (+)-indene oxide **7**, $[\alpha]^{24}_D$ +2.6 (*c* 0.9, $CHCl_3$). The epoxide **7** was then reacted with fuming sulfuric acid (30% of SO_3) in acetonitrile[21b] to yield the intermediary oxazoline derivative, which was hydrolyzed without purification in H_2O at 100 °C to provide the desired (−)-7-methyl-*cis*-1-amino-2-indanol (−)-**b** (99% ee, $[\alpha]^{22}_D$ −110.8 (*c* 0.6, $CHCl_3$)] in 52% yield for two steps (Scheme 4).

The synthesis of 7-isopropyl-substituted aminoindanol is as follows. Unfortunately, various attempts to prepare a large quantity of the corresponding isopropyl-substituted 1,3-dienes were unsuccessful when using the same method, which gave a mixture of regio- and stereoisomers on the double bond. Therefore, we selected the corresponding 2-siloxy-4-isopropyl-1,3-butadiene as a reactant for the D−A reaction with cyclopentenone as shown in Scheme 5. Thus, more than 200 g of isobutyraldehyde was treated with 2.5 M solution of sodium hydroxide in acetone to give the corresponding aldol product in 69% yield,[23] which was dehydrated by treatment with *p*-toluensulfonic acid to provide the (*E*)-α,*β*-unsaturated ketone **8** in 75% yield on a 200-g scale. The treatment of **8** with chlorotrimethylsilane and solid lithium bis(trimethylsilyl)amide in a mixed solvent system of THF and toluene (1:2)[24] at −78 °C provided the desired siloxydiene **9** in 79% yield. The purification of all the products so far was successfully done by distillation that enabled us to easily prepare the siloxydiene **9** on more than a 100-g scale. The siloxydiene **9** was then reacted with cyclopentenone in the presence of 2,5-di-*tert*-butylhydroquinone in benzene at 200 °C for 72 h to give the desired cycloadduct, which without purification was immediately hydrolyzed by treatment with *p*-toluenesulfonic acid in acetone to provide the diketone **10** in 69% yield for two steps. The diketone consisted of two stereoisomers based on the ^1H NMR analysis. The oxidative aromatization was successfully achieved by treatment of the diketones **10** with 10% Pd/C in *p*-cymene at 200 °C for 2 days to produce the phenol **11** in 72% yield.[25] To remove the phenolic hydroxy group of **11**, the nickel catalyzed reductive deoxygenation with sodium borohydride was successfully employed.[26] Thus, the tosylate, which was prepared by treatment of the phenol **11** with *p*-toluenesulfonyl chloride and sodium hydride, was reacted with 30 equiv of sodium borohydride in the presence of 1 equiv of nickel(II) chloride hexahydrate in methanol to give the desired alcohol **12** in 84% yield for two steps, the product resulting from the concomitant reduction of the ketone group. The alcohol **12** was also quantitatively dehydrated by a reaction with *p*-toluenesulfonic acid to provide the 4-isopropyl indene **13**. Meanwhile, the application of the same reaction conditions as the Jacobsen's epoxidation for the 4-methyl derivative **6** toward the 4-isopropyl-substituted indene **13** disappointedly gave the indene oxide **14** in both lower chemical yield (∼50%) and enantioselectivity (∼50% ee). Therefore, we attempted the improved Jacobsen's epoxidation protocol under anhydrous and lower temperature conditions.[27] The indene **13** was treated with 2 equiv of *m*-chloroperbenzoic acid and 5 equiv of *N*-methylmorpholine *N*-oxide in the presence of 5 mol % of (*S*,*S*)-(+)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminomanganese-(III) chloride at −78 °C to provide the indene oxide **14** in 86% yield and 56% ee. Unfortunately, recrystallization was not effective for isolating the enantiomerically pure epoxide **14**. Therefore, indene oxide **14** was then directly subjected to the Ritter reaction followed by hydrolysis of the oxazoline intermediate using the same procedure as that utilized for the methyl derivative **7** to provide the isopropyl substituted compound **d** in 77% yield for two steps (39% yield after recrystallization). The enantiomerically homogeneous (−)-**d** (99% ee, $[\alpha]^{20}_D$ −114.2 (*c* 0.5, $CHCl_3$)) was successfully obtained by the recrystallization from toluene. The obtained enantiomeric excess of (−)-**d** was analyzed by chiral HPLC (Scheme 5). Thus, a sufficient amount of the chiral 7-methyl and 7-isopropyl substituted *cis*-aminoindanol, (−)-**b** and (−)-**d**, were prepared, respectively.

Removal of Indanol Chiral Auxiliary by the Novel Manganese Dioxide Oxidation. The removal of the indanol auxiliary of the cyclized products was examined. The system mainly investigated for the optimization of the condition was (−)-**1a** and its derivatives because these compounds were relatively stable and easily treated under a variety of conditions. Contrary to our initial expectation, the removal of the indan auxiliary was found to be troublesome. The conventional catalytic hydrogenolysis (30% palladium/carbon, platinum dioxide, or Willkinson catalyst) or Birch reduction of **1a** resulted in the recovery of the starting material. Also, the same attempts on (−)-diol **15**, $[\alpha]^{24}_D$ −66.9 (*c* 1.1, $CHCl_3$), derived from (−)-**1a** by the lithium aluminum hydride reduction (Scheme 6),[28] did not cleave the benzylic C−N bond of the aminoindanol derivative, but resulted in the decomposition of **15** due to reduction of the 2-position of the piperidine ring, which is activated by two double

(23) Tishchenko, I. G.; Stanishevskii, L. S. *J. Gen. Chem. USSR* **1963**, *33*, 134.

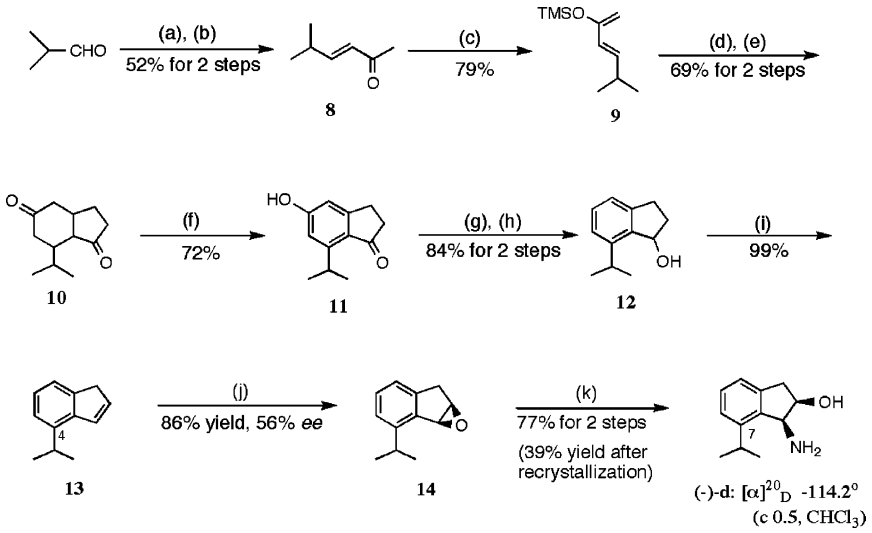
(24) Nagata, T.; Koike, Y.; Nara, K.; Itoh, E.; Arisawa, M.; Naruto, S.; Torisawa, Y.; Hino, T.; Nakagawa, M. *Chem. Pharm. Bull.* **1996**, *44*, 451. (b) Arisawa, M.; Torisawa, Y.; Nakagawa, M. *Synthesis* **1995**, 1371.

(25) (a) Anderson, A. G., Jr.; Nelson, J. A. *J. Am. Chem. Soc.* **1951**, *73*, 232. (b) Turner, R. B.; Nettleton, D. E., Jr.; Ferebee, R. *J. Am. Chem. Soc.* **1956**, *78*, 5923.

(26) Wang, F.; Chiba, K.; Tada, M. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1897.

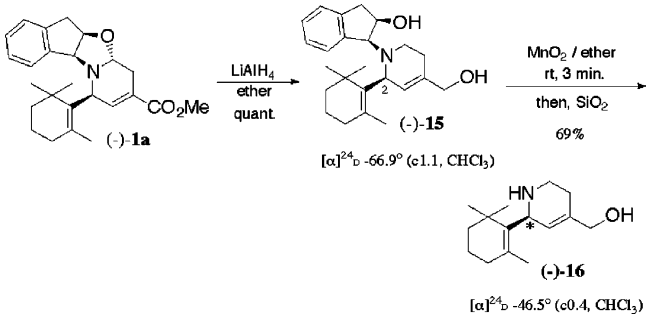
(27) Palucki, M.; Pospisil, P. J.; Zhang, W.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1994**, *116*, 9333.

SCHEME 5[a]



[a] Reagents and conditions: (a) 2.5 M NaOH aq acetone, 0 °C, 2.5 h (2 mol scale); (b) *p*-TsOH (0.005 equiv), Na_2SO_4, benzene, 80 °C; (c) TMSCl, $LiN(TMS)_2$, toluene/THF (2:1), −78 °C; (d) 2-cyclopentenone, 2,5-di-*tert*-butylhydroquinone, benzene, 200 °C, 72 h; (e) *p*-TsOH, acetone; (f) 10% Pd/C, *p*-cymene, 200 °C, 48 h; (g) TsCl, NaH, THF; (h) $NiCl_2$ (1.0 equiv), $NaBH_4$ (30 equiv), MeOH, 0 °C; (i) *p*-TsOH (0.1 equiv), benzene, gradually to 80 °C; (j) *m*-CPBA (2 equiv), NMO (5 equiv), (*S*,*S*)-(+)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminomanganese(III) chloride (5 mol %), CH_2Cl_2, −78 °C; (k) fuming H_2SO_4, CH_3CN, rt, 30 min, then H_2O, 100 °C, 2 h.

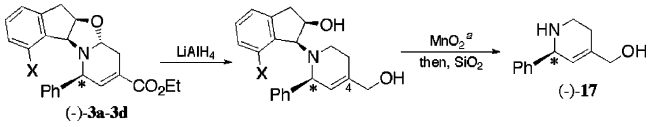
SCHEME 6



bonds and nitrogen. A trial involving the oxidative cleavage[29] of the indanol moiety of **15** by utilizing $Pd(OAc)_4$, KIO_4, and *m*-CPBA also produced a complex mixture of the products. After many trials, this task was finally accomplished by treatment of (−)-**15** with manganese dioxide in ether at room temperature for three minutes, followed by silica gel chromatography to provide the (−)-amino alcohol **16**, $[\alpha]^{24}_D$ −46.5 (*c* 0.4, $CHCl_3$), in 69% yield (Scheme 6).

Similarly, the removal of the chiral indanol moiety in (−)-**3a**−**d** was successfully achieved as shown in Table 3. Thus, (−)-**3a**−**d** were reduced with lithium aluminum hydride to give the corresponding diols in 76−91% yields, which were then treated with manganese dioxide in ether at room temperature followed by silica gel chromatography to provide the corresponding piperidine alcohol (−)-

TABLE 3.



entry	substrate	product	yield of diol (%)	yield of piperidine alcohol (%)
1	(−)-**3a**	(−)-**17**	76[b]	55
2	(−)-**3b**	(−)-**17**	91	55
3	(−)-**3d**	(−)-**17**	91[c]	58

[a] The reaction was performed by treatment of the diols with manganese dioxide (10−20 w/w, chemicals treated, Wako) in ether for a few minutes at room temperature. [b,c] Total yield from aldehyde **3**.

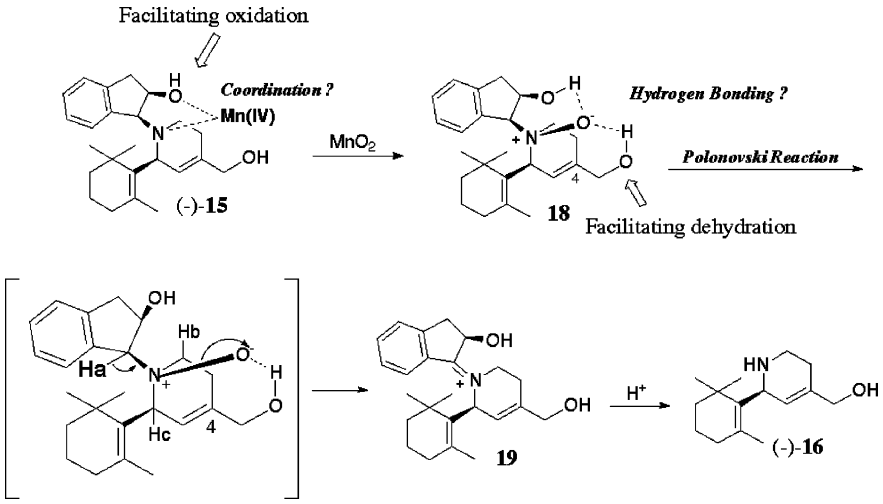
17 in 55−58% yields. Surprisingly, the cleavage of the benzylic C−N bond proceeded under quite mild condition. It was strongly recommended to use ether or acetone as the solvent of the reaction. When the reaction was done in dichloromethane, a complex mixture of products was obtained due to the simultaneous oxidation of the allylic alcohol to the corresponding aldehyde followed by decomposition of the products.

To elucidate the mechanism of this interesting reaction, (−)-diol **15** was treated with manganese dioxide under the same reaction conditions described above. After evaporation of the solvent, and without silica gel chromatography, very unstable *N*-oxide **18** was obtained (Scheme 7). The characterization of the *N*-oxide derivative was conducted for the rather stable *N*-oxide **26** (structure shown in Scheme 8) by MS, IR, and ^{1}H NMR (see the Experimental Section) and compared with those of **18**. The produced *N*-oxide **18** was gradually transformed to the (−)-piperidine alcohol **16** in deuterated chloroform at room temperature, which was also produced when *N*-oxide **18** was subjected to silica gel chromatography. On the basis of the results obtained here, the following mechanism for the removal of the

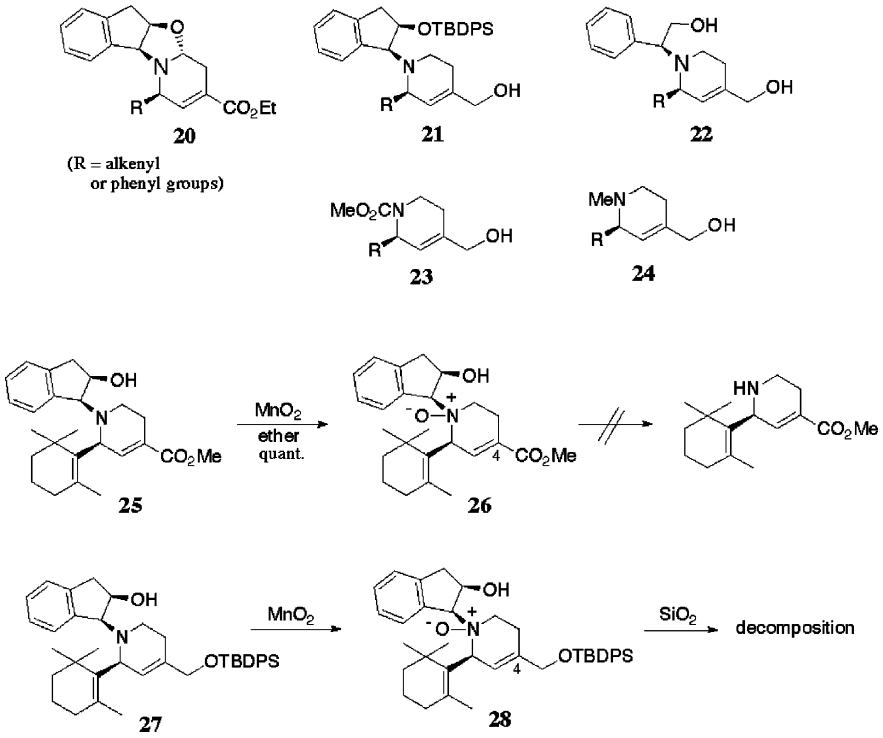
(28) For reduction and alkylation of aminoacetal, see: (a) Yamato, M.; Hashigaki, K.; Ishikawa, S.; Qais, N. *Tetrahedron Lett.* **1988**, *29*, 6949. (b) Higashiyama, K.; Inoue, H.; Takahashi, H. *Tetrahedron Lett.* **1992**, *33*, 235. (c) Higashiyama, K.; Inoue, H.; Takahashi, H. *Tetrahedron* **1994**, *50*, 1083. (d) Higashiyama, K.; Nakahata, K.; Takahashi, H. *J. Chem. Soc., Perkin. Trans. 1* **1994**, 351. (e) Higashiyama, K.; Kyo, H.; Takahashi, H. *Synlett* **1998**, 489. also see the following review; Husson, H.-P.; Royer, J. *Chem. Soc. Rev.* **1999**, *28*, 383.

