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Process Development of a Scaleable Route to (2*R*)-[3-(2-Aminopropyl)-1*H*-indol-7-yloxy]-*N*,*N*-diethylacetamide: A Key Intermediate for AJ-9677, a Potent and Selective Human and Rat β_3-Adrenergic Receptor Agonist

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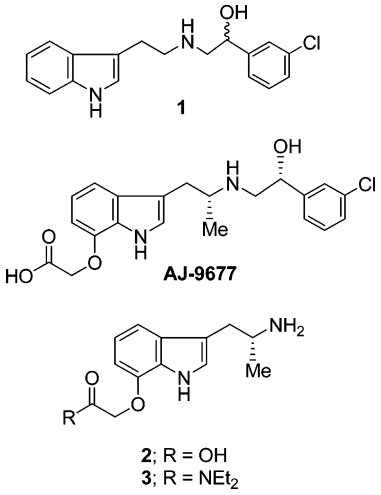
Abstract:

(2*R*)-[3-(2-Aminopropyl)-1*H*-indol-7-yloxy]acetic acid (2) is the left-hand side segment of AJ-9677, which is a potent and selective human and rat β_3-adrenergic receptor agonist. Herein, we describe the process development of a scaleable synthetic route to the corresponding *N*,*N*-diethylacetamide derivative 3 of 2 from 7-benzyloxy-1*H*-indole (4). Reaction of the indole Grignard reagent 12 generated from 4 and methylmagnesium bromide with the *N*-Fmoc-D-alanyl chloride 22, followed by reduction of the resulting crude 3-acylindole 26 with $NaBH_4$ in a mixture of MeCN and 2-PrOH at refluxing temperature and subsequent treatment with oxalic acid gave the oxalate of the *N*-deprotected product, (2*R*)-3-(2-aminopropyl)-7-benzyloxy-1*H*-indole [(*R*)-7] as a crystalline material in 60% yield. After *N*-protection of the (*R*)-7 by Boc group, the (2*R*)-3-[2-(Boc-amino)propyl]-1*H*-indole 30 was hydrogenated to provide the (2*R*)-3-(2-aminopropyl)-7-hydroxy-1*H*-indole 31, which was subsequently alkylated with $ClCH_2CONEt_2$ to give 32 in 91% yield. Finally, treatment of 32 with oxalic acid afforded the desired 3 in 79% in >99% ee.

Introduction

β-Adrenergic receptors (β-ARs) have been subclassified as β_1-, β_2-, and β_3-ARs.[1] The β_3-AR has been shown to mediate various pharmacological and physiological effects such as lipolysis in white adipocytes, thermogenesis in brown adipocytes, and relaxation of urinary bladder detrusor tissue.[2−5] Potent and selective β_3-AR agonists are potential drugs for the treatment of obesity, non-insulin dependent (Type-II) diabetes, frequent urination, and related diseases. At the beginning of 1990 and on the basis of results obtained from random screening for rat β_3-AR agonists, we found a novel 3-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]-ethyl]-1*H*-indole (**1**). In the course of our studies on the structure−activity relationships of **1**, a potent and selective human and rat β_3-AR agonist {3-[(2*R*)-[[(2*R*)-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-1*H*-indol-7-yloxy}-acetic acid (AJ-9677) was finally selected as a promising clinical candidate.[6]



2; R = OH
3; R = NEt_2

The earlier original synthetic route to AJ-9677 from the 7-benzyloxy-1*H*-indole[7] (**4**) via the diastereomers **9** and **10** is shown in Scheme 1.[6] However, this synthetic route has several limitations for large-scale preparation of AJ-9677, for example, the use of $LiAlH_4$, multisteps, low overall yield, and tedious silica gel column chromatography separation of the key diastereomer **10**, which is obtained from reaction of the racemic 3-(2-aminopropyl)-7-benzyloxy-1*H*-indole (**7**) with the commercially available (*R*)-3-chlorostyrene oxide (**8**) and successive protection of the aminoethanol moiety of **9** using *N*,*N*′-carbonyldiimidazole (CDI). Production of a large amount of AJ-9677 is required for the development needs of toxicology, formulation, and pharmacology studies. To meet this production requirement, a process development of a scaleable synthetic route to the left-hand side segment of AJ-9677, (*R*)-[3-(2-aminopropyl)-1*H*-indol-7-yloxy]acetic acid (**2**) is essential. In this contribution, we describe an efficient process used to provide kilogram quantities of the optically active *N*,*N*-diethylacetamide analogue **3** of **2**.

