

Total synthesis of (–)-20-epiuleine via stereocontrolled one-pot asymmetric azaelectrocyclization followed by novel 1,4-addition reaction†

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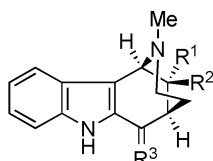
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The first asymmetric total synthesis of an indole alkaloid, (–)-20-epiuleine, containing the 2,3,4-trisubstituted piperidine core, was achieved using a stereocontrolled one-pot asymmetric 6π -azaelectrocyclization followed by a stereoselective 1,4-addition reaction of the unsaturated ester with a Grignard reagent resulting from the novel neighboring participation of the hydroxyl group in *cis*-aminoindanol as a chiral nitrogen source.

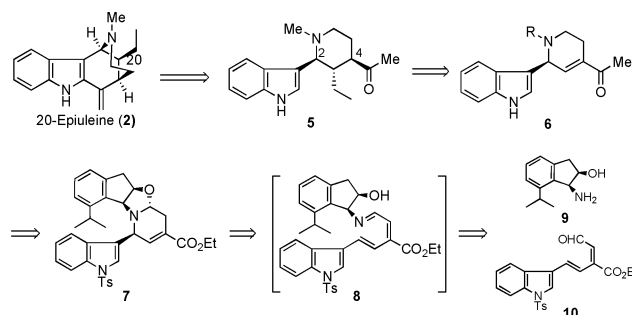
Introduction

Uleine (1), 20-epiuleine (2), dasycarpidone (3) and 20-epidasycarpidone (4) are four related members of the *Strychnos*-type indole alkaloids, which were principally isolated from *Aspidosperma sp* (Fig. 1).¹ These indole alkaloids lack the two-carbon chain from tryptophan. Although a number of synthetic efforts for the racemic 20-epiuleine (2) and epidasycarpidone (4) along with uleine (1) and dasycarpidone (3) were reported in the literature,^{2,3} only a few asymmetric syntheses of these indole alkaloids have been reported.^{4,5} The structural feature of these alkaloids is the 2-aza-bicyclo[3,3,1]nonane skeleton, which has been constructed from the 3-(2-piperidyl)indole derivative 5 by an acid-catalyzed cyclization followed by dehydration (Scheme 1).³ The subject, therefore, is how to efficiently synthesize the optically homogeneous 2-indolyl-3-ethyl-4-carbonyl piperidine compound such as 5, which is classified as a 2,3,4-trisubstituted piperidine skeleton and was obtained in the *dl*-form by the 1,4-addition of the unsaturated ketone 6 (Scheme 1).^{3c,3d}



Uleine (1)	: R ¹ =Et, R ² =H, R ³ =CH ₂
20-Epiuleine (2)	: R ¹ =H, R ² =Et, R ³ =CH ₂
Dasycarpidone (3)	: R ¹ =Et, R ² =H, R ³ =O
20-Epidasycarpidone (4)	: R ¹ =H, R ² =Et, R ³ =O

Fig. 1 *Strychnos*-type indole alkaloids.



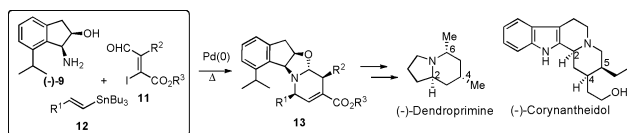
Scheme 1 Synthetic strategy of 20-epiuleine.

Previously, we reported the formal synthesis of the optically active 20-epiuleine (2) utilizing the step-wise asymmetric 6π -azaelectrocyclization, which was developed as a synthetic strategy for substituted piperidines.⁵ This asymmetric azaelectrocyclization includes highly controlling the stereochemistry at the second position of the constructed tetrahydropyridine derivative, such as 7, resulting from a kinetically controlled torquoselective 6π -azaelectrocyclization of a conformationally flexible linear azatriene, such as 8, prepared from *cis*-aminoindanol derivative 9 and dienal 10.⁵ In that formal synthesis, although we synthesized the optically homogeneous 2-indolyl-4-acyl-1,2,5,6-tetrahydropyridine 6, which was identical to the synthetic intermediate of (*dl*)-20-epiuleine reported by Husson's group, the transformation to the corresponding chiral 2,3,4-trisubstituted piperidine derivative 5 was not realized. Thus, the real procedure for the construction of the chiral 2,3,4-trisubstituted piperidine framework has not been yet established.

Most recently, in order to establish asymmetric 6π -azaelectrocyclization as a new strategy for alkaloid synthesis, we realized a one-pot protocol, which enabled the facile and highly stereoselective preparation of chiral 2,4-disubstituted- and 2,4,5-trisubstituted-1,2,5,6-tetrahydropyridine derivatives such as 13 under thermodynamic control (Scheme 2).⁶ Based on the developed protocol, we achieved the stereoselective total synthesis of (–)-dendroprimine,⁷ which possesses a chiral

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† Electronic supplementary information (ESI) available: The experimental details of 27a–d and 29a–c and ¹H and ¹³C NMR spectra of the products. See DOI: 10.1039/c0ob00627k



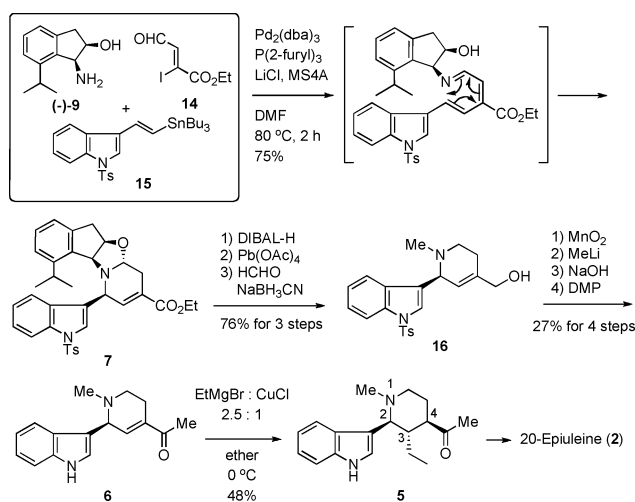
Scheme 2 Alkaloid synthesis *via* 6 π -azaelectrocyclization.

2,4,6-trisubstituted piperidine nucleus, and (-)-corynantheidol,⁸ which has a chiral 2,4,5-trisubstituted piperidine structural unit. In this paper, we describe in detail the stereoselective total synthesis of (-)-20-epiuleine, which consists of a 2,3,4-trisubstituted piperidine structural unit having an indole nucleus *via* the one-pot asymmetric azaelectrocyclization followed by the unique 1,4-addition reaction of the unsaturated ester with Grignard reagents resulting from the novel neighboring participation of the hydroxyl group in *cis*-aminoindanol, which was utilized as a chiral nitrogen source.