(29) For an example of oxidative cleavage of an amino alcohol, see: Higashiyama, K.; Inoue, H.; Yamauchi, T.; Takahashi, H. *J. Chem. Soc., Perkin. Trans. 1* **1995**, 111.

SCHEME 7



SCHEME 8



indan moiety was proposed (Scheme 7). Thus, the nitrogen atom of (−)-**15** would be oxidized by manganese dioxide to produce *N*-oxide **18**, which would be followed by the Polonovski-type reaction:[30] the acid-catalyzed dehydration of **18** followed by hydrolysis of the resulting imminium ion **19**.[31] Time-dependent FAB-MS analysis of the *N*-oxide **18** detected ion peaks corresponding to the imminium ion **19** and the corresponding hydroxylated intermediate, the hemiaminoacetal compound, and supported the proposed mechanism as shown in Scheme 7 (see the Experimental Section). The dehydration of *N*-oxide **18** is possible from three directions: by abstracting either proton H_a, H_b, or H_c. However, proton H_a is selectively removed in this case. This can be rationalized by considering that (1) H_a is a reactive benzylic proton and (2) the C−H_a bond is situated in the antiperiplanar position[32] to the leaving N−O bond in the *N*-oxide **18**. Unfortunately, we could not isolate the cleaved α-hydroxyindanone moiety because it gradually decomposed into several compounds on the basis of TLC analysis.

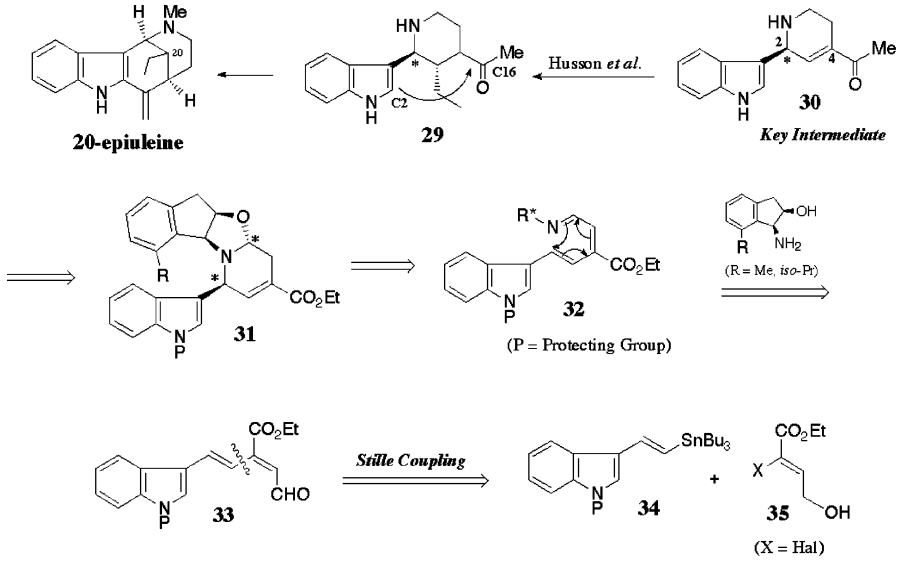
Furthermore, an interesting observation concerning the mechanism of this oxidative removal of the indanol moiety was noted by the following experiments (Scheme 8). Thus, the reaction of **20** with manganese dioxide at

(30) For a review of the Polonovski reaction for alkaloid synthesis, see: Lounasmaa, M. Synthetic Studies in the Field of Indole Alkaloids. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1988; Vol. 1, pp 89−122.

(31) (a) Monkovic, I.; Wong, H.; Bachand, C. *Synthesis* **1985**, 770. (b) Chang, Z.-Y.; Coates, R. M. *J. Org. Chem*. **1990**, *55*, 3475. (c) Blanchet, J.; Bonin, M.; Micouin, L.; Husson, H.-P. *Tetrahedron Lett*. **2000**, *41*, 8279.

(32) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley: New York, 1987.

SCHEME 9



room temperature resulted in only the recovery of **20**. The reactions of **21**−**24** with manganese dioxide cleanly produced the corresponding conjugated aldehydes. Thus, no oxidation of nitrogen was observed with derivatives **20**−**24**. On the other hand, the oxidation of the (−)-ester alcohol **25**, $[\alpha]^{24}_{D}$ −40.0 (*c* 1.0, $CHCl_3$), which was obtained by the sodium borohydride reduction of (−)-**1a**,[28] smoothly gave the corresponding *N*-oxide derivative **26**. However, the *N*-oxide **26** thus produced was found to be stable in $CDCl_3$ for over 24 h or on the silica gel, and conversion of **26** to the corresponding piperidine alcohol such as **16** in Scheme 6 was not observed. In addition, the manganese dioxide oxidation of the compound **27**, of which the C4-hydroxymethyl group was protected as its *tert*-butyldiphenylsilyl ether, produced the corresponding *N*-oxide **28**, which provided a complex mixture of products after silica gel chromatography. On the basis of these results, it was suggested that the hydroxy group of the *cis*-1-amino-2-indanol moiety would contribute to the facile oxidation of the vicinal nitrogen, possibly by the coordination of manganese dioxide to the *cis*-amino alcohol moiety of **15** as shown in Scheme 7. Furthermore, the hydroxymethyl group at the 4-position of the piperidine would facilitate the dehydration, presumably by participating in hydrogen bonding partially with the *N*-oxide moiety, which might be also hydrogen bonded with the vicinal hydroxy group as shown in compound **18** of Scheme 7. This additional hydrogen bonding between the C4-hydroxymethyl group and the *N*-oxide would increase the leaving ability of the N−O bond or would make the conformation favorable to lose the H_a proton, leading to the facile and regioselective Polonovski reaction without any activation of *N*-oxide such as its trifluoroacetate.[30]

Formal Synthesis of 20-Epiuleine. Finally, to apply the thus-established method to the natural products synthesis, we examined the asymmetric synthesis of 20-epiuleine. Uleine, 20-epiuleine, and dasycarpidone, which were principally isolated from *Aspidosperma* sp., constitute a small family of *Strychnos*-type indole alkaloids. These indole alkaloids lack the usual two carbon chain derived from tryptophan (Scheme 9).[33] Although a number of syntheses of racemic uleine derivatives were reported in the literature,[34,35] a few asymmetric syntheses have been reported including the recent synthesis of (+)-uleine by Ogasawara and co-workers.[36] One of the common approaches toward the construction of the 2-azabicyclo[3.3.1]nonane structure, which is characteristic for the *Strychnos* indole alkaloids, includes the C2−C16 bond formation of 3-(2-piperidyl)indoles as shown in Scheme 9.[33] For example, Husson and co-workers succeeded in the synthesis of (±)-20-epiuleine by the acid-catalyzed cyclization of the racemic 2,3,4-trisubstituted piperidine derivative **29**, which was prepared by the conjugate addition of ethylmagnesium bromide to the unsaturated ketone **30**.[35c] Therefore, when the synthesis of the optically active *Strychnos* indole alkaloids is planned,[37] an efficient and stereoselective synthesis of the optically active 2- and 4-substituted piperidine derivative such as chiral **30** would be required, the construction method of which has not yet been established. We envisioned the synthesis of the optically active piperidine **30** using our asymmetric azaelectrocyclization method as shown in Scheme 9. The key intermediate **30** would be derived from **31** by the functional group manupulations, and **31** was thought to be prepared by the asymmetric azaelectrocyclization of azatriene **32**, which would be derived from (*E*)-3-carbonyltrienal **33** and the developed chiral 7-alkyl-*cis*-aminoindanol derivatives. Thereby, the indole ring and the ester substituent of the azatriene **32** would

(33) Bosch, J.; Bonjoch, J. Pentacyclic *Strychnos* Indole Alkaloids. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1988; Vol. 1, pp 31−88.

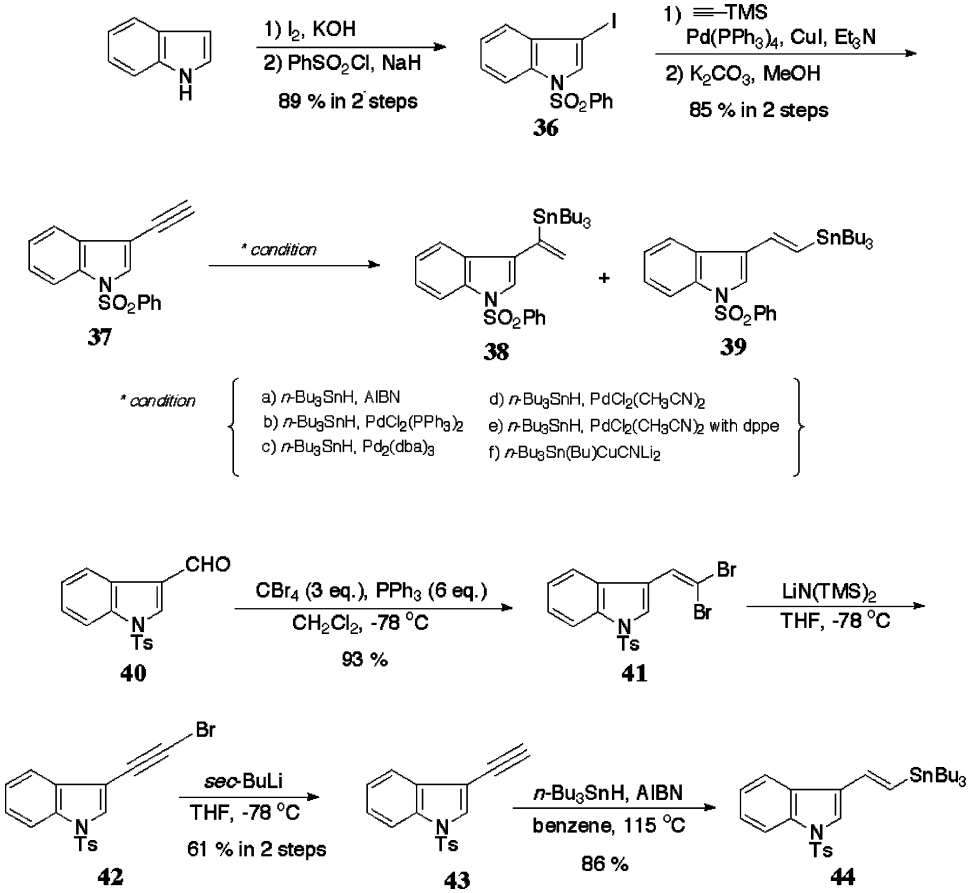
(34) Synthesis of uleine: (a) Jackson, A.; Wilson, N. D. V.; Gaskell, A. J.; Joule, J. A. *J. Chem. Soc. C* **1969**, 2738. (b) Buchi, G.; Gould, S. J.; Naf, F. *J. Am. Chem. Soc.* **1971**, *93*, 2492. (c) Kametani, T.; Suzuki, T. *J. Org. Chem.* **1971**, *36*, 129.

(35) Synthesis of 20-epiuleine: (a) Dolby, L. J.; Biere, H. *J. Org. Chem.* **1970**, *35*, 3843. (b) Natsume, M.; Kitagawa, Y. *Tetrahedron Lett.* **1980**, *21*, 839. (c) Harris, M.; Besselievre, R.; Grierson, D. S.; Husson, H.-P. *Tetrahedron Lett.* **1981**, *22*, 331. (d) Grierson, D. S.; Harris, M.; Husson, H.-P. *Tetrahedron* **1983**, *39*, 3683. see also 34.

(36) Saito, M.; Kawamura, M.; Hiroya, K.; Ogasawara, K. *Chem. Commun.* **1997**, 765.

(37) Enantioselective synthesis of *Strychnos* indole alkaloids and related compounds: Bonjoch, J.; Sole, D. *Chem. Rev.* **2000**, *100*, 3455.

SCHEME 10



function not only as the desirable substituents at the 2- and 4-positions of the piperidine **30** but also as the activating groups of the azaelectrocyclization. Trienal **33** could be prepared from (*E*)-vinylstannane **34** and (*Z*)-vinyl halide **35** by our already-established method.[10]

The synthesis of (*E*)-vinylstannane is shown in Scheme 10. Iodide **36**, which was easily prepared according to the reported procedure,[38] was reacted with TMS-acetylene in the presence of tetrakis(triphenylphosphine)palladium-(0), copper iodide, and triethylamine in THF to yield the corresponding indole acetylene. After removal of the TMS group by potassium methoxide treatment in methanol, acetylene **37** was obtained in 85% yield in two steps. However, a small amount of palladium and copper reagents used for the coupling reaction could not be completely removed from **37** by recrystallizations or column chromatography, because of the low solubility of the indole acetylene compounds in any solvents. Therefore, acetylene **37** was continuously subjected to hydrostannylation without further purification. Contrary to our expectation, various possible conditions for the hydrostannylation of **37** provided only a detectable amount of the desired (*E*)-stannane **39**, and surprisingly, the internal stannane **38** was produced as the major product. We later found that a small contaminant of palladium or copper reagents included in **37** catalyzed the addition of $SnBu_3$ species toward the more substituted position of acetylene.[39] This phenomenon is in clear contrast to the hydrostannylation of the ethynyl benzene derivatives, which exclusively produced the external (*E*)-stannanes.[10] Unfortunately, these stannyl regioisomers could not be separated by silica gel chromatography, and another regioselective synthesis for (*E*)-vinylstannane was required, because the pure (*E*)-vinylstannane was essential for the clean Stille coupling reaction with the vinyl halide fragment (see Scheme 11).

As another approach toward the indole-3-acetylene, the conversion from aldehyde **40** was examined. Thus, 3-indolecarbaldehyde **40** protected with an *N*-*p*-toluenesulfonyl group was reacted with carbon tetrabromide (3 equiv) and triphenylphosphine (6 equiv) at −78 °C to provide the dibromide **41** in 93% yield on a 20-g scale, according to the procedure developed by Corey and Fuchs.[40] Compound **41** was then treated with 1.2 equiv of lithium bis-(trimethylsilyl)amide to give the intermediary bromoacetylene **42**, which without purification was treated with 1.5 equiv of *sec*-butyllithium to provide the pure acetylene **43** in 61% yield for two steps after recrystallization. The choice of the bases such as $LiN(TMS)_2$ and *s*-BuLi and their equivalents was crucial for each reaction to be successful. When other bases such as *n*-butyllithium or LDA were used, the indole ring was decomposed due to the simultaneous removal of the *N*-tosyl protecting group. Fortunately, the reaction of the obtained pure acetylene **43** with *n*-Bu_3SnH in the presence of AIBN at 115 °C provided the desired (*E*)-vinylstannane **44** in 86% yield.

