JOC The Journal of Organic Chemistry

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Stereocontrolled Synthesis of Substituted Chiral Piperidines via One-Pot Asymmetric 6π-Azaelectrocyclization: Asymmetric Syntheses of (−)-Dendroprimine, (+)-7-Epidendroprimine, (+)-5-Epidendroprimine, and (+)-5,7-Epidendroprimine

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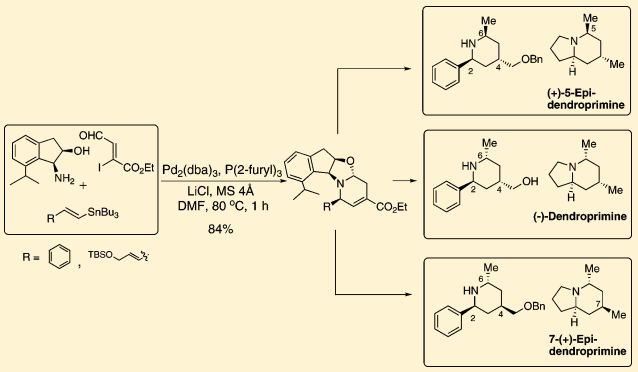
Supporting Information

ABSTRACT: The asymmetric one-pot 6π-azaelectrocyclization of alkenyl vinyl stannane, ethyl (*Z*)-2-iodo-4-oxobutenoate, and (−)-7-isopropyl-*cis*-aminoindanol in the presence of a Pd(0) catalyst stereoselectively produced the tetracyclic aminoacetal compounds, resulting from the four-bond formation accompanying by controlling the stereochemistry at the two asymmetric centers. The produced cyclic aminoacetals can be regarded as synthetic precursors of substituted chiral piperidines, and the syntheses of 2,4- and 2,4,6-substituted piperidines were realized from the obtained aminoacetals by the stereoselective hydrogenation of the double bond conjugated with the C-4 ester group and alkylation at the aminoacetal moiety. In addition, the stereoselective synthesis of an indolizidine alkaloid, (−)-dendroprimine, and its three stereoisomers, (+)-7-epidendroprimine, (+)-5-epidendroprimine, and (+)-5,7-epidendroprimine, were achieved.



INTRODUCTION

The substituted piperidines can be regarded as one of the core structures of naturally occurring alkaloids, including the indol alkaloid (Figure 1).[1] These functionalized six-member nitrogen heterocycles have drawn a great deal of attention due to their attractive pharmacological activities. Therefore, the stereocontrolled synthesis of polysubstituted piperidines has been a current topic in the synthetic community.[2,3] When enantiomerically pure polysubstituted piperidines are easily accessible resulting from the successful introduction of the desired alkyl substituents to the desired positions of a chiral piperidine ring, a widely applicable synthetic strategy for alkaloids consisting of a polysubstitued piperidine ring will be envisioned.[2c,4]

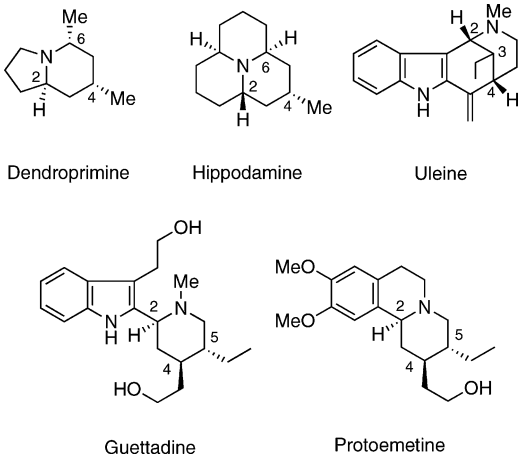


Figure 1. Alkaroids including piperidine core.

Recently, we achieved the highly stereoselective asymmetric 6π-azaelectrocyclization of conformationally flexible linear 1-azatrienes by utilizing 7-alkylsubstituted *cis*-aminoindanol derivatives.[5−7] Our asymmetric azaelectrocyclization is based on the discovery that the remarkable frontier-orbital interaction between the HOMO and LUMO of 1-azatrienes significantly accelerates the azaelectrocyclization in the presence of the C-4 carbonyl and C-6 alkenyl or aryl substituents.[8,9] This asymmetric azaelectrocyclization provided the chiral tetracyclic 2,4-disubstituted 1,2,5,6-tetrahydropyridine in a high yield with a high diastereoselectivity.

To establish the asymmetric 6π-azaelectrocyclization as a new strategy for alkaloid synthesis, we reinvestigated our previous method in terms of the operation, scale up, and the

Received: November 22, 2011
Published: January 19, 2012

   dx.doi.org/10.1021/jo202350z | *J. Org. Chem.* 2012, 77, 1812−1832

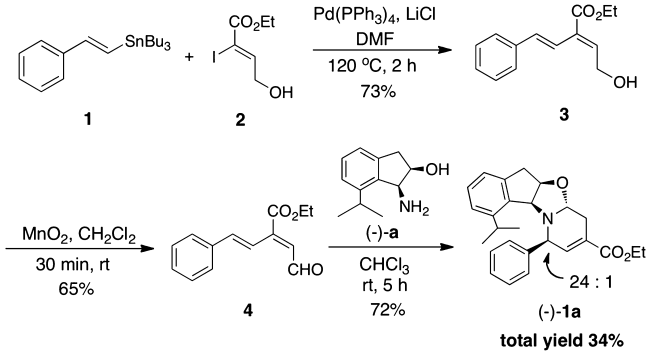
substrate preparation for this azaelectrocyclization. We succeeded in the unique one-pot asymmetric 6π-azaelectrocyclization, which led to the facile and stereocontrolled preparation of the chiral tetrahydropyridine derivatives bearing a variety of aromatic substituents at the C-2 position.[10]

To further pursue the possibility of our one-pot procedure for natural product syntheses, we investigated the synthesis of substituted chiral piperidines. Quite recently, this one-pot protocol was applied to the synthesis of (−)-20-epiuleine possessing the 2,3,4-trisubstituted piperidine core[11] and (−)-corynantheidine and (−)-corynantheidol possessing the 2,4,5-trisubstituted piperidine core.[12] We now report in detail[10,13] the stereoselective synthesis of 2,4-disubstituted and 2,4,6-trisubstituted chiral piperidines and also describe the stereoselective total syntheses of an indolizidine alkaloid, (−)-dendroprimine, and its three diastereomers, (+)-5-epidendroprimine, (+)-7-epidendroprimine, and (+)-5,7-epidendroprimine by the one-pot asymmetric azaelectrocyclization protocol in addition to the correction of the stereochemistry of the previously reported (+)-5-epidendroprimin. We also describe in this paper the analysis results of the extremely high stereoselectivity caused by the one-pot procedure.

RESULTS AND DISCUSSION

One-pot Azaelectrocyclization. We previously reported the stepwise synthesis of tetracyclic 2,4-disubstituted tetrahydropyridine (−)-**1a**,[5] a promising precursor for the preparation of substituted piperidine derivatives, in 34% yield in three steps, as shown in Scheme 1. The sequence involves the following

Scheme 1. Previous Asymmetric 6π-Azaelectrocyclization Method toward Chiral Piperidines

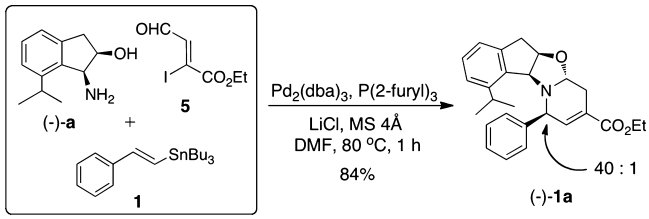


steps: the Stille-Migita coupling of vinyl stannane **1** with vinyl iodide **2**, oxidation of the resulting allylic alcohol **3** by manganese dioxide, and the reaction with the produced aldehyde **4** and (−)-7-isopropyl-*cis*-1-amino-2-indanol (−)-**a**, with resulted in the highly stereoselective 6π-azaelectrocyclization followed by an aminoacetal formation.

To more conveniently demonstrate our asymmetric azaelectrocyclization reaction for natural alkaloid synthesis, we investigated a tandem one-pot procedure as a rapid and easy preparation procedure for the polysubstituted chiral piperidine synthesis by mixing the three components of vinyl stannane **1**, ethyl (*Z*)-2-iodo-4-oxobutenoate **5**, and (−)-7-isopropyl-*cis*-1-amino-2-indanol (−)-**a** in the presence of a palladium catalyst.

After various evaluations of solvents, additives, Pd(0) catalysts and also the mixing order of the substrates, we finally found the optimized conditions. Namely, vinyl iodide **5** and aminoindanol (−)-**a** were first mixed in DMF at room temperature in the presence of MS 4 A to give the corresponding protected aminoacetal. This procedure was followed by the Stille-Migita coupling with vinyl stannanes **1** using the $Pd_2(dba)_3$/trifurylphospine catalyst in the presence of LiCl at 80 °C to provide the corresponding tetrahydropyridine (−)-**1a** in 84% yield as an almost single isomer (40:1 by ^{1}H NMR analysis) (Scheme 2). The spectral data of (−)-**1a** were

Scheme 2. One-pot Azaelectrocyclization using (−)-7-Isopropyl *cis*-1-Amino-2-indanol



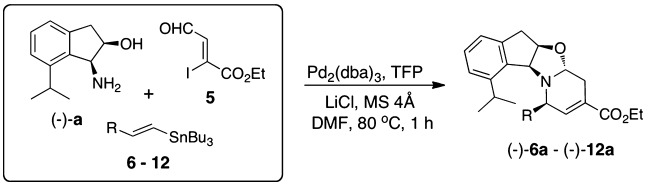
in good agreement with those of the compound previously obtained by the stepwise protocol.[5] Note that this one-pot procedure successfully simultaneously created four new bonds and produced better results than the previously developed stepwise procedure[5] shown in Scheme 1 (84% and 40:1 for the one-pot protocol vs 34% and 24:1 for the stepwise method).[10]

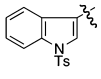
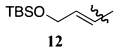
The developed one-pot procedure for the asymmetric azaelectrocyclization was tolerated for the various aromatic substituents at the C-2 position of the piperidines (Table 1). Thus, a small chiral piperidine library bearing indolyl (entries 1 and 2), quinolyl (entry 3), pyridyl (entries 4 and 5), thiophenyl (entry 6) and siloxyallyl derivatives (entry 7), were successfully prepared. Noteworthy is the fact that all the tetracyclic heterocycles could be efficiently obtained with a high diastereoselectivity (from >12:1 to >20:1) and satisfactory yields (67−80%).

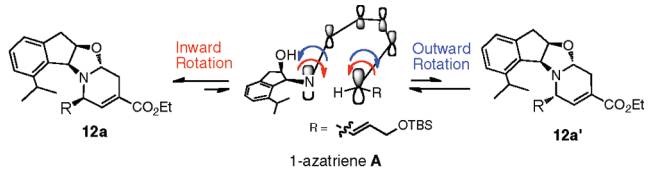
High Diastereoselectivity of the One-pot Procedure. The one-pot procedure afforded compound (−)-**1a** with a higher diastereoselectivity (>40:1) than the stepwise procedure (24:1), and other 2-aryl-substituted derivatives (−)-**6a** ∼ (−)-**12a** were also produced with a high stereoselectivity. In comparison to the stepwise procedure, which was believed to be a kinetically controlled one, because the reaction was completed within 5 min at 24 °C in chloroform and the asymmetric cyclization using (−)-**a** also proceeded at 24 °C, the one-pot procedure required heating at 80 °C in DMF, and therefore the cyclization step of this three-component one-pot procedure must occur under thermodynamically controlled conditions. We then tried to independently isomerize both products of the cyclization, the major and minor products. Both **12a** and **12a′** were isolated by column chromatography and, in particular, **12a′** was collected from the reaction mixture of many cyclization experiments. On the other hand, **12a** was used for the natural dendroprimin synthesis. The compound **12a′** was dissolved in deuterated DMF in a NMR sample tube, and then the time-course of its isomerization at both 70 and 80 °C was monitored by ^{1}H NMR. The results are shown in Figure 2. Heated at 70 °C, a small amount of **12a** was detected in a large amount of **12a′** by the ^{1}H NMR after 90 min. Heated at 80 °C, **12a′** gradually changed and **12a** was clearly observed and the ratio of the both compounds was 1:1 after 30 min. After 90 min, the amount of **12a** increased and the ratio was 4:1, and compound **12a** became major with the ratio of >8:1 after 120 min. On the other hand, although **12a** was heated at 80 °C,

dx.doi.org/10.1021/jo202350z | J. Org. Chem. 2012, 77, 1812−1832

Table 1. One-Pot Azaelectrocyclization Utilizing Variously Substituted Vinyl Stannanes with Heterocycles



entry	R	product	yield	dr (at 2-position)
1	 6	(-)-**6a**	72%	> 16 : 1
2	 7 R = SO_2Ph	(-)-**7a**	67%	> 12 : 1
3	 8	(-)-**8a**	68%	> 15 : 1
4	 9	(-)-**9a**	80%	> 16 : 1
5	 10	(-)-**10a**	78%	> 17 : 1
6	 11	(-)-**11a**	74%	> 15 : 1
7	 12	(-)-**12a**	78%	> 20 : 1



Temperature	Time	12a	:	12a'	Temperature	Time	12a	:	12a'
70 °C	0 min.	0	:	100	80 °C	30 min.	1	:	1
	90 min.	1	:	9		90 min.	4	:	1
	120 min.	1	:	4		120 min.	> 8	:	1

Figure 2. Equilibrium experiments of the cyclized products.

12a′ was not detected at all. These results obviously indicated that the equilibrium existed between **12a** and **12a′** at 80 °C, and the equilibrium moved and almost converged to the more stable **12a** through the inward rotation of the disrotatory 6π-azaelectrocyclization of the 1-azatirene **A** generated by the ring-opening of **12a′**. Thus, it was concluded that in the one-pot procedure at 80 °C, the thermodynamically more stable compound **12a** was exclusively produced resulting from converging the equilibrium of the 6π-azaelectrocyclization.

To analyze the stable conformation **12a**, the molecular modeling was performed by Spartan '02 (Wave function, Inc., Irvine, CA),[14] using default parameters and convergence criteria. The conformations were caluculated with Merck force field (MMFF94s) using the Monte Carlo conformational search method with 1000 iteration steps. The calculation gave the most stable conformation as shown in Figure 3.[15,16] In this

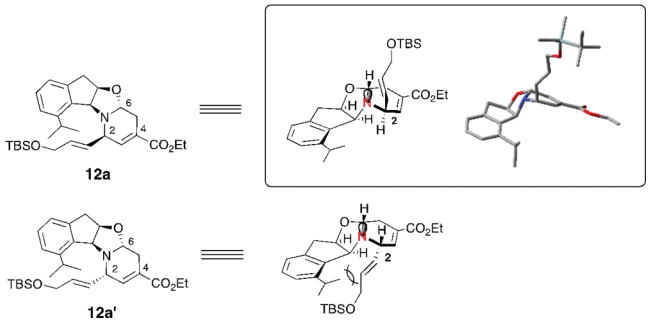


Figure 3. Conformational analysis of the cyclized products.

conformer, the substituent at the C-2 position on the piperidine ring is the α-axial orientation, and no severe steric interaction exists. On the other hand, in the case of minor isomer **12a′**, the substituent at the C-2 position on the tetrahydropyridine ring is situated in β-equatorial. In this conformer, the steric interaction between the isopropyl substitutent on the indan ring and the alkoxypropenyl group at the C-2 position of the tetrahydropyridine ring apparently exists. Thus, the major isomer **12a** is much more stable than **12a′**, and hence **12a** must be preferentially produced in the one-pot procedure. In addition, rough energy estimation of the stable conformations **12a** and **12a′** by Spartan '02, showed that the conformation **12a** is more stable than that of **12a′** by 7.8 kcal/mol. The fact that the tendency of the diastereoselectivity of the electrocyclization depended on the substituent at the C-2 position could also be explained by the conformational analysis described above.

Stereoselective Reduction of the Conjugated Ester Group and Synthesis of 2,4-Disubstituted Piperidines. To synthesize the 2,4-disubstituted piperidines, we examined the stereoselective reduction of the conjugated double bond in the intermediate (−)-**1a**, which can be readily prepared using the one-pot azaelectrocyclization protocol (Scheme 2). Although the substrate was decomposed by using Pd/C as a hydrogenetion catalyst and both the conjugated double bond and the aminoacetal moiety were reduced by applying PtO_2 to the hydrogenation, fortunately the chemoselective hydrogenation of (−)-**1a** with W-2 Raney-Nickel was successful to produce the desired C-4 β-ester **13** as a single stereoisomer in 87% yield. Meanwhile, when (−)-**1a** was treated with magnesium in methanol, the C-4 α-isomer **15** was stereoselectively produced as a major product in the ratio of 5:1.[17] Since both diastereoisomers, **13** and **15**, were selectively obtained by choosing the reducing reagent, the next step was the removal of the Indane moiety. The obtained saturated compounds **13** and **15** were treated with DIBAL-H at −78 °C to provide the corresponding diols in 79% and 83% yield, respectively, which were treated with lead tetraacetate[18] in the presence of *n*-propylamine at −50 °C to afford the desired piperidine compounds **14** and **16** in 75 and 69% yield, respectively (Scheme 3). At the procedure of the oxidative cleavage of the Indane moiety, in the absence of *n*-propylamine, the yield was much lower. The added *N*-propylamine would not only catch the liberated acetic acids to keep the reaction media to a basic condition but also catch the produced aldehyde **17** resulting from the oxidative cleavage of the aminoindanol moiety by lead tetraacetate

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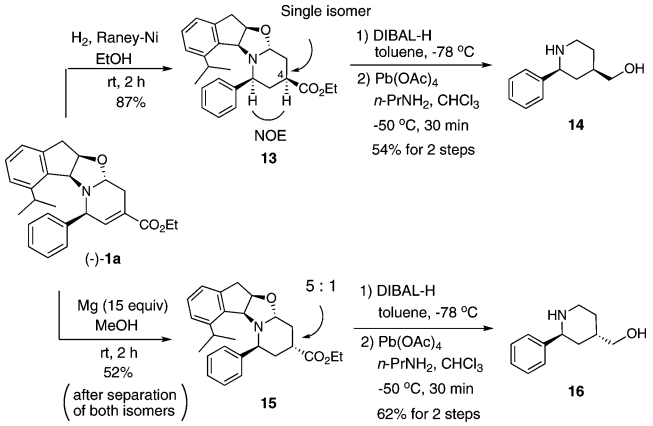
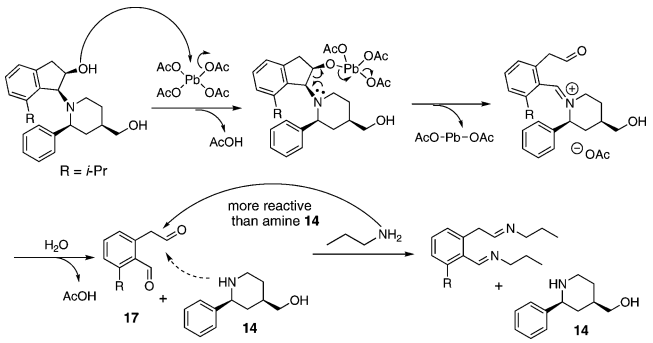
Scheme 3. Stereocontrolled Synthesis of 2,4-Disubstituted Piperidines



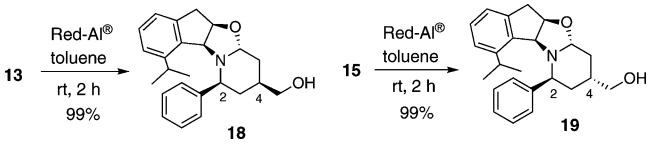
oxidation to avoid the further reaction of the generated aldehyde **17** with the desired second amine **14** as described in the plausible mechanism in Scheme 4. Thus, the synthetically practical route for providing chiral 2,4-disubstituted tetrahydropyridines was established.

Scheme 4. Plausible Mechanism for Oxidative Cleavage of Indane Moiety



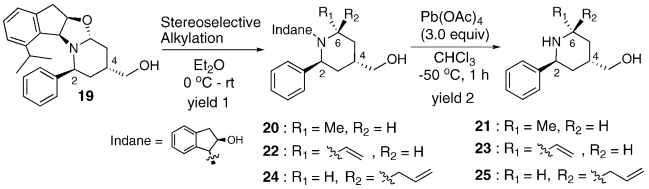
Stereoselective Alkylation of C-4 α-Hydroxymethyl and C-4 α-Benzyloxy Derivatives. Next, we planned to synthesize the 2,4,6-trisubstituted piperidines by the stereoselective alkylation of the aminoacetal moiety. To realize these alkylations by alkyllithium and Grignard reagents in a stereoselective manner, the chemoselective reduction of the C-4 ester group in both **13** and **15** was required. Fortunately, we found that treatment of aminoacetal compounds **13** and **15** with Red-Al at room temperature clearly produced the desired alcohols **18** and **19** in 99% yield, respectively (Scheme 5), although LAH and DIBAL gave the corresponding diols.