Results and Discussion

Sato and Kozikowski[8] and Isobe et al.[9] have reported a novel tryptophan synthesis via Lewis acid-promoted coupling

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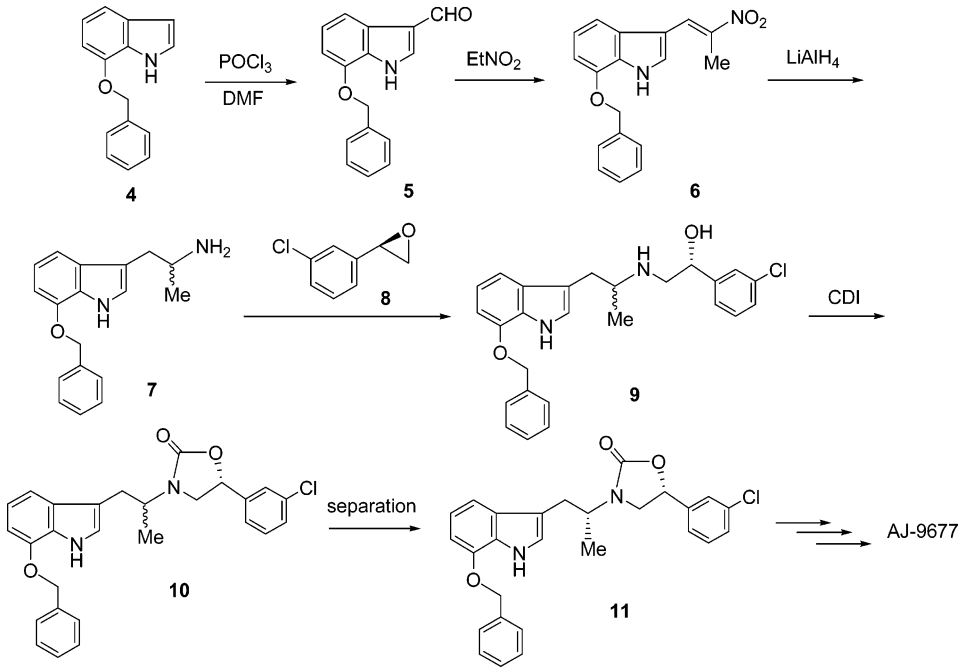
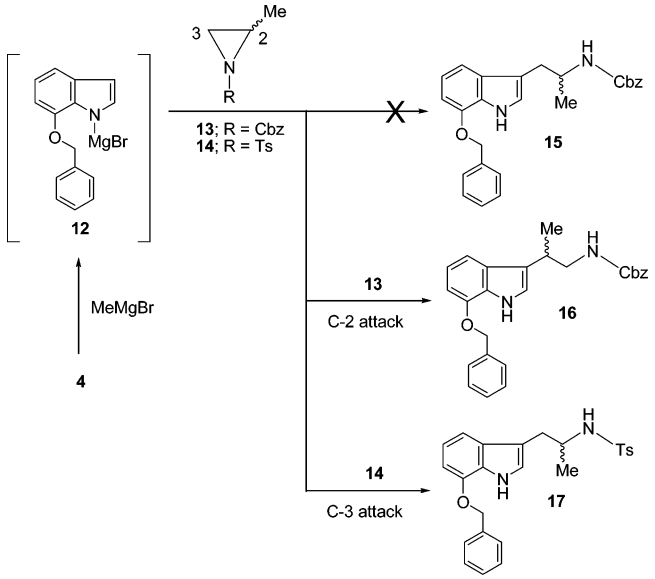
Scheme 1



reaction of indole with the optically active aziridine carboxylate ester. To extend the application of this synthesis, we examined the reaction of 7-benzyloxy-1*H*-indole (**4**) with racemic 2-methylaziridines as C-3 units having different *N*-protecting groups. Initial attempts at reaction of the indole Grignard reagent **12** generated from **4** and methylmagnesium bromide with 1-benzyloxycarbonyl (Cbz)-2-methylaziridine (**13**) in the presence of Lewis acids, such as $Me_2S/CuBr$,[10] $BF_3{\cdot}Et_2O$, or $Zn(OTf)_2$ failed to afford the expected 3-aziridine ring-opening product **15**. Only the inefficient regioisomer **16** of **15** was obtained in 20−30% yield, and **4** was recovered in ca. 50% yield. A similar reaction between **12** and 1-(4-toluenesulfonyl) (Ts)-2-methylaziridine (**14**) under the same conditions and silica gel purification of the reaction mixture afforded the 3-aziridine ring-opening product **17** in only ca. 30% yield together with a large amount of by-products (Scheme 2). To improve the yield, other methods were tried.

Although a large number of synthetic routes to 3-acylindoles using Friedel−Crafts acylation[11−13] and Vilsmeier acylation[14] have been reported, reaction of the indole Grignard reagent with acid chlorides is the most general and useful method.[15] Ames et al. have reported the preparation of 3-(2-amino-1-hydroxyethyl)-5-hydroxy-1*H*-indole from 5-benzyloxy-1*H*-indole using the reaction of indolylmagnesium iodide with benzyloxycarbonylglycinyl chloride and subsequent reduction of the resulting 3-acylindole with $LiBH_4$.[16] Although the yield of this preparation was relatively low, we focused our attention on the nucleophilic substitution

Scheme 2



reaction of the indole Grignard reagent **12** with acid chlorides.