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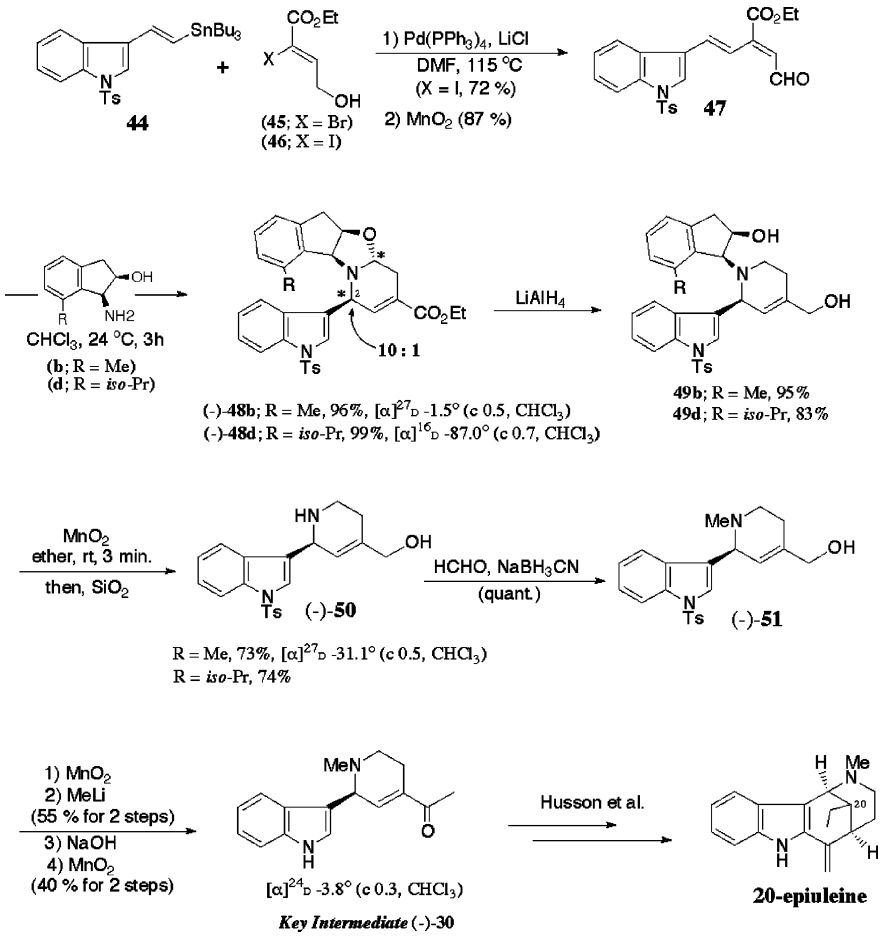
SCHEME 11



The regioselectivity is completely different from the case of the previous attempts. It is an interesting observation that the two regioisomeric stannanes **38** and **44** could be respectively prepared by only changing the catalyst: (i) AIBN for the synthesis of the external (*E*)-stannane **44** and (ii) the presumable complex derived from the palladium and cuprous species for the synthesis of the internal stannane **38**.[39]

Unfortunately, the Stille coupling between stannane **44** and bromide **45** in the presence of $Pd(PPh_3)_4$ and LiCl in DMF only provided the corresponding dimeric product of **44** (Scheme 11).[41] However, the reaction of **44** with the more reactive iodide **46**, which was prepared by the same procedure as the bromide **45** (see Experimental Section), successfully provided the coupling product in 72% yield, which was oxidized with manganese dioxide to yield **47** in 87% yield. The next step is our asymmetric azaelectrocyclization as the key step of the synthesis. Thus, (*E*)-3-carbonyltrienal **47** was reacted with the chiral (−)-*cis*-aminoindanol **b** in chloroform at 24 °C to produce (−)-**48b**, $[\alpha]^{27}_D$ −1.5 (*c* 0.5, $CHCl_3$), in 96% yield as a 10:1 mixture of the stereoisomers at the 2-position of the piperidine ring. The stereoselectivity was surprisingly sensitive to the temperature, and when the reaction was performed even at 33 °C, a 1:1 mixture of the stereoisomers was produced. The quite sensitive diastereoselectivity to the temperature observed is not due to the amine-catalyzed epimerization at the C-2 position since the treatment of pure (−)-**48b** with amine bases such as triethylamine or DBU at 33 °C did not cause the epimerization. After separation of the minor isomer by medium-pressure chromatography, the aminoacetal and ester groups of (−)-**48b** were reduced by lithium aluminum hydride to give the diol **49b** in 95% yield. The removal of the indanol moiety was successfully achieved according to the previously established method. Thus, the treatment of **49b** with manganese dioxide in ether at room temperature for three minutes followed by silica gel column chromatography provided the indole substituted piperidine (−)-**50**, $[\alpha]^{27}_D$ −31.1 (*c* 0.5, $CHCl_3$) in 73% yield. An aminoindanol (−)-**d** similarly provided (−)-**50** via **48d** and **49d** as shown in Scheme 11. The selective *N*-methylation was successfully achieved by treatment of (−)-**50** with 37% aqueous HCHO solution (6 equiv) and sodium cyanoborohydride (2 equiv) in acetonitrile to quantitatively give (−)-**51**. Finally, the conversion to the key intermediate (−)-**30** and the formal synthesis of 20-epiuleine was successfully achieved by the conventional functional group manipulation, which involved the oxidation of the primary alcohol by manganese dioxide, methylation of the aldehyde with methyllithium (55% yield for two steps), deprotection of the indole *N*1-sulfonyl group with sodium methoxide, and oxidation of the secondary alcohol with manganese dioxide (40% yield for two steps). The spectral characteristics of the synthesized

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30 were in good agreement with those reported by Husson and co-workers.

Summary

In summary, we have developed novel chiral 7-alkyl-substituted *cis*-aminoindanol derivatives such as (−)-**b** and (−)-**d**, and achieved the highly stereoselective azaelectrocyclization by reaction with the linear trienals such as **1**−**3** and **47**. The *cis*-aminoindanol derivatives are acting not only as a "chiral auxiliary" but also as a "nitrogen source" for this asymmetric azaelectrocyclization. In addition, the *cis*-hydroxy group of the aminoindanol displays the following important roles: (i) it contributes to improving the diastereoselectivity of the azaelectrocyclization, (ii) stabilizes the notoriously unstable *N*-alkyl 1,2-dihydropyridine nucleus by its aminoacetal formation, and (iii) facilitates the oxidation of the vicinal nitrogen which resulted in the removal of the chiral indanol auxiliary under very mild conditions. It is worthwhile mentioning that this asymmetric azaelectrocyclization can be quite easily carried out by simply mixing aldehydes and the amine in chloroform at room temperature, leaving the mixture for the completion of the reaction, and then evaporating the solvent. This was demonstrated by the formal synthesis of 20-epiuleine. Further application of the developed asymmetric azaelectrocyclization is now ongoing in our laboratory toward achieving a new strategy for natural product synthesis.

Experimental Section

(−)-1,2,5,6-Tetrahydropyridine (1a). To a solution of methyl (*E*,*E*)-4-oxo-2-[(2,6,6-trimethylcyclohex-1-enyl)vinyl]-but-2-enoate **1** (1.19 g, 4.52 mmol) in chloroform (30 mL) was added (1*S*,2*R*)-(−)-*cis*-1-amino-2-indanol **a** (742 mg, 4.97 mmol) at room temperature, and the mixture was stirred for 1 h at this temperature. The reaction mixture was concentrated in vacuo to give the crude products which were purified by column chromatography on silica gel (from 9% to 17% ethyl acetate in hexane) to afford **1a** as a single stereoisomer (1.78 g, 100%) as a yellow oil: $[\alpha]^{24}_{D}$ −45.4 (*c* 1.1, $CHCl_3$); IR (neat, cm^{-1}) 1719, 1460, 1435, 1252, 1119, 1028; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11 (brs, 3H), 1.19 (s, 3H), 1.48−1.68 (m, 4H), 1.86 (s, 3H), 2.07−2.12 (m, 2H), 2.67 (brs, 2H), 3.18 (d, 1H, J = 17.6 Hz), 3.27 (dd, 1H, J = 18.3, 6.1 Hz), 3.76 (s, 3H), 3.82 (brs, 1H), 4.40−4.42 (m, 1H), 4.87 (dd, 1H, J = 6.1, 6.1 Hz), 4.95 (d, 1H, J = 5.4 Hz), 6.88 (brs, 1H), 7.21−7.26 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.5, 21.7, 25.6, 28.4, 29.5, 34.6, 35.3, 39.6, 40.5, 51.7, 54.1, 73.9, 75.3, 87.4, 123.7, 124.6, 125.8, 127.0, 128.1, 135.4, 135.9, 141.0, 141.6, 143.0, 166.8; EI HRMS *m*/*e* calcd for $C_{25}H_{31}NO_3$ ($M^{+\bullet}$) 393.2302, found 393.2308.

(−)-Carboxylic Acid Derivative of 1a. To a solution of (−)-1,2,5,6-tetrahydropyridine **1a** (950 mg, 2.41 mmol) in methanol (20 mL) was added a 2 N KOH solution (1.45 mL, 2.90 mmol) at room temperature. After the mixture was heated to 80 °C and vigorously stirred for 2.5 h, a 1 N HCl solution was added, and the resulting mixture was extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give the crude products. Rough column chromatography on silica gel twice (33−40% ethyl acetate in hexane, and then 25−33% ethyl acetate in hexane) gave the corresponding acid (870 mg, 88%) as a white solid, which was then recrystallized from THF, methanol, and ethyl acetate for the X-ray crystallographic analysis. The carboxylic acid thus obtained narrowly dissolved in $CDCl_3$ to analyze its ^{1}H NMR, and the following very similar signals to those of **1a** indicated that no epimerization occurred during the hydrolysis of (−)-**1a**: mp 163−164 °C; $[\alpha]^{24}_{D}$ −38.0 (*c* 0.3, MeOH); IR (KBr disk, cm^{-1}) 3449, 1690, 1653, 1283; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (brs, 3H), 1.16 (s, 3H), 1.46−1.63 (m, 4H), 1.83 (s, 3H), 2.03−2.10 (m, 2H), 2.64 (brs, 2H), 3.16 (d, 1H, J = 17.8 Hz), 3.24 (dd, 1H, J = 17.8, 5.9 Hz), 3.82 (brs, 1H), 4.38−4.39 (m, 1H), 4.85 (dd, 1H, J = 5.6, 5.6 Hz), 4.93 (d, 1H, J = 5.6 Hz), 6.97 (brs, 1H), 7.17−7.26 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) (as a mixture with its presumable rotamers and its corresponding dihydropyridine) δ 19.0, 20.7, 21.4, 25.3, 27.1, 28.0, 28.7, 29.2, 34.1, 34.3, 34.9, 53.7, 57.5, 59.7, 66.3, 70.6, 73.4, 74.6, 85.3, 86.6, 123.6, 124.5, 125.2, 125.3, 126.3, 126.6, 126.9, 127.5, 128.0, 134.0, 135.7, 136.1, 139.9, 140.8, 141.3, 142.9, 166.7, 167.1; EI HRMS *m*/*e* calcd for $C_{24}H_{29}NO_3$ ($M^{+\bullet}$) 379.2146, found 379.2155.

Representative Procedure of the Stereoselective 6π-Azaelectrocyclization by the Reaction between (*E*)-3-Ethoxycarbonyl-2,4,6-trienals (2 and 3) and *cis*-Aminoindanols (a−e) (Table 2). Unless noted, all the reactions were performed by the following representative procedure to examine the diastereoselectivity of the azaelectrocyclyzation: To a $CDCl_3$ (0.5 mL) solution of the aldehydes **2** or **3** (0.0267 mmol) was added *cis*-aminoindanol derivatives **a**−**e** (0.0267 mmol) at 24 °C. Each reaction was monitored by ^{1}H NMR, and the diastereomeric mixture of the piperidine derivatives were quantitatively produced over 3 h. The mixture was concentrated in vacuo to give the crude products, from which the major isomer was isolated by preparative thin-layer chromatography on silica gel (17% ethyl acetate in hexane).

For the reactions of entries 1−3, the crude cyclized products prepared by the same procedure were directly reduced with lithium aluminum hydride (1.0 equiv, in ether), purified by column chromatography on silica gel (33% to 50% ethyl acetate in hexane), and then the ratio of the resulting two diastereomeric dialcohols were analyzed by ^{1}H NMR, respectively. Furthermore, these diastereomers were successfully separated by preparative thin-layer chromatography on silica gel (45% ethyl acetate in hexane).

Reaction between 2 and (−)-a (Entry 1 of Table 2). The reaction provided the four inseparable mixtures of the piperidine derivatives **2a** (namely, **w**, **x**, **y**, and **z**) in a ratio of 15:5:3:1 (judged by ^{1}H NMR) as a colorless oil: characteristic ^{1}H NMR signals in their vinyl protons (400 MHz, $CDCl_3$) δ 6.73−6.74 (m, proton **w**), 6.68 (dd, proton **x**, J = 2.4, 2.4 Hz), 6.79−6.82 (m, proton **y**), 6.63−6.64 (m, proton **z**).

Dialcohols Prepared from the Cyclized Products of 2a by $LiAlH_4$ Reduction. (Major/minor = 3:1, determined by both ^{1}H NMR and their isolated yields.) Data for the major isomer: $[\alpha]^{26}_{D}$ −41.4 (*c* 0.5, $CHCl_3$); IR (neat, cm^{-1}) 3403, 1256, 1121, 1084, 1061; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.11 (s, 3H), 0.12 (s, 3H), 0.94 (s, 9H), 1.91 (dd, 1H, J = 17.3, 3.2 Hz), 2.14−2.19 (m, 1H), 2.22−2.30 (m, 1H), 2.57−2.64 (m, 1H), 2.66−2.72 (m, 1H), 3.19−3.25 (m, 1H), 3.78 (brs, 1H), 4.03 (d, 1H, J = 16.6 Hz), 4.07 (d, 1H, J = 13.4 Hz), 4.21−4.27 (m, 2H), 4.29−4.38 (m, 2H), 5.59−5.60 (m, 1H), 5.72 (dt, 1H, J = 15.4, 4.9 Hz), 5.97 (ddt, 1H, J = 15.1, 8.8, 1.7 Hz), 7.13−7.25 (m, 3H), 7.37 (d, 1H, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ-5.3, 18.4, 25.9, 26.3, 41.1, 41.7, 61.1, 62.9, 66.3, 66.8, 69.7, 123.7, 125.2, 126.4, 126.8, 128.2, 128.3, 132.4, 136.7, 139.0, 142.2; EI HRMS *m*/*e* calcd for $C_{24}H_{37}NO_3Si$ ($M^{+\bullet}$) 415.2541, found 415.2551. Data for the minor isomer: $[\alpha]^{25}_{D}$ +107.1 (*c* 0.9, $CHCl_3$); IR (neat, cm^{-1}) 3416, 1460, 1256, 1086, 1055, 970; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.08 (s, 3H), 0.09 (s, 3H), 0.91 (s, 9H), 1.84 (brd, 1H, J = 16.6 Hz), 2.13 (ddd, 1H, J = 11.0, 11.0, 3.7 Hz), 2.24 (brd, 1H, J = 14.2 Hz), 2.29−2.35 (m, 1H), 2.82 (dd, 1H, J = 16.6, 7.1 Hz), 3.32 (dd, 1H, J = 16.6, 8.3 Hz), 3.98 (d, 1H, J = 13.4 Hz), 4.04 (d, 1H, J = 13.2 Hz), 4.18−4.27 (m, 3H), 4.39 (dd, 1H, J = 15.4, 8.1 Hz), 4.57 (d, 1H, J = 8.3 Hz), 5.47 (brs, 1H), 5.52 (ddt, 1H, J = 15.4, 9.0, 1.7 Hz), 5.88 (dt, 1H, J = 15.4, 4.6 Hz), 7.17−7.31 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.1, 18.4, 25.9, 26.3, 41.8, 44.9, 62.8, 63.3, 64.4, 66.0, 68.9, 124.1, 125.5, 126.0, 126.4, 128.4, 131.9, 133.4, 136.8, 139.2, 141.7; EI HRMS *m*/*e* calcd for $C_{24}H_{37}NO_3Si$ ($M^{+\bullet}$) 415.2541, found 415.2537.

Reaction between 3 and (−)-a (Entry 2 of Table 2). (Major/minor = 3:1, determined by ^{1}H NMR.) Data for the major isomer (−)-**3a**: $[\alpha]^{21}_D$ −63.8 (*c* 0.5, $CHCl_3$); IR (neat, cm^{-1}) 1715, 1269, 1244, 1032; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (t, 3H, *J* = 7.1 Hz), 2.72−2.75 (m, 2H), 3.15 (d, 1H, *J* = 17.8 Hz), 3.23 (dd, 1H, *J* = 18.1, 6.1 Hz), 4.16 (qm, 2H, *J* = 7.3 Hz), 4.23 (dd, 1H, *J* = 6.1, 3.7 Hz), 4.50 (dd, 1H, *J* = 3.2, 3.2 Hz), 4.75 (d, 1H, *J* = 5.6 Hz), 4.93 (ddd, 1H, *J* = 5.9, 5.9, 1.5 Hz), 6.79 (dd, 1H, *J* = 4.1, 2.0 Hz), 7.13−7.23 (m, 4H), 7.33−7.37 (m, 1H), 7.45 (ddm, 2H, *J* = 7.3, 7.3 Hz), 7.58 (dm, 2H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 25.6, 39.5, 60.6, 61.2, 74.9, 75.4, 86.7, 124.1, 124.4, 125.5, 127.0, 127.8, 128.3, 128.4, 128.8, 138.8, 140.0, 142.3, 142.9, 166.1; EI HRMS *m/e* calcd for $C_{23}H_{23}NO_3$ ($M^{+\bullet}$) 361.1677, found 361.1676. Data for the minor isomer: $[\alpha]^{20}_D$ +129.3 (*c* 0.3, $CHCl_3$); IR (KBr disk, cm^{-1}) 1713, 1250, 1051, 1038; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (t, 3H, *J* = 7.1 Hz), 2.36 (dddd, 1H, *J* = 15.4, 8.3, 4.1, 2.7 Hz), 2.84 (ddd, 1H, *J* = 16.3, 3.2, 3.2 Hz), 3.13−3.24 (m, 2H), 4.12 (dd, 1H, *J* = 4.1, 4.1 Hz), 4.13 (qm, 2H, *J* = 7.3 Hz), 4.73−4.75 (m, 1H), 4.86 (d, 1H, *J* = 5.9 Hz), 5.11 (ddd, 1H, *J* = 5.6, 5.6, 2.7 Hz), 6.70 (dd, 1H, *J* = 2.4, 2.4 Hz), 7.09 (d, 1H, *J* = 7.3 Hz), 7.13−7.17 (m, 1H), 7.23−7.24 (m, 2H), 7.36 (dddd, 1H, *J* = 6.8, 6.8, 1.2, 1.2 Hz), 7.46 (dd, 2H, *J* = 7.3, 7.3 Hz), 7.60 (d, 2H, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 31.0, 39.7, 59.8, 60.7, 65.9, 80.2, 85.5, 125.2, 126.2, 126.6, 127.8, 127.9, 128.5, 129.1, 129.9, 136.4, 139.8, 140.8, 143.7, 166.4; EI HRMS *m/e* calcd for $C_{23}H_{23}NO_3$ ($M^{+\bullet}$) 361.1677, found 361.1685.