Results and Discussion

Usual 1,4-addition reaction of unsaturated methyl ketone with cuprate

As previously reported, the tetracyclic aminoacetal derivative **7** was stereoselectively synthesized by the one-pot asymmetric 6 π -azaelectrocyclization (Scheme 3).⁶ Thus, the *cis*-aminoindanol derivative (-)-**9**, trisubstituted vinyl iodide **14** and MS4A were stirred in DMF at room temperature. After checking the consumption of **14** by TLC, indolyl vinyl stannane **15**, Pd₂(dba)₃, tri(2-furyl)phosphine and LiCl were added, and the resulting mixture was heated at 80 °C for 2 h to produce the desired aminoacetal **7** in 75% yield resulting from the successive Migita-Stille coupling, 1-azatriene formation, 6 π -azaelectrocyclization and aminoacetal formation. The stereoselectivity at the second position and the total yield were better than those obtained by the previously developed stepwise procedure (75% yield and >16:1 stereoselectivity for the one-pot protocol *vs.* 62% yield and 10:1 stereoselectivity for the stepwise method).^{5,6} The transformation from **7** to methyl ketone **6** through **16** was accomplished by the

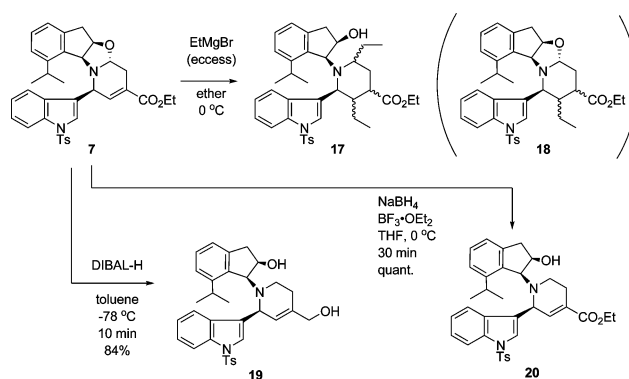


Scheme 3 Synthesis of 20-epiuleine through unsaturated methyl ketone **6**.

sequence of DIBAL-H reduction, lead tetraacetate oxidation in the presence of *n*-propylamine, reductive *N*-methylation (HCHO, NaBH₃CN in CH₃CN), MnO₂ oxidation, methylation with MeLi, hydrolysis of the *N*-tosyl group in the indole ring and then DMP oxidation as previously reported.⁵ We thus obtained the optically active methyl ketone derivative **6**, which was a key synthetic intermediate of (\pm)-20-epiuleine as reported by Husson's group. We then attempted the 1,4-addition reaction of (-)-**6** under the reaction conditions described in the literature.^{3c} After a detailed investigation of the reaction conditions, we obtained the desired 2,3,4-trisubstituted piperidine compound **5** in 48% yield using excess reagents of ethylmagnesium bromide and copper(I) chloride in a ratio of 2.5:1 in ether. When the one to one ratio of ethylmagnesium bromide and copper(I) was used, we did not obtain the desired product and recovered the starting materials. As the solvent of this 1,4-addition reaction, the yield in ether was rather better than in THF. Although we obtained the derived **5**, this 1,4-addition reaction was troublesome and sometimes not reproducible. The yield varied from 48% to 13% under the same conditions employed. We then examined another method for this 1,4-addition reaction.

Novel 1,4-addition reaction of the unsaturated ester with the Grignard reagent to produce 2,3,4-trisubstituted piperidine derivatives; Improved synthesis of (-)-20-epiuleine

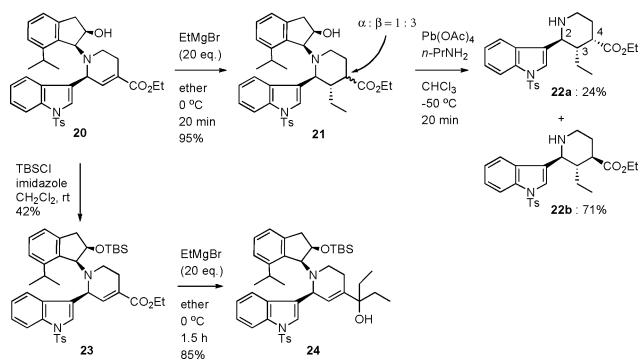
Since it was preferable to construct the 2,3,4-trisubstituted piperidine nucleus of 20-epiuleine at the earlier stage, we attempted the 1,4-addition reaction of the aminoacetal derivative **7**, which was easily obtained by the one-pot asymmetric azaelectrocyclization of the three components.⁶ Surprisingly, the treatment of **7** with an excess amount of the Grignard reagent at 0 °C spontaneously provided the dialkylated ester **17** as a mixture of stereoisomers, and no 1,4-addition product **18** was detected in the mass spectrum (Scheme 4). Even though one equivalent of the Grignard reagent was used, the dialkylated product **17** was admitted as the major product in the mass spectra along with the starting material **7**. We postulated that the 1,4-addition of an ethyl group to the unsaturated ester moiety would occur after the alkylation at the acetal moiety proceeded. We then decided to attempt the 1,4-addition reaction for the aminoindanol derivative **20**, which would be obtained from the aminoacetal **7** by chemoselective reduction, with ethylmagnesium bromide. The reduction of **7** with LAH or DIBAL-H gave the corresponding diol **19**, and Red-Al[®]



Scheme 4 Alkylation and reduction of **7**.

in toluene chemoselectively reduced the ester group to give the primary alcohol as a mixture of olefin isomers, while the saturated derivative gave the corresponding primary alcohol.⁶ Fortunately, we found that the treatment of **7** with NaBH₄ in the presence of BF₃·OEt₂ in THF at 0 °C successfully and quantitatively provided the desired alcohol **20**.⁹ After obtaining **20**, we attempted the 1,4-addition reaction.

The reaction of **20** with an excess amount of ethylmagnesium bromide in ether at 0 °C for 20 min cleanly proceeded to expectedly afford the 1,4-addition product **21** in 95% yield as a mixture of stereoisomers, which could not be separately isolated at this stage (Scheme 5). Removal of the indanol moiety in **21** with lead tetraacetate under the established condition⁶ produced the 2,3,4-trisubstituted piperidine **22a** and **22b** in 24% and 71% yields, respectively, which were cleanly separated from each other. The stereochemistry of **22b** was determined as 2β, 3α, 4β in the piperidine ring and that of **22a** as 2β, 3α, 4α by a detailed analysis of the NMR data. Although various attempts of isomerization at the ester group of **22a** (*t*-BuOK in BuOH, DBU in DMF, *etc.*) were not successful, isomerization of the corresponding methyl ketone **5** was successful in literature,^{3c,d} and hence the present synthesis can be regarded as the stereocontrolled one. On the contrary, the reaction of compound **23**, which was derived from the hydroxyl compound **20** with TBSCl and imidazole, gave tertiary alcohol **24** with ethylmagnesium bromide resulting from the addition of an ethyl group to the ester group. Thus, the secondary hydroxyl group of the aminoindanol moiety is essential for the 1,4-addition reaction.



Scheme 5 1,4-Addition reaction of unsaturated ester.

A plausible mechanism is shown in Fig. 2. The highly stereoselective introduction of an ethyl group at the β-position of the ester group in **20** could be explained by assuming that the coordination

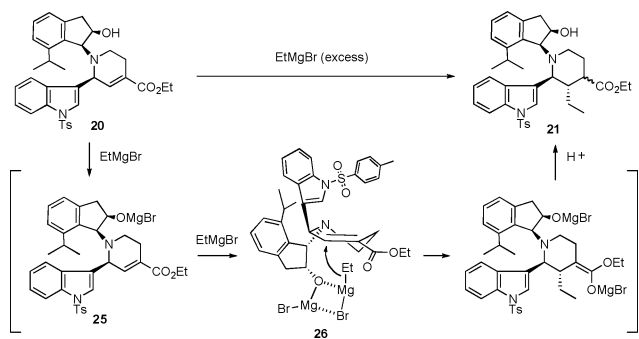


Fig. 2 Plausible mechanism of 1,4-addition reaction.