At the outset of our synthesis, reaction of **12** with acetyl chloride as a simple acid chloride was examined. Treatment of **12** generated from **4** and methylmagnesium bromide with acetyl chloride in CH_2Cl_2 along with a small amount of Et_2O needed for methylmagnesium bromide under ice-cooling or at room temperature and subsequent silica gel column purification produced the expected 3-acetyl-7-benzyloxy-1*H*-indole (**18**) in ca. 80% yield (Scheme 3). On the basis of this good result, reaction of the D-alanyl chlorides **19**−**22** having different *N*-protecting groups with **12** was performed. The required D-alanyl chlorides **19**−**22** were prepared in a usual manner from the readily available *N*-protected D-

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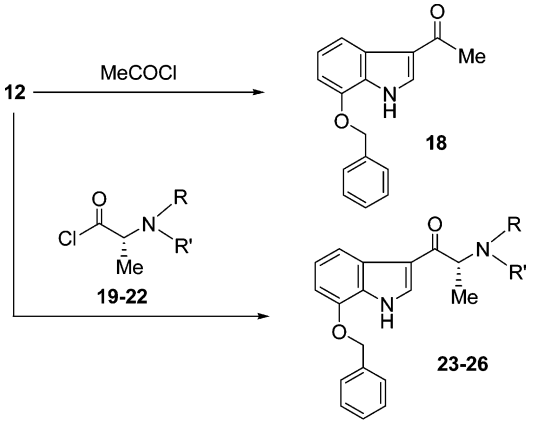
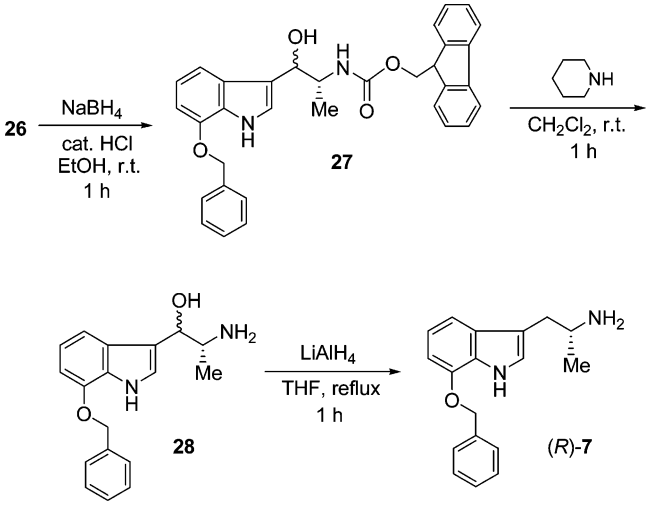
Scheme 3



Scheme 4



alanines. In the case of the *N*-Cbz derivative **19**, only a mixture of by-products was obtained. After this unsuccessful trial, we were delighted to find that the *N*-phthaloyl derivative **20** could react with **12** to furnish the desired product **24** in 39% yield. Treatment of **12** with the D-alanyl chlorides **21** and **22** having trifluoroacetyl and 9-fluorenylmethoxycarbonyl (Fmoc) groups gave the optically active 3-acylindoles **25** and **26** in ca. 40 and ca. 60% yield, respectively (Scheme 3). Although reduction of the carbonyl group at the 3-position of **24** with various reagents did not proceed, the 3-acylindoles **25** and **26** were smoothly reduced. Thus, we chose the *N*-Fmoc group as a promising *N*-protecting group of D-alanyl chlorides.

Reduction of the 7-benzyloxy-3-[2-(Fmoc-amino)propionyl]-1*H*-indole **26** with 3 equiv of $NaBH_4$ in EtOH in the presence of a catalytic amount of aqueous HCl at room temperature for 1 h gave the 3-[1-hydroxy-2-(Fmoc-amino)-propyl]-1*H*-indole **27** in 79% yield. After deprotection of the Fmoc group using piperidine in CH_2Cl_2 at room temperature for 1 h, further reduction of the resulting 3-[(2-amino-1-hydroxy)propyl]-1*H*-indole **28** with $LiAlH_4$ was carried out. Reduction of **26** with 3 equiv of $LiAlH_4$ in refluxing THF for 1 h produced the desired optically active (*R*)-**7** in good yield from **27** without racemization (Scheme 4). These preliminary and successful results prompted us to survey in detail the conditions of reaction of **12** with the *N*-Fmoc-D-alanyl chloride[17] **22** and reduction of **26**.