Dialcohols Prepared from the Cyclized Products of Entry 2 by $LiAlH_4$ Reduction. (Major/minor = 3:1, determined by both ^{1}H NMR and their isolated yields.) Data for the major isomer: mp 142−143 °C; $[\alpha]^{25}_D$ −82.5 (*c* 0.6, $CHCl_3$); IR (KBr disk, cm^{-1}) 3405, 3264, 1453, 1385, 1090, 1067; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.09−2.15 (m, 1H), 2.27−2.38 (m, 2H), 2.62 (dd, 1H, *J* = 16.6, 6.3 Hz), 2.77−2.84 (m, 1H), 3.15 (dd, 1H, *J* = 16.1, 5.9 Hz), 4.13 (brs, 2H), 4.37−4.44 (m, 3H), 5.70 (brs, 1H), 5.82 (brd, 1H, *J* = 7.6 Hz), 6.90 (dd, 1H, *J* = 7.8, 7.8 Hz), 7.07−7.13 (m, 2H), 7.32−7.40 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.2, 41.1, 41.9, 62.5, 66.3, 66.6, 70.3, 123.8, 125.0, 126.1, 126.3, 127.9, 128.0, 128.6, 129.4, 136.5, 138.9, 140.9, 141.7; EI HRMS *m/e* calcd for $C_{21}H_{23}NO_2$ ($M^{+\bullet}$) 321.1727, found 321.1733. Data for the minor isomer: $[\alpha]^{25}_D$ +240.2 (*c* 0.5, $CHCl_3$); IR (KBr disk, cm^{-1}) 3395, 1454, 1080; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.93 (brd, 1H, *J* = 15.6 Hz), 2.23−2.30 (m, 1H), 2.38−2.49 (m, 2H), 2.84 (dd, 1H, *J* = 16.6, 6.8 Hz), 3.24 (dd, 1H, *J* = 16.6, 8.3 Hz), 3.98 (d, 1H, *J* = 13.4 Hz), 4.04 (d, 1H, *J* = 13.2 Hz), 4.11−4.17 (m, 1H), 4.26 (d, 1H, *J* = 8.1 Hz), 4.75 (brs, 1H), 5.53 (brs, 1H), 7.19−7.31 (m, 4H), 7.35−7.42 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.2, 41.7, 45.4, 64.4, 65.2, 65.9, 68.7, 125.52, 125.54, 125.9, 126.4, 127.8, 128.4, 128.9, 135.3, 139.1, 141.6, 142.5; EI HRMS *m/e* calcd for $C_{21}H_{23}NO_2$ ($M^{+\bullet}$) 321.1727, found 321.1731.

Reaction between 2 and (−)-b (Entry 3 of Table 2). (Major/minor = 5:1, determined by ^{1}H NMR.) Data for the major isomer (−)-**2b**: $[\alpha]^{21}_D$ −32.1 (*c* 1.2, $CHCl_3$); IR (neat, cm^{-1}) 1717, 1464, 1254, 1113, 1034; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.10 (s, 6H), 0.93 (s, 9H), 1.27 (t, 3H, *J* = 7.3 Hz), 2.37 (s, 3H), 2.55−2.71 (m, 2H), 3.13 (d, 1H, *J* = 17.6 Hz), 3.21 (dd, 1H, *J* = 17.8, 5.9 Hz), 3.60−3.63 (m, 1H), 4.19 (q, 2H, *J* = 7.3 Hz), 4.25−4.26 (m, 2H), 4.37 (d, 1H, *J* = 4.4 Hz), 4.85 (ddd, 1H, *J* = 5.7, 5.7, 1.5 Hz), 4.93 (d, 1H, *J* = 5.6 Hz), 5.82−5.92 (m, 2H), 6.73−6.74 (m, 1H), 6.99 (d, 1H, *J* = 8.3 Hz), 7.01 (d, 1H, *J* = 8.3 Hz), 7.13 (dd, 1H, *J* = 7.6, 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.3, 14.2, 18.3, 19.1, 25.5, 25.9, 39.6, 59.8, 60.5, 62.8, 74.1, 75.0, 86.3, 121.7, 124.8, 128.31, 128.35, 130.1, 132.9, 136.6, 137.8, 137.9, 143.2, 166.1; EI HRMS *m/e* calcd for $C_{27}H_{39}NO_4Si$ ($M^{+\bullet}$) 469.2646, found 469.2649. Data for the minor isomer: representative signals in its ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.07 (d, 6H, *J* = 2.0 Hz), 0.90 (s, 9H), 1.28 (t, 3H, *J* = 7.1 Hz), 2.38 (s, 3H), 2.57 (brd, 1H, *J* = 20.0 Hz), 2.85 (dddd, 1H, *J* = 19.3, 7.1, 1.2, 1.2 Hz), 3.08 (d, 1H, *J* = 18.1 Hz), 3.21 (dd, 1H, *J* = 18.1, 6.8 Hz), 4.17−4.26 (m, 5H), 4.41 (dd, 1H, *J* = 6.4, 1.0 Hz), 4.50 (ddd, 1H, *J* = 7.6, 7.6, 1.5 Hz), 4.86 (d, 1H, *J* = 6.1 Hz), 5.52 (ddt, 1H, *J* = 15.1, 10.0, 1.5 Hz), 5.86 (dt, 1H, *J* = 15.4, 5.1 Hz), 6.97−7.01 (m, 3H), 7.13 (dd, 1H, *J* = 7.6, 7.6 Hz).

Dialcohols Prepared from the Cyclized Products of Entry 3 by $LiAlH_4$ Reduction. (Major/minor = 5:1, determined by their isolated yields.) These dialcohols existed as their rotamers at 24 °C in $CDCl_3$, and most of the signals in their ^{1}H and ^{13}C NMR spectra were broadened. Data for the major isomer: $[\alpha]^{21}_D$ −64.3 (*c* 0.8, $CHCl_3$); IR (neat, cm^{-1}) 3387, 1470, 1381, 1256, 1121, 1092, 970; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.05 (d, 6H, *J* = 1.5 Hz), 0.90 (s, 9H), 2.30 (s, 3H), 2.66 (dd, 1H, *J* = 15.6, 8.1 Hz), 3.11 (dd, 1H, *J* = 15.6, 7.3 Hz), 4.04 (s, 2H), 4.29−4.38 (m, 2H), 5.47 (brs, 1H), 5.58 (brs, 1H), 5.73−5.85 (brm, 1H), 6.94−7.00 (m, 2H), 7.14 (dd, 1H, *J* = 7.6, 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.3, 18.3, 20.4, 25.9, 27.1, 29.7, 29.8, 40.9, 60.1, 63.0, 66.2, 68.2, 72.1, 122.1, 124.5, 128.0, 128.6, 132.1, 136.2, 136.5, 138.4; EI HRMS *m/e* calcd for $C_{25}H_{39}NO_3Si$ ($M^{+\bullet}$) 429.2697, found 429.2693. Data for the minor isomer: $[\alpha]^{21}_D$ +115.9 (*c* 0.3, $CHCl_3$); IR (neat, cm^{-1}) 3412, 1464, 1256, 1090; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.09 (d, 6H, *J* = 5.4 Hz), 0.91 (s, 9H), 1.84 (brd, 1H, *J* = 13.4 Hz), 2.17−2.34 (m, 3H), 2.36 (s, 3H), 2.69 (dd, 1H, *J* = 16.1, 8.3 Hz), 3.25 (dd, 1H, *J* = 16.1, 8.1 Hz), 3.99−4.07 (m, 2H), 4.19−4.25 (m, 4H), 4.48 (d, 1H, *J* = 7.8 Hz), 4.87 (brs, 1H), 5.46 (brs, 1H), 5.53 (dd, 1H, *J* = 15.4, 9.0 Hz), 5.85 (dt, 1H, *J* = 15.1, 4.9 Hz), 7.01−7.04 (m, 2H), 7.16 (dd, 1H, *J* = 7.6, 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.1, 18.4, 21.5, 25.9, 26.7, 41.9, 44.7, 63.2, 63.4, 63.8, 66.1, 69.1, 122.7, 124.4, 128.0, 128.6, 132.4, 133.2, 135.6, 136.8, 139.1, 142.5; EI HRMS *m/e* calcd for $C_{25}H_{39}NO_3Si$ ($M^{+\bullet}$) 429.2697, found 429.2697.

Reaction between 3 and (−)-b (Entry 4 of Table 2). (Major/minor = 12:1, determined by ^{1}H NMR.) Data for the major isomer (−)-**3b**: mp 41−43 °C; $[\alpha]^{23}_D$ −13.5 (*c* 0.6, $CHCl_3$), IR (KBr disk, cm^{-1}) 1717, 1671, 1456, 1265, 1242; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.5 (t, 3H, *J* = 7.1 Hz), 1.75 (s, 3H), 2.71 (dddd, 1H, *J* = 19.3, 4.6, 4.6, 2.1 Hz), 2.78 (ddd, 1H, *J* = 19.3, 2.0, 2.0 Hz), 3.14−3.24 (m, 2H), 4.11 (dd, 1H, *J* = 6.1, 3.4 Hz), 4.18 (qm, 2H, *J* = 7.1 Hz), 4.47 (dd, 1H, *J* = 4.9, 1.2 Hz), 4.87 (d, 1H, *J* = 5.4 Hz), 4.98 (ddd, 1H, *J* = 5.1, 5.1, 2.7 Hz), 6.80 (dd, 1H, *J* = 3.7, 2.2 Hz), 6.87 (d, 1H, *J* = 7.3 Hz), 6.98 (d, 1H, *J* = 7.6 Hz), 7.08 (dd, 1H, *J* = 7.6, 7.6 Hz), 7.31−7.45 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 18.3, 25.5, 39.6, 60.6, 62.1, 74.6, 75.1, 86.7, 121.6, 124.0, 127.9, 128.3, 128.37, 128.44, 129.5, 136.8, 138.3, 138.4, 141.7, 143.2, 166.2; EI HRMS *m/e* calcd for $C_{24}H_{25}NO_3$ ($M^{+\bullet}$) 375.1833, found 375.1845. Data for the minor isomer: representative signals in its ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.06 (dd, 1H, *J* = 3.9, 2.9 Hz), 6.62−6.64 (m, 1H).

Reaction between 2 and c (Entry 5 of Table 2). (Major/minor = 7:1, determined by ^{1}H NMR.) Data for the major isomer **2c**: IR (neat, cm^{-1}) 1717, 1462, 1254, 1113, 1032; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.10 (d, 6H, *J* = 1.0 Hz), 0.93 (s, 9H), 1.17 (t, 3H, *J* = 7.6 Hz), 1.27 (t, 3H, *J* = 7.1 Hz), 2.53−2.61 (m, 1H), 2.65−2.89 (m, 3H), 3.14 (brd, 1H, *J* = 17.3 Hz), 3.21 (dd, 1H, *J* = 17.8, 5.9 Hz), 3.58−3.63 (m, 1H), 4.19 (q, 2H, *J* = 7.1 Hz), 4.26 (d, 2H, *J* = 3.4 Hz), 4.38 (d, 1H, *J* = 4.6 Hz), 4.85 (ddd, 1H, *J* = 5.6, 5.6, 1.5 Hz), 4.96 (d, 1H, *J* = 5.6 Hz), 5.79−5.92 (m, 2H), 6.72−6.74 (m, 1H), 7.01−7.04 (m, 2H), 7.19 (dd, 1H, *J* = 7.6, 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.3, 14.2, 15.1, 18.4, 25.3, 25.5, 25.9, 39.6, 59.9, 60.6, 62.9, 73.9, 75.0, 86.3, 121.8, 124.8, 126.8, 128.6, 129.9, 133.1, 137.2, 137.9, 142.9, 143.3, 166.1; EI HRMS *m/e* calcd for $C_{28}H_{41}NO_4Si$ ($M^{+\bullet}$) 483.2802, found 483.2810. Data for the minor isomer: representative signals in its ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.42 (dd, 1H, *J* = 7.8, 1.5 Hz), 4.49 (ddd, 1H, *J* = 7.3, 7.3, 1.5 Hz), 4.92 (d, 1H, *J* = 6.1 Hz), 5.52 (ddt, 1H, *J* = 15.4, 10.0, 1.7 Hz).

Reaction between 3 and c (Entry 6 of Table 2). (Major/minor = 20:1, determined by ^{1}H NMR.) Data for the major isomer **3c**: IR (neat, cm^{-1}) 1717, 1265, 1242, 1030; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.73 (t, 3H, *J* = 7.3 Hz), 1.25 (t, 3H, *J* =

7.1 Hz), 2.05−2.27 (m, 2H), 2.70 (dddd, 1H, J = 19.3, 6.8, 2.2, 2.2 Hz), 2.79 (dm, 1H, J = 19.3 Hz), 3.15−3.24 (m, 2H), 4.11 (dd, 1H, J = 6.3, 3.9 Hz), 4.18 (qm, 2H, J = 7.1 Hz), 4.48 (dd, 1H, J = 4.6, 1.0 Hz), 4.91 (d, 1H, J = 5.4 Hz), 4.96−5.01 (m, 1H), 6.80 (dd, 1H, J = 3.7, 2.0 Hz), 6.91 (d, 1H, J = 7.3 Hz), 7.00 (d, 1H, J = 7.1 Hz), 7.14 (dd, 1H, J = 7.3, 7.3 Hz), 7.27−7.45 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 14.7, 24.8, 25.5, 39.5, 60.6, 62.1, 74.4, 75.0, 86.8, 121.7, 124.0, 126.8, 128.0, 128.5, 128.6, 129.4, 136.9, 138.4, 141.6, 143.0, 143.3, 166.3; EI HRMS *m/e* calcd for $C_{25}H_{27}NO_3$ ($M^{+\bullet}$) 389.1989, found 389.1983. Data for the minor isomer: representative signals in its ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.07 (dd, 1H, J = 3.2, 3.2 Hz), 6.61−6.62 (m, 1H).

Reaction between 2 and (−)-d (Entry 7 of Table 2). (Major/minor = 10:1, determined by ^{1}H NMR.) Data for the major isomer (−)-**2d**: $[\alpha]^{21}_D$ −49.6 (*c* 0.5, $CHCl_3$), IR (neat, cm^{-1}) 1717, 1462, 1254, 1113; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.11 (d, 6H, J = 0.7 Hz), 0.94 (s, 9H), 1.15 (d, 3H, J = 6.8 Hz), 1.22 (d, 3H, J = 6.8 Hz), 1.28 (t, 3H, J = 7.3 Hz), 2.52−2.60 (m, 1H), 2.68 (dd, 1H, J = 19.3, 3.2 Hz), 3.14 (brd, 1H, J = 17.3 Hz), 3.20 (dd, 1H, J = 17.8, 5.6 Hz), 3.54 (qq, 1H, J = 6.8, 6.8 Hz), 3.58−3.63 (m, 1H), 4.20 (q, 2H, J = 7.1 Hz) 4.26 (d, 2H, J = 4.2 Hz), 4.38 (d, 1H, J = 4.6 Hz), 4.84 (ddd, 1H, J = 5.6, 5.6, 2.0 Hz), 4.98 (d, 1H, J = 5.4 Hz), 5.80 (ddt, 1H, J = 15.1, 8.8, 1.5 Hz), 5.89 (dt, 1H, J = 15.4, 4.4 Hz), 6.72−6.73 (m, 1H), 7.02 (d, 1H, J = 7.3 Hz), 7.13 (d, 1H, J = 7.6 Hz), 7.22 (dd, 1H, J = 7.6, 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.3, 14.2, 18.4, 23.4, 23.5, 25.5, 26.0, 28.6, 39.6, 60.0, 60.6, 62.9, 74.0, 75.0, 86.4, 121.7, 123.5, 124.7, 128.7, 129.8, 133.2, 136.6, 137.9, 143.2, 147.6, 166.2; EI HRMS *m/e* calcd for $C_{29}H_{43}NO_4Si$ ($M^{+\bullet}$) 497.2959, found 497.2952. Data for the minor isomer: representative signals in its ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.42 (dd, 1H, J = 7.3, 1.0 Hz), 4.47 (ddd, 1H, J = 7.6, 7.6, 1.5 Hz), 4.95 (d, 1H, J = 6.1 Hz), 5.52 (ddt, 1H, J = 15.1, 10.0, 1.5 Hz).