Table 1 1,4-Addition reaction of unsaturated carbonyl compounds

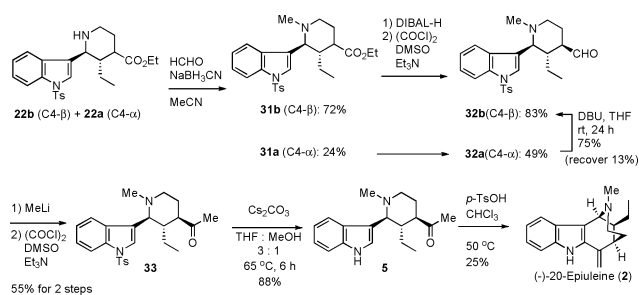
Entry	27	29	R ¹	R ²	Yield	Ratio α : β	By-product
1	20	22		CO ₂ Et	95%	1 : 3.0	
2	27a	29a		CO ₂ Et	82%	1 : 2.7	
3	27b	29b		CO ₂ Et	75%	1 : 3.8	
4	27c	29c			41%	1 : 2.2	

of the Grignard reagent with the OMgBr group prepared from the Grignard reagent and the hydroxyl group in the *cis*-aminoindanol moiety was generated during the alkylation process,¹⁰ and then the ethyl group attacked from the opposite direction of the indole group as shown in structure **26**.

In order to investigate the generality of this novel 1,4-addition reaction assisted by the neighboring hydroxyl group, we applied the reaction to a phenyl derivative **27a** instead of an *N*-tosyl indole compound as a representative compound (Table 1). As expected, the reaction under the same conditions gave the corresponding 1,4-addition product **29a** through **28a** in 82% yield with the single stereoisomer at the ethyl group and the similar stereoselectivity at the ester group. The thiophene derivative **27b**⁶ gave **29b** through **28b** in 75% yield and a rather better stereoselectivity at the ester group. On the contrary, attempts of the 1,4-addition reaction of the corresponding methyl ketone derivative **27c**, which was easily derived from amide **27d**, gave the 1,2-addition product **30c** along with 1,4-addition product **29c** in 26% and 41% yields, respectively. In the case of the amide derivative **27d**, which was obtained by the same one-pot azaelectrocyclization using the corresponding Weinreb amide instead of **14** in Scheme 3 (see experimental), the reaction gave a complex mixture and **29d** was not isolated. Thus, the unsaturated ester group was appropriate for the desired 1,4-addition reaction.

Total synthesis of (–)-20-epiuleine by the one-pot asymmetric 6π-azaelectrocyclization followed by the novel 1,4-addition

To achieve the total synthesis of 20-epiuleine (Scheme 6), the obtained **22b** was transformed into the methyl ketone **5**. Thus, the reductive *N*-methylation of a mixture of **22b** and **22a** was performed by treatment with a 37% aqueous HCHO solution and sodium cyanoborohydride in acetonitrile to produce **31b** and **31a** as a mixture of easily separable epimers. Each of them was transformed into the aldehyde **32b** and **32a** by DIBAL-H reduction followed by Swern oxidation. At this stage, the undesired isomer **32a** was epimerized to the desired **32b** by a DBU treatment in THF



Scheme 6 Synthesis of (–)-20-epiuleine.

at room temperature. The obtained aldehyde **32b** was transformed into the methyl ketone **5** through **33** by methylation with MeLi, Swern oxidation and then hydrolysis of the *N*-tosyl group of the indole moiety with Cs₂CO₃ in THF and MeOH (3 : 1). Finally, the treatment of **5** with *p*-TsOH in chloroform completed the total synthesis of (–)-20-epiuleine (**2**) in 25% yield. The spectral data (¹H NMR, ¹³C NMR, IR, HRMS) were in good agreement with those of the natural product. The value of [α]_D of the synthesized compound was –30.1 (CHCl₃, c 0.9), which is reported for the first time.

Summary

In summary, we achieved the first asymmetric total synthesis of (–)-20-epiuleine (**2**) using a three-component one-pot 6π-azaelectrocyclization. The construction of the 2,3,4-trisubstituted piperidine as the core structure of the indole alkaloid was established by utilizing the highly stereoselective 1,4-addition reaction only with the Grignard reagent. This unique 1,4-addition reaction was due to the novel neighboring participation of the hydroxyl group of the characteristic aminoindanol moiety, which was employed as a chiral nitrogen source. The total yield of the first route *via* Husson's enone obtained from the three components in a one-pot reaction was 1.3% for 10 steps, while that of the second route was 5.0% for 11 steps.

Experimental

General Procedure

All commercially available reagents were used without further purification. All solvents were used after distillation. Tetrahydrofuran, diethyl ether and toluene were refluxed over and distilled from sodium. Dichloromethane was refluxed over and distilled from P₂O₅. Dimethylformamide (DMF) was distilled from CaH₂. Preparative separation was usually performed by column chromatography on silica gel. The ¹H NMR and ¹³C NMR spectra were recorded using a 400 MHz spectrometer, and chemical shifts were represented as δ-values relative to the internal standard TMS. The IR spectra were recorded by a FT-IR spectrometer. The high-resolution mass spectra (HRMS) were measured by a ESI-TOF MS.

(2*S*,3*S*,4*R*)-(–)-3-Ethyl-4-(acetyl)-*N*-methyl-2-(indol-3-yl)piperidine (5**).** To a suspension of copper(I) chloride (148 mg, 1.49 mmol) in ether (1.0 ml) was added ethyl magnesium bromide (1.25 ml, 3.74 mmol, 3.0 M in ether) at 0 °C. After the mixture was stirred for 1 h at this temperature, a solution of **6** (22 mg,

1.20 mmol) in ether (5.0 ml) was added. After the mixture was stirred at this temperature for 30 min, saturated aqueous NH₄Cl and NaHCO₃ solutions were successively added and the resulting mixture was extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over MgSO₄, filtered and concentrated *in vacuo* to give the crude products. Column chromatography on silica gel (from 0% to 9% methanol in chloroform) gave **5** (12 mg, 48%) as a yellow amorphous solid: [α]_D²² –22.1 (c 1.1, CHCl₃); IR (KBr disk, cm^{–1}) 2928, 2793, 1714, 1458, 1136, 1067, 733; ¹H NMR (400 MHz, CDCl₃) δ 8.14–8.26 (br s, 1H), 7.76–7.88 (br s, 1H), 7.37 (d, 1H, *J* = 8.0 Hz), 7.15 (m, 3H), 3.13 (ddd, 1H, *J* = 11.7, 3.2, 3.2 Hz), 3.03 (d, 1H, *J* = 8.7 Hz), 2.59 (ddd, 1H, *J* = 11.5, 11.5, 4.6 Hz), 2.40–2.28 (br s, 1H), 2.16–2.24 (m, 4H), 2.02 (s, 3H), 1.84–1.99 (m, 2H), 1.03–1.20 (m, 2H), 0.62 (t, 3H, *J* = 7.6 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 211.8, 136.3, 122.5, 122.0, 119.4, 116.4, 111.1, 56.5, 54.2, 44.6, 29.2, 28.2, 23.1, 9.2; ESI HRMS *m/z* calcd for C₁₈H₂₄N₂O₁ (M+H)⁺ 285.1967, found 285.1977.