Influence of the reaction solvent and the solvent of methylmagnesium bromide on the preparation of **26** was first examined (Table 1). The area % of **26** and that of the unreacted starting material **4** were determined by HPLC on the crude reaction mixture at 254 nm, prior to workup and purification. Reaction of the indole Grignard reagent **12** generated from **4** and a solution of methylmagnesium

Table 1. **Influence of the reaction solvent and the solvent of MeMgBr on the preparation of 26**

4 $\xrightarrow[\text{room temperature, solvent, 1 h}]{\text{MeMgBr (}\times\text{ 1 equiv) in solvent}}$ **12** $\xrightarrow[\text{solvent}]{\textbf{22}\ (\times\ 1\ \text{equiv})}$ **26**

run	solvent	MeMgBr in solvent	conditions	**26** (%)[b]	**4** (%)[b]
1	THF	THF	rt, 3 day	N.D.[c]	57
2	THF	toluene/THF (75/25)	reflux, 1 day	18	19
3	toluene	toluene/THF (75/25)	rt, 1 day	15	48
4	CH_2Cl_2	Et_2O	rt, 3 h	36	28
5	CH_2Cl_2	Et_2O	reflux, 2 h	33	35
6	$CHCl_3$	Et_2O	rt, 3 h	24	40
7	Et_2O	Et_2O	rt, 3 h	10	39

[a] All reactions were carried out using 1.0 g of **4**, 10 mL of solvent, and a solution of **22** in 20 mL of solvent. [b] The reaction mixture mainly contained **22**, **4**, and 1-methylfluorene. The yield was determined area % by HPLC at 254 nm on the crude reaction mixture, perior to purification. See in Experimental Section. [c] Not detected.

bromide in THF with **22** in THF as solvent at room temperature did not proceed even for 3 day (run 1). Likewise, the same reaction in THF using a commercially available methylmagnesium bromide solution in a mixture of toluene and THF (75/25) did not proceed at room temperature. On the other hand, under refluxing temperature for 1 day the reaction proceeded to give **26** in 18% area. However, the amount of unreacted **4** was significantly reduced (19%, run 2). This may have been due to decomposition of the indole Grignard reagent **12** under the new reaction conditions. In the case of toluene (run 3), the reaction of **12** with **22** at room temperature for 1 day gave **26** (15%) along with unreacted **4** (48%). Surprisingly, the use of CH_2Cl_2 as a solvent and a solution of methylmagnesium bromide in Et_2O led to a good result with the reaction at room temperature for 3 h producing 36% of **26** and 28% of unreacted **4** (run 4). On the other hand, raising the reaction temperature (refluxing temperature) resulted in a slight decrease in area % of **26** (33%, run 5). Using $CHCl_3$ (run 6) and Et_2O (run 7) instead of CH_2Cl_2 caused a decrease in area % of **26** (24 and 10%, respectively). Although the reaction in run 4 did

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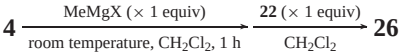
Table 2. **Influence of MeMgX on the preparation of 26**



run	X (in solvent)	**26** (%)[b]
1	Br (Et_2O)	36
2	Cl (THF)	26
3	I (Et_2O)	30

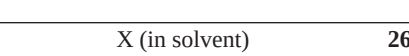
[a] All reactions were carried out using 1.0 g of **4**, 10 mL of CH_2Cl_2, and a solution of **22** in 20 mL of CH_2Cl_2. The mixture was stirred at room temperature for 3 h. [b] The reaction mixture mainly contained **22**, **4**, and 1-methylfluorene. The yield was determined area % by HPLC at 254 nm on the crude reaction mixture, perior to purification. See in Experimental Section.

not go to completion, the conditions of this run were chosen for further preparations.

Next, reaction of the indole Grignard reagent **12** generated from **4** and several methylmagnesium halides with the *N*-Fmoc-D-alanyl chloride **22** was examined (Table 2). Treatment of **4** with a solution of methylmagnesium bromide in Et_2O in CH_2Cl_2, followed by reaction of the resultant **12** with **22** produced the 3-acylindole **26** in 36% (run 1). On the other hand, the use of a commercially available solution of methylmagnesium chloride in THF or methylmagnesium iodide in Et_2O resulted in a decrease of the area of **26** (26% or 30%, runs 2 and 3). As a result, the solution of methylmagnesium bromide in Et_2O was selected as the best methylmagnesium halide in the reaction of **12** with **22**. Although Bergman et al. have reported that reaction of α-bromopropionyl bromide with 1*H*-indole in the presence of 1 equiv of pyridine in dioxane at 60 °C produced 3-(2-bromopropionyl)-1*H*-indole in 60% yield,[18] treatment of **4** with **22** under the same conditions was unsuccessful in our hands. Furthermore, Bergman and Venemalm have reported that reaction of the zinc salt of 1*H*-indole derived from indole Grignard reagent and $ZnCl_2$ with a number of acid chloride gave 3-acylindoles in yields superior to those obtained with indole Grignard reagent alone.[19] However, a similar reaction between **12** and **22** in the presence of $ZnCl_2$ resulted in a decrease in the yield of **26**. Subsequently the reaction of **12** with *N*-Fmoc-D-alanyl chloride **22** was studied in depth by varying the amount of methylmagnesium bromide and **22**. As shown in Table 3, the yield of **26** remained essentially unchanged as the amount of methylmagnesium bromide was increased to 3 equiv (runs 1−3). Using 1.5 equiv of **22** along with 3 equiv of methylmagnesium bromide provided a favorable result (run 4). However, when larger amounts of methylmagnesium bromide and **22** were used, the yield plummeted to 31% (run 5). From the results of Tables 1−3, the reaction of indole Grignard reagent **12** generated from **4** and 3 equiv of a solution of methylmagnesium bromide in Et_2O with 1.5 equiv of **22** in CH_2Cl_2 was found to be the most suitable, from a yield viewpoint, for large-scale synthesis of **26**.