Reaction between 3 and (−)-d (Entries 8 and 9 of Table 2). (Major/minor = 24:1 at 24 °C and >40:1 at 13 °C, determined by ^{1}H NMR.) Data for the major isomer (−)-**3d**: $[\alpha]^{19}_D$ −58.7 (*c* 0.3, $CHCl_3$); IR (neat, cm^{-1}) 1717, 1267, 1242, 1032; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.59 (d, 3H, J = 7.1 Hz), 1.01 (d, 3H, J = 6.8 Hz), 1.25 (t, 3H, J = 7.1 Hz), 2.62 (qq, 1H, J = 6.8, 6.8 Hz), 2.70 (dddd, 1H, J = 19.3, 6.6, 2.2, 2.2 Hz), 2.79 (dm, 1H, J = 19.3 Hz), 3.15−3.25 (m, 2H), 4.12 (dd, 1H, J = 6.1, 3.7 Hz), 4.18 (qm, 2H, J = 7.3 Hz), 4.48 (d, 1H, J = 4.4 Hz), 4.92 (d, 1H, J = 5.6 Hz), 4.96−5.01 (m, 1H), 6.80 (brs, 1H), 6.99 (d, 1H, J = 8.1 Hz), 7.01 (d, 1H, J = 8.8 Hz), 7.17 (dd, 1H, J = 7.6, 7.6 Hz), 7.33−7.43 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 22.8, 23.5, 25.5, 28.0, 39.6, 60.6, 62.2, 74.4, 75.0, 86.7, 121.6, 123.5, 124.0, 128.0, 128.4, 128.8, 129.4, 136.3, 138.3, 141.5, 143.1, 147.8, 166.3; EI HRMS *m/e* calcd for $C_{26}H_{29}NO_3$ ($M^{+\bullet}$) 403.2146, found 403.2137. Data for the minor isomer: representative signals in its ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.85 (d, 1H, J = 6.0 Hz), 5.12 (dd, 1H, J = 3.2, 3.2 Hz), 6.60 (brs, 1H).

Reaction between 2 and e (Entry 10 of Table 2). (Major/minor = 5:1, determined by ^{1}H NMR.) Data for the major isomer **2e**: IR (neat, cm^{-1}) 1717, 1464, 1256, 1113; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.10 (d, 6H, J = 1.7 Hz), 0.93 (s, 9H), 1.27 (t, 3H, J = 7.1 Hz), 1.46 (s, 9H), 2.44−2.52 (m, 1H), 2.69 (brdd, 1H, J = 19.0, 2.9 Hz), 3.07 (dd, 1H, J = 17.3, 5.6 Hz), 3.23 (d, 1H, J = 17.6 Hz), 3.65−3.70 (m, 1H), 4.19 (q, 2H, J = 7.1 Hz), 4.24 (d, 2H, J = 2.7 Hz), 4.37 (dd, 1H, J = 4.9, 1.0 Hz), 4.79 (dd, 1H, J = 5.4, 5.4 Hz), 5.22 (d, 1H, J = 4.9 Hz), 5.79−5.88 (m, 2H), 6.70−6.71 (m, 1H), 7.08 (d, 1H, J = 7.3 Hz), 7.20 (dd, 1H, J = 7.6, 7.6 Hz), 7.30 (d, 1H, J = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.3, 14.2, 18.4, 25.7, 26.0, 31.1, 36.5, 38.8, 60.58, 60.60, 62.9, 75.0, 77.3, 87.2, 122.9, 124.3, 125.3, 128.4, 130.4, 133.0, 136.6, 138.2, 145.0, 150.0, 166.2; EI HRMS *m/e* calcd for $C_{30}H_{45}NO_4Si$ ($M^{+\bullet}$) 511.3116, found 511.3117. Data for the minor isomer: representative signals in its ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.39 (d, 1H, J = 5.9 Hz), 5.21 (d, 1H, J = 4.4 Hz), 5.54 (ddt, 1H, J = 15.1, 10.0, 1.5 Hz), 6.91 (ddd, 1H, J = 5.6, 1.7, 1.7 Hz).

Reaction between 3 and e (Entry 11 of Table 2). (Major/minor = 17:1, determined by ^{1}H NMR.) Data for the major isomer **3e**: IR (neat, cm^{-1}) 1717, 1263, 1244, 1036; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (s, 9H), 1.25 (t, 3H, J = 7.3 Hz), 2.62 (dddd, 1H, J = 19.0, 6.6, 2.4, 2.4 Hz), 2.80 (dm, 1H, J = 18.8 Hz), 3.09 (dd, 1H, J = 17.3, 5.6 Hz), 3.28 (d, 1H, J = 17.6 Hz), 4.14−4.24 (m, 3H), 4.47 (dd, 1H, J = 4.6, 1.2 Hz), 4.95 (dd, 1H, J = 5.1, 5.1 Hz), 5.19 (d, 1H, J = 4.6 Hz), 6.81−6.82 (m, 1H), 7.07 (d, 1H, J = 7.1 Hz), 7.16 (dd, 1H, J = 7.3, 7.3 Hz), 7.22 (d, 1H, J = 7.8 Hz), 7.31−7.41 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 25.7, 30.1, 36.1, 38.7, 60.6, 62.9, 75.0, 78.1, 87.7, 122.9, 123.1, 125.2, 128.1, 128.4, 128.6, 130.1, 136.3, 138.7, 140.8, 144.9, 150.2, 166.3; EI HRMS *m/e* calcd for $C_{27}H_{31}NO_3$ ($M^{+\bullet}$) 417.2302, found 417.2301. Data for the minor isomer: representative signals in its ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.06−5.09 (m, 1H), 5.12 (d, 1H, J = 5.6 Hz), 6.52−6.54 (m, 1H).

4-Methylindene (6). To a solution of lithium aluminum hydride (2.60 g, 68.4 mmol) in ether (240 mL) was slowly added a solution of 7-methyl-1-indanone **5** (10.0 g) in ether (50 mL) at 0 °C. After the mixture was warmed to room temperature and stirred for an additional 10 min, H_2O was carefully added over 30 min. The resulting mixture was filtered and concentrated in vacuo to give the crude alcohol which was dehydrated without further purification.

To a solution of the crude alcohol obtained above in benzene (200 mL) was added *p*-toluenesulfonic acid monohydrate (1.30 g, 6.84 mmol) at room temperature. After the mixture was gradually heated to 100 °C with vigorous stirring over 30 min, saturated aqueous $NaHCO_3$ solution was added, and the resulting mixture was extracted with ether. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give the crude products. Column chromatography on silica gel (gradually 2% to 3% ethyl acetate in hexane) gave the corresponding indene **6** (8.56 g, 96%) as a colorless oil: IR (neat, cm^{-1}) 1603, 1476, 1458, 1393, 1312, 1202, 1071, 947; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.45 (s, 3H), 3.39−3.40 (m, 2H), 6.54 (ddd, 1H, J = 5.6, 2.1, 2.1 Hz), 6.98 (dm, 1H, J = 5.6 Hz), 7.05−7.11 (m, 2H), 7.30 (dd, 1H, J = 6.8, 0.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.6, 39.3, 121.1, 124.6, 127.2, 130.2, 133.5, 143.5, 143.7.

(+)-7-Methylindene Oxide (7). To a dichloromethane (5 mL) solution of 4-methylindene **6** (1.0 g, 7.68 mmol), (*S*,*S*)-(+)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminomanganese(III) chloride (58.5 mg, 0.0922 mmol), and 4-phenylpyridine *N*-oxide (78.9 mg, 0.461 mmol) was added dropwise a cold sodium hypochlorite (NaOCl) solution (18.7 mL, 9.99 mmol, 1.6 M, 0.2 M in sodium hydroxide) at 0 °C over 30 min. After the mixture was gradually warmed to room temperature and stirred for an additional 5 h, H_2O was added, and the resulting mixture was extracted with $CHCl_3$. The organic layers were combined, washed with H_2O, brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give the crude products. Column chromatography on aluminum oxide (gradually from 1% to 4% ethyl acetate in hexane) gave the corresponding epoxides (750 mg, 67%, 85% ee). The enantiomeric excess of the epoxide was determined by HPLC analysis using a Chiracel OD column (25 cm × 4.6 mm, Daicel) eluted with 2-propanol/hexanes (5:95) at 1 mL/min, while monitoring at 254 nm. The retention times of the epoxide enantiomers are 6.9 (major isomer **7**) and 7.4 (minor isomer) min. The products were further recrystallized from ether and hexane to provide the enantiomerically pure **7** as a colorless needle: mp 53 °C; $[\alpha]^{24}_D$ +2.6 (*c* 0.9, $CHCl_3$); IR (neat, cm^{-1}) 1597, 1478, 1460, 1233, 1028, 988; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.47 (s, 3H), 2.96 (dd, 1H, J = 18.1, 2.9 Hz), 3.19 (d, 1H, J = 18.1 Hz), 4.08−4.09 (m, 1H), 4.33−4.34 (m, 1H), 6.98 (dd, 1H, J = 7.6, 0.5 Hz), 7.04 (d, 1H, J = 7.3 Hz), 7.13 (dd, 1H, J = 7.6, 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.3, 34.7, 57.2, 57.6, 123.3, 127.4, 128.5, 135.1, 139.5, 143.4.

(1*S*,2*R*)-(−)-*cis*-1-Amino-7-methylindan-2-ol ((−)-b). To a solution of fuming sulfuric acid (0.729 mL, 13.7 mmol, 30% SO_3) in acetonitrile (5 mL) was added dropwise a solution of epoxide (+)-**7** (1.0 g, 6.84 mmol) in hexane (10 mL) and acetonitrile (2 mL) at 0 °C. After the biphasic mixture was warmed to room temperature and stirred for an additional 1 h, H_2O was carefully added, and the resulting mixture was stirred for 30 min at this temperature. The lower aqueous phase was separated and diluted with H_2O (5 mL), and acetonitrile was removed by distillation at atmospheric pressure to a head temperature of 100 °C. The resulting mixture was heated to reflux for 2 h, and 50% aqueous NaOH solution was added until the reaction mixture reached pH 12 and the white solid of aminoindanol free base precipitated. After the precipitate was completely dissolved in $CHCl_3$, the resulting mixture was extracted with $CHCl_3$. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give the crude products. The obtained white solid was dissolved in hot toluene (6 mL), and the resulting solution was allowed to cool to room temperature and then further cooled to 0 °C. The resulting white solid was collected by vacuum filtration, washed with cold toluene, and dried under reduced pressure to provide the desired (−)-**b** (585 mg, 52%) as a white solid: mp 101−102 °C; $[\alpha]^{22}_D$ −110.8 (*c* 0.6, $CHCl_3$); IR (KBr disk, cm^{-1}) 3314−2571 (br), 1593, 1474, 1346, 1098; ^1H NMR (400 MHz, $CDCl_3$) δ 2.39 (s, 3H), 2.81 (dd, 1H, J = 15.9, 7.6 Hz), 3.13 (dd, 1H, J = 15.9, 7.3 Hz), 4.22 (d, 1H, J = 6.6 Hz), 4.35 (ddd, 1H, J = 7.1, 7.1, 7.1 Hz), 7.00−7.03 (m, 2H), 7.14 (dd, 1H, J = 7.6, 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.4, 39.3, 55.6, 71.2, 122.7, 128.26, 128.32, 134.5, 140.7, 142.6; EI HRMS *m*/*e* calcd for $C_{10}H_{13}NO$ ($M^{+\bullet}$) 163.0996, found 163.1001.

5-Methylhex-3-en-2-one (8). To a solution of acetone (270 mL) and 2.5 M aqueous NaOH solution (100 mL) was added a solution of isobutyraldehyde (138 mL, 1.52 mol) in acetone (270 mL) at an inner temperature of 8.5 °C over 1.5 h. After the mixture was stirred at room temperature for an additional 1 h, 6 N aqueous HCl solution (40 mL) was added, and the pH of the solution was adjusted toward 7. After the bulk of acetone was removed in vacuo to 300 mL, the resulting mixture was extracted with ether. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give the crude products. Distillation under reduced pressure (75−89 °C/7.0 mmHg) gave the corresponding β-hydroxy ketone (316 g, 69%) which was used without further purification.

To a benzene (350 mL) solution of the β-hydroxyketone obtained above (147 g, 1.13 mol) were added *p*-toluenesulfonic acid monohydrate (1.07 g, 5.64 mmol) and Na_2SO_4 (75.0 g) at room temperature. After the mixture was stirred for 5 h at 90 °C, saturated aqueous $NaHCO_3$ solution was added, and the resulting mixture was extracted with ether. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give the crude products. Distillation under reduced pressure (54−68 °C/20 mmHg) gave the corresponding α,β-unsaturated ketone **8** (89.3 g, 71%) as a colorless oil: IR (neat, cm^{-1}) 1676, 1626, 1362, 1260; ^1H NMR (400 MHz, $CDCl_3$) δ 1.08 (d, 6H, J = 6.8 Hz), 2.25 (s, 3H), 2.48 (qdm, 1H, J = 6.8, 6.8 Hz), 6.03 (dd, 1H, J = 15.9, 1.2 Hz), 6.77 (dd, 1H, J = 16.1, 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 26.9, 31.1, 128.5, 154.5, 199.1.

5-Methyl-2-trimethylsiloxyhexa-1,3-diene (9). To a solution of α,β-unsaturated ketone **8** (60.0 g, 535 mmol) and chlorotrimethylsilane (74.7 mL, 588 mmol) in toluene (520 mL) and THF (260 mL) was slowly added lithium bis(trimethylsilyl)amide (116 g, 695 mmol) at −78 °C, and the resulting solution was stirred for 30 min at this temperature. After the mixture was gradually warmed to room temperature and stirred for an additional 40 min, H_2O was added, and the resulting mixture was extracted with ether. The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo to give the crude products which were purified by distillation under reduced pressure (65−79 °C/10.0 mmHg) to afford the corresponding trimethylsilyl enol ether (78.4 g, 79%) as a colorless oil: IR (neat, cm^{-1}) 1655, 1593, 1464, 1334, 1308, 1253; ^1H NMR (400 MHz, $CDCl_3$) δ 0.23 (s, 9H), 1.02 (d, 6H, J = 6.8 Hz), 2.35 (qd, 1H, J = 6.6, 6.6 Hz), 4.23−4.24 (m, 2H), 5.66 (dd, 1H, J = 15.4, 1.0 Hz), 5.92 (dd, 1H, J = 15.4, 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 0.0, 22.2, 30.5, 94.2, 124.7, 138.6, 155.1.

5-Hydroxy-7-isopropyl-1-indanone (11). The benzene solution (58 mL) of the silyl enol ether **9** (85.2 g, 376 mmol), 2-cyclopenenone (30.9 g, 376 mmol), and 2,5-di-*tert*-butylhydroquinone (3.95 g) in a sealed tube was heated at 200 °C for 56 h. The resulting mixture was concentrated in vacuo to give the crude products which were hydrolyzed without any purification.

To an acetone (1.5 L) solution of the crude Diels−Alder adducts obtained above was added *p*-toluenesulfonic acid monohydrate (7.16 g, 37.6 mmol) at room temperature. After the mixture was stirred at room temperature for 30 min, the bulk of the methanol was removed in vacuo, saturated aqueous $NaHCO_3$ solution was added, and the resulting mixture was extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to precipitate one diastereomer of diketone **10** (14.2 g) as a white crystal. Then, column chromatography of the residues on silica gel (gradually 9% to 33% ethyl acetate in hexane) provided the other diastereomer as a white solid (29.6 g, total 60% for two steps).

To a solution of a mixture of the diketone diastereomers **10** obtained above (5.64 g, 29.0 mmol) in *p*-cymene (140 mL) was added 30% palladium carbon (1.20 g) at room temperature, and the mixture was stirred for 45 h at 200 °C. The precipitate was dissolved in acetone, and palladium carbon was filtered off. Concentration of the residues in vacuo to precipitate the phenol **11** (4.12 g, 75%) as a brown solid: IR (KBr disk, cm^{-1}) 2965, 1651, 1607, 1566, 1312, 1273; ^1H NMR (400 MHz, acetone-d_6) δ 1.16 (d, 6H, J = 6.8 Hz), 2.49−2.53 (m, 2H), 2.95−2.98 (m, 2H), 4.11 (qm, 1H, J = 6.8 Hz), 6.72 (brs, 1H), 6.76 (brs, 1H); ^{13}C NMR (100 MHz, acetone-d_6) δ 23.1, 25.7, 27.7, 37.5, 110.6, 112.6, 126.5, 152.6, 160.4, 164.0, 205.1.