Ethyl (2*S*)-1-[(1*S*,2*R*)-2-hydroxyl-7-isopropylindan-1-yl]-2-(*N*-*p*-toluenesulfonylindol-3-yl)-1,2,5,6-tetrahydropiperidine-4-carboxylate (20**).** To a solution of aminoacetal **7** (6.78 g, 11.4 mmol) in THF (110 ml) were added sodium borohydride (2.15 g, 56.8 mmol) and trifluoroborane etherate complex (1.43 ml, 11.4 mmol) at 0 °C. After the mixture was stirred at 0 °C for 30 min, saturated aqueous NaHCO₃ solution was added, and the resulting mixture was extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over MgSO₄, filtered and concentrated *in vacuo* to give the crude products. Column chromatography on silica gel (from 25% to 33% ethyl acetate in hexane) gave the product **20** (5.85 g, 86%) as a yellow amorphous solid: [α]_D²² –116.4 (c 1.0, CHCl₃); IR (KBr disk, cm^{–1}) 2961, 2867, 1711, 1375, 1258, 677; ¹H NMR (400 MHz, CDCl₃, 55 °C) δ 7.99 (d, 1H, *J* = 8.5 Hz), 7.78 (d, 2H, *J* = 8.5 Hz), 7.38–7.70 (br d, 2H), 7.31 (dd, 1H, *J* = 7.3, 7.3 Hz), 7.18–7.24 (m, 4H), 7.00 (d, 1H, *J* = 7.8 Hz), 6.88 (d, 1H, *J* = 6.6 Hz), 6.81(s, 1H), 5.15–5.67 (br s, 1H), 4.45–4.63 (br s, 1H), 4.32 (d, 1H, *J* = 6.6 Hz), 4.12–4.27 (m, 2H), 2.31–3.10 (br m, 7H), 2.30 (s, 3H), 1.27 (t, 3H, *J* = 7.9 Hz), 0.91–1.07 (br s, 3H), 0.25–0.57 (br s, 3H); ¹³C NMR (100 MHz, CDCl₃, 55 °C) δ 166.7, 147.7, 145.0, 139.4, 136.7, 135.6, 135.5, 129.9, 129.4, 129.0, 126.9, 124.8, 123.5, 123.1, 121.9, 120.9, 113.7, 60.5, 54.9, 41.3, 26.3, 25.7, 23.8, 22.5, 21.5, 14.2; ESI HRMS *m/z* calcd for C₃₅H₃₈N₂O₅S₁ (M+Na)⁺ 621.2399, found 621.2377.

Ethyl (2*S*,3*S*)-3-ethyl-1-[(1*S*,2*R*)-2-hydroxyl-7-isopropylindan-1-yl]-2-(*N*-*p*-toluenesulfonylindol-3-yl)-piperidine-4-carboxylate (21**).** To a solution of **20** (3.27 g, 5.46 mmol) in ether (50 ml) was slowly added ethyl magnesium bromide (109 ml, 109 mmol, 1.0 M in ether) at 0 °C. After the mixture was stirred for 20 min, H₂O and a 1 N HCl solution were carefully added, and the resulting mixture was extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over MgSO₄, filtered and concentrated *in vacuo* to give the crude product **21** (3.26 g, 95%): [α]_D²⁴ –31.7 (c 1.1, CHCl₃); IR (KBr disk, cm^{–1}) 2963, 2869, 1732, 1449, 1374, 1177, 750; ¹H and ¹³C NMR was not corrected; ESI HRMS *m/z* calcd for C₃₇H₄₄N₂O₅S₁ (M+Na)⁺ 651.2869, found 651.2850.

Ethyl (2*S*,3*S*,4*S*)-(-)-3-ethyl-2-(*N*-*p*-toluenesulfonylindol-3-yl)-piperidine-4-carboxylate (22a) and Ethyl (2*S*,3*S*,4*R*)-(-)-3-ethyl-2-(*N*-*p*-toluenesulfonylindol-3-yl)-piperidine-4-carboxylate (22b). To a solution of **21** (924 mg, 1.47 mmol, mixture of diastereomers) and *n*-propylamine (1.09 ml, 13.2 mmol) in chloroform (15 ml) was added lead tetraacetate (2.61 mg, 5.88 mmol) at -50 °C. After the mixture was stirred for 15 min, it was added to an ice-1 *N* aqueous NaOH solution. The resulting mixture was filtered and extracted with chloroform. The organic layers were combined, washed with H₂O, dried over MgSO₄, filtered and concentrated *in vacuo* to give the crude products of a 3.0:1 mixture of C4 stereoisomers. Column chromatography on silica gel (from 0% to 2.8% methanol in chloroform) gave **22a** (159 mg, 24%) as a yellow amorphous solid and **22b** (476 mg, 71%) as a yellow amorphous solid. Data for **22a**: [α]_D²⁴ -8.1 (*c* 0.7, CHCl₃); IR (KBr disk, cm⁻¹) 2959, 2934, 2876, 1724, 1370, 1177, 749; ¹H NMR (400 MHz, CDCl₃) δ 7.97 (d, 1H, *J* = 8.2 Hz), 7.70–7.75 (m, 3H), 7.54 (s, 1H), 7.29 (dd, 1H, *J* = 8.2, 7.3 Hz), 7.16–7.23 (m, 3H), 4.39 (d, 1H, *J* = 9.4 Hz), 4.11–4.25 (m, 2H), 3.13 (ddd, 1H, *J* = 11.9, 10.1, 3.0 Hz), 2.99 (dd, 1H, *J* = 8.9, 4.4 Hz), 2.93 (ddd, 1H, *J* = 11.9, 3.9, 3.9 Hz), 2.32 (s, 1H), 1.78–2.00 (m, 3H), 1.02–1.33 (m, 5H), 0.69 (t, 3H, *J* = 7.3 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 174.3, 144.7, 135.3, 135.2, 130.3, 130.0, 126.7, 124.6, 123.8, 123.0, 120.7, 113.7, 60.4, 60.0, 53.6, 45.2, 42.5, 40.3, 28.6, 22.5, 21.5, 21.0, 14.3, 14.2, 11.6; ESI HRMS *m/z* calcd for C₂₅H₃₀N₂O₄S₁ (M+H)⁺ 455.2005, found 455.1996. Data for **22b**: [α]_D²² -29.1 (*c* 1.1, CHCl₃); IR (KBr disk, cm⁻¹) 2936, 2812, 1728, 1371, 1175, 749; ¹H NMR (400 MHz, CDCl₃) δ 7.97 (d, 1H, *J* = 8.2 Hz), 7.79 (d, 1H, *J* = 7.8 Hz), 7.72 (d, 2H, *J* = 8.4 Hz), 7.52 (s, 1H), 7.30 (dd, 1H, *J* = 7.3, 7.1 Hz), 7.22 (dd, 1H, *J* = 8.2, 7.3 Hz), 7.18 (d, 2H, *J* = 8.5 Hz), 4.08–4.29 (m, 2H), 3.67 (d, 1H, *J* = 10.3 Hz), 3.17 (ddd, 1H, *J* = 11.7, 3.4, 2.7 Hz), 2.76 (ddd, 1H, *J* = 11.5, 11.2, 3.4 Hz), 2.45 (ddd, 1H, *J* = 11.2, 11.2, 4.9 Hz), 2.11 (dddd, 1H, *J* = 10.8, 10.8, 4.1, 4.1 Hz), 1.82–1.96 (m, 2H), 1.26 (t, 3H, *J* = 7.3 Hz), 1.11–1.21 (m, 1H), 0.97–1.09 (m, 1H), 0.59 (t, 3H, *J* = 7.6 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 175.1, 144.8, 135.4, 135.1, 130.0, 126.7, 124.7, 124.3, 123.9, 123.0, 121.0, 113.7; ESI HRMS *m/z* calcd for C₂₅H₃₀N₂O₄S₁ (M+H)⁺ 455.2005, found 455.1986.