Scheme 5. Chemoselective Reduction of Ester Group



With compounds **18** and **19** in hand, we attempted the stereoselective alkylation of the aminoacetal moiety of the three compounds, β-hydroxymethyl **18**, α-hydroxymethyl **19** and α-benzyloxymethyl **26** derivatives.[19] First, in the case of **19**,

Table 2. Stereocontrolled Synthesis of (2β,4α,6α)-Trisubstituted Piperidine

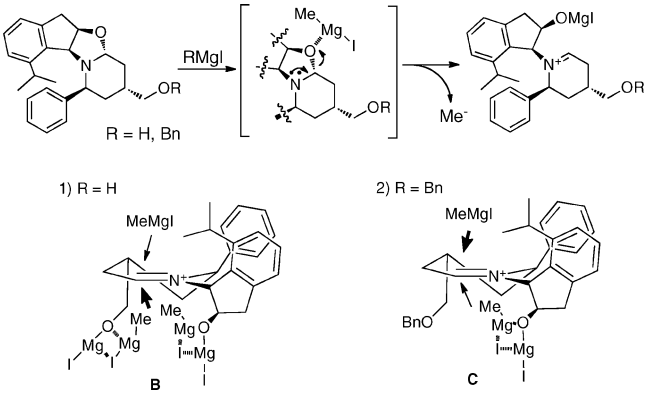


entry	alkylating agent	yield 1	α : β (C-6 position)[c]	yield 2
1	MeLi (excess)	-	-	-
2	MeLi (excess), BF_3-Et_2O (3 equiv)	-	-	-
3	MeLi (excess), $MgBr_2$ (3 equiv)	-	-	-
4	MeMgI (25 equiv)	58%[a]	40 : 1	-
5	MeMgI (20 equiv), CuI (20 equiv)	81%[a]	50 : 1	64%
6	Me_3Al (15 equiv)[d]	88%[b]	2 : 1	-
7	Me_2Zn (15 equiv)[e]	-	-	-
8	MgBr (excess)	82%	α-isomer only	76%
9	MgBr (excess)	78%	β-isomer only	77%

[a]Isolated yields of α-isomer. [b]Yield for mixture of isomers. [c]Determined by ^{1}H NMR analysis of crude mixtures. [d]Reaction was carried out in toluene. [e]Reaction was performed in DMF.

methyl lithium itself and even in the combination with a Lewis acid gave no reaction, and **19** was almost recovered (Table 2, entries 1−3). On the other hand, the Grignard reagent produced the alkylated product with high stereoselectivity (entry 4 and 5). Thus, C-6 α-methyl derivative **20** was exclusively obtained in 58% yield by a reaction with the Grignard reagent (entry 4), and furthermore, when **19** was treated with methylmagnesium iodide (20 equiv) and CuI (20 equiv) in ether (entry 5), the α-methyl isomer **20** was also obtained in 81% yield. The high stereoselectivity of the methylation of **19** could be explained by assuming that the alkylation proceeded through the aggregated species of a methylmetal (Mg or Cu) complex coordinating to the C-4 α-hydroxymethyl group in addition to the hydroxyindane moiety of the intermediary iminium ion (Scheme 6B), and the similar

Scheme 6. Plausible Mechanism of Alkyation on Aminoacetal Moiety



interpretation was applied to the highly stereoselective 1,4-addition to the unsaturated ester moiety of the hydroxyindane derivative **D** derived from (−)-**6a** (Figure 4).[20] The hydroxyindane moiety of the methylated compound **20** was

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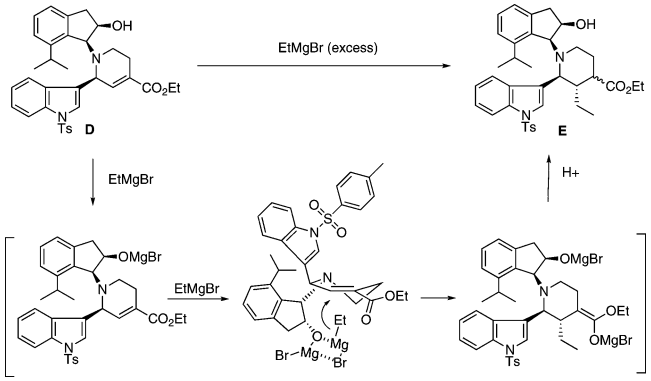


Figure 4. Other example of neighboring group participation by the hydroxy group on indane.

then removed by a treatment with lead tetraacetate at −50 °C in chloroform to produce (2*β*,4*α*,6*α*)-trisubstituted piperidine **21**, the relative configurations of which were determined based on NOE (Figure 5). The addition of n-propylamine was not

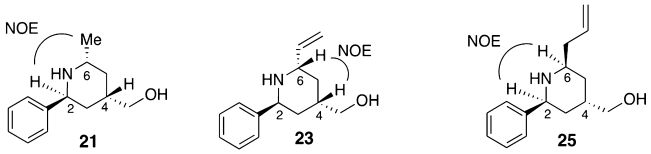
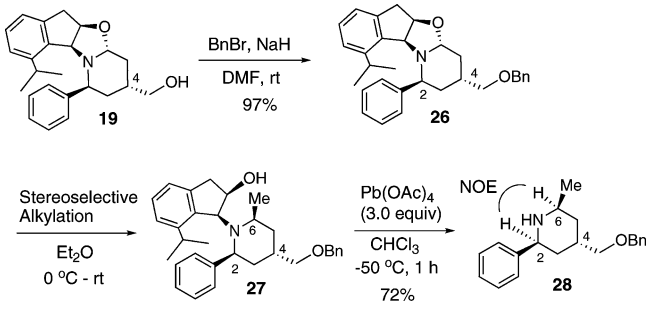


Figure 5. NOE studies of compounds **21**, **23**, and **25**.

necessary in this case probably because of the crowded moiety of the piperidine nitrogen. Other alkylating reagents, such as trimethylaluminium gave low stereoselectivity and dimethylzinc did not react (entries 6 and 7 of Table 2). Furthermore, the reaction of **19** with vinylmagnesium bromide in the absence of CuI provided the corresponding alkylated product **22** as a sole stereoisomer, whose hydroxyindane moiety was removed with lead tetraacetate to produce the vinyl derivative **23** in 62% yield for 2 steps (entry 8). Surprisingly, the reaction of **19** with allyl magnesium bromide afforded the *β*-oriented allyl derivative **25** in 60% yield after removing the hydroxyindane moiety by a lead tetraacetate treatment. In this case, the alkylation obviously proceeded from the opposite side of the C-4 hydroxymethyl group, and therefore the aggregation of the Grignard reagent around the C-4 hydroxymethyl group might not be formed.

To explore the effect of the C-4 hydroxymethyl group to the highly stereoselective alkylation, we protected the hydroxyl group of the compound **19** by a benzyl group to give compound **26**. The methylation of the compound **26** mainly proceeded from the opposite site of the C-4 benzyloxymethyl group (Table 3). Thus, a treatment with MeMgI selectively provided C-6 *β*-methyl isomer **27** in a ratio of 3:1 (entry 2), although no methylated product could be detected again by the reaction with MeLi (entry 1), and the CuI additive did not increase stereoselectivity (entry 3). The treatment of **26** with Me_3Al in ether provided the same C-6*β* isomer **27** with the highest selectivity of 5:1 (entry 4). Apparently, the steric factor due to the benzyl protecting group overrode the coordination of the Grignard reagent to the oxygen function at the C-4 position (Scheme 6C). Another stereoisomer, (2*β*,4*α*,6*β*)-trisubstituted piperidine derivative **28**, was obtained in 72% yield after removal of the hydroxyindane moiety by a lead tetraacetate treatment of the isolated **27**.

Table 3. Stereoselective Synthesis of (2*β*,4*α*,6*α*)-Trisubstituted Piperidine

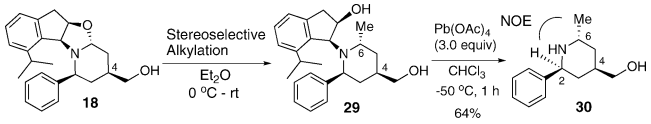


entry	alkylating agent	yield[a] (%)	*α*:*β* (C-6 position)[b]
1	MeLi (excess)		
2	MeMgI (3 equiv)	84	1:3
3	MeMgI (3 equiv), CuI (3 equiv)	79	1:2
4	Me_3Al (5 equiv)[c]	82	1:5

[a]Yield for mixture of isomers. [b]Determined by ^{1}H NMR analysis of crude mixtures. [c]Reaction was carried out in toluene.

Stereoselective Alkylation of *β*-Hydroxymethyl and *β*-Benzyloxyl Derivatives. We also attempted the reaction of C-4 *β*-derivatives **18** and **31** with alkyl agents. In the case of compound **18**, the reaction with MeMgI and Me_3Al gave the almost same results with the 4:1 diastereoselectivity (Table 4).

Table 4. Stereoselective Synthesis of (2*β*,4*α*,6*α*)-Trisubstituted Piperidine



entry	alkylating agent	yield[a] (%)	*α*:*β* (C-6 position)[b]
1	MeLi (excess)		
2	MeMgI (20 equiv)	68	4:1
3	Me_3Al (15 equiv)[c]	69	4:1

[a]Yield for mixture of isomers. [b]Determined by ^{1}H NMR analysis of crude mixtures. [c]Reaction was carried out in toluene.

On the other hand, the reaction of C-4 *β*-benzyloxymethyl derivative **31** with MeMgI stereoselectively provided C-6 *α*-methyl isomer **32** in a ratio of 10:1, and (2*β*,4*β*,6*α*)-trisubstitutedpiperidine **33** was obtained in 58% yield by an oxidative cleavage of **32** with lead tetraacetate (Scheme 7).

Thus, we established the synthetic method of the three chiral 2,4,6-trisubstituted piperidine diastereomers **21**, **28** and **33** from the common intermediate (−)-**1a**, which was easily obtained by the one-pot azaelectrocyclization reaction.

Synthesis of (−)-Dendroprimine (34): Retrosynthetic Analysis of (−)-Dendroprimine (34). To demonstrate the established protocol for the polysubstituted piperidine synthesis, we examined the asymmetric synthesis of an indolizidine alkaloid, (−)-dendroprimine (**34**), which was isolated from *Dendrobium primulinum* Lindl (*Orchidaceae*) and characterized by Luning and his co-workers in 1965.[1a] The relative configuration of the stereogenic centers of dendroprimine was determined by the synthesis of the four racemic diastereomers of this indolizidine alkaloid, and the absolute

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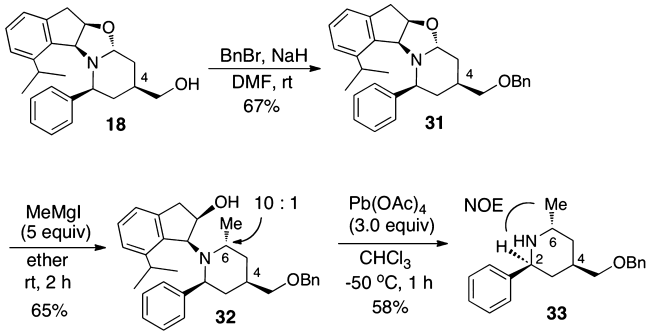
Scheme 7. Stereoselective Synthesis of (2β,4α,6α)-Trisubstituted Piperidine



configuration was also determined by the same group in 1972.[1b,c] The enantioselective synthesis of (−)-dendroprimine (**34**) and its two isomers were reported by Gelas-Mialhe in 2004,[21] and the synthesis of (−)-5,7-epi-dendroprimene (**54**) was reported by other two groups.[22]

Our synthetic analysis of (−)-dendroprimine (**34**) is shown in Figure 6. We envisioned that dendroprimine (**34**) could be

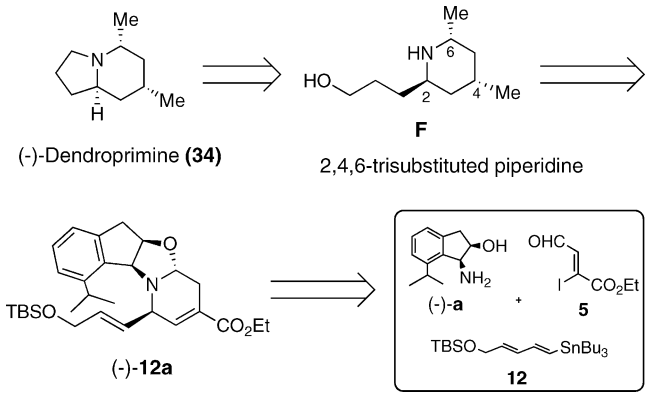


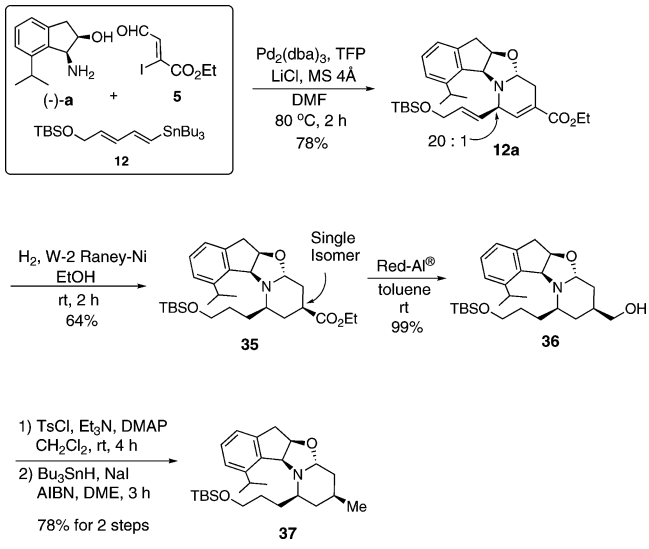
Figure 6. Synthetic strategy for (−)-dendroprimine (**34**) by one-pot azaelectrocyclization protocol.

synthesized from 2,4,6-trisubstituted piperidine **F**, which was prepared from the one-pot azaelectrocyclization product (−)-**12a** by applying the established method for the 2,4,6-trisubstituted piperidine synthesis.

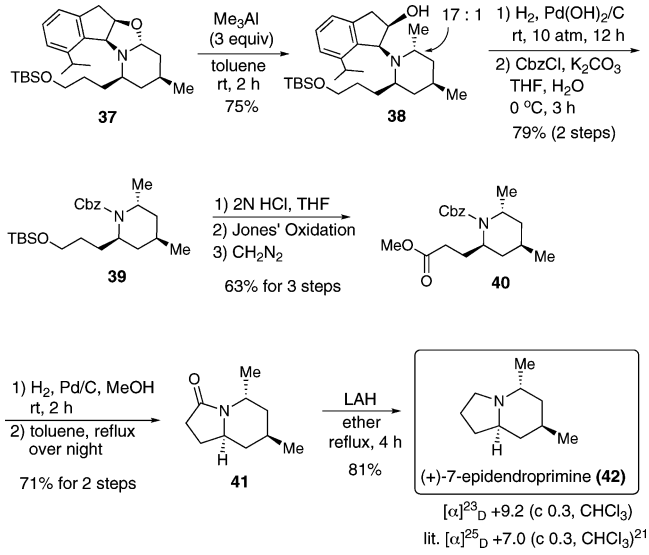
Synthesis of 7-Epidendroprimine (42) from C-4 β-Ester 35. The catalytic hydrogenation of (−)-**12a**, which can be readily prepared using the one-pot azaelectrocyclization protocol (Table 1, entry 7), with Raney-Nickel provided C-4 β-ester **35** as a single stereoisomer in 64% yield. The ester **35** was treated with Red-Al at room temperature to provide the corresponding alcohol **36** in 99% yield resulting from the chemoselective reduction of the ester group as similar to the previously obtained result (Scheme 5). Considering the results on the stereoselectivity described in Table 4 and Scheme 7, we first converted the hydroxymethyl group to a methyl group to obtain the better stereoselectivity at the methylation of the aminoacetal moiety. This conversion was performed by the Ueno's method;[23] tosylation of **36** followed by iodination and radical reduction in one-pot provided methyl derivative **37** in 79% yield for 2 steps (Scheme 8).

Synthesis of (+)-7-epidendroprimine from **37** was achieved as shown in Scheme 9. Thus, C-4 methyl derivative **37** was

Scheme 8. Synthesis of C-4 β-Methyl Compound 37 via One-Pot Azaelectrocyclization



Scheme 9. Stereocontrolled Synthesis of (+)-7-Epidendroprimine (42)



treated with Me_3Al to provide the C-6 α-methyl derivative **38** with 17:1 diastereoselectivity in 67% yield. The removal of the hydroxyl Indane moiety in **38** was successful by a catalytic hydrogenation in the presence of palladium hydroxide, and the resulting piperidine nitrogen was protected with Cbz in 79% yield for two steps. The terminal TBS ether group was converted into the corresponding methyl ester by a sequence of removing TBS, Jones oxidation and esterification. The removal of the Cbz group followed by heating the resulting amine in toluene caused smooth cyclization to produced the corresponding lactam derivative **41**.[24] Finally, the reduction of the lactam carbonyl group of **41** with $LiAlH_4$ under ether reflux condition provided (+)-7-epidendroprimine (**42**) (Scheme 9), whose spectral data were in good corresponding with those of the reported ones.[21]

Synthesis of (−)-Dendroprimine (34) and (+)-5-Epidendroprimine (55) from C-4 α-Ester 43. According to the procedure established in Scheme 3, reduction of the

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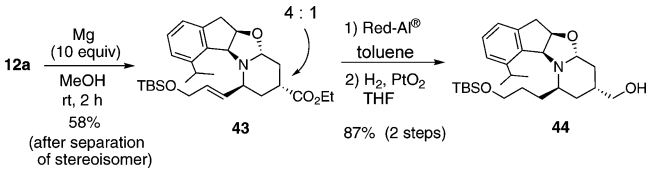
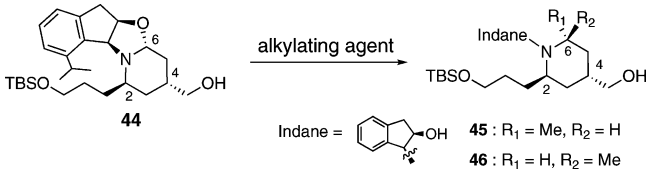
conjugated ester double bond of **12a** with magnesium in methanol selectively provided the C-4 α-isomer **43** at a ratio of 4:1. The relative stereochemistry of the major isomer **43** was unambiguously determined by X-ray crystallographic analysis (see Supporting Information). Reduction of the ester group of the isolated **43** with Red-Al followed by catalytic hydrogenation using PtO_2 afforded the corresponding alcohol **44** in 87% yield for 2 steps (Scheme 10).

Scheme 10. Stereoselective Reduction of Conjugated Ester



To selectively obtain the C-6 α-methyl isomer as described in Table 2, the methylation of the hydroxymethyl derivative **44** using MeMgI unexpectedly gave a 1:1 mixture of diastereomers **45** and **46**, and the reaction with MeMgI and CuI provided the compound **45** with the higher selectivity of 3:1, which were isolable by column chromatography. Surprisingly, the reaction with Me_3Al exclusively produced the undesired C-6 β-methyl isomer **46** (Table 5).

Table 5. Stereoselective Synthesis of C-6 Methyl Isomers 45 and 46



entry	alkylating agent	yield(%)	45:46[b]
1	MeMgI (15 equiv)	73[a]	1:1
2	MeMgI (20 equiv), CuI (20 equiv)	60	3:1
3	Me_3Al (15 equiv)[c]	82	46 only

[a]Yield for mixture of isomers. [b]Determined by ^{1}H NMR analysis of crude mixtures. [c]Reaction was carried out in toluene.

Obviously, the substituents at the C-2 position of the piperidine ring influenced the stereoselectivity of the methylation (compare **19** and **44** in Table 2 and Table 5). The difference of the stereoselectivity might be caused by the location of the hydroxyindane moiety. When the intermediary iminium ion was generated from the aminoacetal group, in the case of the siloxyallyl derivative, the Indane moiety would be situated upside of the iminium ion in order to avoid the steric interaction with the siloxyallyl group at the C-2 position (Figure 7, G and Figure 8). On the other hand, in the case of the phenyl derivative, the Indane moiety would exist downside of the iminium ion, due to the $\pi-\pi$ stacking with the phenyl group at the C-2 position (Figure 7, H).[25]

Thus, since we obtained the two kinds of stereoisomers at the C-6 position, we planned to synthesize (−)-dendroprimine (**34**) and 5-epidendroprimine (**55**) from **45** and **46**, respectively. The removal of the hydroxyl Indane moiety in **45** was achieved by a catalytic hydrogenation, and the resulting piperidine nitrogen was protected by a Cbz group in 80% yield

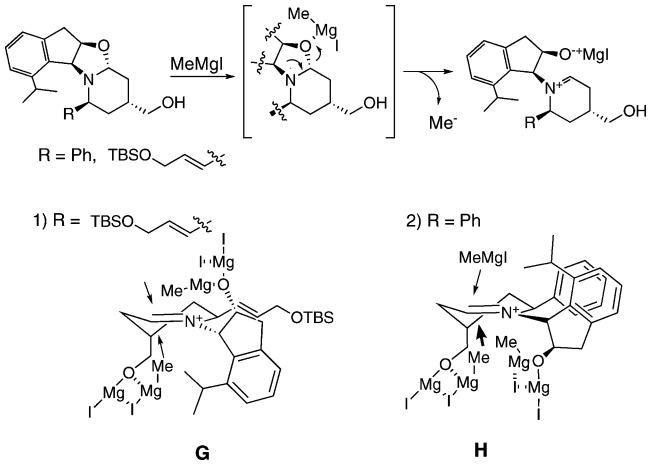


Figure 7. Presumption of stereoselectivity of alkyation on aminoacetal moiety.

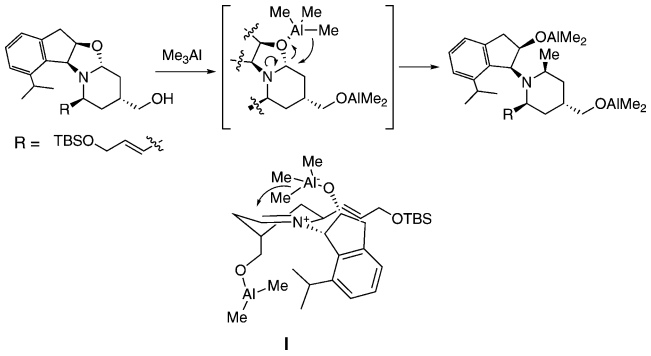


Figure 8. Suggested selectivity of alkyation on aminoacetal moiety.

for two steps. Interconversion of the hydroxymethyl group of the obtained **47** to the methyl group of **48** was successful by the Puglis's method,[26] although the Ueno's procedure applied to **47** was unsuccessful. Thus, **47** was treated with CBr_4/PPh_3 followed by $NaBH_4$ reduction in DMSO to successfully produce the methyl derivative **48** in 72% yield. The total synthesis of (−)-dendroprimine (**34**) was achieved by the same procedure to that of (+)-7-epidendroprimine (**42**) as shown in Scheme 11.

The spectral data (^{1}H and ^{13}C NMR) of the synthesized (−)-dendroprimine (**34**) were in good agreement with those published in the literature.[1a,21] From C-6 β-methyl compound **46**, we also synthesized the (+)-5-epidendroprimine (**55**) by the same procedure to that of (−)-dendroprimine (**34**) as show in Scheme 12.

In the case of (+)-7-epidendroprimine (**42**), although the values of ^{1}H chemical shifts of the both methyl groups were slightly different from those of the reported data by Gelas-Mialhe, these were well corresponded and the spectral data of ^{13}C NMR were in good agreement with those of the reported one. However, the spectral data of the synthesized (+)-5-epidendroprimine (**55**) were not in agreement with, in particular, both the chemical shift and coupling constant assigned to the 7-methyl group and the every values of the chemical shift of ^{13}C NMR were clearly different each other as shown in Table 6.

The synthesis of (−)-dendroprimine (**34**) reported by Gelas-Mialhe is shown in Scheme 13. They synthesized a mixture of

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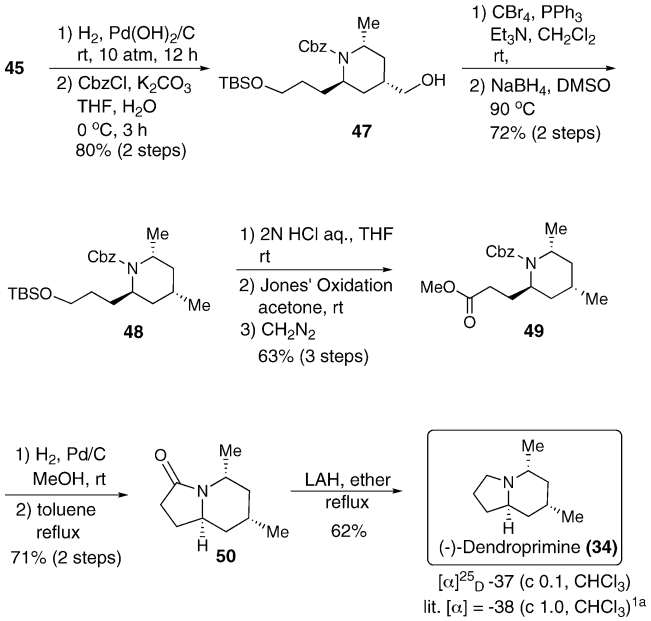
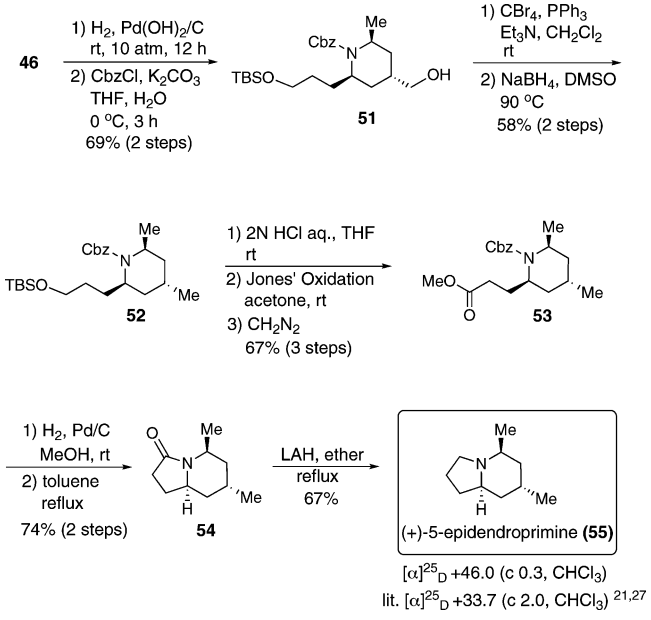
Scheme 11. Synthesis of (−)-Dendroprimine (34)



Scheme 12. Synthesis of (+)-5-Epidendroprimine



compound **57** and **58** from **56** by employing the intramolecular cyclization of the generated intermediary acyliminium ion, which possessed the side chain substituted by an allylsilyl group as an internal π-nucleophile. The catalytic hydrogenation of the mixture of compounds **57** and **58** gave a mixture of lactam derivatives **59**, **60** and **61**. The reduction of the mixture of these compounds gave the corresponding indorizidine alkaloids including (−)-dendroprimine (**34**). In their paper, however, the determination of the relative configuration of the lactam **61**, which was the precursor of (−)-5-epidendroprimine *ent*-(**55**), was not described. We then presumed that the correct stereochemistry of the C-7 methyl group in lactam **61** would not be C-7 β but C-7 α as shown in **62**, and hence it was supposed that they would synthesize not 5-epidendroprimine *ent*-(**55**) but 5,7-epidendroprimine *ent*-(**63**) as shown in Scheme 14.