5-*p*-Toluenesulfonoxy-7-isopropyl-1-indanone. To a solution of the phenol **11** (7.78 g, 40.9 mmol) in THF (400 mL) was added sodium hydride (1.88 g, 49.1 mmol, 62.5%) at room temperature. The mixture was stirred for 20 min, and *p*-toluenesulfonyl chloride (8.57 g, 45.0 mmol) was added at this temperature. After the resulting mixture was stirred for an additional 2.5 h, H_2O was added, and the resulting mixture was extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give the crude products. Column chromatography on silica gel (5% to 25% ethyl acetate in hexane) gave the corresponding tosylate (13.7 g, 97%) as a yellow solid: IR (KBr disk, cm^{-1}) 1701, 1593, 1377, 1192, 1179; ^1H NMR (400 MHz, $CDCl_3$) δ1.05 (d, 6H, J = 6.8 Hz), 2.46 (s, 3H), 2.66−2.69 (m, 2H), 3.04−3.07 (m, 2H), 4.08 (qq, 1H, J = 6.8, 6.8 Hz), 6.63−6.64 (m, 1H), 7.06−7.07 (m, 1H), 7.34 (dd, 2H, J = 8.5, 0.5 Hz), 7.73 (d, 2H, J = 8.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 22.6, 25.4, 26.9, 37.2, 117.8, 118.3, 128.6, 129.8, 131.7, 132.2, 145.7, 152.3, 154.0, 158.1, 206.1.

7-Isopropylindanol (12). To a methanol solution (15 mL) of the tosylate obtained above (500 mg, 1.45 mmol) and nickel(II) chloride hexahydrate (345 mg, 1.45 mmol) was slowly added sodium borohydride (1.65 g, 43.6 mmol) at 0 °C over 2 h. After the mixture was stirred at room temperature for an additional 1 h, the bulk of methanol was removed in vacuo, 2 N HCl solution was added, and the resulting mixture was extracted with ether. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give the crude products. Column chromatography on silica gel (5% to 9% ethyl acetate in hexane) provided the corresponding alcohol **12** (221 mg, 87%) as a white solid: IR (KBr disk, cm^{-1}) 3331, 3243, 1047, 783; ^1H NMR (400

MHz, $CDCl_3$) δ 1.25 (d, 3H, J = 6.8 Hz), 1.30 (d, 3H, J = 6.8 Hz), 1.64 (brs, 1H), 2.06 (dddd, 1H, J = 13.7, 7.8, 2.7, 2.0 Hz), 2.28−2.37 (m, 1H), 2.81 (ddd, 1H, J = 16.1, 9.0, 2.7 Hz), 3.15 (ddd, 1H, J = 16.3, 8.3, 8.3 Hz), 3.33 (qq, 1H, J = 6.8, 6.8 Hz), 5.36 (brd, 1H, J = 6.3 Hz), 7.09 (d, 1H, J = 7.8 Hz), 7.15 (d, 1H, J = 7.8 Hz), 7.26 (dd, 1H, J = 7.3, 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.9, 24.1, 29.8, 30.1, 35.2, 74.9, 122.3, 123.2, 129.2, 141.7, 144.0, 146.3.

4-Isopropylindene (13). To a solution of the alcohol **12** (1.98 g, 11.2 mmol) prepared above in benzene (110 mL) was added *p*-toluenesulfonic acid monohydrate (213 mg, 1.12 mmol) at room temperature. After the mixture was gradually heated to 100 °C with vigorous stirring over 40 min, saturated aqueous $NaHCO_3$ solution was added, and the resulting mixture was extracted with ether. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give the crude products. Column chromatography on silica gel (2% ethyl acetate in hexane) gave the corresponding indene **13** (1.87 g, 100%) as a colorless oil: IR (neat, cm^{-1}) 1476, 1431, 1391, 953; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (d, 6H, J = 6.8 Hz), 3.27 (qq, 1H, J = 6.8, 6.8 Hz), 3.40 (brs, 2H), 6.55 (ddd, 1H, J = 5.6, 2.0, 2.0 Hz), 7.06 (dm, 1H, J = 5.6 Hz), 7.16−7.17 (m, 2H), 7.31−7.33 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.4, 30.8, 39.3, 121.3, 122.5, 124.9, 130.0, 133.5, 141.1, 142.5, 143.7.

7-Isopropylindene Oxide (14). To a dichloromethane (6.0 mL) solution of 4-isopropylindene **13** (100 mg, 0.63 mmol), (*S*,*S*)-(+)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2cyclohexanediaminomanganese(III) chloride (20.1 mg, 0.032 mmol), and 4-methylmorpholine *N*-oxide (370.2 mg, 3.16 mmol) was added 3-chloroperoxybenzoic acid (218 mg 1.26 mmpl), at −78 °C. After the mixture was stirred for 1 h at −78 °C, dimethyl sulfide (0.3 mL) in CH_2Cl_2 (1.5 mL) and NaOH solution (6 mL) were added, and the resulting mixture was extracted with $CHCl_3$. The organic layers were combined, washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give the crude products. Column chromatography on aluminum oxide (gradually from 2% to 3% ethyl acetate in hexane) gave the corresponding epoxide **14** (95 mg, 86%, 56% ee) as a colorless oil which was used for the next reaction without further purification. The enantiomeric excess of the epoxide was determined by HPLC analysis using a Chiracel OD column (25 cm × 4.6 mm, Daicel) eluted with 2-propanol/hexanes (3:97) at 1 mL/min, while monitoring at 254 nm. The retention times of the epoxide enantiomers are 6.3 (major isomer **14**) and 6.7 (minor isomer) min: IR (neat, cm^{-1}) 1753, 1460, 1447, 1084, 1036, 1009; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (d, 3H, J = 7.1 Hz), 1.33 (d, 3H, J = 7.1 Hz), 2.97 (dm, 1H, J = 18.1 Hz), 3.20 (d, 1H, J = 18.1 Hz), 3.29 (qq, 1H, J = 7.1, 7.1 Hz), 4.09−4.11 (m, 1H), 4.40−4.41 (m, 1H), 7.05 (d, 1H, J = 7.3 Hz), 7.09 (d, 1H, J = 7.6 Hz), 7.20 (dd, 1H, J = 7.6, 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.5, 23.9, 30.7, 34.7, 57.4, 57.5, 122.8, 123.4, 128.8, 138.4, 143.5, 146.2.

(1*S*,2*R*)-(−)-*cis*-1-Amino-7-isopropylindan-2-ol ((−)-d). To a solution of fuming sulfuric acid (0.601 mL, 11.3 mmol, 30% SO_3) in acetonitrile (11 mL) was added dropwise a solution of the epoxide **14** (983 mg, 5.64 mmol) in hexane (11 mL) at 0 °C. After the biphasic mixture was warmed to room temperature and stirred for an additional 1 h, H_2O (11 mL) was carefully added, and the resulting mixture was stirred for 30 min at this temperature. The lower aqueous phase was separated and diluted with H_2O (11 mL), and acetonitrile was removed by distillation at atmospheric pressure to a head temperature of 100 °C. The resulting mixture was heated to reflux for 2 h, and 50% aqueous NaOH solution was added until the reaction mixture reached pH 12 and the white solid of aminoindanol free base precipitated. After the precipitate was completely dissolved in $CHCl_3$, the resulting mixture was extracted with $CHCl_3$. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give the crude products. Column chromatography on silica gel (gradually from 5% to 9% methanol in chloroform) gave the corresponding **d** (796 mg, 74%) as a white solid. The mixture of stereoisomers of **d** was dissolved in hot toluene (1.5 mL), the resulting solution was allowed to cool to room temperature and then further cooled to 0 °C. The resulting white solid was collected by vacuum filtration, washed with cold toluene, and dried under reduced pressure to provide the optically pure (−)-**d** as a colorless crystal: mp 90−91 °C; $[\alpha]^{20}_D$ −114.2 (*c* 0.5, $CHCl_3$); IR (KBr disk, cm^{-1}) 3194 (br), 1586, 1480, 1451, 1383, 1333, 1094; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (d, 3H, J = 6.8 Hz), 1.31 (d, 3H, J = 6.8 Hz), 2.31 (brs, 3H), 2.80 (dd, 1H, J = 15.9, 8.3 Hz), 3.14 (dd, 1H, J = 15.6, 7.3 Hz), 3.13−3.21 (m, 1H), 4.29 (brd, 1H, J = 6.1 Hz), 4.34−4.38 (m, 1H), 7.03 (d, 1H, J = 7.3 Hz), 7.14 (d, 1H, J = 7.8 Hz), 7.23 (dd, 1H, J = 7.6, 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.9, 24.2, 30.0, 39.3, 55.0, 71.4, 122.7, 123.6, 128.8, 140.6, 141.3, 145.8; CI HRMS *m*/*z* calcd for $C_{12}H_{18}NO$ $(M + H)^+$ 192.1387, found 192.1383.

(±)-*cis*-1-Amino-7-ethylindan-2-ol (c): mp 118−119 °C; IR (KBr disk, cm^{-1}) 3316−2753 (br), 1591, 1478, 1451, 1345, 1100; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (t, 3H, J = 7.8 Hz), 2.12 (brs, 3H), 2.74 (qm, 2H, J = 7.6 Hz), 2.80 (dd, 1H, J = 15.6, 7.8 Hz), 3.14 (dd, 1H, J = 15.6, 7.3 Hz), 4.26 (brd, 1H, J = 6.3 Hz), 4.36 (brddd, 1H, J = 7.1, 7.1, 7.1 Hz), 7.04 (d, 1H, J = 7.6 Hz), 7.07 (d, 1H, J = 7.6 Hz), 7.20 (dd, 1H, J = 7.6, 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.1, 25.3, 39.3, 55.2, 71.4, 122.8, 126.4, 128.6, 140.7, 140.8, 142.1; CI HRMS *m*/*e* calcd for $C_{11}H_{16}NO$ $(M + H)^+$ 178.1231, found 178.1234.

(±)-*cis*-1-Amino-7-*tert*-butyl-indan-2-ol (e): mp 61−62 °C; IR (neat, cm^{-1}) 3341 (br), 1580, 1480, 1364, 1206, 1092; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (s, 9H), 2.28 (brs, 3H), 2.79 (dd, 1H, J = 15.1, 9.3 Hz), 3.02 (dd, 1H, J = 15.4, 7.3 Hz), 4.31 (brddd, 1H, J = 7.1, 7.1, 7.1 Hz), 4.42 (brd, 1H, J = 5.9 Hz), 7.07 (d, 1H, J = 7.1 Hz), 7.18 (dd, 1H, J = 7.8, 7.3 Hz), 7.24 (d, 1H, J = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.7, 32.2, 37.8, 57.0, 72.5, 123.5, 124.8, 128.3, 142.1, 147.4; EI HRMS *m*/*e* calcd for $C_{13}H_{19}NO$ ($M^{+\bullet}$) 205.1466, found 205.1460.

(1*S*,2*R*)-(−)-*cis*-1-[(2*R*)-4-Hydroxymethyl-2-(2,6,6-trimethylcyclohex-1-enyl)-1,2,5,6-tetrahydropyridin-1-yl]indan-2-ol ((−)-15). To a solution of the ester (−)-**1a** prepared in Scheme 2 (119 mg, 0.302 mmol) in ether (3.0 mL) was added lithium aluminum hydride (11.5 mg, 0.302 mmol) at 0 °C. After the mixture was warmed to room temperature and stirred for an additional 5 min, H_2O was carefully added over 30 min. The resulting mixture was filtered and concentrated in vacuo to give the crude products which were purified by column chromatography on silica gel (40% ethyl acetate in hexane) to afford the corresponding (−)-dialcohol **15** (112 mg, 100%) as a white foam: mp 70−71 °C; $[\alpha]^{24}_D$ −66.9 (*c* 1.1, $CHCl_3$); IR (KBr disk, cm^{-1}) 3387, 1460, 1047; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12 (s, 3H), 1.20 (s, 3H), 1.41−1.55 (m, 4H), 1.90 (s, 3H), 1.90−1.92 (m, 3H), 2.21−2.29 (m, 1H), 2.83 (dd, 1H, J = 16.3, 2.4 Hz), 3.03−3.10 (m, 2H), 3.17 (dd, 1H, J = 11.5, 4.6 Hz), 4.01 (d, 1H, J = 12.9 Hz), 4.05 (d, 1H, J = 12.9 Hz), 4.41 (d, 1H, J = 5.1 Hz), 4.48 (brs, 1H), 4.86 (brs, 1H), 5.54 (s, 1H), 7.19−7.26 (m, 3H), 7.32 (d, 1H, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.5, 21.1, 27.4, 28.2, 29.3, 34.7, 35.5, 40.9, 41.2, 45.1, 58.0, 65.4, 66.9, 77.6, 125.1, 125.5, 126.4, 126.8, 127.1, 133.8, 134.3, 135.3, 139.6, 142.9; EI HRMS *m*/*e* calcd for $C_{24}H_{33}NO_2$ ($M^{+\bullet}$) 367.2510, found 367.2514.

(2*R*)-(−)-4-Hydroxymethyl-2-(2,6,6-trimethylcyclohex-1-enyl)-1,2,5,6-tetrahydropyridine ((−)-16). To a solution of the (−)-alcohol **15** prepared from (−)-**1a** as mentioned above (100 mg, 0.271 mmol) in ether (3.0 mL) was added manganese dioxide (1.0 g) at room temperature, and the resulting mixture was stirred for 3 min. The reaction mixture was filtered and concentrated in vacuo to give the corresponding unstable *N*-oxide (major isomer/minor isomer = 3:1): representative signals in their ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.40 (brs, major) and 4.34 (brs, minor), 5.55 (brs, major) and 5.53 (brs, minor), 5.58 (brs, major) and 5.74 (brs, minor), 5.12 (dd, major, J = 8.4, 2.4 Hz) and 5.58−5.60 (m, minor).

The unstable *N*-oxide thus obtained were immediately (otherwise decomposed) subjected to column chromatography on silica gel (11% methanol in chloroform) to afford (−)-**16** (44 mg, 69%) as a colorless oil: $[\alpha]^{24}_D$ −46.5 (*c* 0.4, $CHCl_3$); IR (neat, cm^{-1}) 3329, 1454, 1427, 1024; ^1H NMR (400 MHz, $CDCl_3$) δ 1.00 (s, 3H), 1.07 (s, 3H), 1.38−1.48 (m, 2H), 1.52−1.58 (m, 2H), 1.69 (s, 3H), 1.84−1.96 (m, 2H), 2.00 (brd, 1H, *J* = 16.6 Hz), 2.18−2.27 (m, 1H), 2.44 (brs, 2H), 2.91 (ddd, 1H, *J* = 11.7, 11.7, 4.4 Hz), 3.30 (ddd, 1H, *J* = 12.2, 5.6, 1.0 Hz), 3.96−4.03 (m, 3H), 5.58 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.3, 20.6, 25.4, 27.9, 28.2, 34.0, 35.3, 39.7, 44.1, 54.0, 66.6, 127.2, 132.2, 134.4, 138.3; EI HRMS *m/e* calcd for $C_{15}H_{25}NO$ ($M^{+\bullet}$) 235.1935, found 235.1933.

Characterization of the *N*-Oxide Derivative and the Mechanistic Insight Concerning the Removal of the Indan Auxiliary by Manganese Dioxide Oxidation. In the oxidative removal of the indan auxiliary by the reaction with manganese dioxide (Scheme 6 and Table 3), the *N*-oxide intermediate was characterized by the following experiment and spectroscopic data of rather stable *N*-oxide **26**: To a solution of the (−)-ester alcohol **25** (20 mg, 0.0506 mmol) derived from (−)-**1a** by sodium borohydride reduction (see below) in dichloromethane (2.0 mL) was added manganese dioxide (200 mg) at room temperature, and the mixture was stirred for 5 min. The reaction mixture was filtered and concentrated in vacuo to give the corresponding *N*-oxide **26** as a yellow oil (major isomer/minor isomer = 3:1). IR (KBr disk, cm^{-1}) 3451, 1717, 972; representative signals in their ^1H NMR (400 MHz, $CDCl_3$) δ 4.52 (brs, major) and 4.45 (brs, minor), 6.79 (brs, major) and 6.77 (brs, minor), 5.59 (brs, major) and 5.74 (brs, minor), 5.12 (dd, major, *J* = 8.4, 3.2 Hz) and 5.59−5.61 (m, minor); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.2, 19.3, 21.45, 21.50, 25.1, 26.3, 27.6, 29.2, 29.3, 34.4, 34.5, 34.6, 35.8, 35.9, 36.5, 40.4, 40.5, 42.3, 42.4, 51.6, 56.56, 56.65, 82.0, 86.8, 91.9, 92.0, 125.5, 125.9, 126.56, 126.63, 126.8, 127.4, 127.6, 128.8, 129.0, 132.7, 134.1, 134.16, 134.23, 135.3, 135.4, 135.8, 142.36, 142.41, 144.3, 167.57, 167.60; EI HRMS *m/e* calcd for $C_{25}H_{33}NO_4$ ($M^{+\bullet}$) 411.2408, found 411.2410.

Furthermore, the time-dependent EIMS analyses of thus obtained *N*-oxide **26** detected the ion peaks corresponding to the imminium ion [$(M - H)^{+\bullet}$ = 393] and its hydroxylated product ($M^{+\bullet}$ = 411) under the MS-measurement condition.