Ethyl (2*S*)-1-[(1*S*,2*R*)-*cis*-2-(*t*-butyldimethylsilyloxy)-7-isopropylindan-1-yl]-2-(*N*-*p*-toluenesulfonylindol-3-yl)-1,2,5,6-tetrahydropyridine-4-carboxylate (23). To a solution of **20** (251 mg, 0.419 mmol) in dimethylformamide (4.0 ml) were added triethylamine (0.6 ml, 8.23 mmol) and *t*-butyldimethylchlorosilane (126 mg, 0.84 mmol) and 4,4-dimethylamino-4-pyridine (26 mg, 0.21 mmol) at 0 °C. After the mixture was stirred at room temperature for 20 h, a saturated aqueous NaHCO₃ solution was added, and the resulting mixture was extracted with ethyl acetate. The organic layers were combined, washed twice with water for twice and with brine, dried over MgSO₄, filtered and concentrated *in vacuo* to give the crude products. Column chromatography on silica gel (from 6.3% to 33% ethyl acetate in hexane) gave the product **23** (101 mg, 34%) as a yellow amorphous solid and recover of the starting material **20** (98 mg): [α]_D²⁴ -76.1 (*c* 0.7, CHCl₃); IR (KBr disk, cm⁻¹) 2930, 2856, 1713, 1377, 1257, 1097; ¹H NMR (400 MHz, CDCl₃) δ 8.00 (d, 1H, *J* = 8.2), 7.76 (d, 2H, *J* = 8.2), 7.59 (s, 1H), 7.54 (d, 1H, *J* = 7.8), 7.31 (dd, 1H, *J* = 7.3, 7.3), 7.12–7.22 (m, 4H), 6.90–6.96 (m, 2H), 6.72–6.75 (br m, 1H), 5.80–5.85

(br d, 1H, *J* = 2.7), 4.63 (ddd, 1H, *J* = 8.2, 8.0, 8.0), 4.21 (d, 1H, *J* = 7.1), 4.09–4.21 (m, 2H), 3.18 (ddd, 1H, *J* = 11.2, 11.0, 2.7), 3.06 (dd, 1H, *J* = 15.3, 8.0), 2.96 (dd, 1H, *J* = 15.6, 9.4), 2.79 (dd, 1H, *J* = 11.3, 3.6), 2.32–2.49 (m, 2H), 2.18–2.30 (m, 4H), 1.24 (t, 3H, *J* = 7.1), 1.04 (s, 9H), 0.83 (d, 3H, *J* = 6.9), 0.31 (s, 3H), 0.22 (s, 3H), 0.05 (d, 3H, *J* = 6.9); ¹³C NMR (100 MHz, CDCl₃) δ 167.0, 147.9, 144.9, 140.5, 140.0, 137.3, 135.8, 135.2, 129.9, 129.8, 128.4, 126.7, 125.9, 124.6, 123.6, 122.8, 122.2, 122.1, 121.2, 113.5, 60.5, 60.4, 55.4, 42.2, 42.1, 27.6, 26.4, 26.1, 25.6, 23.1, 21.4, 18.0, 14.2, -3.6, -4.0; ESI HRMS *m/z* calcd for C₄₁H₅₂N₂O₅Si₁ (M+Na)⁺ 735.3264, found 735.3232.

3-[(2*S*)-1-[(1*S*,2*R*)-*cis*-1-(*t*-butyldimethylsilyloxy)-7-isopropylindan-1-yl]-2-(*N*-*p*-toluenesulfonylindol-3-yl)-1,2,5,6-tetrahydropyridin-4-yl]pentan-3-ol (24). To a solution of **23** (53 mg, 0.074 mmol) in ether (2.1 ml) was slowly added ethyl magnesium bromide (1.2 ml, 1.19 mmol, 1.0 M in ether) at 0 °C. After the mixture was stirred for 3 h, H₂O and saturated aqueous NH₄Cl solution were carefully added, and the resulting mixture was extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over MgSO₄, filtered and concentrated *in vacuo* to give the crude products. Column chromatography on silica gel (from 6.3% to 12% ethyl acetate in hexane) gave the product **24** (37 mg, 69%) as a yellow amorphous solid: [α]_D²⁵ -80.3 (*c* 1.0, CHCl₃); IR (KBr disk, cm⁻¹) 2960, 2930, 2855, 1375, 1174, 1099; ¹H NMR (400 MHz, CDCl₃) δ 8.00 (d, 1H, *J* = 8.5), 7.76 (d, 2H, *J* = 8.2), 7.69 (d, 1H, *J* = 7.6), 7.55 (s, 1H), 7.29 (dd, 1H, *J* = 7.8, 7.8), 7.12–7.18 (m, 4H), 6.89–6.96 (m, 2H), 5.71–5.75 (br s, 1H), 5.49–5.52 (m, 1H), 4.65 (dd, 1H, *J* = 16.0, 8.2), 4.22 (d, 1H, *J* = 7.1), 3.25 (ddd, 1H, *J* = 11.0, 11.0, 2.7), 3.06 (dd, 1H, *J* = 15.6, 8.0), 2.96 (dd, 1H, *J* = 15.1, 8.0), 2.72 (dd, 1H, *J* = 15.1, 9.2), 2.48–2.60 (br m, 1H), 2.26 (s, 1H), 1.82–2.10 (m, 1H), 1.80 (d, 1H, *J* = 16.0), 1.44–1.63 (m, 4H), 1.03 (s, 9H), 0.81–0.89 (m, 6H), 0.76 (t, 3H, *J* = 7.6), 0.30 (s, 1H), 0.21 (s, 1H), 0.03–0.13 (br m, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 147.9, 144.8, 140.6, 139.4, 137.9, 135.9, 135.3, 130.1, 129.8, 129.7, 128.2, 126.7, 125.4, 124.6, 124.4, 123.8, 123.5, 122.3, 121.1, 113.5, 77.5, 69.7, 55.2, 42.7, 42.2, 32.1, 31.2, 27.6, 27.3, 26.1, 26.0, 25.6, 23.1, 22.8, 21.4, 17.9, 7.8, 7.6 -4.0, -4.7; ESI HRMS *m/z* calcd for C₄₃H₅₈N₂O₄Si₁ (M+Na)⁺ 749.3784, found 749.3752.