Our attention was then focused on a facile hydride reduction of **26** (Table 4). As described above, treatment of **26** with $NaBH_4$ in EtOH at room temperature for 1 h afforded

Table 3. **Influence of the amount of MeMgBr and 22 on the preparation of 26**



run	Y_1 (equiv)	Y_2 (equiv)	**26** (%)[b]
1	1	1	36
2	2	1	34
3	3	1	36
4	3	1.5	41
5	4	2	31

[a] All reactions were carried out using 1.0 g of **4**, 10 mL of CH_2Cl_2, and a solution of **22** in 20 mL of CH_2Cl_2. The mixture was stirred at room temperature for 3 h. [b] The reaction mixture mainly contained **22**, **4**, and 1-methylfluorene. The yield was determined area % by HPLC at 254 nm on the crude reaction mixture, perior to purification. See in Experimental Section.

Table 4. **Reaction conditions for hydride reduction of *2*6 (1)**

run	reagent	equiv	solvent	time	main product(s)
1	$NaBH_4$	10	EtOH	1 day	**28**
2	$NaBH_4$	10	2-PrOH	4 h	(*R*)-**7**
3	$LiBH_4$	2	2-PrOH	6 h	**29**
4	vitride (in toluene)	4	THF[c]	5 h	(*R*)-**7**[d]
5[b]	BH_3−THF	2	THF	1 day	(*R*)-**7** + **28**

[a] All reactions were carried out using 1.0 g of **26** and 10 mL of solvent unless otherwise noted. [b] 0.2 g of **26** was employed. [c] 20 mL was employed. [d] A number of by-products were produced.

the 3-[[2-(*N*-protected amino)-1-hydroxy]propyl]-1*H*-indole **27**. On the other hand, reduction of **26** with 10 equiv of $NaBH_4$ in EtOH at refluxing temperature for 1 day gave the (2*R*)-3-[(2-amino-1-hydroxy)propyl]-7-benzyloxy-1*H*-indole (**28**) as main product (run 1). A similar reaction of **26** in refluxing 2-PrOH for 4 h directly produced (*R*)-**7** as main product (run 2). Analysis of the reaction mixture in run 2 by HPLC revealed formation of the (2*R*)-3-(2-aminopropionyl)-7-benzyloxy-1*H*-indole (**29**) and the intermediate **28** along with (*R*)-**7**. An authentic sample of **29** was obtained by treatment of **26** with piperidine. When $LiBH_4$ was used, the reduction did not proceed, and the *N*-deprotected product **29** was produced as main product (run 3). Reduction of **26** with a solution of vitride in toluene or BH_3 in refluxing THF provided the desired product (*R*)-**7** or (*R*)-**7** along with **28**, respectively (runs 4 and 5). The use of vitride, however, led to a remarkable increase of by-products. As a result, reduction of **26** with 10 equiv of $NaBH_4$ in refluxing 2-PrOH for 4 h gave the optically active (*R*)-**7** as a powder in 36% isolated yield without chromatographic purification. Additionally, the oxalate of (*R*)-**7** [(*R*)-**7**·$(CO_2H)_2$] was isolated from the resulting filtrate in AcOEt in 12% yield without further purification (Table 5, run 1).[20] The total yield of (*R*)-**7** thus isolated was 48%. To decrease the amount of $NaBH_4$, a similar reduction using 5 equiv of $NaBH_4$ was carried out. As shown in Table 5, the yield of (*R*)-**7** was essentially the same as that of run 1 (run 2). On the other hand, further

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(19) Bergman, J.; Venemalm, L. *Tetrahedron* **1990**, *46*, 6061.
(20) The hydrochloride and fumarate of (*R*)-**7** from the filtrate were not obtained as a crystalline material.

Table 5. **Reaction conditions for hydride reduction of 26 (2)**

$$\mathbf{26} \xrightarrow[\text{2-PrOH, reflux, 4 h}]{\text{NaBH}_4\ (\times\ Z_1\ \text{equiv})} (R)\text{-}\mathbf{7}$$

run	Z_1 (equiv)	(*R*)-**7** (%)[b]
1	10	36 + 12[c]
2	5	36[d]
3	4	32[e]

[a] All reactions were carried out using 1.0 g of **26** and 20 mL of 2-PrOH. [b] Isolated yield. [c] The yield of second crop as the oxalate of (*R*)-**7**. [d] The second crop of (*R*)-**7** from the filtrate was not isolated. [e] The yield of the oxalate of (*R*)-**7**.