To confirm this hypothesis, we attempted the synthesis of 5,7-epidendroprimine (**63**) from **64**, which might be obtained by a reaction of compound **37** with the Grignard reagent. Thus, the isolated C-4 methyl derivative **37** was treated with MeMgI to produce the C-6 methyl derivatives as a 1:1 mixture of diastereoisomers in 67% yield. Both stereoisomers were isolated by column chromatography, and we completed the synthesis of (+)-5,7-epidendroprimine (**63**) from compound **64** by the same procedure to the synthesis of other diastereomers as shown in Scheme 15. All the spectral data of (+)-5,7-epidendroprimine (**63**) synthesized by us were in good agreement with the data, which were reported as (+)-5-epidendroprimine (**55**) by Gelas-Mialhe and co-workers (Table 7).[21,27]

As described above, we have concluded that, in Gelas-Mialhe's synthesis,[21,27] the hydrogenation of compound **58** did not produce the lactam **61** but **62** as a single stereoisomer and 5,7-epidendroprimine *ent*-(**63**) was derived from the lactam **62**.

SUMMARY

In summary, we achieved the stereocontrolled synthesis of the chiral 2,4-disubstitiuted and 2,4,6-trisubstituted piperidines from the common synthetic intermediate which was obtained by the unique one-pot protocol of the highly stereoselective asymmetric azaelectrocyclization. The method was applied to the synthesis of a natural indolizidine alkaloid, (−)-dendroprimine (**34**), and its three diastereomers. In particular, in the synthesis of (+)-7-epidendroprimine (**42**), we could realize the complete stereocontrol. Although generality in the stereocontrolled introduction of the desired substituents on the piperidine ring has not still been satisfactory such as from **45** to **46**, the one-pot asymmetric 6π-azaelectrocyclization can be regarded as a powerful method for alkaloid synthesis and also synthesis of polysubstituted chiral piperidines which have a variety of substituents at the C-2 position. Further applications to the synthesis of 2,4,6-trisubsitituted piperidine derivatives and also alkaloids consisted of this core structure, are currently in progress in our laboratory.

EXPERIMENTAL SECTION

General. All commercially available reagents were used without further purification. All solvents were used after distillation. Diethylether, and benzene were refluxed over and distilled from sodium. Dichloromethane and acetonitrile were refluxed over and distilled from P_2O_5. Preparative separation was usually performed by column chromatography on silica gel (60−200 mesh) and on aluminum oxide deactivated with 5 w/% of H_2O. ^1H NMR and ^{13}C NMR spectra were recorded on 400 MHz spectrometer and chemical shifts were represented as δ-values relative to the internal standard TMS. IR spectra were obtained on a FT-IR Spectrometer. Optical rotations were measured on a polarimeterat a wavelength of 589 nm. High resolution mass spectra (HRMS) were obtained by either an electronspray ionization (ESI) or a fast atom bombardment (FAB), and theoretical monoisotopic molecular masses were typically ≤5 ppm. Melting point was uncorrected.

One-pot Reaction by Using (−)-a, 1 and 5. To a solution of the vinyliodide **5** (1.33 g, 5.23 mmol) and molecular sieve 4 Å (5.23 g) in DMF (52 mL) was added (1S, 2R)-(−)-*cis*-1-amino-7-isopropylindan-2-ol (−)-**a** (1.0 g, 5.23 mmol) at room temperature, and the mixture was stirred for 30 min at this temperature. Then to this solution was added lithium chloride (443 mg, 10.46 mmol), Tri(2-furyl)phosphine (97 mg, 0.418 mmol) and Tris(dibenzylideneacetone)dipalladium(0) (96 mg, 0.105 mmol) at room temperature, and the mixture was

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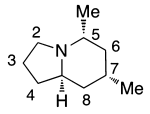
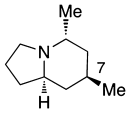
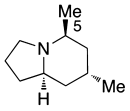
Table 6. Spectral Data of (−)-Dendroprimine (34), (+)-5-Epidendroprimine (55)

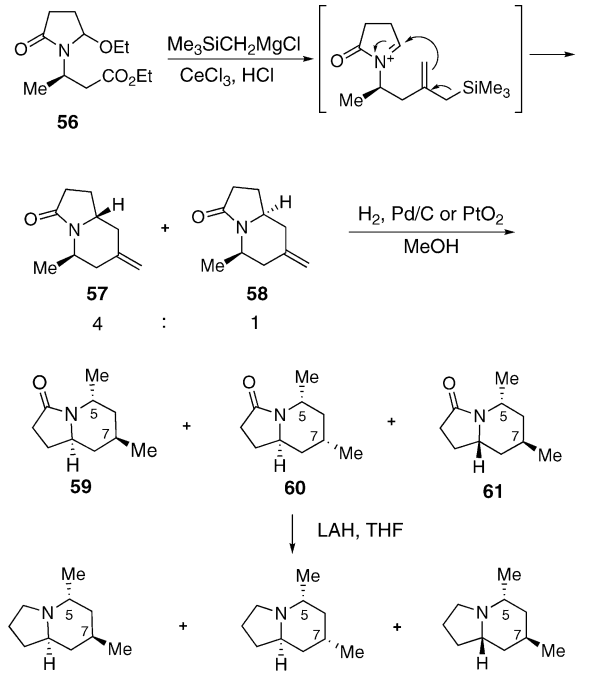
		Optical rotation	^{1}H NMR ($CDCl_3$) 5-methyl	^{1}H NMR ($CDCl_3$) 7-methyl	^{13}C NMR ($CDCl_3$)
 (-)-Dendroprimine **(34)**	Synthetic compound	$[\alpha]^{23}_D$ -36.9 (c 0.1, $CHCl_3$)	1.04 ppm (J = 5.9 Hz)	0.91 ppm (J = 6.3Hz)	δ 60.0, 50.9, 49.8, 42.9, 35.1 26.6, 25.3, 22.1, 21.9, 21.8
	Literature[21]	$[\alpha]^{25}_D$ -37.5 (c 1.3, $CHCl_3$)	1.00 ppm (J = 6.0 Hz)	0.88 ppm (J = 6.3Hz)	δ 60.8, 51.7, 50.6, 43.7, 35.9 27.4, 26.1, 22.9, 22.7, 22.6
	Natural product[1a]	$[\alpha]_D$ -38 (c 1.0, $CHCl_3$)	1.01 ppm (J = 6.0 Hz)	0.89 ppm (J = 5.0 Hz)	

		Optical rotation	^{1}H NMR 5-methyl	^{1}H NMR 7-methyl	^{13}C NMR ($CDCl_3$)
 (+)-7-epidendroprimine **(42)**	Synthetic compound	$[\alpha]^{23}_D$ +9.2 (c 0.3, $CHCl_3$)	0.97 ppm (J = 6.8 Hz)	0.91 ppm (J = 6.3Hz)	δ 54.1, 49.9, 48.5, 40.5, 39.9 30.7, 25.5, 22.3, 21.0, 9.8
	Literature[21]	$[\alpha]^{25}_D$ +7.0 (c 0.4, $CHCl_3$)	0.92 ppm (J = 6.7 Hz)	0.85 ppm (J = 6.4 HZ)	δ 54.2, 49.9, 48.6, 40.6, 40.0 30.8, 25.6, 22.4, 21.1, 9.7

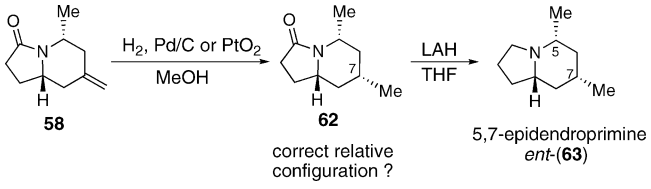
		Optical rotation	^{1}H NMR 5-methyl	^{1}H NMR 7-methyl	^{13}C NMR ($CDCl_3$)
 (+)-5-epidendroprimine **(55)**	Synthetic compound	$[\alpha]^{25}_D$ +46.0 (c 0.3, $CHCl_3$)	1.07 ppm (J = 6.1 Hz)	1.00 ppm (J = 7.3Hz)	δ 58.5, 53.3, 51.6, 40.3, 36.9 30.7, 26.8, 21.2, 20.3, 18.8
	Literature[21, 27]	$[\alpha]^{25}_D$ +33.7 (c 2.0, $CHCl_3$)	1.10 ppm (J = 6.4 Hz)	0.90 ppm (J = 6.4Hz)	δ 64.7, 58.1, 51.4, 43.1, 39.5 31.3, 30.3, 21.9, 21.6, 21.0

Disagreement

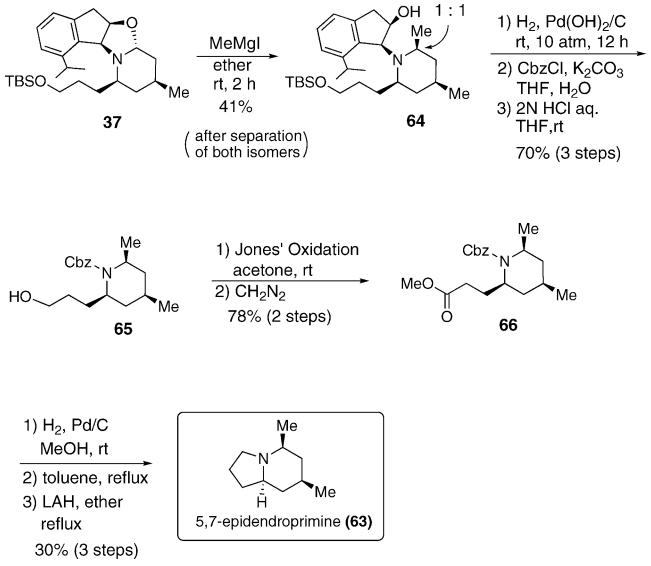
Scheme 13. Synthesis of (−)-Dendroprimine and its Two Isomers by Gelas-Mialhe



Scheme 14. Presumption of Relative Configuration of the Letam Obtained by Hydrogenation of 58



Scheme 15. Synthesis of (+)-5,7-Epidendroprimine (63)



stirred for 10 min at this temperature, then vinylstannane **1** (4.11 g, 10.46 mmol) was added to this solution. After the reaction mixture was stirred at 80 °C for 1 h, 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 a 40:1 mixture of two stereoisomers crude products. These isomers were successfully separated by column

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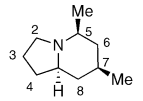
Table 7. Spectral Data of (+)-5,7-Epidendroprimine (63)



(+)-5,7-epidendroprimine **(63)**

	Synthetic compound	reported data as 5-epidendroprimine[21,27]
Optical rotation	$[\alpha]^{23}_D$ +53.7 (c 0.2, $CHCl_3$)	$[\alpha]^{25}_D$ +33.7 (c 2.0, $CHCl_3$)
^{1}H NMR ($CDCl_3$)		
5-methyl	1.10 ppm (J = 6.2 Hz)	1.10 ppm (J = 6.4 Hz)
7-methyl	0.93 ppm (J = 6.6 Hz)	0.90 ppm (J = 6.4 Hz)
^{13}C NMR ($CDCl_3$)	δ 64.7, 58.1, 51.4, 43.2, 39.6 31.4, 30.4, 22.0, 21.0, 20.7	δ 64.7, 58.1, 51.4, 43.1, 39.5 31.3, 30.3, 21.9, 21.6, 21.0

chromatography on silica gel (from 5 to 9% ethyl acetate in hexane) to give the 1,2,5,6-tetrahydropyridine derivative (−)-**1a** (1.77 g, 84%) as a yellow oil: $[\alpha]^{19}_D$ −58.7 (c = 0.3, $CHCl_3$); IR (neat, cm^{-1}) 1717, 1267, 1242, 1032; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.33 (m, 5H), 7.17 (dd, 1H, J = 7.6, 7.6 Hz), 7.01 (d, 1H, J = 8.8 Hz), 6.99 (d, 1H, J = 8.1 Hz), 6.80 (brs, 1H), 5.01−4.96 (m, 1H), 4.92 (d, 1H, J = 5.6 Hz), 4.48 (d, 1H, J = 4.4 Hz), 4.18 (m, 2H), 4.12 (dd, 1H, J = 6.1, 3.7 Hz), 3.15−3.25 (m, 2H), 2.79 (m, 1H), 2.70 (dddd, 1H, J = 19.3, 6.6, 2.2, 2.2 Hz), 2.62 (qq, 1H, J = 6.8, 6.8 Hz), 1.25 (t, 3H, J = 7.1 Hz), 1.01 (d, 3H, J = 6.8 Hz), 0.59 (d, 3H, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 147.8, 143.1, 141.5, 138.3, 136.3, 129.4, 128.8, 128.4, 128.0, 124.0, 123.5, 121.6, 86.7, 75.0, 74.4, 62.2, 60.6, 39.6, 28.0, 25.5, 23.5, 22.8, 14.2; EI-HRMS m/z calcd for $C_{26}H_{29}NO_3$ [M^+] 403.2146, found 403.2137.

One-pot Reaction by using (−)-a, 5 and 6. To a solution of the vinyliodide **5** (100 mg, 0.394 mmol) and molecular sieve 4 Å (394 mg) in DMF (2 mL) was added (1S, 2R)-(−)-*cis*-1-amino-7-isopropylindan-2-ol (−)-**a** (90 mg, 0.473 mmol) at room temperature, and the mixture was stirred for 30 min at this temperature. Then to this solution was added lithium chloride (33 mg, 0.788 mmol), Tri(2-furyl)phosphine (7 mg, 0.03 mmol) and Tris(dibenzylideneacetone)-dipalladium(0) (7 mg, 0.008 mmol) at room temperature, and the mixture was stirred for 10 min at this temperature then vinylstannane **6** (462 mg, 0.788 mmol) was added to this solution. After the reaction mixture was stirred at 80 °C for 1 h, 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 a 16:1 mixture of two stereoisomers crude products. These isomers were successfully separated by column chromatography on silica gel (from 5 to 25% ethyl acetate in hexane) to give the 1,2,5,6-tetrahydropyridine derivative (−)-**6a** (0.169 g, 72%) as a yellow foam: $[\alpha]^{16}_D$ −87.0 (*c* 0.7, $CHCl_3$); IR (KBr disk, cm^{-1}) 1715, 1447, 1373, 1260, 1175, 1113, 1030; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, 1H, J = 8.5 Hz), 7.84 (ddd, 2H, J = 8.8, 2.0, 2.0 Hz), 7.66 (s, 1H), 7.55 (d, 1H, J = 7.8 Hz), 7.35 (m, 1H), 7.28−7.18 (m, 3H), 7.13 (dd, 1H, J = 7.6, 7.6 Hz), 6.98 (d, 1H, J = 7.6 Hz), 6.89 (d, 1H, J = 7.6 Hz), 6.80 (dd, 1H, J = 3.7, 2.0 Hz), 5.00−4.94 (m, 2H), 4.52 (dd, 1H, J = 4.6, 1.2 Hz), 4.34 (dd, 1H, J = 6.3, 3.9 Hz), 4.17 (m, 2H), 3.23 (dd, 1H, J = 18.1, 5.9 Hz), 3.17 (d, 1H, J = 17.1 Hz), 2.84 (m, 1H), 2.77 (dddd, 1H, J = 19.5, 4.4, 4.4, 2,0 Hz), 2.52 (qq, 1H, J = 6.8, 6.8 Hz), 2.32 (s, 3H), 1.24 (t, 3H, J = 7.1 Hz), 0.52 (d, 3H, 6.6 Hz), 0.05 (d, 3H, J = 7.1 Hz): ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 147.6, 145.1, 143.1, 137.4, 136.0, 135.6, 135.2, 130.0, 129.5, 128.8, 126.9, 125.0, 124.4, 123.3, 121.8, 121.6, 113.4, 86.6, 74.9, 74.3, 60.7, 54.4, 39.5, 27.6, 25.6, 22.5, 22.2, 21.5; EI HRMS m/z calcd. For $C_{35}H_{36}N_2O_5S$[M^+] 596.2343, found 596.2345: representative signals in its ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.68 (brs, 1H), 0.93 (d, 1H, J = 6.9 Hz).

One-pot Reaction by using (−)-a, 5 and 7. To a solution of the vinyliodide **5** (100 mg, 0.394 mmol) and molecular sieve 4 Å (394 mg) in DMF (2 mL) was added (1S, 2R)-(−)-*cis*-1-amino-7-isopropylindan-2-ol (−)-**a** (90 mg, 0.473 mmol) at room temperature, and the mixture was stirred for 30 min at this temperature. Then to this solution was added lithium chloride (33 mg, 0.788 mmol), Tri(2-furyl)phosphine (7 mg, 0.03 mmol) and Tris(dibenzylideneacetone)-dipalladium(0) (7 mg, 0.008 mmol) at room temperature, and the mixture was stirred for 10 min at this temperature, then vinylstannane **7** (451 mg, 0.788 mmol) was added to this solution. After the reaction mixture was stirred at 80 °C for 1 h, 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 a 12:1 mixture of two stereoisomers crude products. These isomers were not separated by column chromatography on silica gel to give the 1,2,5,6-tetrahydropyridine derivative (−)-**7a** and isomer (0.154 g, 67%) as a yellow foam. Data for the major isomer (−)-**7a**: $[\alpha]^{26}_D$ −37.5 (c = 0.1, $CHCl_3$); IR (KBr disk cm^{-1}) 1716, 1448, 1371, 1255, 1172, 1030; ^{1}H NMR(400 MHz, $CDCl_3$) δ 8.34 (1H, d, J = 8.5), 7.73 (dd, 2H, J = 8.7, 1.4), 7.52 (m, 1H), 7.43−7.36 (m, 3H), 7.31 (dd, 1H, J = 7.3, 7.3 Hz), 7.17 (dd, 1H, J = 7.6, 7.6 Hz), 6.99 (d, 2H, J = 6.6), 6.89 (s, 1H), 6.57 (m, 1H), 5.23 (dd, 1H, J = 6.0, 3.0 Hz), 4.94 (m, 1H), 4.87 (d, 1H, J = 5.5 Hz), 4.47 (d, 1H, J = 4.6 Hz), 4.14 (m, 2H), 3.17 (m, 1H), 2.91 (qq, 1H, J = 6.9, 6.9 Hz), 2.77 (m, 1H), 2.60 (dddd, 1H, J = 19.0, 11.0, 3.9, 2.5 Hz), 1.25 (m, 3H), 1.02 (d, 3H, J = 6.9 Hz), 0.54 (d, 3H, J = 7.1 Hz): ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 147.6, 143.3, 141.6, 139.1, 137.7, 136.2, 136.1, 134.1, 129.4, 128.9, 126.1, 125.1, 124.2, 124.1, 123.5, 121.8, 120.7, 115.5, 114.0, 86.7, 75.6, 75.5, 60.7, 53.9, 39.4, 28.1, 25.3, 23.5, 23.0, 14.2; ESI HRMS m/z calcd for $C_{34}H_{34}N_2O_5S$ [M^+ + Na] 605.2086, found 605.2077; representative signals in its ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (dd, 1H, J = 8.5, 0.69 Hz), 8.20 (d, 1H, J = 8.5 Hz), 8.14 (d, 1H, J = 8.5 Hz), 6.12 (brs, 1H).

One-pot Reaction by using (−)-a, 5 and 8. To a solution of the vinyliodide **5** (70 mg, 0.276 mmol) and molecular sieve 4 Å (276 mg) in DMF (2.8 mL) was added (1S, 2R)-(−)-*cis*-1-amino-7-isopropylindan-2-ol (−)-**a** (63 mg, 0.331 mmol) at room temperature, and the mixture was stirred for 30 min at this temperature. Then to this solution was added lithium chloride (23 mg, 0.552 mmol), Tri(2-furyl)phosphine (5 mg, 0.022 mmol) and Tris(dibenzylideneacetone)-dipalladium(0) (5 mg, 0.006 mmol) at room temperature, and the mixture was stirred for 10 min at this temperature, then vinylstannane **8** (245 mg, 0.552 mmol) was added to this solution. After the reaction mixture was stirred at 80 °C for 1 h, 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 a 15:1 mixture of two stereoisomers crude products. These isomers were successfully separated by column chromatography on silica gel (from 5 to 25% ethyl acetate in hexane) to give the 1,2,5,6-tetrahydropyridine derivative (−)-**8a** (0.119 g, 74%) as a yellow oil. Data for the major isomer (−)-**8a**: $[\alpha]^{27}_D$ −34.3 (*c* 1.02, $CHCl_3$); IR (neat, cm^{-1}) 2961, 1714, 1670, 1475, 1460, 1258, 1115, 1032; ^{1}H NMR(400 MHz, $CDCl_3$) δ 8.96 (d, 1H, J = 2.1 Hz), 8.21 (d, 1H, J = 2.1 Hz), 8.17 (m, 1H), 7.85 (dd, 1H, J = 8.2, 1.1 Hz), 7.76 (ddd, 1H, J = 8.2, 6.8, 1.3 Hz), 7.60 (ddd, 1H, J = 8.0, 6.8, 1.1 Hz), 7.16 (dd, 1H, J = 7.6, 7.5 Hz), 6.98 (d, 2H, J = 8.0 Hz), 6.82 (dd, 1H, J = 3.4, 2.3 Hz), 5.04 (ddd, 1H, J = 5.1, 5.2, 2.2 Hz), 4.91 (d, 1H, J = 5.5 Hz), 4.55 (dd, 1H, J = 4.8, 0.9 Hz), 4.36 (dd, 1H, J = 6.2, 3.4 Hz), 4.20 (qd, 2H, J = 7.1, 1.4 Hz), 3.22 (m, 1H), 2.86 (m, 1H), 2.78 (dddd, 1H, J = 19.4, 11.2, 4.8, 2.3 Hz), 2.49 (qq, 1H, J = 6.9, 6.9 Hz), 1.26 (t, 3H, J = 7.1 Hz), 1.0 (d, 3H, J = 6.9 Hz), 0.31 (d, 3H, J = 6.9 Hz) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 151.8, 148.0, 147.6, 143.2, 136.8, 135.8, 135.7, 134.3, 129.7, 129.3, 128.9, 127.7, 127.6, 127.0, 125.1, 123.5, 121.7, 86.5, 75.1, 74.5, 60.8, 60.2, 39.6, 28.3, 25.5, 23.3, 22.4, 14.2; ESI HRMS m/z calcd for $C_{29}H_{30}N_2O_3$ [M^+ + Na] 477.2154, found 477.2160; representative signals in its ^{1}H NMR(400 MHz, $CDCl_3$) δ 8.93 (dd, 1H, J = 5.0, 0.92 Hz), 6.78 (d, 1H, J = 3.0 Hz), 1.14 (d, 3H, J = 6.6 Hz).