Ethyl (2*S*,3*S*,4*S*)-(-)-3-ethyl-*N*-methyl-2-(*N*-*p*-toluenesulfonylindol-3-yl)-piperidine-4-carboxylate (31a) and Ethyl (2*S*,3*S*,4*R*)-(-)-3-ethyl-*N*-methyl-2-(*N*-*p*-toluenesulfonylindol-3-yl)-piperidine-4-carboxylate (31b). To a solution of **22a**, **22b** (448 mg, 0.985 mmol, mixture of diastereomers) and 37% aqueous formaldehyde (400 ml, 4.93 mmol) in acetonitrile (9.8 ml) was added sodium cyanoborohydride (124 mg, 1.97 mmol) at room temperature. After the mixture was stirred at this temperature for 30 min, a saturated aqueous NaHCO₃ solution was added, and the resulting mixture was extracted with chloroform. The organic layers were combined, dried over MgSO₄, filtered and concentrated *in vacuo* to give the crude products. Column chromatography on silica gel (from 0% to 1.0% methanol in chloroform) gave the alcohol product **31a** (111 mg, 24%) as a yellow amorphous solid and **31b** (334 mg, 72%) as a yellow amorphous solid. Data for **31a**: [α]_D²² -30.0 (*c* 1.1, CHCl₃); IR (KBr disk, cm⁻¹) 2939, 2878, 2793, 1727, 1447, 1372, 1177, 749; ¹H NMR (400 MHz, CDCl₃) δ 7.98 (d, 1H, *J* = 8.3 Hz), 7.87 (d, 1H, *J* = 7.3 Hz), 7.69 (d, 2H, *J* = 8.5 Hz), 7.47 (s, 1H), 7.27

(dd, 1H, $J = 8.0, 7.3$ Hz), 7.12–7.20 (m, 3H), 4.11–4.19 (m, 2H), 3.64 (d, 1H, $J = 10.1$ Hz), 2.92 (dd, 1H, $J = 7.6, 5.0$ Hz), 2.81 (ddd, 1H, $J = 11.9, 3.4, 3.4$ Hz), 2.51 (ddd, 1H, $J = 11.9, 11.9, 3.4$ Hz), 2.27 (s, 3H), 1.81–2.14 (m, 6H), 1.26 (t, 3H, $J = 7.6$ Hz), 1.05–1.17 (m, 1H), 0.79–0.92 (m, 1H), 0.58 (t, 3H, $J = 7.3$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 173.9, 144.6, 135.5, 134.9, 129.6, 129.5, 129.6, 124.6, 124.5, 122.9, 120.9, 62.1, 59.8, 23.2, 22.8, 22.7, 21.4; ESI HRMS m/z calcd for $\text{C}_{26}\text{H}_{32}\text{N}_2\text{O}_4\text{S}_1$ (M+H) $^+$ 469.2161, found 469.2143. Data for **31b**: $[\alpha]_{\text{D}}^{22} -75.6$ (c 1.2, CHCl_3); IR (KBr disk, cm^{-1}) 2940, 2784, 1728, 1369, 1177, 749; ^1H NMR (400 MHz, CDCl_3) δ 7.98 (d, 1H, $J = 8.2$ Hz), 7.77–7.94 (br s, 1H), 7.69 (d, 2H, $J = 8.2$ Hz), 7.40–7.54 (br s, 1H), 7.29 (dd, 1H, $J = 8.2, 7.1$ Hz), 7.20 (dd, 1H, $J = 7.6, 7.3$ Hz), 7.15 (d, 2H, $J = 8.2$ Hz), 4.06–4.18 (m, 2H), 3.03 (ddd, 1H, $J = 11.0, 3.2, 2.8$ Hz), 2.89 (d, 1H, $J = 9.8$ Hz), 2.38 (ddd, 1H, $J = 13.5, 11.4, 3.9$ Hz), 2.29 (s, 3H), 1.87–2.24 (m, 7H), 1.23 (t, 3H, $J = 7.2$ Hz), 1.02–1.14 (m, 1H), 0.76–0.94 (m, 1H), 0.57 (t, 3H, $J = 7.6$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 175.1, 144.7, 135.7, 134.9, 129.8, 129.6, 126.5, 124.8, 124.5, 123.4, 123.1, 113.8, 65.5, 60.2, 55.9, 46.1, 44.5, 41.3, 29.3, 23.0, 21.4, 14.2, 9.0; ESI HRMS m/z calcd for $\text{C}_{26}\text{H}_{32}\text{N}_2\text{O}_4\text{S}_1$ (M+H) $^+$ 469.2161, found 469.2145.

(2S,3S,4R)-(-)-3-Ethyl-4-formyl-N-methyl-2-(N-p-toluenesulfonylindol-3-yl)-piperidine (32b). To a solution of **31b** (300 mg, 0.64 mmol) in toluene (6.4 ml) was added diisobutylaluminium hydride solution (3.2 mg, 3.2 mmol, 1.0 M in toluene) at -78 °C. After the mixture was stirred at this temperature for 2.5 h, a saturated aqueous potassium sodium tartrate tetrahydrate solution was carefully added. The resulting mixture was stirred at room temperature for 1 h, and 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. Column chromatography on silica gel (from 0% to 6.3% methanol in chloroform) gave the alcohol product (237 mg, 87%) as a yellow amorphous solid: $[\alpha]_{\text{D}}^{22} -86.4$ (c 1.0, CHCl_3); IR (KBr disk, cm^{-1}) 2938, 2880, 2786, 1597, 1447, 1370, 1174, 749, 689; ^1H NMR (400 MHz, CDCl_3) δ 7.98 (d, 1H, $J = 8.5$ Hz), 7.74–7.82 (br s, 1H), 7.70 (d, 2H, $J = 8.2$ Hz), 7.49 (s, 1H), 7.27 (dd, 1H, $J = 7.8, 7.6$ Hz), 7.11–7.20 (m, 3H), 3.50 (dd, 1H, $J = 10.5, 3.0$ Hz), 3.47 (dd, 1H, $J = 10.5, 7.1$ Hz), 3.03 (br d, 1H, $J = 11.5$ Hz), 2.93 (br d, 1H, $J = 10.3$ Hz), 2.54–2.79 (br s, 1H), 2.26 (s, 3H), 2.11 (dd, 1H, $J = 11.4, 10.3$ Hz), 1.85–1.97 (m, 3H), 1.50–1.81 (m, 3H), 1.15–1.27 (m, 1H), 0.86–0.91 (br s, 1H), 0.58 (t, 3H, $J = 7.6$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 144.7, 134.8, 129.5, 126.4, 124.6, 124.4, 124.2, 123.0, 113.7, 64.9, 56.6, 44.6, 40.0, 28.8, 21.3, 20.9, 8.7; ESI HRMS m/z calcd for $\text{C}_{24}\text{H}_{30}\text{N}_2\text{O}_3\text{S}_1$ (M+H) $^+$ 427.2055, found 427.2055.