(−)-Ester 25. To a solution of the ester (−)-**1a** (200 mg, 0.508 mmol) in methanol (5.0 mL) was added sodium borohydride (28.8 mg, 0.762 mmol) at 0 °C. After the mixture was stirred for an additional 15 min at this temperature, the resulting mixture was concentrated in vacuo to give the crude products which were purified by column chromatography on silica gel (gradually from 4% to 12% ethyl acetate in hexane) to afford (−)-ester alcohol **25** (159 mg, 79%) as a white solid: $[\alpha]^{24}_D$ −40.0 (*c* 1.0, $CHCl_3$); IR (KBr disk, cm^{-1}) 3486, 1701, 1260; 1H NMR (400 MHz, CDCl3) δ 1.17 (s, 3H), 1.23 (s, 3H), 1.48−1.63 (m, 4H), 1.88 (s, 3H), 1.94−1.95 (m, 2H), 2.31−2.37 (m, 2H), 2.86 (dd, 1H, *J* = 16.3, 2.9 Hz), 3.01−3.06 (m, 1H), 3.10 (dd, 1H, *J* = 16.6, 6.1 Hz), 3.13−3.18 (m, 1H), 3.75 (s, 3H), 4.42 (d, 1H, *J* = 5.1 Hz), 4.65 (brs, 1H), 4.86 (brs, 1H), 6.79 (s, 1H), 7.24−7.30 (m, 4H); 13C NMR (100 MHz, CDCl3) δ 19.4, 21.1, 26.1, 28.0, 29.2, 34.7, 35.6, 40.7, 41.4, 44.6, 51.6, 58.4, 65.0, 77.4, 125.1, 125.5, 126.7, 127.0, 127.3, 133.7, 135.4, 139.6, 142.0, 142.5, 167.8; EI HRMS *m/e* calcd for $C_{25}H_{33}NO_3$ ($M^{+\bullet}$) 395.2459, found 395.2462.

(2*R*)-(−)-4-Hydroxymethyl-2-phenyl-1,2,5,6-tetrahydropyridine ((−)-17) (Experimental Procedure for Entry 1 of Table 3). To a solution of the dialcohol prepared from (−)-**3a** (see entry 2 of Table 2) (80 mg, 0.249 mmol) in ether (4.0 mL) and THF (1.0 mL) was added manganese dioxide (1.0 g) at room temperature, and the mixture was stirred for 5 min. The reaction mixture was filtered and concentrated in vacuo to give the crude products which were purified by column chromatography on silica gel (gradually from 0% to 33% methanol in chloroform) to afford (−)-**17** (26 mg, 55%) as a colorless oil: $[\alpha]^{19}_D$ −67.4 (*c* 0.8, $CHCl_3$); IR (neat, cm^{-1}) 3424, 1051, 1032; ^1H NMR (400 MHz, $CDCl_3$) δ 2.10 (brd, 1H, *J* = 17.3 Hz), 2.20−2.28 (m, 1H), 2.68 (brs, 2H), 2.95 (ddd, 1H, *J* = 13.2, 8.3, 4.9 Hz), 3.14 (ddd, 1H, *J* = 12.2, 5.1, 5.1 Hz), 4.07 (brs, 2H), 4.50 (brs, 1H), 5.72 (brs, 1H), 7.24−7.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.6, 41.3, 57.9, 66.4, 123.6, 127.5, 127.8, 128.5, 137.6, 142.7; EI HRMS *m/e* calcd for $C_{12}H_{15}NO$ ($M^{+\bullet}$) 189.1153, found 189.1160.

(1*S*,2*R*)-(−)-*cis*-1-[(2*R*)-4-Hydroxymethyl-2-phenyl-1,2,5,6-tetrahydropyridin-1-yl]-7-methylindan-2-ol (Experimental Procedure of Entry 2 of Table 3). To a solution of the ester (−)-**3b** prepared in entry 4 of Table 2 (370 mg, 0.985 mmol) in ether (4.0 mL) and THF (2.0 mL) was added lithium aluminum hydride (56.1 mg, 1.48 mmol) at 0 °C. After the mixture was warmed to room temperature and stirred for 5 min, H_2O was carefully added over 30 min. The resulting mixture was filtered and concentrated in vacuo to give the crude products which were purified by column chromatography on silica gel (from 33% to 50% ethyl acetate in hexane) to produce the corresponding (−)-dialcohol (300 mg, 91%) as a white foam: mp 83−85 °C; $[\alpha]^{19}_D$ −1.8 (*c* 0.6, $CHCl_3$); IR (KBr disk, cm^{-1}) 3410, 1468, 1456, 1399, 1159, 1030; EI HRMS *m/e* calcd for $C_{22}H_{25}NO_2$ ($M^{+\bullet}$) 335.1884, found 335.1892. The obtained dialcohol existed as its rotamers at 24 °C in $CDCl_3$, and all the signals in its ^1H and ^{13}C NMR spectra were broadened.

(2*R*)-(−)-4-Hydroxymethyl-2-phenyl-1,2,5,6-tetrahydropyridine ((−)-17). To a solution of the (−)-dialcohol prepared from (−)-**3b** as mentioned above (80 mg, 0.238 mmol) in ether (2.0 mL), THF (0.5 mL), and acetone (0.1 mL) was added manganese dioxide (2.0 g) at room temperature, and the mixture was stirred for 1 min. The reaction mixture was filtered and concentrated in vacuo to give the crude products which were purified by preparative thin-layer chromatography on silica gel (13% methanol in chloroform) to afford (−)-**17** (25 mg, 55%) as a colorless oil, whose spectral data were good agreement with those obtained from (−)-**3a**.

(1*S*,2*R*)-(−)-*cis*-1-[(2*R*)-4-Hydroxymethyl-2-phenyl-1,2,5,6-tetrahydropyridin-1-yl]-7-isopropylindan-2-ol (Experimental Procedure for Entry 3 of Table 3). To a solution of the crude ester (−)-**3d** prepared in entry 9 of Table 2 (theoretical; 3.37 mmol) in ether (15 mL) and THF (15 mL) was added lithium aluminum hydride (256 mg, 6.75 mmol) at 0 °C. After the mixture was warmed to room temperature and stirred for further 10 min, H_2O was carefully added over 30 min. The resulting mixture was filtered and concentrated in vacuo to give the crude products which were purified by column chromatography on silica gel (from 33% to 50% ethyl acetate in hexane) to afford the corresponding (−)-dialcohol (1.12 g, 91% for 2 steps) as a white foam: mp 40−42 °C; $[\alpha]^{20}_D$ −162.9 (*c* 0.5, $CHCl_3$); IR (KBr disk, cm^{-1}) 3393, 1454, 1383, 1080; EI HRMS *m/e* calcd for $C_{24}H_{29}NO_2$ ($M^{+\bullet}$) 363.2196, found 363.2195. The dialcohol thus obtained existed in a mixture of rotamers at 24 °C in $CDCl_3$, and all the signals of its ^1H and ^{13}C NMR spectra were broadened.

(2*R*)-(−)-4-Hydroxymethyl-2-phenyl-1,2,5,6-tetrahydropyridine ((−)-17). To a solution of the (−)-dialcohol prepared from (−)-**3d** as mentioned above (80 mg, 0.220 mmol) in ether (3.0 mL) was added manganese dioxide (2.0 g) at room temperature, and the mixture was stirred for 1 min. The reaction mixture was filtered and concentrated in vacuo to give the crude products which were purified by column chromatography on silica gel (gradually from 0% to 33% methanol in chloroform) to afford (−)-**17** (24 mg, 58%) as a colorless oil, whose spectral data were good agreement with those obtained from (−)-**3a** and (−)-**3b**.

3-(2,2-Dibromovinyl)-*N*-*p*-toluenesulfonylindole (41). To a solution of triphenylphosphine (52.6 g, 200 mmol) in CH_2Cl_2 (200 mL) was added carbon tetrabromide (33.2 g, 100 mmol) at −20 °C. After the mixture was stirred for 10 min at −20 °C, a solution of *N*-*p*-toluenesulfonylindole-3-carboxaldehyde **40** (10.0 g, 33.4 mmol) in CH_2Cl_2 (60 mL) was slowly added at −78 °C, and stirring was continued for an additional

5 min. After the reaction mixture was gradually warmed to room temperature, a bulk of hexane (200 mL) was added. The resulting precipitate was filtered, and the filtrate was concentrated in vacuo to give the crude solids, which were then completely dissolved in chloroform. The resulting black solution was again concentrated in vacuo to give the crude products as an oil which were rapidly purified by column chromatography on silica gel (gradually 25% to 50% ethyl acetate in hexane) to provide the corresponding dibromide **41** (14.1 g, 93%) as a white solid: mp 129−130 °C; IR (KBr disk, cm^{-1}) 1447, 1372, 1173, 1138, 1123, 1094, 972; ^1H NMR (400 MHz, $CDCl_3$) δ 2.34 (s, 3H), 7.22−7.24 (m, 2H), 7.27 (dd, 1H, J = 8.1, 8.1 Hz), 7.35 (dd, 1H, J = 7.3, 7.3 Hz), 7.51 (d, 1H, J = 8.1 Hz), 7.53 (s, 1H), 7.77−7.80 (m, 2H), 7.98 (d, 1H, J = 8.3 Hz), 8.29 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 90.3, 113.6, 117.3, 118.8, 123.6, 124.9, 125.4, 126.8, 126.9, 129.4, 130.0, 134.0, 134.8, 145.3; EI HRMS *m/e* calcd for $C_{17}H_{13}Br_2NO_2S$ ($M^{+\bullet}$) 452.9033, found 452.9040.

3-Ethynyl-*N*-*p*-toluenesulfonylindole (43). To a solution of the dibromide prepared above (4.5 g, 9.89 mmol) in THF (80 mL) was added lithium bis(trimethylsilyl)amide (1.0 M in THF, 21.8 mL, 21.8 mmol) at −78 °C. After the reaction mixture was stirred for 20 min at this temperature, saturated aqueous NH_4Cl solution was rapidly added, and the resulting mixture was extracted with ethyl acetate. The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo to give the corresponding crude ethynyl bromide **42** as a white solid which was subjected to the next reaction without any purification.

To a solution of the crude ethynyl bromide **42** in THF (80 mL) was added *sec*-butyllithium (1.0 M in cyclohexane, 14.8 mL, 14.8 mmol) at −78 °C. After the reaction mixture was stirred for 5 min at this temperature, saturated aqueous NH_4Cl solution was rapidly added, and the resulting mixture was extracted with ethyl acetate. The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo to give the crude products which were purified by recrystallization from hexane and ethyl acetate to afford the corresponding acetylene derivative **43** (1.79 g, 61% in two steps) as a white solid: mp 161−162 °C; IR (KBr disk, cm^{-1}) 3266, 3131, 1595, 1449, 1375, 1175, 1138, 1094, 966; ^1H NMR (400 MHz, $CDCl_3$) δ 2.34 (s, 3H), 3.26 (s, 1H), 7.22−7.34 (m, 3H), 7.36 (dd, 1H, J = 7.3, 7.3 Hz), 7.64 (d, 1H, J = 7.8 Hz), 7.76−7.79 (m, 3H), 7.97 (d, 1H, J = 8.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 74.9, 81.5, 104.0, 113.5, 120.5, 123.8, 125.5, 126.9, 129.9, 130.0, 130.7, 134.0, 134.8, 145.4; EI HRMS *m/e* calcd for $C_{17}H_{13}NO_2S$ ($M^{+\bullet}$) 295.0666, found 295.0654.

(*E*)-(*N*-*p*-Toluenesulfonylindol-3-yl)-tributyltin (44). To a solution of 3-ethynyl-*N*-*p*-toluenesulfonylindole **43** (1.45 g, 4.91 mmol) and tri-*n*-butyltin hydride (1.42 mL, 5.40 mmol) in benzene (50 mL) was added 2,2′-azobisisobutyronitrile (AIBN) (32 mg, 0.196 mmol) at room temperature. After being stirred at 115 °C for 3 h, the reaction mixture was concentrated in vacuo to give the crude products which were purified by column chromatography on aluminum oxide (gradually from 1% to 4% ethyl acetate in hexane) to give (*E*)-vinylstannane **44** (2.88 g, 84%) as a colorless oil: IR (KBr, cm^{-1}) 1599, 1447, 1375, 1130; ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, 1H, J = 8.1 Hz), 7.80 (d, 1H, J = 8.3 Hz), 7.70 (d, 2H, J = 8.3 Hz), 7.58 (s, 1H), 7.32 (ddd, 1H, J = 7.8, 1.0, 1.0 Hz), 7.26 (ddd, 1H, J = 7.4, 1.0, 1.0 Hz) 7.21 (d, 1H, J = 8.1 Hz), 6.94 (d, 1H, J = 19.8 Hz), 6.83 (d, 1H, J = 19.8 Hz), 2.33 (s, 1H), 1.52−1.59 (m, 6H), 1.30−1.39 (m, 6H), 0.96−1.00 (m, 6H), 0.89−0.93 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9, 136.5, 135.5, 135.2, 131.7, 129.9, 129.0, 126.8, 124.8, 123.5, 123.4, 122.7, 120.4, 113.7, 29.1, 27.3, 21.5, 13.7, 9.60; EI HRMS *m/e* calcd for $C_{29}H_{40}NO_2S^{119}Sn$ ($M - H$)$^{+\bullet}$ 585.1811, found 585.1816.

Ethyl (*Z*)-4-Hydroxy-2-iodo-2-butenoate (46). To a dichloromethane (140 mL) solution of tetrahydropyranyloxyethanal (3.74 g, 25.9 mmol) was added triphenylcarbethoxyiodomethylenephosphorane (14.8 g, 31.1 mmol) at room temperature. After the reaction mixture was stirred at room temperature for 12 h, the bulk of dichloromethane was removed in vacuo, H_2O was added, and the resulting mixture was extracted with ether. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give the crude products. Column chromatography on silica gel (17% ethyl acetate in hexane) gave an inseparable 10:1 mixture of (*Z*)- and (*E*)-conjugated ester derivatives (5.69 g, 65%) as an orange oil, which was used for the next step without further purification.

To a methanol (100 mL) solution of a (*Z*)- and (*E*)-mixture of the conjugated ester obtained above (7.78 g, 22.9 mmol) was added *p*-toluenesulfonic acid monohydrate (435 mg, 2.29 mmol) at room temperature. After the mixture was stirred at room temperature for 40 min, saturated aqueous $NaHCO_3$ solution was added, and the resulting mixture was extracted with ether. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give the crude products. Column chromatography on silica gel (gradually from 9% to 29% ethyl acetate in hexane) gave (*Z*)-vinyl iodide **46** (4.94 g, 84%) as an orange oil: IR (neat, cm^{-1}) 3447, 1717, 1618, 1256; ^1H NMR (400 MHz, $CDCl_3$) δ 1.33 (t, 3H, J = 7.1 Hz), 4.28 (q, 2H, J = 7.1 Hz), 4.36 (d, 2H, J = 5.1 Hz), 7.50 (t, 1H, J = 5.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 63.0, 67.4, 144.8, 151.6, 162.3; EI HRMS *m/e* calcd for $C_6H_9IO_3$ ($M^{+\bullet}$) 255.9596, found 255.9601.

Ethyl (*E*,*E*)-4-Oxo-2-[(*N*-*p*-toluenesulfonylindol-3-yl)-vinyl]but-2-enoate (47). To a solution of the (*E*)-stannane **44** (11.0 g, 18.8 mmol) and the vinyl iodide **46** (4.94 g, 19.3 mmol) in DMF (160 mL) were added tetrakis(triphenylphosphine)palladium(0) (1.08 g, 0.938 mmol) and lithium chloride (1.59 g, 37.5 mmol) at room temperature. After the reaction mixture was stirred at 115 °C for 30 min, 10% aqueous NH_3 solution was added, and the resulting mixture was extracted with ether. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo to give the crude products. Rough purification by column chromatography on silica gel (from 25% to 50% ethyl acetate in hexane) gave the corresponding alcohol (5.14 g, 64%) as a yellow oil which was oxidized without further purification.

To a solution of the crude alcohol thus obtained (750 mg, 1.76 mmol) in dichloromethane (20 mL) was added manganese dioxide (20 g) at room temperature, and the mixture was stirred for 13 min. The reaction mixture was filtered and concentrated in vacuo to give the crude products which were purified by column chromatography on silica gel (gradually from 17% to 25% ethyl acetate in hexane) to afford the desired aldehyde **47** (500 mg, 67%) as a yellow oil: IR (neat, cm^{-1}) 1723, 1672, 1613, 1447, 1373, 1175, 1127, 976; ^1H NMR (400 MHz, $CDCl_3$) δ 1.39 (t, 3H, J = 7.1 Hz), 2.35 (s, 3H), 4.37 (q, 2H, J = 7.3 Hz), 6.67 (d, 1H, J = 6.8 Hz), 7.22−7.27 (m, 3H), 7.32−7.41 (m, 2H), 7.54 (d, 1H, J = 16.1 Hz), 7.79−7.82 (m, 4H), 8.02 (d, 1H, J = 8.1 Hz), 10.17 (d, 1H, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 21.6, 62.1, 113.9, 119.6, 119.9, 120.5, 124.1, 125.5, 127.0, 127.2, 128.0, 130.1, 130.4, 132.7, 134.7, 135.6, 145.5, 145.7, 166.3, 191.2; EI HRMS *m/e* calcd for $C_{23}H_{21}NO_5S$ ($M^{+\bullet}$) 423.1139, found 423.1144.