diminishment of the amount of $NaBH_4$ (4 equiv) resulted in a slight decrease in the isolated yield of (*R*)-**7** and its oxalate (run 3), presumably because of decomposition of $NaBH_4$ in refluxing 2-PrOH. To avoid the decomposition of $NaBH_4$ in alcohol solvent, we examined the reduction of **26** with $NaBH_4$ in a mixed solvent at refluxing temperature (Table 6). Reaction with 4 equiv of $NaBH_4$ in dimethoxyethane in the presence of 3 equiv of 2-PrOH for 4 h gave 67% of (*R*)-**7** (area %) along with 4% of **28** and 7% of **29** (run 1). The use of 3 equiv of $NaBH_4$ and elongation of the reaction time led to a slight increase of (*R*)-**7** (run 2). A similar reaction with further decrease in $NaBH_4$ (2 equiv) and 2-PrOH (2 equiv) essentially retained the yield of (*R*)-**7** but increased the formation of **29** as compared with run 2 (run 3). In this reaction, (*R*)-**7**·$(CO_2H)_2$ was isolated in 54% yield. When reduction of **26** in AcOEt (run 4) or toluene (run 5) was carried out under conditions similar to those of run 2, the area % of (*R*)-**7** decreased with an isolated yield in run 4 of 36%. On the other hand, the use of MeCN as solvent increased the area % of (*R*)-**7** and decreased that of **29** with an isolated yield for (*R*)-**7**·$(CO_2H)_2$ of 56−61% (runs 6−8). Although the use of EtOH in place of 2-PrOH gave essentially the same results as those of run 8, the reaction proceeded violently (run 9). On the basis of the results in Tables 4−6, the preparation of (*R*)-**7**·$(CO_2H)_2$ was accomplished by reaction of **26** with 3 equiv of $NaBH_4$ in refluxing MeCN in the presence of 4 equiv of 2-PrOH (Scheme 5).

Because of conversion of the benzyl group of 1*H*-indole ring to an *N*,*N*-diethylacetamide, the amino group of the optically active (*R*)-**7** was again protected by Boc group. i.e., di-*tert*-butyl dicarbonate was added to a solution of (*R*)-**7**·$(CO_2H)_2$ in a mixture of aqueous K_2CO_3 solution and AcOEt at ca. 5 °C to give **30** in excellent yield (Scheme 6). Hydrogenation of the (2*R*)-7-benzyloxy-3-[2-(Boc-amino)-propyl]-1*H*-indole **30** in the presence of Pd/C produced the corresponding 7-hydroxy-1*H*-indole **31**, which was treated with $ClCH_2CONEt_2$ in the presence of K_2CO_3 and KI in refluxing acetone to afford the desired **32** as a crystalline material in excellent yield. Treatment of **31** with a haloacetic acid ester, such as methyl, ethyl, or benzyl ester instead of $ClCH_2CONEt_2$ resulted in intramolecular cyclization to give the lactam **33**, which was converted into the ring-opening product **34** in aqueous conditions. Finally, deprotection of the Boc group of **32** was examined. Reaction of **32** with a mineral acid such as hydrochloric acid or sulfuric acid gave the desired deprotected **3** in good yield, but not as a crystalline material. On the other hand, treatment of **32** with ca. 3 equiv of oxalic acid in refluxing MeCN for 4 h produced the oxalate of **3** as a crystalline material. In this reaction, the use of MeOH, EtOH, or 2-PrOH as a solvent was unfavorable as the reaction did not proceed. In addition, the use of AcOEt and DMF or diminishment of the amount of oxalic acid was also unfavorable as the reaction required a long time before completion. Treatment of the oxalate of **3** with aqueous K_2CO_3 solution gave **3** in 79% yield in >99% ee as a crystalline material (Scheme 7).

Conclusions

In summary, we have found an effective process for large-scale preparation of the optically active 1*H*-indole derivative, (2*R*)-[3-(2-aminopropyl)-1*H*-indole-7-yloxy]-*N*,*N*-diethylacetamide (**3**) from **4** in five steps in 43% overall yield without chromatographic purification. This new efficient process is based on the following: (1) the convenient reaction of indole Grignard reagent **12** with *N*-(9-fluorenylmethoxycarbonyl)-D-alanyl chloride (**22**) derived from the commercially available D-alanine. (2) reduction of the 3-acylindole **26** with $NaBH_4$ in refluxing MeCN in the presence of 2-PrOH. This reduction leads not only to transformation of the carbonyl group to methylene but also to deprotection of the *N*-Fmoc group, thereby conveniently yielding the optically active (*R*)-**7** from which the desired 1*H*-indole **3** with high optical purity (>99% ee) was prepared.

Experimental Section

General Procedures. All melting points were determined on a Yanagimoto micromelting point apparatus without correction. IR spectra were recorded on a Shimadzu FTIR-8200 spectrometer with KBr disks. Atmospheric pressure chemical ionization mass spectra were obtained on a Hitachi M-1000 spectrometer. ^{1}H NMR spectra were recorded on a Varian Gemini-200 (200 MHz) or a JEOL JNM-LA300 (300 MHz) using dilute solution in $CDCl_3$ unless otherwise stated, and coupling constants (*J*) are given in Hz. Chemical shifts are expressed as δ (ppm) values from Me_4Si as an internal standard. Optical rotations were measured at 589 nm with a Jasco P-1020 digital polarimeter. Analytical HPLC was performed with a Shimadzu LC-6A, SPD-6A instruments. Organic extracts were dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure. Merck silica gel 60 (70−230 mesh), Fuji Silysia FL60D silica gel (60 μm), or Fuji Silysia basic silica gel (100−200 mesh) was used for column chromatography.