To a solution of oxalyl chloride (0.162 mL, 5.74 mmol) in dichloromethane (8.0 ml) was added DMSO (0.307 mL, 6.89 mmol) at -78 °C. After the mixture was stirred for 10 min at this temperature, a solution of the produced alcohol (980 mg, 2.30 mmol) in dichloromethane (10.0 ml) was added. After the mixture was stirred for 40 min, triethylamine (1.32 mL, 11.5 mmol) was added. After the mixture was stirred for 5 min at this temperature, then stirred for an additional 20 min at room temperature, H_2O was added, and the resulting mixture was extracted with chloroform. The organic layers were combined, washed with a saturated aqueous NaHCO_3 solution and brine, dried over MgSO_4 , filtered and concentrated *in vacuo* to give the crude products. Column

chromatography on silica gel (from 0% to 9.9% methanol in chloroform) gave the aldehyde product **32b** (926 mg, 95%) as a yellow amorphous solid: $[\alpha]_{\text{D}}^{24} -72.4$ (c 1.1, CHCl_3); IR (KBr disk, cm^{-1}) 2944, 2784, 2705, 1447, 1370, 750; ^1H NMR (400 MHz, CDCl_3) δ 9.58 (d, 1H, $J = 4.1$ Hz), 7.99 (d, 1H, $J = 8.2$ Hz), 7.78–7.86 (br d, 1H, $J = 7.3$ Hz), 7.70 (d, 2H, $J = 8.2$ Hz), 7.48 (s, 1H), 7.30 (ddd, 1H, $J = 7.3, 7.1, 1.1$ Hz), 7.20 (ddd, 1H, $J = 7.1, 7.1, 1.0$ Hz), 7.16 (d, 2H, $J = 8.2$ Hz), 3.08 (ddd, 1H, $J = 11.5, 3.4, 3.0$ Hz), 2.92 (d, 1H, $J = 10.3$ Hz), 2.26–2.39 (m, 4H), 2.09–2.22 (m, 2H), 1.76–1.93 (m, 5H), 1.07–1.19 (m, 1H), 0.86–0.98 (m, 1H), 0.56 (t, 3H, $J = 7.6$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 204.0, 145.1, 136.0, 135.2, 130.0, 126.9, 125.2, 125.0, 123.5, 123.3, 121.6, 114.2, 65.1, 55.5, 52.3, 44.8, 40.3, 26.1, 23.1, 21.7, 9.5; ESI HRMS m/z calcd for $\text{C}_{24}\text{H}_{28}\text{N}_2\text{O}_3\text{S}_1$ (M+H) $^+$ 425.1899, found 425.1902.

(2S,3S,4S)-(-)-3-Ethyl-4-formyl-N-methyl-2-(N-p-toluenesulfonylindol-3-yl)-piperidine (32a). To a solution of **31a** (73 mg, 0.28 mmol) in toluene (2.8 ml) was added diisobutylaluminium hydride solution (1.39 mL, 1.39 mmol, 1.0 M in toluene) at -78 °C. After the mixture was stirred at this temperature for 2 h, a saturated aqueous potassium sodium tartrate tetrahydrate solution was carefully added. The mixture was stirred at room temperature for 1 h, and 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. Column chromatography on silica gel (from 0% to 9.1% methanol in chloroform) gave the alcohol product (51 mg, 78%) as a white amorphous solid: $[\alpha]_{\text{D}}^{26} -33.3$ (c 0.9, CHCl_3); IR (KBr disk, cm^{-1}) 2955, 2915, 2789, 1597, 1447, 1370, 1174, 749, 683; ^1H NMR (400 MHz, CDCl_3) δ 7.98 (d, 1H, $J = 8.2$ Hz), 7.72–7.79 (br d, 1H, $J = 7.1$ Hz), 7.70 (d, 2H, $J = 8.2$ Hz), 7.44 (s, 1H), 7.27 (dd, 1H, $J = 8.2, 7.1$ Hz), 7.14–7.22 (m, 3H), 3.82 (dd, 1H, $J = 10.3, 10.1$ Hz), 3.73 (dd, 1H, $J = 10.5, 4.6$ Hz), 3.05 (d, 1H, $J = 9.8$ Hz), 2.83 (ddd, 1H, $J = 11.9, 3.9, 3.7$ Hz), 2.41 (dd, 1H, $J = 12.1, 10.1$ Hz), 2.31 (s, 3H), 1.91–2.18 (m, 7H), -0.89 – 1.04 (m, 1H), 0.76–0.89 (m, 1H), 0.64 (t, 3H, $J = 7.3$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 144.7, 135.6, 135.0, 129.7, 129.6, 126.6, 124.7, 124.3, 123.1, 121.9, 121.0, 113.9, 63.0, 59.1, 51.1, 44.5, 40.0, 26.5, 22.0, 21.5, 11.4; ESI HRMS m/z calcd for $\text{C}_{24}\text{H}_{30}\text{N}_2\text{O}_3\text{S}_1$ (M+H) $^+$ 427.2055, found 427.2059.

To a solution of oxalyl chloride (0.02 mL, 0.77 mmol) in dichloromethane (2.0 mL) was added DMSO (0.04 mL, 0.93 mmol) at -78 °C. After the mixture was stirred for 10 min at this temperature, a solution of the produced alcohol (132 mg, 0.31 mmol) in dichloromethane (2.0 mL) was added. After the mixture was stirred for 40 min, triethylamine (0.18 mL, 1.55 mmol) was added. After the mixture was stirred for 5 min at this temperature, it was stirred for an additional 20 min at room temperature, then H_2O was added, and the resulting mixture was extracted with chloroform. The organic layers were combined, washed with a saturated aqueous NaHCO_3 solution and brine, dried over MgSO_4 , filtered and concentrated *in vacuo* to give the crude products. Column chromatography on silica gel (from 0% to 9.9% methanol in chloroform) gave **32a** (83 mg, 63%) as a white amorphous solid: $[\alpha]_{\text{D}}^{26} -37.1$ (c 1.3, CHCl_3); IR (KBr disk, cm^{-1}) 2960, 2788, 1717, 1447, 1370, 750; ^1H NMR (400 MHz, CDCl_3) δ 9.94 (s, 1H), 7.99 (d, 1H, $J = 8.5$ Hz), 7.78 (d, 1H, $J = 7.9$ Hz), 7.71 (d, 2H, $J = 8.5$ Hz), 7.46 (s, 1H), 7.31 (dd, 1H, $J = 7.1, 7.1$ Hz), 7.15–7.23 (m, 3H) 3.28 (d, 1H, $J = 10.3$ Hz), 2.15–2.36 (m, 5H), 1.91–2.11

(m, 5H), 1.24–1.39 (m, 1H), 0.87–1.00 (m, 1H), 0.64 (t, 3H, $J = 7.3$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 204.5, 144.8, 135.7, 135.0, 129.7, 126.7, 124.9, 124.5, 123.8, 123.1, 121.1, 114.0, 64.3, 52.7, 46.0, 44.3, 43.9, 25.6, 22.3, 21.5, 11.7; ESI HRMS m/z calcd for $\text{C}_{24}\text{H}_{28}\text{N}_2\text{O}_3\text{S}_1$ ($\text{M}+\text{H}$) $^+$ 425.1899, found 425.1898.

(2S,3S,4R)-(-)-3-Ethyl-4-formyl-N-methyl-2-(N-p-toluenesulfonylindol-3-yl)-piperidine (32b). To a solution of **32a** (83 mg, 0.20 mmol) in THF (4 ml) was added DBU (0.05 ml, 0.29 mmol) at room temperature. After the mixture was stirred for 24 h, a saturated aqueous 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 (from 0% to 9.9% methanol in chloroform) gave the epimerized product **32b** (62 mg, 75%) as a yellow amorphous solid, and the recovered starting material **32a** (11 mg, 13%) as a yellow amorphous solid.