One-pot Reaction by using (−)-a, 5 and 9. To a solution of the vinyliodide **5** (100 mg, 0.394 mmol) and molecular sieve 4 Å (394 mg)

dx.doi.org/10.1021/jo202350z | J. Org. Chem. 2012, 77, 1812−1832

in DMF (2 mL) was added (1S, 2R)-(−)-*cis*-1-amino-7-isopropylindan-2-ol (−)-**a** (90 mg, 0.473 mmol) at room temperature, and the mixture was stirred for 30 min at this temperature. Then to this solution was added lithium chloride (33 mg, 0.788 mmol), Tri(2-furyl)phosphine (7 mg, 0.03 mmol) and Tris(dibenzylideneacetone)-dipalladium(0) (7 mg, 0.008 mmol) at room temperature, and the mixture was stirred for 10 min at this temperature, then vinylstannane **9** (311 mg, 0.788 mmol) was added to this solution. After the reaction mixture was stirred at 80 °C for 1 h, 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 a 16:1 mixture of two stereoisomers crude products. These isomers were successfully separated by column chromatography on silica gel (from 5 to 25% ethyl acetate in hexane) to give the 1,2,5,6-tetrahydropyridine derivative (−)-**9a** (0.127 g, 80%) as a yellow oil. Data for the major isomer (−)-**9a**: $[\alpha]^{27}_D$ −50.9 (*c* 1.02, $CHCl_3$); IR (neat, cm^{-1}) 2961, 1714, 1473, 1114, 1032; ^1H NMR(400 MHz, $CDCl_3$) δ 8.60 (ddd, 1H, *J* = 5.0, 1.8, 0.92), 7.78 (ddd, 1H, *J* = 7.8, 7.6, 1.8 Hz), 7.50 (ddd, 1H, *J* = 7.8, 2.1, 1.2 Hz), 7.29 (ddd, 1H, *J* = 7.6, 5.0, 1.2 Hz), 7.17 (dd, 1H, *J* = 7.6, 7.6 Hz), 7.00 (d, 1H, *J* = 7.1 Hz), 6.99 (d, 1H, *J* = 7.3 Hz), 6.88 (dd, 1H, *J* = 2.3, 1.2 Hz), 5.11 (d, 1H, *J* = 5.5 Hz), 5.02 (ddd, 1H, *J* = 5.5, 5.3, 2.3 Hz), 4.49 (d, 1H, *J* = 4.4 Hz), 4.40 (dd, 1H, *J* = 6.4, 3.4 Hz), 4.20 (m, 2H), 3.20 (m, 1H), 2.82 (m, 1H), 2.69 (m, 1H), 2.51 (qq, 1H, *J* = 7.1, 6.9 Hz), 1.26 (t, 3H, *J* = 7.1 Hz), 1.00 (d, 3H, *J* = 6.6 Hz), 0.63 (d, 3H, *J* = 7.1 Hz), ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 161.4, 148.7, 147.4, 143.3, 136.6, 136.5, 136.2, 128.8, 124.7, 124.2, 123.4, 122.9, 121.7, 86.4, 75.2, 74.5, 64.1, 60.7, 39.5, 28.2, 25.4, 23.3, 23.0, 14.2; ESI HRMS *m*/*z* calcd for $C_{25}H_{28}N_2O_3$ [M^+ + Na] 427.1998, found 427.1990; representative signals in its ^1H NMR(400 MHz, $CDCl_3$) δ 6.12 (d, 1H, *J* = 7.6 Hz), 5.57 (d, 1H, *J* = 7.1 Hz), 3.90 (ddd, 1H, *J* = 7.8, 7.6, 1.8 Hz).

One-pot reaction by using (−)-a, 5 and 10. To a solution of the vinyliodide **5** (100 mg, 0.394 mmol) and molecular sieve 4 Å (394 mg) in DMF (2 mL) was added (1S, 2R)-(−)-*cis*-1-amino-7-isopropylindan-2-ol (−)-**a** (90 mg, 0.473 mmol) at room temperature, and the mixture was stirred for 30 min at this temperature. Then to this solution was added lithium chloride (33 mg, 0.788 mmol), Tri(2-furyl)phosphine (7 mg, 0.03 mmol) and Tris(dibenzylideneacetone)-dipalladium(0) (7 mg, 0.008 mmol) at room temperature, and the mixture was stirred for 10 min at this temperature, then vinylstannane **10** (311 mg, 0.788 mmol) was added to this solution. After the reaction mixture was stirred at 80 °C for 1 h, 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 a 17:1 mixture of two stereoisomers crude products. These isomers were successfully separated by column chromatography on silica gel (from 5 to 25% ethyl acetate in hexane) to give the 1,2,5,6-tetrahydropyridine derivative (−)-**10a** (0.124 g, 78%) as a yellow oil. Data for the major isomer (−)-**10a**: $[\alpha]^{27}_D$ −35.8 (*c* 0.3, $CHCl_3$); IR (neat, cm^{-1}) 2959, 1712, 1476, 1030; ^1H NMR(400 MHz, $CDCl_3$) δ 8.67 (dd, 1H, *J* = 2.2, 0.73 Hz), 8.64 (dd, 1H, *J* = 4.6, 1.7 Hz), 7.78 (ddd, 1H, *J* = 7.8, 4.2, 2.0 Hz), 7.38 (ddd, 1H, *J* = 7.8, 4.6, 0.73 Hz), 7.19 (dd, 1H, *J* = 7.6, 7.6 Hz), 7.01 (d, 2H, *J* = 7.8 Hz), 6.73 (dd, 1H, *J* = 3.7, 2.2 Hz), 4.99 (ddd, 1H, *J* = 5.4, 5.1, 2.4 Hz), 4.85 (d, 1H, *J* = 5.4 Hz), 4.49 (d, 1H, *J* = 4.1 Hz), 4.24−4.16 (m, 3H), 3.21 (m, 1H), 2.81 (m, 1H), 2.70 (dddd, 1H, *J* = 19.0, 11.2, 4.6, 2.4 Hz), 2.53 (qq, 1H, *J* = 6.8, 6.8 Hz), 1.27 (t, 3H, *J* = 7.1 Hz), 1.04 (d, 3H, *J* = 6.8 Hz), 0.63 (d, 3H, *J* = 7.1 Hz), ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 150.2, 149.5, 147.5, 143.1, 137.2, 137.0, 136.8, 135.7, 128.9, 124.9, 123.5, 123.4, 121.7, 86.4, 75.0, 74.4, 60.7, 59.8, 39.5, 28.2, 25.4, 23.3, 22.6, 14.1; ESI HRMS *m*/*z* calcd for $C_{25}H_{28}N_2O_3$ [M^+ + Na] 427.1998, found 427.1991; representative signals in its ^1H NMR(400 MHz, $CDCl_3$) δ 6.86 (dd, 1H, *J* = 1.7, 0.7 Hz), 1.45 (t, 3H, *J* = 7.1 Hz), 0.45 (d, 3H, *J* = 7.1 Hz).

One-pot Reaction by using (−)-a, 5 and 11. To a solution of the vinyliodide **5** (100 mg, 0.394 mmol) and molecular sieve 4 Å (394 mg) in DMF (2 mL) was added (1S, 2R)-(−)-*cis*-1-amino-7-isopropylindan-2-ol (−)-**a** (90 mg, 0.473 mmol) at room temperature, and the mixture was stirred for 30 min at this temperature. Then to this solution was added lithium chloride (33 mg, 0.788 mmol), Tri(2-furyl)phosphine (7 mg, 0.03 mmol) and Tris(dibenzylideneacetone)dipalladium(0) (7 mg, 0.008 mmol) at room temperature, and the mixture was stirred for 10 min at this temperature, then vinylstannane **11** (315 mg, 0.788 mmol) was added to this solution. After the reaction mixture was stirred at 80 °C for 1 h, 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 a 15:1 mixture of two stereoisomers crude products. These isomers were successfully separated by column chromatography on silica gel (from 5 to 25% ethyl acetate in hexane) gave the 1,2,5,6-tetrahydropyridine derivative (−)-**11a** (0.119 g, 74%) as a yellow oil. Data for the major isomer (−)-**11a**: $[\alpha]^{27}_D$ −51.8 (*c* 0.8, $CHCl_3$); IR (neat, cm^{-1}) 1714, 1475, 1253, 1114, 1032; ^1H NMR(400 MHz, $CDCl_3$) δ 7.37 (dd, 1H, *J* = 5.0, 3.0 Hz), 7.30 (dd, 1H, *J* = 3.0, 1.2 Hz), 7.18 (dd, 1H, *J* = 7.6, 7.6 Hz), 7.13 (dd, 1H, *J* = 5.0, 1.2 Hz), 7.03 (d, 1H, *J* = 7.6 Hz), 6.99 (d, 1H, *J* = 7.6 Hz), 6.79 (dd, 1H, *J* = 3.7, 2.1 Hz), 4.97 (d, 1H, *J* = 5.7 Hz), 4.95 (dd, 1H, *J* = 5.7, 2.1 Hz), 4.45 (d, 1H, *J* = 4.4 Hz), 4.28 (dd, 1H, *J* = 6.0, 3.7 Hz), 4.19 (m, 2H), 3.20 (m, 1H), 2.67−2.79(m, 3H), 1.26 (t, 3H, *J* = 7.1 Hz), 1.0 (d, 3H, *J* = 6.6 Hz), 0.74 (d, 3H, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 147.8, 143.1, 142.4, 137.7, 136.3, 128.8, 128.2, 126.0, 124.3, 123.5, 123.3, 121.6, 86.5, 74.9, 74.4, 60.6, 57.1, 39.6, 28.2, 25.5, 23.6, 22.9, 14.2; ESI HRMS *m*/*z* calcd for $C_{24}H_{27}NO_3S$ [M^+ + Na] 432.1609, found 432.1598; representative signals in its ^1H NMR(400 MHz, $CDCl_3$) δ 3.90 (dd, 1H, *J* = 9.2, 5.5 Hz), 3.84 (ddd, 1H, *J* = 6.0, 5.7, 2.8 Hz), 0.91 (d, 3H, *J* = 6.9 Hz).

One-pot Reaction using (−)-a, 5 and 12. To a solution of the vinyliodide **5** (1.5 g, 5.91 mmol) and molecular sieve 4 Å (5.91 g) in DMF (60 mL) was added (1*S*, 2*R*)-(−)-*cis*-1-amino-7-isopropylindan-2-ol (−)-**a** (1.13 g, 5.91 mmol) at room temperature, and the mixture was stirred for 30 min at this temperature. Then to this solution was added lithium chloride (500 mg, 11.81 mmol), Tri(2-furyl)phosphine (110 mg, 0.472 mmol) and Tris(dibenzylideneacetone)dipalladium(0) (108 mg, 0.118 mmol) at room temperature, and the mixture was stirred for 10 min at this temperature, then vinylstannane **12** (5.76 g, 11.81 mmol) was added to this solution. After the reaction mixture was stirred at 80 °C for 1 h, 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 a 20:1 mixture of two stereoisomer crude products. These isomers were successfully separated by column chromatography on silica gel (from 5 to 9% ethyl acetate in hexane) to give the 1,2,5,6-tetrahydropyridine derivative (−)-**12a** (2.28 g, 78%) as a yellow oil: $[\alpha]^{21}_D$ −49.6 (c = 0.5, $CHCl_3$), IR (neat, cm^{-1}) 1717, 1462, 1254, 1113; ^1H NMR (400 MHz, $CDCl_3$) δ 7.22 (dd, 1H, *J* = 7.6, 7.6 Hz), 7.13 (d, 1H, *J* = 7.6 Hz), 7.02 (d, 1H, *J* = 7.3 Hz), 6.73−6.72 (m, 1H), 5.89 (dt, 1H, *J* = 15.4, 4.4 Hz), 5.80 (ddt, 1H, *J* = 15.1, 8.8, 1.5 Hz), 4.98 (d, 1H, *J* = 5.4 Hz), 4.84 (ddd, 1H, *J* = 5.6, 5.6, 2.0 Hz), 4.38 (d, 1H, *J* = 4.6 Hz), 4.26 (d, 2H, *J* = 4.2 Hz), 4.20 (q, 2H, *J* = 7.1 Hz), 3.63−3.58 (m, 1H), 3.54 (qq, 1H, *J* = 6.8, 6.8 Hz), 3.20 (dd, 1H, *J* = 17.8, 5.6 Hz), 3.14 (brd, 1H, *J* = 17.3 Hz), 2.68 (dd, 1H, *J* = 19.3, 3.2 Hz), 2.60−2.52 (m, 1H), 1.28 (t, 3H, *J* = 7.3 Hz), 1.22 (d, 3H, *J* = 6.8 Hz), 1.15 (d, 3H, *J* = 6.8 Hz), 0.94 (s, 9H), 0.11 (d, 6H, *J* = 0.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 147.6, 143.2, 137.9, 136.6, 133.2, 129.8, 128.7, 124.7, 123.5, 121.7, 86.4, 75.0, 74.0, 62.9, 60.6, 60.0, 39.6, 28.6, 26.0, 25.5, 23.5, 23.4, 18.4, 14.2, −5.3; EI-HRMS *m*/*z* calcd for $C_{29}H_{43}NO_4Si$ [$M]^+$ 497.2959, found 497.2952. Representative signals in its ^1H NMR (400 MHz, $CDCl_3$) δ 5.52 (ddt, 1H, *J* = 15.1, 10.0, 1.5 Hz), 4.95 (d, 1H, *J* = 6.1 Hz), 4.47 (ddd, 1H, *J* = 7.6, 7.6, 1.5 Hz), 4.42 (dd, 1H, *J* = 7.3, 1.0 Hz).

(−)-(*β*)-Ethylester Piperidine Derivative (−)-13. To a solution of (−)-**1a** (402 mg, 0.99 mmol) in ethanol (3.0 mL) was added Raney-Ni W2 (excess amount) at a room temperature. After the reaction mixture was stirred under H_2 atmosphere for 2 h, the catalyst was removed by filtration and the filtrate was concentrated *in vacuo* to give crude products, which were purified by column chromatography on silica gel (5−13% ethyl acetate in hexane) gave the piperidine (*β*)-ester derivative (−)-**13** (349 mg, 87%) as a colorless oil: $[\alpha]^{26}_D$ −56.5 (c = 0.68, $CHCl_3$); IR (neat, cm^{-1}) 1732, 1593, 1315, 1179; ^1H NMR (400 MHz, $CDCl_3$) δ7.48 (d, 1H, *J* = 7.1 Hz), 7.39−7.35 (m, 1H),

dx.doi.org/10.1021/jo202350z | J. Org. Chem. 2012, 77, 1812−1832

7.33−7.28 (m, 1H), 7.15 (dd, 1H, J = 7.6 Hz), 7.02 (d, 1H, J = 7.3 Hz), 6.96 (m, 1H), 4.93−4.90 (m, 1H), 4.73 (d, 1H, J = 5.4 Hz), 4.39 (dd, 1H, J = 2.7, 2.7 Hz), 4.11 (q, 2H, J = 7.1 Hz), 3.52 (dd, J = 12.0, 2.9 Hz), 3.19−3.05 (m, 2H), 3.01 (qq, 1H, J = 6.8, 6.8 Hz), 2.88 (dddd, 1H, J = 12.4, 12.4, 3.7, 3.7 Hz), 2.29 (dddd, 1H, J = 14.4, 4.2, 2.4, 2.4 Hz), 2.07 (ddd, 1H, J = 13.4, 5.9, 2.9 Hz), 2.00−1.86 (m, 2H), 1.21 (t, 3H, J = 7.1 Hz), 1.19 (d, 3H, J = 7.1 Hz), 0.66 (d, 3H, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 147.7, 142.8, 142.7, 136.7, 128.8, 128.5, 128.1, 127.8, 123.5, 121.8, 89.0, 75.4, 73.3, 62.8, 60.4, 39.6, 36.3, 36.1, 29.0, 28.1, 23.7, 22.7, 14.2; ESI-HRMS m/z for calcd for $C_{26}H_{32}NO_3$ $[M + H]^+$ 406.2382, found 406.2379.

(2*S*,4*R*)-(−)-4-Hydroxymethyl-2-phenylpiperidine (−)-14. To a solution of compound (−)-**13** (150 mg, 0.370 mmol) of dichloromethane (3.7 mL) was slowly added diisobutylaluminium hydride (1.5 mL, 1.48 mmol, 1 M in toluene) at −78 °C. After the mixture was stirred at this temperature for 1 h, H_2O and saturated aqueous potassium sodium tartrate tetrahydrate solution was carefully added, and the resulting mixture was extracted with diethyl ether. 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 (20−50% ethyl acetate in hexane) to give the diol (117 mg, 79%) as a colorless oil.

To a solution of diol obtained above (128 mg, 0.350 mmol) in $CHCl_3$ (1.75 mL) was added *n*-propylamine (0.14 mL) and lead tetraacetate (465 mg, 1.05 mmol) at −50 °C. After the mixture was stirred at this temperature for 30 min, it was added to ice-1N aqueous NaOH solution 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 (from 0 to 20% methanol in chloroform) to give (−)-**14** (43 mg, 69%) as a white amorphous solid: $[\alpha]^{23}_D$ −40.6 (*c* 0.3, MeOH); IR (neat, cm^{-1}) 3289, 3165, 1262, 1096, 1044, 802; ^{1}H NMR(400 MHz, CD_3OD) δ 7.37−7.30 (m, 4H), 7.26−7.21 (m, 1H), 3.65 (dd, 1H, J = 11.4, 2.1 Hz), 3.43 (dd, 2H, J = 6.0, 2.5 Hz), 3.21 (ddd, 1H, J = 12.4, 3.9, 1.8 Hz), 2.81 (ddd, 1H, J = 12.6, 2.3 Hz), 1.93−1.88 (m, 1H), 1.84−1.73 (m, 2H), 1.30−1.19 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 145.2, 129.5, 128.4, 127.8, 68.2, 62.5, 40.7, 38.2, 29.5; FAB-HRMS m/z calcd for $C_{12}H_{18}NO$ $[M + H]^+$ 192.1388, found 192.1388.

(−)-(α)-Ethylester Piperidine Derivative (−)-15. To magnesium turning (1.21 g, 49.7 mmol) in methanol (5.0 mL) was added a solution of the (−)-**1a** (1.34 g, 3.32 mmol) in methanol (28 mL) at room temperature. After the mixture was stirred at this temperature for 2 h, H_2O and 2N aqueous HCl solution was carefully added, and the pH of the solution was adjusted toward 7. 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 a 5:1 mixture (determined by ^{1}H NMR) of two stereoisomer crude products. These isomers were successfully separated by column chromatography on silica gel (from 5 to 13% ethyl acetate in hexane) to give the piperidine (α)-ester derivative (−)-**15** (704 mg, 52%) as a white crystalline solid: mp = 86−89 °C, $[\alpha]^{23}_D$ −52.4 (c 1.0, $CHCl_3$); IR (KBr disk, cm^{-1}) 1730, 1454, 1188, 1086; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (m, 1H), 7.38 (m, 1H), 7.30 (dddd, 1H, J = 6.3, 6.3, 1.2, 1.2 Hz), 7.13 (dd, 1H, J = 7.3, 7.3 Hz), 7.01 (d, 1H, J = 7.3 Hz), 6.94 (d, 1H, J = 6.8 Hz), 4.78 (dd, 1H, J = 5.6, 5.6 Hz), 4.30−4.16 (m, 3H), 3.84 (dd, 1H, J = 12.0, 3.2 Hz), 3.16−2.98 (m, 3H), 2.66−2.61 (m, 2H), 2.25 (ddd, 1H, J = 13.7, 5.6, 2.7 Hz), 2.06 (ddd, 1H, J = 9.8, 6.6, 2.9 Hz), 1.84 (ddd, 1H, J = 12.0, 4.4, 1.7 Hz), 1.33 (t, 3H, J = 7.1 Hz), 1.15 (d, 3H, J = 6.8 Hz), 0.66 (d, 3H, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 147.6, 143.6, 143.1, 136.8, 128.9, 128.4, 128.1, 127.5, 123.3, 121.7, 88.6, 75.4, 73.6, 60.3, 59.1, 39.3, 34.2, 33.8, 28.1, 28.0, 23.6, 22.7, 14.2; FAB-HRMS m/z calcd for $C_{26}H_{32}NO_3$ $[M + H]^+$ 406.2382, found 406.2394; Data for minor isomer **15′**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.93 (dd, 1H, J = 5.3, 5.3 Hz), 4.74 (d, 1H, J = 5.3 Hz), 3.67 (s, 3H), 1.20 (d, 3H, J = 6.6 Hz), 0.67 (d, 3H, J = 6.9 Hz).

(2*S*,4*S*)-(−)-4-Hydroxymethyl-2-phenylpiperidine (−)-16. To a solution of compound (−)-**15** (111 mg, 0.274 mmol) of dichloromethane (2.7 mL) was slowly added diisobutylaluminium hydride (1.1 mL, 1.10 mmol, 1 M in toluene) at −78 °C. After the mixture was stirred at this temperature for 1 h, H_2O and saturated aqueous potassium sodium tartrate tetrahydrate solution was carefully added, and the resulting mixture was extracted with diethyl ether. 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 (20−50% ethyl acetate in hexane) to give the diol (83 mg, 83%) as a colorless oil.

To a solution of diol obtained above (69 mg, 0.254 mmol) in $CHCl_3$ (1.27 mL) was added *n*-propylamine (0.10 mL) and lead tetraacetate (340 mg, 0.763 mmol) at −50 °C. After the mixture was stirred at this temperature for 30 min, added to ice-1N aqueous NaOH solution 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 (from 0 to 20% methanol in chloroform) to give the (−)-**16** (27 mg, 75%) as a white amorphous solid: $[\alpha]^{23}_D$ −12.8 (*c* 0.3, MeOH); IR (KBr disk, cm^{-1}) 3263, 3117(br), 1605, 1451, 1325, 1059, 1038; ^{1}H NMR(400 MHz, $CDCl_3$) δ 7.39 − 7.37 (m, 2H), 7.34−7.30 (m, 2H), 7.25−7.21 (m, 1H), 3.88 (dd, 1H, J = 9.8, 3.2 Hz), 3.77−3.75 (m, 2H), 2.96−2.93 (m, 2H), 2.08−2.00 (m, 1H), 1.94−1.87 (m, 1H), 1.86−1.77) (m, 2H), 1.67−1.61 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.5, 128.4, 126.9, 126.9, 64.2, 56.1, 42.2, 35.0, 34.8, 27.0; ESI HRMS m/z calcd for $C_{12}H_{18}NO$ $[M + H]^+$ 192.1388, found 192.1391.

(−)-(β)-Hydroxymethyl Piperidine Derivative (−)-18. To a solution of compound (−)-**13** (304 mg, 0.75 mmol) of toluene (4 mL) was slowly added Red-Al (0.58 mL, >65 wt.% in toluene) at 0 °C. After the mixture was stirred at this temperature for 30 min, H_2O and saturated aqueous potassium sodium tartrate tetrahydrate solution was carefully 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, which were purified by column chromatography on silica gel (20−50% ethyl acetate in hexane) to give the piperidine (β)-hydroxymethyl derivative (−)-**18** (270 mg, 99%) as a white crystalline solid: mp = 109−114 °C, $[\alpha]^{25}_D$ −63.7 (c = 0.88, $CHCl_3$); IR (KBr disk, cm^{-1}) 3378(br), 1593, 1454, 1190, 1038; ^{1}H NMR (400 MHz, $CDCl_3$) δ7.48 (d, 1H, J = 7.5 Hz), 7.37 (m, 1H), 7.29 (ddd, 1H, J = 7.2, 1.4, 1.4 Hz), 7.15 (dd, 1H, J = 7.6, 7.6 Hz), 7.02 (d, 1H, J = 7.6 Hz), 6.97 (d, 1H, J = 7.4, Hz), 4.92 (dd, 1H, J = 6.2, 5.7 Hz), 4.74 (d, 1H, J = 5.2 Hz), 4.39 (dd, 1H, J = 2.6, 2.6 Hz), 3.57−3.47 (m, 3H), 3.19−3.07 (m, 2H), 3.04 (qq, 1H, J = 7.0, 7.0 Hz), 2.11−2.06 (m, 2H), 1.88 (ddd, 1H, J = 12.9, 5.6, 2.7 Hz), 1.59−1.50 (m, 3H), 1.19 (d, 3H, J = 6.8 Hz), 0.66 (d, 3H, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.7, 143.4, 142.9, 137.0, 128.7, 128.5, 128.1, 127.6, 123.4, 121.8, 89.5, 75.3, 73.3, 67.5, 63.1, 39.6, 37.1, 33.0, 29.5, 28.1, 23.7, 22.7; ESI-HRMS m/z calcd for $C_{24}H_{30}NO_2$ $[M + H]^+$ 364.2277, found 364.2269.