(−)-1,2,5,6-Tetrahydropyridine derivative ((−)-48b). To a solution of the aldehyde **47** (500 mg, 1.18 mmol) in chloroform (10 mL) was added (1*S*,2*R*)-(−)-*cis*-1-amino-7-methylindan-2-ol, (−)-**b** (193 mg, 1.18 mmol) at 23 °C, and the mixture was stirred for 12 h at this temperature. The reaction mixture was concentrated in vacuo to give the crude products which were purified by column chromatography on silica gel (from 5% to 25% ethyl acetate in hexane) to afford a 10:1 mixture of (−)-**48b** and its stereoisomer (643 mg, 96%) as a yellow oil. The major stereoisomer (−)-**48b** was then successfully isolated by medium-pressure liquid chromatography (14% ethyl acetate in hexane): $[\alpha]^{27}_D$ −1.5 (*c* 0.5, $CHCl_3$); IR (KBr disk, cm^{-1}) 1715, 1447, 1372, 1258, 1175; ^1H NMR (400 MHz, $CDCl_3$) δ 1.17 (s, 3H), 1.24 (t, 3H, J = 7.1 Hz), 2.29 (s, 3H), 2.76 (dm, 1H, J = 19.3 Hz), 2.85 (dm, 1H, J = 19.3 Hz), 3.16 (d, 1H, J = 17.6 Hz), 3.23 (dd, 1H, J = 18.1, 5.9 Hz), 4.17 (qm, 2H, J =

7.1 Hz), 4.35 (dd, 1H, J = 6.1, 3.4 Hz), 4.47 (d, 1H, J = 4.4 Hz), 4.87 (d, 1H, J = 5.4 Hz), 4.99 (ddd, 1H, J = 5.9, 5.9, 1.2 Hz), 6.72 (d, 1H, J = 7.3 Hz), 6.80 (brs, 1H), 6.97 (d, 1H, J = 7.3 Hz), 7.05 (dd, 1H, J = 7.3, 7.3 Hz), 7.16−7.20 (m, 3H), 7.34 (dd, 1H, J = 7.8, 7.8 Hz), 7.53 (d, 1H, J = 8.1 Hz), 7.65 (s, 1H), 7.78−7.81 (m, 2H), 8.03 (d, 1H, J = 8.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 17.4, 21.5, 25.5, 39.6, 54.4, 60.7, 74.7, 75.0, 86.4, 113.8, 121.3, 121.6, 122.6, 123.2, 124.7, 125.0, 125.1, 126.8, 128.1, 128.4, 129.8, 129.9, 135.1, 135.8, 136.5, 137.2, 137.3, 143.1, 145.1, 166.0; EI HRMS *m/e* calcd for $C_{33}H_{32}N_2O_5S$ ($M^{+\bullet}$) 568.2030, found 568.2028.

(2*S*)-(−)-4-Hydroxymethyl-2-(*N*-*p*-toluenesulfonylindol-3-yl)-1,2,5,6-tetrahydropyridine ((−)-50). To a solution of the ester (−)-**48b** (1.10 g, 1.93 mmol) in ether (15 mL) and THF (5 mL) was added lithium aluminum hydride (100 mg, 2.64 mmol) at 0 °C over 10 min. After the mixture was warmed to room temperature and stirred for an additional 5 min, H_2O was carefully added over 30 min. The resulting mixture was filtered and concentrated in vacuo to give the crude products which were roughly purified by column chromatography on silica gel (from 40% to 67% ethyl acetate in hexane) to afford the corresponding diol (969 mg, 95%) as a white foam, which was oxidized without further purification.

To a solution of the crude alcohol thus obtained (150 mg, 0.284 mmol) in ether (5.0 mL) was added manganese dioxide (2.0 g) at room temperature, and the mixture was stirred for 3 min. The reaction mixture was filtered and concentrated in vacuo to give the crude products which were purified by column chromatography on silica gel (gradually from 5% to 14% methanol in chloroform) to afford (−)-**50** (79 mg, 73%) as a white foam: mp 79−80 °C; $[\alpha]^{27}_D$ −31.1 (*c* 0.5, $CHCl_3$); IR (KBr disk, cm^{-1}) 3320, 3131, 3052, 2920, 1449, 1370, 1173, 1123; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.07 (brs, 2H), 2.15 (brs, 2H), 2.33 (s, 3H), 2.91−2.97 (m, 1H), 3.01−3.07 (m, 1H), 4.10 (brs, 2H), 4.75 (brs, 1H), 5.82 (brs, 1H), 7.19−7.33 (m, 4H), 7.45 (s, 1H), 7.60 (d, 1H, J = 7.6 Hz), 7.74−7.77 (m, 2H), 7.96 (d, 1H, J = 8.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 26.0, 40.7, 49.7, 66.4, 113.7, 119.9, 122.2, 123.2, 123.9, 124.1, 124.8, 126.8, 129.4, 129.8, 135.2, 135.5, 138.3, 144.9; EI HRMS *m/e* calcd for $C_{21}H_{22}N_2O_3S$ ($M^{+\bullet}$) 382.1350, found 382.1354.

(−)-1,2,5,6-Tetrahydropyridine derivative ((−)-48d). To a solution of the aldehyde **47** (600 mg, 1.42 mmol) in chloroform (20 mL) was added (1*S*,2*R*)-(−)-7-*cis*-1-amino-7-isopropylindan-2-ol, (−)-**d** (271 mg, 1.42 mmol), at 12 °C, and the mixture was stirred for 8.5 h at this temperature. The resulting mixture was concentrated in vacuo to give the crude products which were purified by column chromatography on silica gel (33% ethyl acetate in hexane) to afford a 10:1 mixture of (−)-**48d** and its stereoisomer (840 mg, 99%) as a yellow oil. The major stereoisomer (−)-**48d** was then successfully isolated by column chromatography on silica gel (gradually from 17% to 29% ethyl acetate in hexane): $[\alpha]^{16}_D$ −87.0 (*c* 0.7, $CHCl_3$); IR (KBr disk, cm^{-1}) 1715, 1447, 1373, 1260, 1175, 1123, 1030; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.05 (d, 3H, J = 7.1 Hz), 0.52 (d, 3H, J = 6.6 Hz), 1.24 (t, 3H, J = 7.1 Hz), 2.32 (s, 3H), 2.52 (qq, 1H, J = 6.8, 6.8 Hz), 2.77 (dddd, 1H, J = 19.5, 4.4, 4.4, 2.0 Hz), 2.84 (dm, 1H, J = 19.5 Hz), 3.17 (d, 1H, J = 17.1 Hz), 3.23 (dd, 1H, J = 18.1, 5.9 Hz), 4.17 (qm, 2H, J = 7.1 Hz), 4.34 (dd, 1H, J = 6.3, 3.9 Hz), 4.52 (dd, 1H, J = 4.6, 1.2 Hz), 4.94−5.00 (m, 2H), 6.80 (dd, 1H, J = 3.7, 2.0 Hz), 6.89 (d, 1H, J = 7.6 Hz), 6.98 (d, 1H, J = 7.6 Hz), 7.13 (dd, 1H, J = 7.6, 7.6 Hz), 7.18−7.28 (m, 3H), 7.35 (ddm, 1H, J = 7.3, 7.3 Hz), 7.55 (d, 1H, J = 7.8 Hz), 7.66 (s, 1H), 7.84 (ddd, 2H, J = 8.8, 2.0, 2.0 Hz), 8.02 (d, 1H, J = 8.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 21.5, 22.2, 22.5, 25.6, 27.6, 39.5, 54.4, 60.7, 74.3, 74.9, 86.6, 113.4, 121.6, 121.8, 123.0, 123.3, 124.4, 125.0, 125.4, 126.9, 128.8, 129.5, 130.0, 135.2, 135.6, 136.0, 137.4, 143.1, 145.1, 147.6, 166.0; EI HRMS *m/e* calcd for $C_{35}H_{36}N_2O_5S$ ($M^{+\bullet}$) 596.2343, found 596.2345.

(2*S*)-(−)-4-Hydroxymethyl-2-(*N*-*p*-toluenesulfonylindol-3-yl)-1,2,5,6-tetrahydropyridine ((−)-50). To a solution of the ester (−)-**48d** (315 mg, 0.528 mmol) in ether (3.0 mL) and THF (2.0 mL) was added lithium aluminum hydride (30.0 mg, 0.792 mmol) at 0 °C over 10 min. After the mixture was warmed to room temperature and stirred for an additional 5 min, H_2O was carefully added over 30 min. The resulting mixture was filtered and concentrated in vacuo to give the crude products which were roughly purified by column chromatography on silica gel (from 33% to 50% ethyl acetate in hexane) to afford the corresponding dialcohol (244 mg, 83%) as a white foam, which was oxidized without further purification.

To a solution of the crude alcohol thus obtained (200 mg, 0.359 mmol) in ether (6.0 mL) was added manganese dioxide (2.3 g) at room temperature, and the mixture was stirred for 3 min. The reaction mixture was filtered and concentrated in vacuo to give the crude products which were purified by column chromatography on silica gel twice (gradually from 5% to 14% methanol in chloroform) to afford (−)-**50** (102 mg, 74%), whose spectral data were good agreement with those obtained from (−)-**48b**.

(2*S*)-(−)-4-Hydroxymethyl-*N*-methyl-2-(*N*-*p*-toluenesulfonylindol-3-yl)-1,2,5,6-tetrahydropyridine (51). To a solution of (−)-**50** (154 mg, 0.403 mmol) and 37% aqueous formaldehyde (0.16 mL, 2.01 mmol) in acetonitrile (4.0 mL) was added sodium cyanoborohydride (50.3 mg, 0.805 mmol) at room temperature. After the reaction mixture was stirred for 5 min, saturated aqueous NH_4Cl solution was added, and the resulting mixture was extracted with chloroform. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give the crude products which were purified by column chromatography on silica gel (gradually from 5% to 11% methanol in chloroform) to afford the corresponding (−)-*N*-methyl derivative **51** (159 mg, 100%) as a colorless oil: $[\alpha]^{26}_D$ −82.4 (*c* 0.3, $CHCl_3$); IR (KBr disk, cm^{-1}) 3399, 1447, 1368, 1175, 1121; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.08−2.12 (m, 1H), 2.17 (s, 3H), 2.32 (s, 3H), 2.43−2.52 (m, 2H), 2.95−3.02 (m, 1H), 3.94 (brs, 1H), 4.01−4.17 (m, 2H), 5.52 (brs, 1H), 7.16−7.21 (m, 3H), 7.26−7.30 (m, 1H), 7.48 (s, 1H), 7.63 (d, 1H, J = 7.8 Hz), 7.73−7.75 (m, 2H), 7.95 (d, 1H, J = 8.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 26.0, 43.6, 51.4, 59.4, 66.0, 113.6, 120.9, 123.0, 123.1, 123.4, 124.5, 124.6, 126.7, 126.9, 129.8, 135.1, 135.6, 136.3, 144.8; EI HRMS *m/e* calcd for $C_{22}H_{24}N_2O_3S$ ($M^{+\bullet}$) 396.1506, found 396.1511.

(2*S*)-(−)-4-(1-Hydroxyethyl)-*N*-methyl-2-(*N*-*p*-toluenesulfonylindol-3-yl)-1,2,5,6-tetrahydropyridine. To a solution of the (−)-*N*-methyl derivative **51** obtained above (60 mg, 0.151 mmol) in dichloromethane (2 mL) was added manganese dioxide (1.2 g) at room temperature, and the mixture was stirred for 5 min. The reaction mixture was filtered and concentrated in vacuo to give the crude aldehyde which was reacted with methyllithium without any purification.

To a solution of the crude aldehyde thus obtained in ether (2 mL) and THF (1 mL) was added methyllithium (1.5 M solution in ether, 0.20 mL, 0.303 mmol) at 0 °C. After the reaction mixture was stirred for 5 min at 0 °C, saturated aqueous NH_4Cl solution was added, and the resulting mixture was extracted with chloroform. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give the crude products which were purified by column chromatography on silica gel (gradually from 5% to 9% methanol in chloroform) to afford the corresponding (−)-secondary alcohol as a 1:1 mixture of stereoisomers (34 mg, 55% in two steps) as a colorless oil: $[\alpha]^{24}_D$ −68.8 (*c* 0.4, $CHCl_3$); IR (neat, cm^{-1}) 3391, 1447, 1372, 1175, 1121; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (d, 3H, J = 6.3 Hz), 2.10−2.17 (m, 1H), 2.17 (s, 3H), 2.33 (s, 3H), 2.44−2.49 (m, 2H), 2.97−3.05 (m, 1H), 3.91−3.93 (m, 1H), 4.19−4.27 (m, 1H), 5.51 (brd, 1H, J = 11.0), 7.16−7.21 (m, 3H), 7.25−7.30 (m, 1H), 7.47 (s, 1H), 7.63 (dd, 1H, J = 9.0, 9.0 Hz), 7.73−7.75 (m, 2H), 7.95 (d, 1H, J = 8.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 21.5, 21.8, 24.1, 25.3, 43.67, 43.73, 51.7, 51.9, 59.7, 59.8, 70.7, 70.9, 113.7, 120.9, 121.0, 121.7, 123.0, 123.6, 124.5, 124.6,

126.8, 129.79, 129.84, 135.2, 135.7, 140.1, 144.8; EI HRMS *m/e* calcd for $C_{23}H_{26}N_2O_3S$ ($M^{+\bullet}$) 410.1662, found 410.1662.

(2*S*)-(−)-2-(Indol-3-yl)-*N*-methyl-4-methyloxo-1,2,5,6-tetrahydropyridine ((−)-30). To a solution of the (−)-secondary alcohol obtained above (21.5 mg, 0.0524 mmol) in methanol (1.5 mL) was added an 50% aqueous NaOH solution (0.3 mL) at room temperature, and the mixture was stirred for 7 h at 80 °C. The reaction mixture was directly concentrated in vacuo to give the crude products which were roughly purified by column chromatography on silica gel (gradually from 13% to 25% methanol in chloroform) to afford the corresponding indole N−H derivative. It was oxidized without further purification.

To a solution of the roughly purified indole N−H derivative thus obtained in dichloromethane (2.0 mL) was added manganese dioxide (800 mg) at room temperature, and the mixture was stirred for 30 min. The reaction mixture was filtered and concentrated in vacuo to give the crude products which were purified by column chromatography on silica gel (gradually from 3% to 9% methanol in chloroform) to afford (−)-**30** (5.3 mg, 40% for two steps) as a yellow oil: $[\alpha]^{24}_D$ −3.8 (*c* 0.3, $CHCl_3$); IR (neat, cm^{-1}) 3355, 1665, 1254, 1236, 1094; ^1H NMR (400 MHz, $CDCl_3$) δ 2.25 (s, 3H), 2.28 (s, 3H), 2.45−2.51 (m, 1H), 2.55−2.59 (m, 2H), 3.07 (ddd, 1H, J = 11.2, 4.4, 4.4 Hz), 4.26 (brs, 1H), 6.74−6.76 (m, 1H), 7.12 (ddd, 1H, J = 8.1, 8.1, 1.0 Hz), 7.158−7.163 (m, 1H), 7.22 (ddd, 1H, J = 8.1, 8.1, 1.0 Hz), 7.40 (d, 1H, J = 8.3 Hz), 7.67 (d, 1H, J = 8.1 Hz), 8.20 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.0, 25.2, 43.6, 51.4, 59.8, 111.2, 111.3, 119.6, 119.8, 122.4, 123.2, 123.4, 126.7, 136.4, 141.6, 198.9; EI HRMS *m/e* calcd for $C_{16}H_{18}N_2O$ ($M^{+\bullet}$) 254.1418, found.

Acknowledgment. We thank Dr. Kayoko Saiki at the Kobe Pharmaceutical University for her high-resolution mass spectra measurements. We also thank Mr. Tamotsu Yamamoto at the Institute for Life Science Research at Asahi Chemical Industry Co., Ltd., for his X-ray crystallographic measurements. This study was supported by a Grant-in-Aid for Scientific Research 09480145 from the Ministry of Education, Science, Sports and Culture of Japan. K.T. is grateful to the JSPS for a Research Fellowship for Young Scientists.

Supporting Information Available: Copies of ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

JO049381F