(2*R*)-7-Benzyloxy-3-[[2-(9-fluorenylmethoxycarbonylamino)-1-hydroxy]propyl]-1*H*-indole (27). To a mixture of (2*R*)-7-benzyloxy-3-[2-(9-fluorenylmethoxycarbonylamino)propionyl]-1*H*-indole (described later) (**26**, 0.19 g, 0.37 mmol), $NaBH_4$ (42 mg, 1.1 mmol), and EtOH (5 mL) was added concentrated HCl (1 drop) at room temperature. Although vigorous foam was observed, the mixture was stirred at the same temperature for 1 h. The solvent was evaporated, and H_2O and AcOEt were added to the residue. The organic layer was separated, washed with brine, and

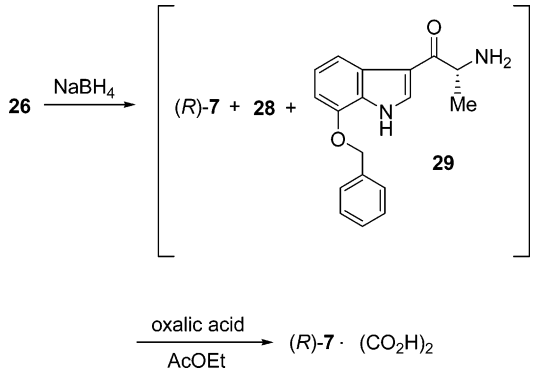
Table 6. **Reaction conditions for hydride reduction of 26 (3)**

$$\mathbf{26} \xrightarrow[\text{solvent} + \text{ROH} (\times Z_2 \text{ equiv}), \text{reflux}]{\text{NaBH}_4 (\times Z_1 \text{ equiv})} (R)\text{-}\mathbf{7} + \mathbf{28} + \mathbf{29}$$

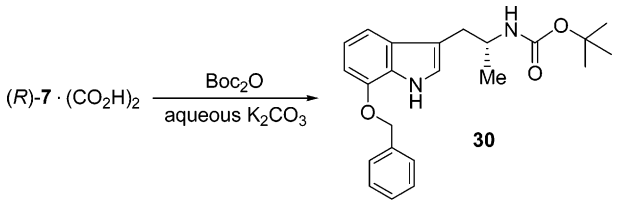
run	Z_1 (equiv)	solvent	ROH (Z_2 equiv)	time (h)	(*R*)-**7**:**28**:**29** (%)[b]	(*R*)-**7** (%)[c]
1	4	dimethoxyethane	2-PrOH (3)	4	67:4:7	N.I.[d]
2	3	dimethoxyethane	2-PrOH (3)	6	73:2:6	N.I.[d]
3	2	dimethoxyethane	2-PrOH (2)	6	74: −: 12	54
4	3	AcOEt	2-PrOH (3)	6	58:4:9	36
5	3	toluene	2-PrOH (3)	6	63:3:4	N.I.[d]
6	3	MeCN	2-PrOH (3)	4	80:5:2	56
7	2	MeCN	2-PrOH (3)	4	86:4:2	57
8	3	MeCN	2-PrOH (4)	5	85:6:2	61
9	3	MeCN	EtOH (4)	3	86:3:1	N.I.[d]

[a] All reactions were carried out using 1.0 g of **26** and 5 mL of solvent. [b] Area % by HPLC at 215 nm. See Experimental Section. [c] Isolated yield of the oxalate of (*R*)-**7**. [d] Not isolated.