(−)-(α)-Hydroxymethyl Piperidine Derivative (−)-19. To a solution of compound (−)-**15** (407 mg, 1.00 mmol) of toluene (5 mL) was slowly added Red-Al (0.67 mL, >65 wt.% in toluene) at 0 °C. After the mixture was stirred at this temperature for 2 h, H_2O and saturated aqueous potassium sodium tartrate tetrahydrate solution was carefully 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, which were purified by column chromatography on silica gel (20−50% ethyl acetate in hexane) to give the piperidine (α)-hydroxymethyl derivative (−)-**19** (362 mg, 99%) as a white crystalline solid: mp = 119−112 °C, $[\alpha]^{23}_D$ −60.9 (c 1.0 $CHCl_3$), IR (KBr disk, cm^{-1}) 3416 (br), 1454, 1152, 1054; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (m, 1H), 7.37 (m, 1H), 7.29 (dddd, 1H, J = 7.3, 7.3, 1.5, 1.5 Hz), 7.15 (dd, 1H, J = 7.6, 7.6 Hz), 7.03 (d, 1H, J = 7.6 Hz), 6.96 (d, 1H, J = 7.3 Hz), 4.87 (dd, 1H, J = 5.1, 5.1 Hz), 4.74 (d, 1H, J = 5.1 Hz), 4.33 (dd, 1H, J = 2.7, 2.7 Hz), 3.87−3.78 (m, 2H), 3.74 (dd, 1H, J = 11.5, 2.9 Hz), 3.18−3.02 (m, 3H), 2.10−1.99 (m, 3H), 1.89 (dddd, 1H, J = 13.4, 3.2, 1.7, 1.7 Hz), 1.20 (d, 3H, J = 6.6 Hz), 0.67 (d, 3H, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.7, 143.5, 142.7, 136.7, 128.9,

dx.doi.org/10.1021/jo202350z | J. Org. Chem. 2012, 77, 1812−1832

128.5, 128.1, 127.6, 123.5, 121.8, 89.0, 75.2, 73.5, 66.5, 58.8, 39.3, 35.6, 32.3, 28.1, 27.9, 23.7, 22.7; FAB-HRMS m/z calcd for $C_{24}H_{30}NO_2$ $[M + H]^+$ 364.2277, found 364.2267.

(1*S*,2*R*)-(−)-*cis*-1-[(2*S*,4*S*,6*R*)-4-Hydroxymethyl-6-methyl-2-phenylpiperidin-1-yl]-7-isopropylindan-2-ol (−)-20. To a solution of compound (−)-**18** (186 mg, 0.512 mmol) in ether (5.8 mL) was added a 1.0 M solution of methylmagnesium iodide in ether (11.5 mL, 11.5 mmol) prepared from methyl iodide (1.24 mL, 19.9 mmol), magnesium turning (440 mg, 18.1 mmol), and ether (18.1 mL) at 0 °C. After the mixture was stirred at room temperature for 3 h, 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 a 40:1 mixture (determined by ^1H NMR) of two stereoisomers crude products. These isomers were successfully separated by column chromatography on silica gel (from 5 to 50% ethyl acetate in hexane) to give the piperidine (−)-**20** (113 mg, 58%) as a white amorphous solid: $[\alpha]^{23}_D$ −134.8 (c = 1.0, $CHCl_3$); IR (KBr disk, cm^{-1}) 3416(br), 1447, 1387, 1080, 1049; ^1H NMR (400 MHz, $CDCl_3$) δ7.31−7.16 (m, 7H), 6.95 (d, 1H, J = 7.3, Hz), 4.76 (d, 1H, J = 7.3 Hz), 4.19−4.15 (m, 1H), 3.81−3.74 (m, 2H), 3.50−3.39 (m, 4H), 2.91 (dd, 1H, J = 15.6, 7.6 Hz), 2.27 (dd, 1H, J = 15.6, 9.3 Hz), 1.92−1.81 (m, 1H), 1.76 (m, 1H), 1.67 (m, 1H), 1.41 (d, 3H, J = 6.6 Hz), 1.40 (d, 3H, J = 6.8 Hz), 1.17 (d, 3H, J = 6.8 Hz),1.11(ddd, 1H, J = 12.9, 12.9, 6.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.9, 144.7, 142.7, 137.9, 129.1, 128.7, 127.2, 126.4, 123.1, 122.6, 74.1, 68.4, 59.0, 56.0, 50.4, 40.6, 36.8, 34.0, 31.5, 29.6, 25.9, 21.5, 21.3; FAB-HRMS m/z calcd for $C_{25}H_{34}NO_2$ $[M + H]^+$ 380.2590, found 380.2580.

(2*S*,4*S*,6*R*)-(+)-4-Hydroxymethyl-6-methyl-2-phenylpiperidine (+)-21. To a solution of compound (−)-**20** (113 mg, 0.298 mmol) in $CHCl_3$ (3 mL) was added lead tetraacetate (396 mg, 0.893 mmol) at −50 °C. After the mixture was stirred at this temperature for 30 min, added to ice-1N aqueous NaOH solution 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 (from 0 to 20% methanol in chloroform) to give the (+)-**21** (39 mg, 64%) as a yellow oil: $[\alpha]^{24}_D$ 9.2 (c = 0.77, $CHCl_3$); IR (neat, cm^{-1}) 3314(br), 1454, 1377, 1053; ^1H NMR (400 MHz, $CDCl_3$) δ7.42 (m, 2H), 7.35 (m, 2H), 7.21 (m, 1H), 4.39 (d, 1H, J = 3.9 Hz), 3.48 (d, 2H, J = 6.1 Hz), 2.88 (ddq, 1H, J = 13.4, 6.4, 2.9 Hz), 2.40−2.36 (m, 1H), 1.79 (dddd, 1H, J = 18.8, 12.9, 6.6, 3.7 Hz), 1.69 (m, 1H), 1.62 (ddd, 1H, J = 12.4, 12.4, 5.4 Hz), 1.10 (d, 3H, J = 6.3 Hz), 0.92(ddd, 1H, J = 12.0, 12.0, 12.0 Hz), ^{13}C NMR (100 MHz, CDCl3) δ 142.7, 128.5, 126.7, 126.2, 68.3, 54.0, 45.2, 37.6, 34.3, 31.6, 22.9; EI-HRMS m/z calcd for $C_{13}H_{19}NO$ $[M]^+$ 205.1467, found 205.1467.

(2*S*,4*S*,6*S*)-(−)-4-Hydroxymethyl-2-phenyl-6-vinylpiperidine 23. To a solution of compound **19** (95 mg, 0.261 mmol) in ether (2.6 mL) was added a 1.0 M solution of vinylmagnesium bromide in THF (5.23 mL, 5.23 mmol) prepared from vinyl bromide (1.6 g, 15.0 mmol), magnesium turning (243 mg, 10.0 mmol), and THF (10 mL). After the mixture was stirred at room temperature for 4 h, 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 crude products, which were purified by column chromatography on silica gel (from 5 to 50% ethyl acetate in hexane) to give the piperidine **22** (84 mg, 82%) as a yellow amorphous.

To a solution of diol obtained above (56 mg, 0.143 mmol) in $CHCl_3$ (1.0 mL) was added *n*-propylamine (0.06 mL) and lead tetraacetate (190 mg, 0.429 mmol) at −50 °C. After the mixture was stirred at this temperature for 30 min, added to ice-1N aqueous NaOH solution 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 (from 0 to 20% methanol in chloroform) to give the **23** (24 mg, 76%) as a yellow oil: $[\alpha]^{22}_D$ −5.7 (c = 0.26, $CHCl_3$); IR(neat, cm^{-1}) 3328(br), 1641, 1601, 1449, 1030; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42−7.34 (m, 4H), 7.24−7.21 (m, 1H), 5.85 (ddd, 1H, J = 17.2, 10.5, 6.2 Hz), 5.18 (m, 1H), 5.06 (m, 1H), 4.42−4.40 (m, 1H), 3.51 (d, 2H, J = 6.2 Hz), 3.36−3.31 (m, 1H), 2.38 (m, 1H, J = 13.5 Hz), 1.88−1.80 (m, 1H), 1.79−1.73 (m, 1H), 1.65 (ddd, 1H, J = 13.8, 13.8, 5.3 Hz), 1.06 (q, 1H, J = 11.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.7, 141.5, 128.5, 126.6, 126.2, 114.1, 68.1, 53.6, 52.4, 35.4, 34.1, 31.6; ESI-HRMS m/z calcd for $C_{14}H_{20}NO$ $[M + H]^+$ 218.1545, found 218.1551.

(2*S*,4*S*,6*R*)-(−)-6-Allyl-4-Hydroxymethyl-2-phenylpiperidine 25. To a solution of compound **19** (56 mg, 0.154 mmol) in ether (1.5 mL) was added a 1.0 M solution of allylmagnesium bromide in THF (3.08 mL, 3.08 mmol). After the mixture was stirred at room temperature for 2 h, 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 crude products which were purified by column chromatography on silica gel (from 5 to 50% ethyl acetate in hexane) to give the piperidine **24** (49 mg, 78%) as a yellow oil.

To a solution of diol obtained above (43 mg, 0.118 mmol) in $CHCl_3$ (0.6 mL) was added *n*-propylamine (0.05 mL) and lead tetraacetate (160 mg, 0.354 mmol) at −50 °C. After the mixture was stirred at this temperature for 30 min, added to ice-1N aqueous NaOH solution 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 (from 0 to 20% methanol in chloroform) to give the **25** (21 mg, 77%) as a white amorphous solid: $[\alpha]^{22}_D$ −34.6 (c = 0.25, $CHCl_3$); IR(neat, cm^{-1}) 3432(br), 3265, 1640, 1445, 1327, 1042; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38−7.37 (m, 2H), 7.31 (dd, 2H, J = 7.1, 7.1 Hz), 7.25−7.22 (m, 1H), 5.76 (dddd, 1H, J = 16.9, 10.1, 8.2, 6.4 Hz), 5.10 (d, 1H, J = 16.9 Hz), 5.05 (d, 1H, J = 10.1 Hz), 3.82 (d, 2H, J = 7.8 Hz), 3.79−3.78 (m, 1H), 2.92−2.85 (m, 1H), 2.24−2.18 (m, 1H), 2.15−2.08 (m, 2H), 1.85−1.68 (m, 3H), 1.46 (ddd, 1H, J = 12.6, 12.6, 5.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9, 135.3, 128.4, 127.2, 126.7, 117.6, 64.0, 57.0, 51.7, 41.6, 35.6, 35.4, 32.7; ESI-HRMS m/z calcd for $C_{15}H_{22}NO$ $[M + H]^+$ 232.1701, found 232.1701.

(−)-(α)-Benzyl Ether Piperidine Derivative (−)-26. To a solution of compound (−)-**19** (104 mg, 0.29 mmol) of DMF (1.5 mL) was added sodium hydride (27 mg, 1.14 mmol) and benzyl bromide (0.05 mL, 0.43 mmol) at 0 °C. After the reaction mixture was stirred at room temperature for 4 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, which were purified by column chromatography on silica gel (2−9% ethyl acetate in hexane) gave the piperidine (α)-benzyl ether derivative (−)-**26** (126 mg, 97%) as a colorless oil: $[\alpha]^{24}_D$ −58.0 (c = 1.00, $CHCl_3$); IR (neat, cm^{-1}) 1454, 1090, 1036, 968; ^1H NMR (400 MHz, $CDCl_3$) δ7.46−7.28 (m, 10H), 7.13 (dd, 1H, J = 7.6, 7.6 Hz), 7.01 (d, 1H, J = 7.6 Hz), 6.94 (d, 1H, J = 7.3 Hz), 4.73 (dd, 1H, J = 5.4, 5.4 Hz), 4.68−4.62 (m, 2H), 4.49 (d, 1H, J = 12.2 Hz), 4.27 (dd, 1H, J = 2.7, 2.7 Hz), 3.88 (dd, 1H, J = 9.5, 9.5 Hz), 3.59 (dd, 1H, J = 9.3, 5.6 Hz), 3.42 (dd, 1H, J = 11.5, 3.2 Hz), 3.14−3.00 (m, 3H), 2.18−2.16 (m, 1H), 2.05−1.90 (m, 4H), 1.20 (d, 3H, J = 6.6 Hz),0.67(d, 3H, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.7, 143.5, 142.9, 138.9, 136.9, 128.9, 128.4, 128.3, 128.0, 127.7, 127.6, 127.4, 123.4, 121.7, 89.3, 77.3, 77.0, 76.7, 74.6, 73.3, 72.8, 71.9, 57.5, 39.5, 34.1, 30.5, 28.1, 27.7, 23.7, 22.7; FAB-HRMS m/z calcd for $C_{31}H_{36}NO_2$ $[M + H]^+$ 454.2746, found 454.2758.

(1*S*,2*R*)-(−)-*cis*-1-[(2*S*,4*S*,6*S*)-4-Benzyloxymethyl-6-methyl-2-phenylpiperidin-1-yl]-7-isopropylindan-2-ol (−)-27. To a solution of compound (−)-**26** (118 mg, 0.260 mmol) in toluene (2.6 mL) was added a ca. 1.4 M trimethylaluminium in *n*-hexane (0.93 mL, 1.30 mmol) at 0 °C. After the mixture was stirred at room temperature for 2 h, H_2O was carefully 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 a 5:1 mixture (determined by ^1H NMR) of two stereoisomers crude products. These isomers were successfully separated by column chromatography on silica gel (from 5 to 17% ethyl acetate in hexane)

dx.doi.org/10.1021/jo202350z | J. Org. Chem. 2012, 77, 1812−1832

to give the piperidine compound (−)-**15** (72 mg, 59%) as a colorless oil; $[\alpha]^{24}_{D}$ −30.5 (c = 1.1, $CHCl_3$); IR (neat, cm^{-1}) 3416(br), 1589, 1452, 1091; ^1H NMR (400 MHz, $CDCl_3$) δ7.38−7.28 (m, 5H), 7.12 (d, 2H, *J* = 4.2 Hz), 7.03−6.99 (m, 3H), 6.71 (d, 2H, *J* = 5.6 Hz), 6.57 (dd, 1H, *J* = 4.2, 4.2 Hz), 4.61−4.46 (m, 3H), 4.17−4.11 (m, 1H), 3.62 (dd, 1H, *J* = 8.5, 8.5 Hz), 3.50 (dd, 1H, *J* = 9.0, 6.6 Hz), 3.37−3.29 (m, 1H), 3.07 (qq, 1H, *J* = 6.8, 6.8 Hz), 2.68 (dd, 1H, *J* = 15.9, 8.1 Hz), 2.13−2.07 (m, 1H), 1.96−1.91 (m, 1H), 1.77 (ddd, 1H, *J* = 14.6, 10.7, 6.1 Hz), 1.67 (ddd, 1H, *J* = 13.9, 4.2, 4.2 Hz), 1.51−1.47 (m, 1H), 1.42 (d, 3H, *J* = 6.8 Hz), 1.41 (d, 3H, *J* = 6.6 Hz), 1.33 (d, 3H, *J* = 5.9 Hz), 1.12(d, 1H, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.2, 144.9, 143.5, 138.6, 137.8, 128.9, 128.4, 127.6, 127.6, 127.3, 126.2, 122.5, 73.0, 72.1, 69.9, 66.2, 57.8, 53.4, 40.7, 37.1, 35.7, 31.7, 30.2, 25.2, 24.2, 22.1; FAB-HRMS *m*/*z* calcd for $C_{32}H_{40}NO_2$ $[M + H]^+$ 470.3059, found 470.3054.

(2*S*,4*S*,6*S*)-(−)-4-Benzyloxymethyl-6-methyl-2-phenylpiperidine (−)-28. To a solution of compound (−)-**27** (70 mg, 0.149 mmol) in $CHCl_3$ (1.5 mL) was added lead tetraacetate (198 mg, 0.447 mmol) at −50 °C. After the mixture was stirred at this temperature for 40 min, added to ice-1N aqueous NaOH solution 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 (from 0 to 9% methanol in chloroform) to give the (−)-**28** (33 mg, 72%) as a yellow oil: $[\alpha]^{24}_{D}$ −7.0 (c = 1.0, $CHCl_3$); IR (neat, cm^{-1}) 1454, 1368, 1308, 1100; ^1H NMR (400 MHz, $CDCl_3$) δ7.36−7.21 (m, 10H), 4.59−4.52 (m, 2H), 3.77 (dd, 1H, *J* = 12.0, 2.6 Hz), 3.67−3.60 (m, 2H), 2.92 (ddq, 1H, *J* = 12.3, 6.2, 2.6 Hz), 2.29 (dddd, 1H *J* = 12.9, 12.9, 7.4, 2.2 Hz), 1.84 (ddd, 1H, *J* = 13.5, 4.2, 2.2 Hz), 1.73−1.65 (m, 2H), 1.40 (ddd, 1H, *J* = 13.4, 11.9, 5.5 Hz), 1.04 (d, 3H, *J* = 6.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 128.4, 128.4, 127.6, 127.6, 127.1, 126.7, 72.9, 71.4, 57.1, 48.0, 35.1, 34.9, 32.9, 22.9; ESI-HRMS *m*/*z* calcd for $C_{20}H_{26}NO$ $[M + H]^+$ 296.2014, found 296.2024.

(1*S*,2*R*)-(−)-*cis*-1-[(2*S*,4*R*,6*R*)-4-Hydroxymethyl-6-methyl-2-phenylpiperidin-1-yl]-7-isopropylindan-2-ol (−)-29. To a solution of compound (−)-**18** (186 mg, 0.512 mmol) in ether (5.8 mL) was added a 1.0 M solution of methylmagnesium iodide in ether (11.5 mL, 11.5 mmol) prepared from methyl iodide (1.24 mL, 19.9 mmol), magnesium turning (440 mg, 18.1 mmol), and ether (18.1 mL) at 0 °C. After the mixture was stirred at room temperature for 3 h, 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 a 4:1 mixture (this compound existed its rotamers at 24 °C so that the diastereoselectivity determined by ^1H NMR after crude product lead to compound (−)-(**30**) of two stereoisomers crude products. These isomers were successfully separated by column chromatography on silica gel (from 5 to 50% ethyl acetate in hexane) to give the piperidine (−)-**29** (113 mg, 68%) as a white crystalline solid: mp = 134−138 °C, $[\alpha]^{24}_{D}$ (c = 1.0, $CHCl_3$); IR (neat, cm^{-1}) 3427, 2924, 2866, 1591, 1451, 1385, 1085, 762; ^1H NMR (400 MHz, $CDCl_3$) δ 7.13−7.09 (m, 2H), 7.03−6.89 (m, 3H), 6.52−6.44 (m, 3H), 4.50 (d, 1H, *J* = 8.7 Hz), 4.15 (ddd, 1H, *J* = 8.7, 8.7, 8.2 Hz), 3.64 (dd, 1H, *J* = 11.4, 3.7 Hz), 3.46 (d, 2H, *J* = 6.4 Hz), 3.30−3.20 (m, 1H), 3.13 (qq, 1H, *J* = 6.9, 6.9 Hz), 2.60 (dd, 1H, *J* = 16.0, 8.2 Hz), 2.05−1.97 (m, 1H), 1.79−1.68 (m, 2H), 1.54 (d, 3H, *J* = 6.9 Hz), 1.38 (d, 3H, *J* = 6.0 Hz), 1.30−1.08 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.2, 144.3, 143.9, 137.6, 128.9, 128.0, 127.4, 126.4, 122.5, 122.5, 69.0, 67.4, 66.6, 62.4, 59.3, 41.5, 40.6, 38.8, 37.7, 32.1, 24.9, 24.4, 22.2; ESI-HRMS *m*/*z* calcd for $C_{25}H_{33}NNaO_2$ $[M + Na]^+$ 402.2409, found 402.2419.

(2*S*,4*R*,6*R*)-(−)-4-Hydroxymethyl-6-methyl-2-phenylpiperidine (−)-30. To a solution of compound (−)-**29** (113 mg, 0.298 mmol) in $CHCl_3$ (3 mL) were added lead tetraacetate (396 mg, 0.893 mmol) at −50 °C. After the mixture was stirred at this temperature for 30 min, added to ice-1N aqueous NaOH solution 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 (from 0 to 20% methanol in chloroform) to give the (−)-**30** (39 mg, 64%) as a white crystalline solid: mp =137−142 °C, $[\alpha]^{25}_{D}$ −7.5 (c = 0.3, $CHCl_3$); IR (neat, cm^{-1}) 3274, 2928, 2818, 1363, 1305, 1054, 756; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40−7.35 (m, 2H), 7.34−7.28 (m, 2H), 7.26−7.21 (m, 1H), 3.72 (dd, 1H, *J* = 11.4, 2.7 Hz), 3.52 (d, 2H, *J* = 6.0 Hz), 2.92−2.83 (m, 1H,), 1.91−1.73 (m, 3H), 1.21−1.13 (m, 4H), 0.90 (ddd, 1H, *J* = 11.9, 11.4, 11.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9, 128.4, 127.1, 126.7, 68.1, 61.5, 52.3, 39.7, 37.2, 36.8, 22.8; ESI-HRMS *m*/*z* calcd for $C_{13}H_{19}NNaO$ $(M+Na)^+$ 206.1545, found 206.1535.

(−)-(β)-Benzyl Ether Piperidine Derivative (−)-31. To a solution of compound (−)-**18** (162 mg, 0.45 mmol) of DMF (2 mL) was added sodium hydride (43 mg, 1.78 mmol) and benzyl bromide (0.08 mL, 0.67 mmol) at 0 °C. After the reaction mixture was stirred at room temperature for 4 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 which were purified by column chromatography on silica gel (2−9% ethyl acetate in hexane) to give the piperidine benzyl (β)-ether derivative (−)-**31** (154 mg, 76%) as a colorless oil: $[\alpha]^{25}_{D}$ −48.3 (c = 1.11, $CHCl_3$); IR (neat, cm^{-1}) 1452, 1084, 1019, 910; ^1H NMR (400 MHz, $CDCl_3$) δ7.47 (d, 1H, *J* = 7.2 Hz), 7.36 (dd, 2H, *J* = 7.0, 7.0 Hz), 7.33−7.22 (m, 6H), 7.14 (dd, 1H, *J* = 7.6, 7.6 Hz), 7.02 (d, 1H, *J* = 7.6 Hz), 6.96 (d, 1H, *J* = 7.3 Hz), 4.91 (dd, 1H, *J* = 5.3, 5.3 Hz), 4.73 (d, 1H, *J* = 5.2 Hz), 4.51−4.44 (m, 2H), 4.37 (dd, 1H, *J* = 2.7, 2.7 Hz), 3.51 (dd, 1H, *J* = 11.9, 2.9 Hz), 3.38 (dd, 1H, *J* = 9.2, 5.4 Hz), 3.29 (dd, 1H, *J* = 9.2, 6.9 Hz), 3.18−3.09 (m, 2H), 3.04 (qq, 1H, *J* = 6.9, 6.9 Hz), 2.25 (dddd, 1H, *J* = 19.3, 12.4, 7.0, 3.8 Hz), 2.10−2.04 (m, 1H), 1.94 (ddd, 1H, *J* = 13.3, 5.7, 2.8 Hz), 1.61−1.51 (m, 3H), 1.19 (d, 3H, *J* = 6.8 Hz), 0.65 (d, 3H, *J* = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.7, 143.5, 142.9, 138.5, 137.1, 128.8, 128.4, 128.3, 128.0, 127.5, 127.4, 123.3, 121.7, 89.6, 75.3, 74.8, 73.4, 72.9, 63.2, 39.6, 37.6, 30.7, 29.9, 28.0, 23.6, 22.7; ESI-HRMS *m*/*z* calcd for $C_{31}H_{36}NO_2$ $[M + H]^+$ 454.2746, found 454.2740.