(2S,3S,4R) (-)-3-Ethyl-4-acetyl-N-methyl-2-(N-p-toluenesulfonylindol-3-yl)-piperidine (33). To a solution of **32b** (471 mg, 1.11 mmol) in THF (10 ml) and ether (10 ml) was added a methyl lithium solution (6.93 ml, 11.1 mmol, 1.6 M in ether) at -40 °C. After the mixture was stirred at this temperature for 30 min, H_2O was carefully added, and the resulting mixture was extracted with chloroform. The organic layers were combined, washed with brine, dried over MgSO_4 , filtered and concentrated *in vacuo* to give the crude products. Column chromatography on silica gel (from 2% to 4% methanol in chloroform) gave the *sec*-alcohol product (320 mg, 65%) in a 1 : 1 mixture of diastereomers as a yellow amorphous solid: $[\alpha]_{\text{D}}^{24} -90.6$ (c 1.1, CHCl_3); IR (KBr disk, cm^{-1}) 2963, 2785, 1447, 1370, 1175, 749; ^1H NMR (400 MHz, CDCl_3) δ 7.97 (d, 1H, $J = 8.4$ Hz), 7.76–7.87 (br s, 1H), 7.70 (d, 2H, $J = 8.4$ Hz), 7.43–7.50 (br s, 1H), 7.25–7.32 (m, 1H), 7.13–7.23 (m, 3H), 4.00–4.10 (m, 1H), 3.04–3.11 (m, 1H), 2.88–2.96 (m, 1H), 3.32 (s, 3H), 1.53–2.20 (m, 8H), 1.08–1.40 (m, 4H), 0.77–0.94 (br m, 1H), 0.57–0.68 (m, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 144.7, 144.7, 135.7, 135.0, 129.6, 126.6, 124.7, 124.5, 123.1, 113.9, 113.8, 67.3, 66.4, 56.7, 44.7, 44.6, 43.4, 43.2, 23.4, 23.0, 21.5, 21.0, 20.7, 20.5, 17.2, 8.8, 8.4; ESI HRMS m/z calcd for $\text{C}_{25}\text{H}_{32}\text{N}_2\text{O}_3\text{S}_1$ ($\text{M}+\text{H}$) $^+$ 441.2212, found 441.2201.

To a solution of oxalyl chloride (0.085 mL, 3.00 mmol) in dichloromethane (3.0 ml) was added DMSO (0.160 ml, 3.60 mmol) at -78 °C. After the mixture was stirred for 20 min at this temperature, a solution of the produced *sec*-alcohol afforded above (529 mg, 1.20 mmol) in dichloromethane (6.0 ml) was added. After the mixture was stirred for 40 min, triethylamine (0.693 ml, 6.00 mmol) was added. After the mixture was stirred for 5 min at this temperature, it was stirred for an additional 20 min at room temperature, then H_2O was added, and the resulting mixture was extracted with chloroform. The organic layers were combined, washed with a saturated aqueous NaHCO_3 solution, dried over MgSO_4 , filtered and concentrated *in vacuo* to give the crude products. Column chromatography on silica gel (from 0% to 0.5% methanol in chloroform) gave **33** (449 mg, 85%) as a yellow amorphous solid: $[\alpha]_{\text{D}}^{22} -71.6$ (c 1.0, CHCl_3); IR (KBr disk, cm^{-1}) 2938, 2784, 1707, 1447, 1340, 1175, 1121; ^1H NMR (400 MHz, CDCl_3) δ 7.98 (d, 1H, $J = 8.2$ Hz), 7.78–7.90 (br s, 1H), 7.69 (d, 2H, $J = 8.2$ Hz), 7.42–7.50 (br s, 1H), 7.30 (ddd, 1H, $J = 8.5, 6.1, 1.1$ Hz), 7.21 (ddd, 1H, $J = 8.0, 7.1, 0.9$ Hz), 7.16 (d, 2H, $J =$

8.0 Hz), 3.06 (ddd, 1H, $J = 11.7, 3.4, 3.2$ Hz), 2.89 (d, 1H, $J = 10.4$ Hz), 2.52 (ddd, 1H, $J = 11.2, 11.2, 4.8$ Hz), 2.30 (s, 1H), 2.07–2.27 (m, 5H), 1.82–1.92 (m, 5H), 0.98–1.06 (m, 1H), 0.74–0.88 (br s, 1H), 0.53 (t, 3H, $J = 7.6$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 211.5, 145.0, 135.9, 135.2, 129.8, 126.8, 125.1, 124.8, 123.5, 123.4, 121.8, 114.1, 56.3, 53.7, 44.7, 29.3, 28.8, 23.1, 21.7, 9.4; ESI HRMS m/z calcd for $\text{C}_{25}\text{H}_{30}\text{N}_2\text{O}_3\text{S}_1$ ($\text{M}+\text{H}$) $^+$ 439.2055, found 439.2038.

(2S,3S,4R)-(-)-3-Ethyl-4-acetyl-N-methyl-2-(indol-3-yl)-piperidine (5). To a solution of **33** (499 mg, 1.02 mmol) in methanol (7.0 ml) and THF (14.0 ml) was added caesium carbonate (1.33 g, 4.09 mmol) at room temperature. After the mixture was stirred at 65 °C for 6 h, a saturated aqueous 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 (from 1.5% to 9% methanol in chloroform) gave **5** (255 mg, 88%) as a yellow amorphous solid.

(-)-20-Epiuleine (2). To a solution of **5** (17 mg, 0.060 mmol) in chloroform (6.0 ml) was added *p*-toluenesulfonic acid monohydrate (51 mg, 0.299 mmol) at room temperature. After the mixture was stirred at 60 °C for 24 h, an aqueous 10% NH_3 solution was added, and the resulting mixture was extracted with dichloromethane. The organic layers were combined, washed with water, dried over MgSO_4 , filtered and concentrated *in vacuo* to give the crude products. Column chromatography on silica gel (from 50% to 75% ethyl acetate in hexane) gave (-)-20-epiuleine (4 mg, 25%) as a yellow amorphous solid: $[\alpha]_{\text{D}}^{23} -30.1$ (c 0.9, CHCl_3); IR (KBr disk, cm^{-1}) 3422, 2961, 2930, 1447, 1319, 739; ^1H NMR (400 MHz, CDCl_3) δ 8.20–8.28 (br s, 1H), 7.56 (d, 1H, $J = 8.0$ Hz), 7.34 (d, 1H, $J = 8.0$ Hz), 7.19 (ddd, 1H, $J = 8.0, 6.9, 1.2$ Hz), 7.10 (ddd, 1H, $J = 8.0, 6.9, 1.2$ Hz), 5.18 (s, 1H), 4.95 (s, 1H), 4.03 (d, 1H, $J = 2.0$ Hz), 2.62–2.66 (br s, 1H), 2.43 (dd, 1H, $J = 11.2, 4.6$ Hz), 2.19–2.30 (m, 4H), 1.94–2.10 (m, 2H), 1.84–1.90 (m, 1H), 1.64–1.76 (m, 1H), 1.37–1.44 (br d, 1H, $J = 12.4$ Hz), 1.02 (t, 3H, $J = 7.6$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 142.2, 136.5, 135.9, 128.9, 122.7, 119.9, 119.7, 112.2, 110.7, 104.5, 54.8, 46.4, 44.9, 44.7, 38.6, 28.5, 23.6, 12.1; ESI HRMS m/z calcd for $\text{C}_{18}\text{H}_{22}\text{N}_2$ ($\text{M}+\text{H}$) $^+$ 267.1861, found 267.1850.

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