(1*S*,2*R*)-(−)-*cis*-1-[(2*S*,4*R*,6*R*)-4-Benzyloxymethyl-6-methyl-2-phenylpiperidin-1-yl]-7-isopropylindan-2-ol (−)-32. To a solution of compound (−)-**31** (98 mg, 0.270 mmol) in ether (2.7 mL) was added a 1.0 M solution of methylmagnesium iodide in ether (1.35 mL, 1.35 mmol) prepared from methyl iodide (1.24 mL, 19.9 mmol), magnesium turning (440 mg, 18.1 mmol), and ether (18.1 mL) at 0 °C. After the mixture was stirred at room temperature for 2 h, 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 a 10:1 mixture (this compound existed its rotamers at 24 °C so that the diastereoselectivity determined by ^1H NMR after crude product led to compound (−)-**33**) of two stereoisomer crude products. These isomers were successfully separated by column chromatography on silica gel (from 3 to 5% ethyl acetate in hexane) to give the piperidine compound (−)-**32** (68 mg, 65%) as a colorless oil: $[\alpha]^{25}_{D}$ −28.2 (c = 0.56, $CHCl_3$); IR (neat, cm^{-1}) 3451(br), 1738, 1591, 1454, 1364, 1087; The obtained compound existed its rotamers at 24 °C, and all the signals in their 1H and 13C NMR spectra were complex.; ESI-HRMS *m*/*z* calcd for $C_{32}H_{40}NO_2$ $[M + H]^+$ 470.3059, found 470.3063.

(2*S*,4*R*,6*R*)-(−)-4-Benzyloxymethyl-6-methyl-2-phenylpiperidine (−)-33. To a solution of compound (−)-**32** (61 mg, 0.130 mmol) in $CHCl_3$ (1.0 mL) was added lead tetraacetate (173 mg, 0.390 mmol) at −50 °C. After the mixture was stirred at this temperature for 40 min, added to ice-1N aqueous NaOH solution 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 (from 75 to 83% ethyl acetate in hexane) to give the (−)-**33** (22 mg, 58%) as a yellow oil: $[\alpha]^{25}_{D}$ −31.3 (c = 0.14, $CHCl_3$); IR (neat, cm^{-1}) 1602, 1452, 1366, 1105; ^1H NMR (400 MHz, $CDCl_3$) δ7.37−7.20 (m, 10H), 4.51 (d, 1H, *J* = 16.9 Hz), 4.47 (d, 1H, *J* = 17.0 Hz), 4.00 (dd, 1H, *J* = 11.6, 2.5 Hz), 3.56 (ddq, 1H, *J* = 12.2, 6.8, 1.8 Hz), 3.32 (dd, 1H, *J* = 18.3, 9.0 Hz), 3.31 (dd, 1H, *J* = 18.9, 9.0 Hz), 2.20 (dddd, 1H, *J* = 19.2, 13.2, 7.0, 3.8 Hz), 1.99−1.94 (m, 1H), 1.67−1.61 (m, 2H), 1.50 (ddd, 1H, *J* = 12.7, 12.7,

dx.doi.org/10.1021/jo202350z | *J. Org. Chem.* 2012, 77, 1812−1832

5.2 Hz), 1.29 (d, 1H, J = 6.9 Hz), 1.17 (ddd, 1H, J = 12.2, 12.2, 12.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.4, 138.6, 128.3, 127.6, 127.5, 127.0, 126.7, 76.1, 73.1, 53.5, 47.8, 38.9, 33.7, 31.8, 19.1; ESI-HRMS m/z calcd for $C_{20}H_{26}NO$ $[M + H]^+$ 296.2014, found 296.2024.

(−)-(β)-Ester Piperidine Derivative (−)-35. To a solution of (−)-**12a** (1.73 g, 3.49 mmol) in ethanol (15.0 mL) was added Raney-Ni W2 (excess amount) at a room temperature. After the reaction mixture was stirred under H_2 atmosphere for 2 h, the catalyst was removed by filtration and the filtrate was concentrated *in vacuo* to give crude products which were purified by column chromatography on silica gel (5−10% ethyl acetate in hexane) to give the piperidine (β)-ester derivative (−)-**35** (1.12 g, 64%) as a colorless oil: $[\alpha]^{23}_D$ −73.5 (c = 0.70, $CHCl_3$); IR (neat, cm^{-1}) 1736, 1593, 1474, 1256, 1101; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (dd, 1H, J = 7.6, 7.3 Hz), 7.14 (d, 1H, J = 7.8 Hz), 7.02 (m, 1H), 5.04 (d, 1H, J = 5.1 Hz), 4.75 (ddd, 1H, J = 5.1, 5.1, 1.7 Hz), 4.24 (dd, 1H, J = 2.4, 2.4 Hz), 4.12 (q, 2H, J = 7.1 Hz), 3.73−3.57 (m, 3H), 3.17−3.07 (m, 2H), 2.68 (dddd, 1H, J = 12.7, 12.7, 3.2, 3.2 Hz), 2.50−2.43 (m, 1H), 2.19 (dddd, 1H, J = 14.1, 2.7, 2.7, 2.7 Hz), 2.14−2.09 (m, 1H), 1.79−1.68 (m, 2H), 1.53−1.48 (m, 2H), 1.26 (dd, 2H, J = 7.3, 7.1 Hz), 1.24 (t, 3H, J = 7.3 Hz), 1.21 (d, 3H, J = 7.8 Hz), 1.01 (d, 3H, J = 6.8 Hz), 0.90 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 147.5, 143.0, 137.1, 128.6, 123.6, 122.0, 89.0, 75.4, 72.8, 63.1, 60.4, 56.5, 39.6, 35.5, 33.0, 31.4, 29.2, 28.9, 28.4, 25.9, 23.8, 23.7, 18.3, 14.2, −5.3; ESI HRMS m/z calcd for $C_{29}H_{48}NO_4Si$ $[M + H]^+$ 502.3353, found 502.3354.

(−)-(β)-Hydroxymethyl Piperidine Derivative (−)-36. To a solution of compound (−)-**35** (407 mg, 1.00 mmol) of toluene (5 mL) was slowly added Red-Al (0.67 mL, >65 wt.% in toluene) at 0 °C. After the mixture was stirred at this temperature for 2 h, H_2O and saturated aqueous potassium sodium tartrate tetrahydrate solution was carefully 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 which were purified by column chromatography on silica gel (20−50% ethyl acetate in hexane) to give the piperidine (α)-alcohol derivative (−)-**36** (362 mg, 99%) as a white foam: $[\alpha]^{23}_D$ −79.8 (c = 0.7 $CHCl_3$); IR (KBr disk, cm^{-1}) 3420 (br), 1742, 1593, 1472, 1254, 1101; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (dd, 1H, J = 7.6, 7.6 Hz), 7.14 (d, 1H, J = 7.1 Hz), 7.02 (m, 1H), 5.05 (d, 1H, J = 5.1 Hz), 4.75 (ddd, 1H J = 4.9, 4.9, 1.5 Hz), 4.25 (dd, 1H, J = 2.7, 2.7 Hz), 3.67 (qq, 1H, J = 7.0, 6.8 Hz), 3.55−3.43 (m, 3H), 3.17−3.07 (m, 2H), 2.50−2.43 (m, 1H), 2.13−2.07 (m, 1H), 1.99−1.85 (m, 3H), 1.77−1.67 (m, 1H), 1.56−1.43 (m, 2H), 1.22 (d, 3H, J = 6.8 Hz), 1.20 (d, 3H, J = 7.1 Hz), 1.01−0.92 (m, 2H), 0.90 (s, 9H), 0.07 (s, 6H); 13C NMR (100 MHz, $CDCl_3$) δ 147.4, 143.0, 137.4, 128.5, 123.5, 122.0, 89.5, 75.3, 72.9, 67.8, 63.2, 56.7, 39.6, 33.5, 32.2, 31.6, 29.7, 29.0, 28.4, 25.9, 23.7, 18.3, −5.3; ESI HRMS m/z calcd for $C_{27}H_{46}NO_3Si$ $[M + H]^+$ 460.3247, found 460.3270.

Tosylate. To a solution of (−)-**36** (561 mg, 1.22 mmol) in dichloromethane (6 mL) was added 4-(dimethylamino)pyridine (DMAP) (75 mg, 0.610 mmol), triethylamine (0.5 mL, 3.66 mmol), and *p*-toluenesulfonyl chloride (349 mg, 1.83 mmol) at room temperature. After the reaction mixture was stirred at room temperature for 2 h, 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 which were purified by column chromatography on silica gel (10% ethyl acetate in hexane) to give corresponding tosylate (642 mg, 86%) as a colorless oil; $[\alpha]^{24}_D$ −57.8 (c = 0.6 $CHCl_3$); IR (neat, cm^{-1}) 1740, 1597, 1462, 1362, 1252, 1178, 1098; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, 2H, J = 8.4 Hz), 7.33 (d, 2H, J = 8.0 Hz), 7.22 (dd, 1H, J = 7.2, 7.2 Hz), 7.13 (d, 1H, J = 7.6 Hz), 7.00 (d, 1H, J = 5.2 Hz), 5.01 (d, 1H, J = 5.2 Hz), 4.73−4.70 (m, 1H), 4.18 (dd, 1H, J = 2.4, 2.4 Hz), 3.84 (ddd, 1H, J = 15.1, 9.5, 5.6 Hz), 3.71−3.62 (m, 2H), 3.60 (qq, 1H, J = 6.8, 6.8 Hz), 3.13−3.04 (m, 2H), 2.43−2.37 (m, 1H), 2.10−2.01 (m, 2H), 1.85−1.81 (m, 2H), 1.67−1.61 (m, 1H), 1.44 (ddd, 2H, J = 6.3, 6.3, 4.2 Hz), 1.33−1.30 (m, 1H), 1.19 (dd, 6H, J = 6.3, 6.3 Hz), 0.97−0.88 (m, 1H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.4, 144.7, 142.9, 137.0, 132.8, 129.8, 128.5, 127.9, 123.5, 121.9, 88.9, 75.3, 74.2, 72.7, 63.1, 56.4, 39.5, 33.0, 31.4, 29.4, 29.1, 28.9, 28.3, 25.9, 23.7, 21.6, 18.3, −5.3, −5.3; ESI HRMS m/z calcd for $C_{34}H_{51}NNaO_5SSi$ $[M + Na]^+$ 636.3155, found 636.3146.

(−)-(β)-Methyl Piperidine Derivative (−)-37. To a solution of tosylate obtained above (89 mg, 0.145 mmol) and tri*n*-butyltin hydride (0.05 mL, 0.17 mmol) in dimetoxyethane (0.8 mL) was added 2,2′-azobisisobutyronitrile (AIBN) (2 mg, 0.015 mmol) and sodium iodide (43 mg, 0.29 mmol). After the mixture was stirred at 80 °C for 3 h, 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 which were purified by column chromatography on silica gel (2−5% ethyl acetate in hexane) to give (−)-**37** (58 mg, 91%) as a colorless oil; $[\alpha]^{28}_D$ −79.9 (c 1.0 $CHCl_3$); IR (neat, cm^{-1}) 1742, 1593, 1460, 1254, 1102, 1040; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (dd, 1H, J = 7.6, 7.6 Hz), 7.13 (d, 1H, J = 7.6 Hz), 7.01 (d, 1H, J = 7.1 Hz), 5.03 (d, 1H, J = 5.3 Hz), 4.75−4.73 (m, 1H), 4.18 (dd, 1H, J = 2.7, 2.2 Hz), 3.72−3.62 (m, 3H), 3.16−3.06 (m, 2H), 2.47−2.41 (m, 1H), 2.09−2.03 (m, 1H), 1.91 (ddd, 1H, J = 14.7, 5.5, 3.0 Hz), 1.81−1.66 (m, 3H), 1.55−1.31 (m, 2H), 1.22 (d, 3H, J = 6.9 Hz), 1.20 (d, 3H, J = 7.1 Hz), 1.23−1.19 (m, 1H), 0.94−0.87 (m, 1H), 0.90 (s, 9H), 0.89 (m, 3H), 0.07 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.4, 143.0, 137.6, 128.4, 123.4, 121.9, 90.0, 75.2, 72.8, 63.3, 57.1, 39.6, 39.2, 35.2, 29.1, 28.3, 25.9, 24.1, 23.7, 21.8, 18.3, −5.3, −5.3; ESI HRMS m/z calcd for $C_{27}H_{46}NO_2Si$ $[M + H]^+$ 444.3298, found 444.3277.

(1*S*,2*R*)-(−)-*cis*-1-[(2*R*,4*R*,6*R*)-2-(1-tert-Butyldimethylsiloxy-propenyl)-4,6-dimethylpiperidin-1-yl]-7-isopropylindan-2-ol (−)-38. To a solution of (−)-**37** (282 mg, 0.636 mmol) in toluene (3.5 mL) was added trimethylaluminum (10% in hexane, 1.53 mL, 3.18 mmol) at 0 °C. After the mixture was warmed to room temperature and stirred for an additional 2 h, H_2O was added, and the resulting mixture was extracted with AcOEt. The organic layers were combined, washed with H_2O, brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a 17:1 mixture (determined by ^{1}H NMR) of two stereoisomers crude products. These isomers were successfully separated by column chromatography on silica gel (gradually 3−5% ethyl acetate in hexane) to give (−)-**38** (229 mg, 75%) as a colorless oil; $[\alpha]^{24}_D$ −49.9 (c 1.0 $CHCl_3$); IR (neat, cm^{-1}) 1591, 1460, 1385, 1254, 1098, 836; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (dd, 1H, J = 7.6, 7.6 Hz), 7.12 (d, 1H, J = 7.8 Hz), 7.00 (d, 1H, J = 7.3 Hz), 4.51 (d, 1H, J = 6.9 Hz), 4.10−4.05 (m, 1H), 3.74−3.64 (m, 2H), 3.36 (qq, 1H, J = 6.9, 6.9 Hz), 3.34−3.26 (m, 1H), 3.10 (dd, 1H, J = 15.8, 7.8 Hz), 2.70−2.60 (m, 2H), 1.79−1.66 (m, 4H), 1.63−1.49 (m, 2H), 1.37 (d, 3H, J = 6.9 Hz), 1.17 (d, 3H, J = 7.1 Hz), 1.11 (d, 3H, J = 6.9 Hz), 0.95−0.83 (m, 2H), 0.90 (s, 9H), 0.81 (d, 3H, J = 6.1 Hz), 0.56 (ddd, 1H, J = 12.7, 12.7, 5.1 Hz), 0.07 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.8, 142.8, 138.4, 128.9, 123.0, 122.5, 71.4, 63.2, 58.9, 53.6, 48.4, 41.3, 39.5, 36.9, 30.9, 30.8, 29.8, 26.1, 25.9, 25.5, 22.7, 21.3, 18.3, 18.1, −5.3; ESI HRMS m/z calcd for $C_{28}H_{50}NO_2Si$ $[M + H]^+$ 460.3611, found 460,3598.

(2*R*,4*R*,6*R*)-(−)-*N*-Benzyzoxycalboyl-2-(2-(tert-butyldimethyl-silyloxy)ethyl)-4,6-dimethylpiperidine (−)-39. A solution of (−)-**38** (126 mg, 0.27 mmol) and $Pd(OH)_2/C$ (60 mg) in methanol (1.5 mL) was stirred in an autoclave under 10 atmospheric pressure of hydrogen at room temperature for 24 h. Then the catalyst was removed by filtration and the filtrate was concentrated *in vacuo* to give crude products. The crude product was reduced without further purification.

To a solution of the crude piperidine obtained above in tetrahydrofurane (1.5 mL) and H_2O (1.5 mL) was added K_2CO_3 (378 mg, 2.73 mmol) and carbobenzoxy chloride (0.10 mL, 0.55 mmol) at 0 °C. After the mixture was stirred at 0 °C for 2 h, 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 which were purified by column chromatography on silica gel (gradually from 2 to 3.3% ethyl acetate in hexane) to give (−)-**39** (91 mg, 79%) as a colorless oil: $[\alpha]^{24}_D$ −15.8 (c = 0.3, $CHCl_3$); IR (neat, cm^{-1}) 1827, 1696, 1259, 1148, 1100; ^{1}H NMR (400 MHz, $CDCl_3$) δ7.36−7.28 (m, 5H), 5.14−5.08 (m, 2H), 4.22 (dddd, 1H, J = 14.6, 9.8, 6.9, 3.0 Hz),

dx.doi.org/10.1021/jo202350z | J. Org. Chem. 2012, 77, 1812−1832

3.66−3.50 (m, 3H), 1.98−1.78 (m, 3H), 1.68−1.43 (m, 5H), 1.29 (ddd, 1H, J = 19.7, 13.1, 6.0 Hz), 1.24 (d, 3H, J = 6.9 Hz), 0.98 (d, 3H, J = 6.6 Hz), 0.88 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 137.1, 128.4, 127.8, 127.8, 66.6, 63.1, 52.6, 48.4, 36.6, 33.8, 32.0, 26.0, 23.3, 23.1, 19.1, 18.3, −5.3; ESI HRMS m/z calcd for $C_{24}H_{41}NNaO_3Si$ $[M + Na]^+$ 442.2753, found 442.2745.

(2*R*,4*R*,6*R*)-(−)-*N*-Benzyloxycalboyl-4,6-dimethyl-2-hydroxypropylpiperidine. To a solution of (−)-**39** (121 mg, 0.155 mmol) in tetrahydrofurane (1.5 mL) was added 2N aqueous HCl solution (0.75 mL) at 0 °C. After the mixture was stirred at room temperature for 1 h, 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 which were purified by column chromatography on silica gel (gradually from 25 to 50% ethyl acetate in hexane) to give alcohol (84 mg, 95%) as a colorless oil: $[\alpha]^{24}_D$ −9.63 (c = 0.8, $CHCl_3$); IR (neat, cm^{-1}) 3431(br), 1688, 1454, 1410, 1307, 1101, 1070; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.29 (m, 5H), 5.14 (d, 1H, J = 12.4 Hz), 5.10 (d, 1H, J = 12.4 Hz), 4.27−4.20 (m, 1H), 3.70−3.57 (m, 3H), 2.01 (brs, 1H), 1.99−1.85 (m, 3H), 1.70−1.44 (m, 5H), 1.30 (ddd, 1H, J = 13.7, 5.9, 5.9 Hz), 1.23 (d, 3H, J = 6.9 Hz), 0.99 (d, 3H, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 136.9, 128.4, 127.9, 127.9, 66.7, 62.3, 52.1, 48.3, 36.7, 33.9, 31.8, 29.5, 23.4, 22.9, 19.1; ESI HRMS m/z calcd for $C_{18}H_{27}NNaO_3$ $[M + Na]^+$ 328.1889, found 328.1880.

(2*R*,4*R*,6*R*)-(+)-*N*-Benzyzoxycalboyl-4,6-dimethyl-2-methylesterpropylpiperidine (+)-40. To a solution of alcohol obtained above (139 mg, 0.455 mmol) in acetone (1 mL) was added 2.67 N Jones reagent at 0 °C. After the reaction mixture was stirred for 1 h at room temperature, brine was added, and the resulting mixture was extracted with ethyl acetate. The organic layers were combined, washed with 10% $NaHSO_3$ solution and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give the crude products. The crude product was reduced without further purification.

To a solution of the crude carboxylic acid obtained above in ethyl acetate (2.5 mL) was added diazomethane prepared from nitrosomethylurea (117 mg, 1.135 mmol), 30% aqueous NaOH solution (0.5 mL) and ether (2.5 mL) at 0 °C. After the reaction mixture was stirred for 30 min at 0 °C, saturated NH_4Cl 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 which were purified by column chromatography on silica gel (gradually from 6 to 9% ethyl acetate in hexane) to give methyl ester (+)-**40** (101 mg, 66% for 2 steps) as a colorless oil: $[\alpha]^{24}_D$ 1.1 (c = 0.3, $CHCl_3$); IR (neat, cm^{-1}) 1738, 1698, 1437, 1404, 1305, 1265, 1128, 1100; ^{1}H NMR (400 MHz, $CDCl_3$) δ7.37−7.28 (m, 5H), 5.13 (d, 1H, J = 12.4 Hz), 5.09 (d, 1H, J = 12.2 Hz), 4.25 (dqd, 1H, J = 12.0, 6.6, 3.1 Hz), 3.68−3.59 (m, 1H), 3.63 (s, 3H), 2.37−2.33 (m, 2H), 2.31−2.20 (m, 1H), 1.96−1.78 (m, 3H), 1.59 (ddd, 1H, J = 13.7, 5.9, 3.2 Hz), 1.42 (ddd, 1H, J = 13.7, 11.7, 5.4 Hz), 1.28−1.19 (m, 1H), 1.22 (d, 3H, J = 6.8 Hz), 0.96 (d, 3H, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 156.0, 136.9, 128.4, 127.9, 127.9, 66.7, 52.1, 51.4, 48.7, 37.0, 35.5, 31.4, 30.6, 23.9, 23.0, 18.6; ESI HRMS m/z calcd for $C_{19}H_{27}NNaO_4$ $[M + Na]^+$ 356.1838, found 356.1826.

(5*R*,7*R*,8a*R*)-(−)-5,7-Dimethylindolizidine-3-one (−)-41. To a solution of methylester (−)-**40** (84 mg, 0.252 mmol) in methanol (1 mL) was added Pd/C (25 mg) at a room temperature. After the reaction mixture was stirred under H_2 atmosphere for 1 h, the catalyst was removed by filtration and the filtrate was concentrated *in vacuo* to give crude products. The crude product was reduced without further purification.

After solution of the crude amine obtained above in toluene (1 mL) was refluxed for 3 h, the reaction mixture was concentrated *in vacuo* to give the crude products which were purified by column chromatography on silica gel (ethyl acetate) to give indoridizine (−)-**41** (29 mg, 71% for 2 steps) as a colorless oil: $[\alpha]^{24}_D$ −46.5 (c = 0.1, $CHCl_3$); IR (neat, cm^{-1}) 1671, 1422, 1375, 1285; ^{1}H NMR (400 MHz, $CDCl_3$) δ4.36 (dq, 1H, J = 6.6, 6.6 Hz), 3.63−3.55 (m, 1H), 2.36−2.27 (m, 2H), 2.19−2.11 (m, 1H), 1.94−1.75 (m, 2H), 1.56−1.46 (m, 2H), 1.20 (ddd, 1H, J = 12.6, 12.6, 5.7 Hz), 1.11 (d, 3H, J = 7.8 Hz), 0.91 (d, 3H, J = 6.3 Hz), 0.77 (ddd, 1H, J = 12.0, 12.0, 12.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 53.0, 43.5, 42.3, 38.1, 30.6, 25.5, 25.1, 22.0, 16.7; ESI HRMS m/z calcd for $C_{10}H_{17}NNaO$ $[M + Na]^+$ 190.1208, found 190.1215.

(+)-7-Epidendroprimine. To a solution of indoridizine (−)-**41** (18 mg, 0.129 mmol) in ether (2 mL) was added lithium aluminum hydride (14 mg, 0.369 mmol) at 0 °C. After the reaction mixture was refluxed for 6 h, ice was slowly added, and the resulting mixture was extracted with dichloromethane. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude products which were purified by column chromatography on reverse phase silica gel (9% trimethylamine in methanol) gave (+)-7-epidendroprimine (13 mg, 81%) as a yellow oil: $[\alpha]^{24}_D$ 9.2 (c = 0.3, $CHCl_3$); IR (neat, cm^{-1}) 1458, 1373, 1260, 1173, 1154; ^{1}H NMR (400 MHz, $CDCl_3$) δ3.35−3.29 (m, 1H), 2.80 (td, 1H, J = 8.5, 2.7 Hz), 2.53 (q, 1H, J = 8.8 Hz), 2.48−2.41 (m, 1H), 1.86−1.59 (m, 5H), 1.52−1.39 (m, 2H), 1.35−1.23 (m, 2H), 0.97 (d, 3H, J = 6.8 Hz), 0.91 (d, 3H, J = 6.3 Hz), 0.80 (q, 1H, J = 11.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ54.1, 49.9, 48.5, 40.5, 39.9, 30.7, 25.5, 22.3, 21.0, 9.8; ESI HRMS m/z calcd for $C_{10}H_{20}N$ $[M + H]^+$ 154.1596, found 154.1593.

(−)-(α)-Ester Piperidine Derivative (−)-43. To magnesium turning (488 mg, 20.1 mmol) in methanol (5.0 mL) was added a solution of the (−)-**12a** (1.0 g, 2.01 mmol) in methanol (15 mL) at room temperature. After the mixture was stirred at this temperature for 2 h, H_2O and 2N aqueous HCl solution was carefully added, and the pH of the solution was adjusted toward 7. 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 a 4:1 mixture (determined by ^{1}H NMR) of two stereoisomers crude products. These isomers were successfully separated by column chromatography on silica gel (from 5 to 7% ethyl acetate in hexane) to give the piperidine (α)-ester derivative (−)-**43** (581 mg, 58%) as a white crystalline solid: mp = 86−89 °C, $[\alpha]^{24}_D$ −30.0 (c = 1.2, $CHCl_3$), IR (KBr disk, cm^{-1}) 1732, 1471, 1379, 1257, 1128; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (dd, 1H, J = 7.3, 7.3 Hz), 7.10 (d, 1H, J = 7.3 Hz), 6.96 (m, 1H), 5.84 (dt, 1H, J = 15.4, 4.6 Hz), 5.73 (ddt, 1H, J = 15.4, 8.8, 1.5 Hz), 4.93 (d, 1H, J = 5.4 Hz), 4.68 (ddd, 1H, J = 5.4, 5.4, 2.0 Hz), 4.25−4.09 (m, 5H), 3.58 (qq, 1H, J = 6.8, 6.8 Hz), 3.30 (ddd, 1H, J = 11.7, 8.5, 3.2 Hz), 3.12−3.03 (m, 2H), 2.56−2.50 (m, 2H), 2.12 (ddd, 1H, J = 13.7, 5.9, 2.9 Hz), 1.91 (ddd, 1H, J = 14.9, 6.6, 2.9 Hz), 1.55 (ddd, 1H, J = 13.7, 12.0, 4.6 Hz), 1.29 (t, 3H, J = 7.3 Hz), 1.25 (d, 3H, J = 6.8 Hz), 1.14 (d, 3H, J = 7.1 Hz), 0.93 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 147.4, 143.1, 137.3, 133.0, 132.3, 128.3, 123.2, 121.7, 87.7, 75.4, 72.7, 63.2, 60.3, 56.5, 39.6, 33.7, 31.8, 28.5, 27.8, 26.0, 23.5, 23.5, 18.4, 14.2, −5.2; FAB-HRMS m/z calcd for $C_{29}H_{46}NO_4Si$ $[M + H]^+$ 500.3196, found 500.3198.

(−)-(α)-Hydroxymethyl Piperidine Derivative. To a solution of compound (−)-**31** (700 mg, 1.40 mmol) of toluene (7 mL) was slowly added Red-Al (1.13 mL, >65 wt.% in toluene) at 0 °C. After the mixture was stirred at room temperature for 2 h, H_2O and saturated aqueous potassium sodium tartrate tetrahydrate solution was carefully 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 which were purified by column chromatography on silica gel (from 20 to 50% ethyl acetate in hexane) to give the piperidine (α)-alcohol derivative (604 mg, 94%) as a colorless oil: $[\alpha]^{25}_D$ −50.1 (c = 0.4, $CHCl_3$); IR (neat, cm^{-1}) 3370(br), 1593, 1464, 1255, 1037; ^{1}H NMR (400 MHz, $CDCl_3$) δ7.17 (dd, 1H, J = 7.6, 7.6 Hz), 7.12 (d, 1H, J = 7.3 Hz), 6.99 (m, 1H), 5.79 (dt, 1H, J = 15.4, 4.6 Hz), 5.70 (m, 1H, J = 15.4, 8.5 Hz), 5.02 (d, 1H, J = 5.5 Hz), 4.77 (ddd, 1H, J = 5.5, 4.2, 3.2 Hz), 4.20 (m, 2H), 3.80−3.69 (m, 2H), 3.58 (qq, 1H, J = 6.8, 6.8 Hz), 3.22 (ddd, 1H, J = 11.2, 8.5, 4.2 Hz), 3.12 (d, 2H, J = 3.4 Hz), 3.08−3.04 (m, 1H), 1.95−1.92 (m, 2H), 1.77−1.66 (m, 2H), 1.25 (d, 3H, J = 6.8 Hz), 1.15 (d, 3H, J = 6.8 Hz), 0.92 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.5, 142.7, 137.2, 133.3, 132.2, 128.5, 123.4, 121.7, 88.0, 75.2, 72.7, 66.5, 63.2, 56.3, 39.5, 33.7, 31.6, 28.6,

dx.doi.org/10.1021/jo202350z | J. Org. Chem. 2012, 77, 1812−1832

27.7, 26.0, 23.5, 18.4, −5.2; FAB-HRMS *m/z* calcd for $C_{27}H_{44}NO_3Si$ $[M + H]^+$ 458.3090, found 458.3090.

(−)-(α)-Hydroxymethyl Piperidine Derivative (−)-44. To a solution of the alcohol compound obtained above (300 mg, 0.65 mmol) in THF (4.0 mL) was added PtO_2 (30 mg) at room temperature. After the reaction mixture was stirred under H_2 atmosphere for 3 h, the catalyst was removed by filtration and the filtrate was concentrated *in vacuo* to give crude products which were purified by column chromatography on silica gel (from 20 to 50% ethyl acetate in hexane) to give the piperidine (α)-alcohol derivative (−)-**44** (277 mg, 92%) as a colorless oil: $[\alpha]^{25}_D$ −86.5 (c = 0.4, $CHCl_3$); IR (neat, cm^{-1}) 3408(br), 1593, 1472, 1254, 1100, 1038; ^1H NMR (400 MHz, $CDCl_3$) δ7.21 (dd, 1H, *J* = 7.6, 7.6 Hz), 7.14 (d, 1H, *J* = 7.6 Hz), 7.01 (d, 1H, *J* = 7.3 Hz), 5.07 (d, 1H, *J* = 5.4 Hz), 4.71 (ddd, 1H, *J* = 4.9, 4.9, 1.5 Hz), 4.19 (dd, 1H, *J* = 2.9, 2.9 Hz), 3.75−3.66 (m, 4H), 3.65 (qq, 1H, *J* = 6.8, 6.8 Hz), 3.16−3.06 (m, 2H), 3.01 (dd, 1H, *J* = 4.9, 4.9 Hz), 2.64 (dddd, 1H, *J* = 11.5, 8.8, 2.7, 2.7 Hz), 2.11 (dddd, 1H, *J* = 12.9, 12.9, 5.1, 2.7 Hz), 1.98−1.85 (m, 4H), 1.75−1.66 (m, 1H), 1.56−1.35 (m, 3H), 1.22 (d, 3H, *J* = 6.6 Hz), 1.20 (d, 3H, *J* = 7.1 Hz), 0.90 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.4, 142.8, 137.1, 128.5, 123.6, 121.9, 89.0, 75.1, 72.9, 66.2, 63.1, 39.4, 32.0, 31.9, 31.5, 29.0, 28.4, 27.8, 25.9, 23.8, 23.7, 18.3, −5.3; FAB-HRMS *m/z* calcd for $C_{27}H_{46}NO_3Si$ $[M + H]^+$ 460.3247, found 460.3224.

(1*S*,2*R*)-(−)-*cis*-1-[(2*R*,4*S*,6*R*)-2-(3-*tert*-Butyldimethylsiloxypropyl)-4-hydroxymethyl-6-methylpiperidin-1-yl]-7-isopropylindan-2-ol (−)-45M. To copper iodide (3.2 g, 16.8 mmol) in ether (4.0 mL) was added a 1.0 M solution of methylmagnesium iodide in ether (17.0 mL, 16.8 mmol) prepared from methyl iodide (1.24 mL, 19.9 mmol), magnesium turning (440 mg, 18.1 mmol), and ether (18.1 mL) at 0 °C. The reaction mixture was stirred at this temperature for 10 min and a solution of the (−)-**44** (387 mg, 0.84 mmol) in ether (4.0 mL) was added dropwise at 0 °C. After the mixture was stirred at 0 °C for 10 min and an additional 2 h at room temperature, saturated aqueous NH_4Cl 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 a 3:1 mixture (determined by ^1H NMR) of two stereoisomers crude products. These isomers were successfully separated by column chromatography on silica gel (from 25 to 50% ethyl acetate in hexane) to give the piperidine compound (−)-**45** (235 mg, 60%) as a white amorphous solid: $[\alpha]^{23}_D$ −55.8 (c = 0.3, $CHCl_3$); IR (KBr disk, cm^{-1}) 3414(br), 1462, 1389, 1253, 1093; ^1H NMR (400 MHz, $CDCl_3$) δ7.23 (dd, 1H, *J* = 7.6, 7.6 Hz), 7.11 (d, 1H *J* = 7.6 Hz), 7.00 (d, 1H, *J* = 7.3 Hz), 4.54 (d, 1H, 6.6 Hz), 4.11−4.03 (m, 1H), 3.55 (dt, 2H, *J* = 6.6, 1.5 Hz), 3.57−3.53 (m, 1H), 3.40−3.31 (m, 1H), 3.37 (d, 2H, *J* = 5.9 Hz), 3.04 (dd, 1H, *J* = 15.9, 7.6 Hz), 2.63 (dd, 1H, *J* = 15.6, 9.3 Hz), 1.88−1.76 (m, 1H), 1.70 (m, 1H), 1.63−1.55 (m, 1H), 1.37 (d, 3H, *J* = 6.8 Hz), 1.30 (d, 3H, *J* = 6.8 Hz), 1.13 (d, 3H, *J* = 6.8 Hz), 1.17−0.99 (m, 2H), 0.91 (ddd, 2H, *J* = 13.2, 9.0, 3.9 Hz), 0.88 (s, 9H), 0.55(ddd, 1H, *J* = 12.9, 12.9, 5.1 Hz), 0.02(s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.5, 143.0, 138.0, 129.1, 122.9, 122.6, 72.3, 68.6, 63.1, 58.3, 52.8, 48.8, 40.7, 36.6, 33.9, 31.1, 29.8, 28.1, 27.9, 26.0, 21.2, 20.9, 18.3, −5.2; FAB-HRMS *m/z* calcd for $C_{28}H_{50}NO_3Si$ $[M + H]^+$ 476.3560, found 476.3559.

(1*S*,2*R*)-(−)-*cis*-1-[(2*R*,4*S*,6*S*)-2-(3-*tert*-Butyldimethylsiloxypropyl)-4-hydroxymethyl-6-methylpiperidin-1-yl]-7-isopropylindan-2-ol (−)-46. To a solution of compound (−)-**44** (600 mg, 1.31 mmol) in toluene (6.5 mL) was added a ca. 1.4 M trimethylaluminium in *n*-hexane (9.41 mL, 19.6 mmol) at 0 °C. After the mixture was stirred at room temperature for 2 h, H_2O was carefully 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 a crude products which were purified by column chromatography on silica gel (from 25 to 33% ethyl acetate in hexane) gave the piperidine compound (−)-**46** (508 mg, 82%) as a colorless oil; $[\alpha]^{23}_D$ −57.0 (c = 0.6, $CHCl_3$); IR (KBr disk, cm^{-1}) 3435(br), 1742, 1462, 1385, 1254, 1090; ^1H NMR (400 MHz, acetone-d_6) δ7.25−7.16 (m, 2H), 7.00 (d, 1H, *J* = 7.1 Hz), 4.38 (d, 1H, *J* = 6.8 Hz), 4.12−4.06 (m, 1H), 3.55−3.51 (m, 2H), 3.42−3.39 (m, 2H), 3.37−3.30 (m, 1H), 3.25−3.20 (m, 1H), 2.85 (dd, 1H, *J* = 15.6, 7.3 Hz), 2.63 (dd, 1H, *J* = 15.6, 8.8 Hz), 2.42 (m, 1H), 2.07−2.04 (m, 2H), 1.99−1.91 (m, 1H), 1.72−1.65 (m, 2H), 1.63−1.60 (m,2H), 1.51−1.46 (m,1H), 1.45−1.35 (m, 1H), 1.39 (d, 3H, *J* = 7.1 Hz), 1.24−1.05 (m, 2H), 1.15 (d, 3H, *J* = 6.8 Hz), 1.13 (d, 3H, *J* = 6.3 Hz), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, acetone-d_6) δ 147.5, 143.4, 139.6, 129.7, 123.8, 123.1, 72.2, 68.9, 67.7, 63.5, 54.0, 53.1, 41.6, 34.6, 34.5, 32.2, 31.3, 29.0, 26.3, 26.1, 24.6, 22.1, 18.8, −5.1; ESI HRMS *m/z* calcd for $C_{28}H_{50}NO_3Si$ $[M + H]^+$ 476.3560, found 476.3544.

(2*R*,4*S*,6*R*)-(−)-*N*-Benzyzoxycalboyl-2-(3-*tert*-butyldimethylsilyloxypropyl)-4-hydroxymethyl-6-methylpiperidine (−)-47. A solution of (−)-**45** (475 mg, 1.00 mmol) and $Pd(OH)_2/C$ (100 mg) in methanol (5.0 mL) was stirred in an autoclave under 10 atmospheric pressure of hydrogen at room temperature for 12 h. Then the catalyst was removed by filtration and the filtrate was concentrated *in vacuo* to give crude products. The crude product was protected without further purification.

To a solution of the crude piperidine obtained above in tetrahydropyrane (5 mL) and H_2O (5 mL) was added K_2CO_3 (1.38 g, 9.98 mmol) and carbobenzoxy chloride (0.35 mL, 2.00 mmol) at 0 °C. After the mixture was stirred at 0 °C for 2 h, 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 which were purified by column chromatography on silica gel (gradually from 20 to 50% ethyl acetate in hexane) to give (−)-**47** (346 mg, 80%) as a colorless oil: $[\alpha]^{23}_D$ −19.1 (c = 1.0, $CHCl_3$); IR (neat, cm^{-1}) 3449(br), 1688, 1408, 1256, 1100; ^1H NMR (400 MHz, $CDCl_3$) δ7.36−7.27 (m, 5H), 5.12 (d, 1H, *J* = 12.5 Hz), 5.09 (d, 1H, *J* = 12.5 Hz), 4.18−4.16 (m, 1H), 3.71 (dddd, 1H, *J* = 13.9, 6.8, 6.8, 4.4 Hz), 3.62−3.55 (m, 2H), 3.54−3.46 (m, 2H), 2.01 (ddd, 1H, *J* = 19.3, 13.2, 6.6 Hz), 1.88 (ddd, 1H, *J* = 13.9, 6.8, 4.4 Hz), 1.80−1.69 (m, 2H), 1.57−1.40 (m, 4H), 1.37 (d, 3H, *J* = 7.1 Hz), 1.34−1.26 (m, 1H), 0.88 (s, 9H), 0.03(s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 137.0, 128.4, 127.8, 68.2, 66.6, 62.9, 52.4, 47.6, 32.6, 31.7, 29.9, 29.0, 28.5, 25.9, 22.4, 18.3, −5.3; FAB-HRMS *m/z* calcd for $C_{24}H_{42}NO_4Si$ $[M + H]^+$ 436.2883, found 436.2881.

(2*R*,4*S*,6*R*)-(−)-*N*-Benzoxycalboyl-2-(3-*tert*-butyldimethylsilyloxypropyl)-4-bromomethyl-6-methylpiperidine. To a solution of (−)-**47** (222 mg, 0.510 mmol) in dichloromethane (2.5 mL) was added triethylamine (0.283 mL, 2.04 mmol), carbon tetrabromide (507 mg, 1.53 mmol) and triphenylphosphine (535 mg, 2.04 mmol) at 0 °C and stirred, continued for an additional 5 min. After the mixture was stirred at room temperature for 2 h, hexane was added, the resulting precipitate was filtered, and the filtrate was concentrated *in vacuo* to give crude products which were purified by column chromatography on silica gel (gradually from 2 to 5% ethyl acetate in hexane) to give the bromide derivative (224 mg, 88%) as a yellow oil: $[\alpha]^{23}_D$ −11.3 (c = 0.4, $CHCl_3$); IR (neat, cm^{-1}) 1703, 1462, 1404, 1309, 1098; ^1H NMR (400 MHz, $CDCl_3$) δ7.36−7.28 (m, 5H), 5.12 (d, 1H, *J* = 12.5 Hz), 5.09 (d, 1H, *J* = 12.5 Hz), 4.24−4.19 (m, 1H), 3.67−3.60 (m, 1H), 3.63−3.53 (m, 2H), 3.28 (d, 2H, *J* = 6.8 Hz), 2.18−2.09 (m, 1H), 1.94 (ddd, 1H, *J* = 13.9, 6.1, 4.4 Hz), 1.87 (ddd, 1H, *J* = 13.7, 5.1, 2.9 Hz), 1.78−1.68 (m, 1H), 1.53−1.45 (m, 4H), 1.41 (d, 3H, *J* = 6.8 Hz), 1.31 (ddd, 1H, *J* = 13.9, 8.3, 8.3 Hz), 0.88 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 136.9, 128.4, 127.9, 66.7, 62.7, 52.6, 47.7, 39.4, 35.7, 32.5, 31.9, 29.8, 28.0, 25.9, 22.1, 18.3, −5.3; FAB-HRMS *m/z* calcd for $C_{24}H_{41}BrNO_3Si$ $[M^+ + H]$ 498.2039, found 498.2027.

(2*R*,4*S*,6*R*)-(−)-*N*-Benzoxycalboyl-2-(3-*tert*-butyldimethylsilyloxypropyl)-4,6-dimethylpiperidine (−)-48. To a solution of bromide derivative obtained above (215 mg, 0.431 mmol) in dimethylsulfoxide (2.5 mL) was added sodium borohydride (65 mg, 1.73 mmol) at room temperature. After the mixture was stirred at 90 °C for 1 h, 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 which were purified by column chromatography on silica gel (3% ethyl acetate in hexane) to give (−)-**48** (149 mg, 82%) as a

dx.doi.org/10.1021/jo202350z | J. Org. Chem. 2012, 77, 1812−1832

colorless oil: $[\alpha]^{23}_{D}$ −16.3 (c = 0.2, $CHCl_3$); IR (neat, cm^{-1}) 1705, 1458, 1404, 1309, 1258, 1099; ^1H NMR (400 MHz, $CDCl_3$) δ7.35−7.27 (m, 5H), 5.12 (d, 1H, *J* = 12.8 Hz), 5.09 (d, 1H, *J* = 12.8 Hz), 4.20−4.15 (m, 1H), 3.63−3.53 (m, 3H), 1.95−1.70 (m, 3H), 1.66 (ddd, 1H, *J* = 13.7, 4.9, 2.7 Hz), 1.55−1.44 (m, 3H), 1.40 (d, 3H, *J* = 6.8 Hz), 1.34 (ddd, 1H, *J* = 13.7, 12.0, 5.1 Hz), 1.15 (ddd, 1H, *J* = 13.4, 8.3, 8.3 Hz), 0.94 (d, 3H, *J* = 6.6 Hz), 0.88 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 137.1, 128.4, 127.8, 127.7, 66.5, 62.9, 53.1, 48.3, 39.2, 35.1, 29.9, 28.0, 25.9, 24.3, 22.9, 22.2, 18.3, −5.3, FAB-HRMS *m*/*z* calcd for $C_{24}H_{42}NO_3Si$ $[M + H]^+$ 420.2934, found 420.2928.

(2*R*,4*S*,6*R*)-(−)-*N*-Benzoxycalboyl-4,6-dimethyl-2-hydroxypropylpiperidine. To a solution of (−)-**48** (65 mg, 0.155 mmol) in tetrahydrofurane (1.0 mL) was added 2N aqueous HCl solution (0.5 mL) at 0 °C. After the mixture was stirred at room temperature for 1 h, 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 which were purified by column chromatography on silica gel (gradually from 25 to 50% ethyl acetate in hexane) to give alcohol (47 mg, 100%) as a colorless oil: $[\alpha]^{23}_{D}$ −23.2 (c = 0.4, $CHCl_3$); IR (neat, cm^{-1}) 3414(br), 1686, 1454, 1412, 1310, 1268, 1063; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35−7.28 (m, 5H), 5.13 (d, 1H, *J* = 12.4 Hz), 5.08 (d, 1H, *J* = 12.4 Hz), 4.16 (ddq, 1H, *J* = 7.3, 5.1, 2.4 Hz), 3.70−3.63 (m, 1H), 3.63 (t, 2H, *J* = 6.1 Hz), 1.93−1.74 (m, 3H), 1.66 (ddd, 1H, *J* = 15.9, 5.4, 2.4 Hz), 1.59−1.45 (m, 3H), 1.38 (d, 3H, *J* = 6.8 Hz), 1.42−1.35 (m, 1H), 1.17 (ddd, 1H, *J* = 13.7, 7.3, 7.3 Hz), 0.96 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 137.0, 128.4, 127.8, 127.8, 66.6, 62.3, 52.6, 48.2, 38.4, 34.4, 29.4, 28.2, 23.7, 23.1, 22.3; FAB-HRMS *m*/*z* calcd for $C_{18}H_{28}NO_3$ $[M + H]^+$ 306.2069, found 306.2071.

(2*R*,4*S*,6*R*)-(−)-*N*-Benzoxycalboyl-4,6-dimethyl-3-methylesterpropylpiperidine (−)-49. To a solution of alcohol obtained above (47 mg, 0.154 mmol) in acetone (1 mL) was added 2.67 N Jones reagent at 0 °C. After the reaction mixture was stirred for 2 h at room temperature, brine was added, and the resulting mixture was extracted with ethyl acetate. The organic layers were combined, washed with 10% $NaHSO_3$ solution and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give the crude products. The crude product was esterification without further purification.

To a solution of the crude carboxylic acid obtained above in ethyl acetate (1 mL) was added diazomethane prepared from nitrosomethylurea (242 mg, 0.385 mmol), 30% aqueous NaOH solution (1.35 mL) and ether (5.0 mL) at 0 °C. After the reaction mixture was stirred for 30 min at 0 °C, saturated NH_4Cl 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 which were purified by column chromatography on silica gel (gradually from 6 to 9% ethyl acetate in hexane) to give methyl ester (−)-**49** (32 mg, 63% for 2 steps) as a colorless oil: $[\alpha]^{23}_{D}$ −24.9 (c = 0.4, $CHCl_3$); IR (neat, cm^{-1}) 1738, 1705, 1454, 1412, 1307, 1262, 1170, 1061; ^1H NMR (400 MHz, $CDCl_3$) δ7.35−7.28 (m, 5H), 5.11 (d, 1H, *J* = 12.2 Hz), 5.08 (d, 1H, *J* = 12.2 Hz), 4.21 (dqd, 1H, *J* = 9.0, 6.6, 2.9 Hz), 3.62 (s, 3H), 3.58 (dddd, 1H, *J* = 13.7, 10.2, 6.8, 3.7 Hz), 2.31 (t, 2H, *J* = 7.8 Hz), 2.15−2.03 (m, 1H), 1.91−1.71 (m, 3H), 1.63 (ddd, 1H, *J* = 13.2, 4.6, 2.2 Hz), 1.39 (d, 3H, *J* = 6.8 Hz), 1.35 (ddd, 1H, *J* = 13.9, 12.2, 5.4 Hz), 1.15 (ddd, 1H, *J* = 13.4, 8.5, 8.5 Hz), 0.94 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 156.1, 137.0, 128.4, 127.8, 127.8, 66.6, 52.8, 51.5, 48.6, 39.1, 35.4, 31.3, 26.9, 24.7, 22.8, 22.0; FAB-HRMS *m*/*z* calcd for $C_{19}H_{28}NO_4$ $[M + H]^+$ 334.2018, found 334.2015.

(5*R*,7*S*,8a*R*)-(−)-5,7-Dimethylindolizidine-3-one (−)-50. To a solution of methylester (−)-**49** (84 mg, 0.252 mmol) in methanol (1 mL) was added Pd/C (25 mg) at a room temperature. After the reaction mixture was stirred under H_2 atmosphere for 2 h, the catalyst was removed by filtration and the filtrate was concentrated *in vacuo* to give crude products. The crude product was reduced without further purification.

After solution of the crude amine obtained above in toluene (1 mL) was refluxed for 3 h, the reaction mixture was concentrated *in vacuo* to give the crude products which were purified by column chromatography on silica gel (ethyl acetate) to give indorizidinone (−)-**50** (29 mg, 71% for 2 steps) as a colorless oil: $[\alpha]^{23}_{D}$ −80.4 (c = 0.7, $CHCl_3$); IR (neat, cm^{-1}) 1686, 1418, 1375, 1294; ^1H NMR (400 MHz, $CDCl_3$) δ4.15 (dq, 1H, *J* = 13.4, 6.6 Hz), 3.78 (m, 1H), 2.35 (t, 2H, *J* = 8.8 Hz), 2.25−2.16 (m, 1H), 1.94−1.86 (m, 1H), 1.82 (ddd, 1H, *J* = 13.7, 7.1, 4.6 Hz), 1.62−1.48 (m, 3H), 1.27 (ddd, 1H, *J* = 12.7, 6.6, 6.6 Hz), 1.20 (d, 3H, *J* = 6.9 Hz), 1.09 (d, 3H, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 49.0, 44.5, 39.0, 36.1, 30.5, 26.0, 25.9, 21.0, 19.9; FAB-HRMS *m*/*z* calcd for $C_{10}H_{18}NO$ $[M + H]^+$ 168.1388, found 168.1389.

(−)-Dendroprimine (34). To a solution of indorizidinone (−)-**50** (14 mg, 0.084 mmol) in ether (2 mL) was added lithium aluminum hydride (6 mg, 0.158 mmol) at 0 °C. After the reaction mixture was refluxed for 6 h, ice was slowly added, and the resulting mixture was extracted with dichloromethane. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude products which were purified by column chromatography on silica gel on reverse phase silica gel (9% trimethylamine in methanol) to give (−)-dendroprimine (8 mg, 62%) as a yellow oil: $[\alpha]^{23}_{D}$ −36.9 (c = 0.1, $CHCl_3$); IR (neat, cm^{-1}) 1458, 1373, 1100, 1051; ^1H NMR (400 MHz, $CDCl_3$) δ3.16−3.07 (m, 2H), 2.80−2.72 (m, 1H), 2.35 (dddd, 1H, *J* = 11.7, 8.8, 5.9, 2.9 Hz), 1.89−1.50 (m, 8H), 1.04 (d, 3H, *J* = 5.9 Hz), 0.98−0.93 (1H, m), 0.91 (d, 3H, *J* = 6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ60.0, 50.9, 49.8, 42.9, 35.1, 26.6, 25.3, 22.1, 21.9, 21.8; FAB-HRMS *m*/*z* calcd for $C_{10}H_{20}N$ $[M + H]^+$ 154.1596, found 154.1595.

(2*R*,4*S*,6*S*)-(−)-*N*-Benzyzoxycalboyl-2-(3-*tert*-butyldimethylsilyloxypropyl)-4-hydroxymethyl-6-methylpiperidine (−)-51. A solution of (−)-**46** (509 mg, 1.07 mmol) and $Pd(OH)_2/C$ (100 mg) in methanol (5.0 mL) was stirred in an autoclave under 10 atmospheric pressure of hydrogen at room temperature for 12 h. Then the catalyst was removed by filtration and the filtrate was concentrated *in vacuo* to give crude products. The crude product was protected without further purification.

To a solution of the crude piperidine obtained above in tetrahydropyrane (5.5 mL) and H_2O (5.5 mL) was added K_2CO_3 (1.48 g, 10.7 mmol) and carbobenzoxy chloride (0.38 mL, 2.14 mmol) at 0 °C. After the mixture was stirred at 0 °C for 2 h, 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 which was purified by column chromatography on silica gel (gradually from 20 to 50% ethyl acetate in hexane) to give (−)-**51** (323 mg, 69%) as a colorless oil: $[\alpha]^{23}_{D}$ −6.1 (c = 1.0, $CHCl_3$); IR (neat, cm^{-1}) 3457(br), 1694, 1414, 1327, 1254, 1100; ^1H NMR (400 MHz, acetone-d_6) δ7.41−7.28 (m, 5H), 5.11 (m, 2H), 4.49−4.42 (m, 1H), 4.28−4.23 (m, 1H), 3.62−3.61 (m, 2H), 3.40 (d, 2H, *J* = 5.8 Hz), 2.06−1.97 (m, 2H), 1.82−1.79 (m, 1H), 1.68−1.40 (m, 4H), 1.32−1.17 (m, 2H), 1.21 (d, 3H, *J* = 7.1 Hz), 0.89 (s, 9H), 0.04(s, 6H); ^{13}C NMR (100 MHz, acetone-d_6) δ 156.0, 138.5, 129.2, 128.5, 67.9, 67.1, 63.5, 51.5, 47.0, 34.4, 32.7, 32.0, 31.5, 28.8, 26.3, 21.3, 18.8, −5.1; ESI HRMS *m*/*z* calcd for $C_{24}H_{41}NNaO_4Si$ $[M + Na]^+$ 458.2703, found 458.2687.

(2*R*,4*S*,6*S*)-(−)-*N*-Benzoxycalboyl-2-(3-*tert*-butyldimethylsilyloxypropyl)-4,6-dimethylpiperidine (−)-52. To a solution of (−)-**51** (323 mg, 0.741 mmol) in dichloromethane (4.0 mL) was added triethylamine (0.411 mL, 2.966 mmol), carbon tetrabromide (737 mg, 2.22 mmol) and triphenylphosphine (778 mg, 2.966 mmol) at 0 °C and stirred continued for an additional 5 min. After the mixture was stirred at room temperature for 2 h, hexane was added, the resulting precipitate was filtered, and the filtrate was concentrated *in vacuo* to give crude products which was purified by column chromatography on silica gel (gradually from 2 to 5% ethyl acetate in hexane) to give the bromide derivative (293 mg, 79%) as a yellow oil.

To a solution of bromide derivative obtained above (293 mg, 0.588 mmol) in dimethylsulfoxide (3.0 mL) was added sodium borohydride (89 mg, 2.35 mmol) at room temperature. After the mixture was stirred at 90 °C for 1 h, H_2O was added, and the resulting mixture was

dx.doi.org/10.1021/jo202350z | *J. Org. Chem.* 2012, 77, 1812−1832

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 which was purified by column chromatography on silica gel (3% ethyl acetate in hexane) to give (−)-**52** (180 mg, 73%) as a colorless oil: $[\alpha]^{23}_D$ −2.4 (c = 0.2, $CHCl_3$); IR (neat, cm^{-1}) 1696, 1460, 1412, 1323, 1101; ^1H NMR (400 MHz, acetone-d_6) δ7.41−7.28 (m, 5H), 5.14−5.08 (m, 2H), 4.44−4.38 (m, 1H), 4.22−4.17 (m, 1H), 3.61 (m, 2H), 2.06−2.04 (m, 1H), 2.01−1.89 (m, 1H), 1.70−1.37 (m, 5H), 1.28−1.09 (m, 2H), 1.20 (d, 3H, *J* = 6.8 Hz), 0.92 (d, 3H, *J* = 6.4 Hz), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, acetone-d_6) δ 156.1, 138.5, 129.2, 128.5, 67.1, 63.5, 51.8, 47.3, 39.8, 37.3, 32.7, 31.6, 26.3, 22.6, 21.3, 20.5, 18.8, −5.1. ESI HRMS *m/z* calcd for $C_{24}H_{41}NNaO_3Si$ $[M + Na]^+$ 442.2753, found 442.2747.

(2*R*,4*S*,6*S*)-(−)-*N*-Benzoxycalboyl-4,6-dimethyl-3-methylesterpropylpiperidine (−)-53. To a solution of (−)-**52** (165 mg, 0.393 mmol) in tetrahydrofurane (2.0 mL) was added 2N aqueous HCl solution (1.0 mL) at 0 °C. After the mixture was stirred at room temperature for 1 h, 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 which was purified by column chromatography on silica gel (gradually from 25 to 50% ethyl acetate in hexane) to give alcohol as a colorless oil.

To a solution of alcohol obtained above (115 mg, 0.377 mmol) in acetone (2 mL) was added 2.67 N Jones reagent at 0 °C. After the reaction mixture was stirred for 2 h at room temperature, brine was added, and the resulting mixture was extracted with ethyl acetate. The organic layers were combined, washed with 10% $NaHSO_3$ solution and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give the crude products. The crude product was esterification without further purification.

To a solution of the crude carboxylic acid obtained above in ethyl acetate (2 mL) was added diazomethane prepared from nitrosomethylurea (242 mg, 0.385 mmol), 30% aqueous NaOH solution (1.25 mL) and ether (5.0 mL) at 0 °C. After the reaction mixture was stirred for 30 min at 0 °C, saturated NH_4Cl 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 which were purified by column chromatography on silica gel (gradually from 6 to 9% ethyl acetate in hexane) to give methyl ester (−)-**53** (88 mg, 67% for 3 steps) as a colorless oil: $[\alpha]^{23}_D$ −2.8 (c = 0.8, $CHCl_3$); IR (neat, cm^{-1}) 1738, 1691, 1412, 1323, 1271, 1099; ^1H NMR (400 MHz, acetone-d_6) δ7.41−7.29 (m, 5H), 5.15 (d, 1H, *J* = 12.7 Hz), 5.07 (d, 1H, *J* = 12.7 Hz), 4.46−4.39 (m, 1H), 4.23 (m, 1H), 3.58 (s, 3H), 2.38−2.20 (m, 2H), 2.06−1.86 (m, 3H), 1.69−1.65 (m, 1H), 1.59−1.55 (m, 1H), 1.29−1.13 (m, 2H), 1.21 (d, 3H, *J* = 7.1 Hz), 0.92 (d, 3H, *J* = 6.3 Hz); ^{13}C NMR (100 MHz, acetone-d_6) δ 173.7, 156.1, 138.4, 129.2, 128.6, 67.2, 51.5, 51.3, 47.3, 39.6, 37.3, 32.3, 31.3, 22.5, 21.3, 20.5; ESI HRMS *m/z* calcd for $C_{19}H_{27}NNaO_4$ $[M + Na]^+$ 356.1838, found 356.1852.

(5*S*,7*S*,8a*R*)-(−)-5,7-Dimethylindolizidine-3-one (−)-54. To a solution of methylester (−)-**53** (46 mg, 0.138 mmol) in methanol (1 mL) was added Pd/C (15 mg) at a room temperature. After the reaction mixture was stirred under H_2 atmosphere for 1 h, the catalyst was removed by filtration and the filtrate was concentrated *in vacuo* to give crude products. The crude product was reduced without further purification.

After solution of the crude amine obtained above in toluene (1 mL) was refluxed for 3 h, the reaction mixture was concentrated *in vacuo* to give the crude products which were purified by column chromatography on silica gel (ethyl acetate) to give indoridizine (−)-**54** (17 mg, 74% for 2 steps) as a colorless oil: $[\alpha]^{24}_D$ 9.77 (c = 0.6, $CHCl_3$); IR (neat, cm^{-1}) 1686, 1414, 1377, 1312, 1275; ^1H NMR (400 MHz, $CDCl_3$) δ3.79−3.71 (m, 1H), 3.66−3.59 (m, 1H), 2.34−2.29 (m, 2H), 2.18−2.05 (m, 2H), 1.64−1.55 (m, 3H), 1.51−1.44 (m, 2H), 1.42 (d, 3H, *J* = 6.6 Hz), 1.04 (d, 3H, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 53.1, 46.2, 38.1, 37.5, 31.7, 26.7, 23.4, 20.6, 19.8; ESI HRMS *m/z* calcd for $C_{10}H_{17}NNaO$ $[M + Na]^+$ 190.1208, found 190.122.

(+)-5-Epidendroprimine (55). To a solution of indoridizine (−)-**54** (17 mg, 0.102 mmol) in ether (2 mL) was added lithium aluminum hydride (14 mg, 0.369 mmol) at 0 °C. After the reaction mixture was refluxed for 6 h, ice was slowly added, and the resulting mixture was extracted with dichloromethane. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude products which were purified by column chromatography on reverse phase silica gel (9% trimethylamine in methanol) to give (+)-5-epidendroprimine (**55**) (10 mg, 67%) as a yellow oil: $[\alpha]^{25}_D$ 46.0 (c = 0.3, $CHCl_3$); IR (neat, cm^{-1}) 1460, 1377, 1325, 1125; ^1H NMR (400 MHz, $CDCl_3$) δ3.23 (td, 1H, *J* = 8.5, 2.0 Hz), 2.30−2.22 (m, 1H), 2.15−1.97 (m, 3H), 1.82−1.33 (m, 8H), 1.07 (d, 3H, *J* = 6.1 Hz), 1.00 (d, 3H, *J* = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ58.5, 53.3, 51.6, 40.3, 36.9, 30.7, 26.8, 21.2, 20.3, 18.8; ESI HRMS *m/z* calcd for $C_{10}H_{20}N$ $[M + H]^+$ 154.1596, found 154.1589.

(1*S*,2*R*)-(−)-*cis*-1-[(2*R*,4*R*,6*S*)-2-(1-tert-Butyldimethylsiloxypropenyl)-4,6-dimethylpiperidin-1-yl]-7-isopropylindan-2-ol (−)-64. To a solution of compound (−)-**37** (168 mg, 0.379 mmol) in ether (3.8 mL) was added a 1.0 M solution of methylmagnesium iodide in ether (1.90 mL, 1.90 mmol) prepared from methyl iodide (1.24 mL, 19.9 mmol), magnesium turning (440 mg, 18.1 mmol), and ether (18.1 mL) at 0 °C. After the mixture was stirred at room temperature for 2 h, 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 a 1:1 mixture. These isomers were successfully separated by column chromatography on silica gel (from 3 to 5% ethyl acetate in hexane) to give the piperidine compound (−)-**64** (71 mg, 41%) as a colorless oil: $[\alpha]^{23}_D$ −28.3 (c = 0.8 $CHCl_3$); IR (neat, cm^{-1}) 3209, 1589, 1458, 1385, 1254, 1090; ^1H NMR (400 MHz, $CDCl_3$) δ 7.21 (dd, 1H, *J* = 7.6, 7.6 Hz), 7.12 (d, 1H, *J* = 7.6 Hz), 6.99 (d, 1H, *J* = 7.3 Hz), 4.52 (d, 1H, *J* = 8.9 Hz), 4.35−4.29 (m, 1H), 3.37 (dd, 1H, *J* = 17.2, 8.7 Hz), 3.14−2.84 (m, 6H), 2.44−2.37 (m, 1H), 1.87 (ddd, 1H, *J* = 12.8, 6.4, 3.2 Hz), 1.75 (ddd, 1H, *J* = 13.5, 6.4, 3.2 Hz), 1.47−1.37 (m, 1H), 1.38 (d, 3H, *J* = 6.9 Hz), 1.22 (d, 3H, *J* = 6.0 Hz), 1.17−1.09 (m, 1H), 1.12 (d, 3H, *J* = 6.9 Hz), 1.05−0.96 (m, 1H), 0.91 (d, 3H, *J* = 6.4 Hz), 0.88−0.73 (m, 3H), 0.82 (s, 9H), 0.81 (d, 3H, *J* = 6.1 Hz), 0.59−0.48 (m, 1H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.8, 142.4, 137.7, 129.0, 122.9, 122.7, 67.5, 67.4, 63.0, 58.9, 55.8, 44.2, 42.4, 41.3, 33.4, 31.8, 29.3, 29.0, 26.0, 24.8, 24.0, 22.1, 21.9, 18.3, −5.3; ESI HRMS *m/z* calcd for $C_{28}H_{49}NO_2Si$ $[M + H]^+$ 460.3611, found 460,3603.

(2*R*,4*R*,6*S*)-(+)-*N*-Benzyloxycalboyl-4,6-dimethyl-2-hydroxypropylpiperidine (+)-65. A solution of (−)-**64** (204 mg, 0.44 mmol) and $Pd(OH)_2/C$ (57 mg) in methanol (2.7 mL) was stirred in an autoclave under 10 atmospheric pressure of hydrogen at room temperature for 12 h. Then the catalyst was removed by filtration and the filtrate was concentrated *in vacuo* to give crude products. The crude product was reduced without further purification.

To a solution of the crude piperidine obtained above in tetrahydrofurane (2.2 mL) and H_2O (2.2 mL) was added K_2CO_3 (600 mg, 4.45 mmol) and carbobenzoxy chloride (0.16 mL, 0.89 mmol) at 0 °C. After the mixture was stirred at 0 °C for 1 h, 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 which were purified by column chromatography on silica gel (gradually from 2 to 3.3% ethyl acetate in hexane) to give the Cbz compound (177 mg, 95%) as a colorless oil.

To a solution of piperidine derivative obtained above in tetrahydrofurane (2.0 mL) was added 2N aqueous HCl solution (1.0 mL) at room temperature. After the mixture was stirred at room temperature for 2 h, 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 which were purified by column chromatography on silica gel (gradually from 25 to 50% ethyl acetate in hexane) to give (+)-**65** (95 mg, 74%) as a colorless oil: $[\alpha]^{24}_D$ 7.08 (c = 0.28, $CHCl_3$); IR (neat, cm^{-1}) 3441(br), 1690, 1456, 1416, 1321, 1098, 1007; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38−7.28

dx.doi.org/10.1021/jo202350z | *J. Org. Chem.* 2012, 77, 1812−1832

(m, 5H), 5.16−5.09 (m, 2H), 4.28−4,14 (m, 2H), 3.64−3.61 (m, 2H), 2.17−2.10 (m, 1H), 1.95−1.88 (m, 1H), 1.78−1.71 (m, 1H), 1.61−1.44 (m, 4H), 1.23 (d, 3H, J = 6.6 Hz), 1.08−0.94 (m, 2H), 0.92 (d, 3H, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 137.0, 128.4, 127.8, 127.7, 66.9, 62.5, 50.7, 48.4, 38.2, 37.1, 36.2, 29.1, 26.2, 23.9, 21.7; ESI HRMS m/z calcd for $C_{18}H_{27}NNaO_3$ $[M + Na]^+$ 328.1889, found 328.1880.

(2*R*,4*S*,6*S*)-(+)-*N*-Benzyzoxycalboyl-4,6-dimethyl-2-methyl-esterpropylpiperidine (+)-66. To a solution of (+)-**65** (95 mg, 0.311 mmol) in acetone (2 mL) was added 2.67 N Jones reagent at 0 °C. After the reaction mixture was stirred for 1 h at room temperature, brine was added, and the resulting mixture was extracted with ethyl acetate. The organic layers were combined, washed with 10% $NaHSO_3$ solution and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give the crude products. The crude product was reduced without further purification.

To a solution of the crude carboxylic acid obtained above in ethyl acetate (1.7 mL) was added diazomethane prepared from nitrosomethylurea (80 mg, 0.778 mmol), 30% aqueous NaOH solution (0.3 mL) and ether (1.7 mL) at 0 °C. After the reaction mixture was stirred for 30 min at 0 °C, saturated NH_4Cl 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. Column chromatography on silica gel (gradually from 6 to 9% ethyl acetate in hexane) to give methyl ester (+)-**66** (80 mg, 78% for 2 steps) as a colorless oil: $[\alpha]^{24}_D$ 10.6 (c = 1.2, $CHCl_3$); IR (neat, cm^{-1}) 1738, 1692, 1456, 1412, 1319, 1172, 1096, 1015; ^{1}H NMR (400 MHz, $CDCl_3$) δ7.38−7.29 (m, 5H), 5.12 (d, 1H, J = 12.6 Hz), 5.09 (d, 1H, J = 12.6 Hz), 4.30−4.23 (m, 1H), 4.21−4.13 (m, 1H), 3.62 (s, 3H), 2.39−2.26 (m, 2H), 2.18−2.10 (m, 1H), 2.00−1.87 (m, 2H), 1.84−1.75 (m, 1H), 1.58−1.45 (m, 1H), 1.23 (d, 3H, J = 6.6 Hz), 1.11−1.02 (m, 1H), 0.98−0.90 (m, 1H), 0.92 (d, 3H, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 156.4, 136.9, 128.5, 127.8, 127.7, 67.0, 51.6, 50.2, 48.7, 38.0, 36.9, 34.7, 31.1, 26.2, 23.6, 21.7; ESI HRMS m/z calcd for $C_{24}H_{41}NO_3Si$ $[M + Na]^+$ 356.1838, found 356.1838.

(+)-5,7-Epidendroprimine. To a solution of methylester (+)-**66** (80 mg, 0.240 mmol) in methanol (1.2 mL) was added Pd/C (30 mg) at a room temperature. After the reaction mixture was stirred under H_2 atmosphere for 1 h, the catalyst was removed by filtration and the filtrate was concentrated *in vacuo* to give crude products. The crude product was reduced without further purification.

After solution of the crude amine obtained above in toluene (2.0 mL) was refluxed for 5 h, the reaction mixture was concentrated *in vacuo* to give the crude products which were purified by column chromatography on silica gel (ethyl acetate) to give indorizidinone (14 mg, 35% for 2 steps) as a colorless oil: $[\alpha]^{22}_D$ +63.7 (c = 0.4, $CHCl_3$); IR (neat, cm^{-1}) 1694, 1458, 1412, 1377, 1262; ^{1}H NMR (400 MHz, $CDCl_3$) δ3.34−3.26 (m, 1H), 3.24−3.15 (m, 1H), 2.39−2.25 (m, 2H), 2.13−2.05 (m, 1H), 1.80 (ddd, 1H, J = 12.8, 2.1, 2.1 Hz), 1.67 (d, 3H, J = 6.6 Hz), 1.62−1.46 (m, 3H), 1.01−0.83 (m, 2H), 0.95 (d, 3H, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 59.9, 52.7, 43.6, 41.5, 32.2, 30.7, 25.2, 21.8, 19.8; ESI-HRMS m/z calcd for $C_{10}H_{18}NNaO$ $[M + Na]^+$ 190.1208, found 190.1209.

To a solution of indorizidinone obtained above (14 mg, 0.084 mmol) in ether (1.3 mL) was added lithium aluminum hydride (5 mg, 0.132 mmol) at 0 °C. After the reaction mixture was refluxed for 2 h, ice was slowly added, and the resulting mixture was extracted with dichloromethane. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give (+)-5,7-epidendroprimine (11 mg, 86%) as a yellow oil: $[\alpha]^{23}_D$ +53.7 (c = 0.2, $CHCl_3$); IR (neat, cm^{-1}) 1456, 1373, 1205, 1043; ^{1}H NMR (400 MHz, $CDCl_3$) δ3.22 (td, 1H, J = 8.7, 2.1 Hz), 2.07−1.42 (m, 9H), 1.32−1.25 (m, 1H), 1.10 (d, 3H, J = 6.2 Hz), 1.01−0.87 (m, 2H), 0.93 (d, 3H, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ64.7, 58.1, 51.4, 43.2, 39.6, 31.4, 30.4, 22.0, 21.0, 20.7; ESI-HRMS m/z calcd for $C_{10}H_{20}N$ $[M + H]^+$ 154.1596, found 154.1598.

■ ASSOCIATED CONTENT

Supporting Information

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

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Mr. Tamotsu Yamamoto at the Institute for Life Science Research at Asahi Chemical Industry Co., Ltd., for his X-ray crystallographic measurements. This work was financially supported by a Grant-in-Aid for Science Research on Priority Areas 16073222 from the Ministry of Education, Culture, Sports, Science and Technology, Japan, and JSPS (Research Fellowship for T.K.).

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