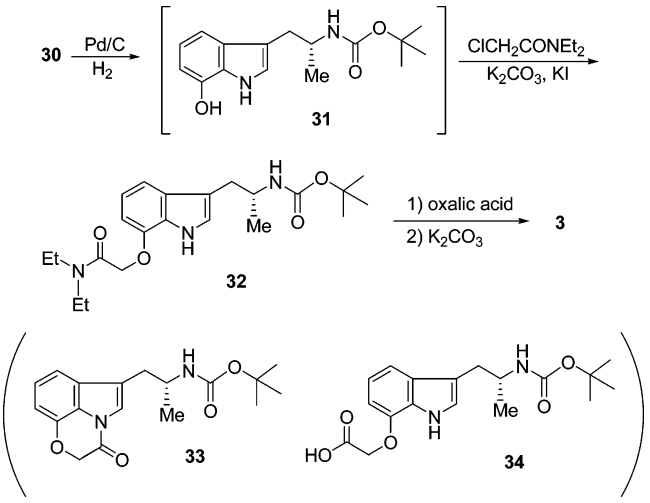
Scheme 5



Scheme 6



Scheme 7



dried over anhydrous $MgSO_4$. The solvent was evaporated to give 0.15 g (79%) of **27** as an amorphous solid. ^{1}H NMR [dimethyl sulfoxide (DMSO)-d_6, 200 MHz] δ 1.05 (d, 3H, J = 7), 3.9 (m, 1H), 4.1−4.3 (m, 3H), 4.91 (t, 1H, J = 4.4), 5.05 (d, 1H, J = 5.0), 5.23 (s, 2H), 6.71 (d, 1H, J = 7.4), 6.86 (td, 1H, J = 7.8, 3.6), 7.02−7.48 (m, 9H), 7.56 (dd, 2H, J = 8.0, 1.6), 7.67 (d, 2H, J = 7.2), 7.88 (d, 2H, J = 7.2), 10.98 (s, 1H). MS *m*/*z*: 519 (MH^+).

(2*R*)-3-[(2-Amino-1-hydroxy)propyl]-7-benzyloxy-1*H*-indole (28). Piperidine (82 mg, 0.97 mmol) was added to a solution of **27** (0.50 g, 0.97 mmol) in CH_2Cl_2 (3 mL). The mixture was stirred at room temperature for 1 h and concentrated to dryness. The residue was chromatographed on basic silica gel with $CHCl_3$/MeOH = 30/1 to give 0.19 g (65%) of **28** as an amorphous solid. ^{1}H NMR (200 MHz) δ 1.07 (d, 3H, J = 6.4), 1.8 (br, 2H), 2.75 (br, 1H), 3.34 (quint, 1H, J = 6.2), 4.74 (d, 1H, J = 5.4), 5.17 (s, 2H), 6.71 (d, 1H, J = 7.6), 7.00 (t, 1H, J = 7.8, 7.8), 7.09 (s, 1H), 7.24−7.50 (m, 6H), 8.94 (br s, 1H). MS *m*/*z*: 297 (MH^+).

(2*R*)-3-(2-Aminopropyl)-7-benzyloxy-1*H*-indole [(*R*)-7]. $LiAlH_4$ (0.05 g, 1.3 mmol) was added to a solution of **28** (0.13 g, 0.44 mmol) in anhydrous THF (20 mL) at room temperature. The mixture was heated to reflux for 1 h and cooled to ca. 5 °C. After careful addition of H_2O (0.3 mL), the whole was stirred at room temperature for 5 min. Anhydrous $MgSO_4$ was added, and the mixture was filtered through Celite. The filtrate was concentrated to dryness to give 0.12 g (quantitative yield) of (*R*)-**7**.

(2*R*)-3-(2-Aminopropionyl)-7-benzyloxy-1*H*-indole (29). In a manner similar to that described for the preparation of **28**, **26** was converted into **29** in quantitative yield. ^{1}H NMR (DMSO-d_6, 200 MHz) δ 1.21 (d, 3H, J = 7), 2.20 (br, 2H), 4.25 (q, 1H, J = 7), 5.30 (s, 2H), 6.87 (d, 1H, J = 7.5), 7.09 (dd, 1H, J = 7.5, 7.5), 7.28−7.48 (m, 3H), 7.54−7.63 (m, 2H), 7.80 (d, 1H, J = 7.5), 8.29 (s, 1H), 11.75 (br s, 1H). MS *m*/*z*: 295 (MH^+).

(2*R*)-3-(2-Aminopropyl)-7-benzyloxy-1*H*-indole [(*R*)-7]· Oxalate. Methylmagnesium bromide (3.0 M solution in Et_2O, 50 mL, 0.15 mol) was added dropwise to a solution of 7-benzyloxy-1*H*-indole (**4**, 11.2 g, 50 mmol) in CH_2Cl_2 (100 mL) at ca. 5 °C under argon atmosphere. The mixture was warmed at room temperature and stirred for 1 h [preparation of 7-benzyloxy-1*H*-indole magnesium bromide (**12**)]. A solution of *N*-(9-fluorenylmethoxycarbonyl)-D-alanyl chloride

(described later) (**22**) in CH_2Cl_2 (200 mL) was gradually added to the cold solution (ca. 5 °C) at argon atmosphere. The mixture was warmed to room temperature and stirred for 1 h. After addition of 5% aqueous HCl (100 mL) under ice-cooling, the whole was stirred at the same temperature for ca. 15 min and warmed to room temperature. The organic layer was separated, washed successively with water and brine, and dried over anhydrous $MgSO_4$. The solvent was evaporated to leave a mixture (ca. 40.1 g) of **26**, **4**, and *N*-(9-fluorenylmethoxycarbonyl)-D-alanine as a purple amorphous solid, which was used in the next step without further purification. The analysis of the mixture was carried out by HPLC [column, Shiseido capcell pak C_{18} (Shiseido Co., Ltd., Japan); 4.6 mm i.d. × 150 mm; eluent, water containing 0.05% CF_3CO_2H/MeCN = 3/7; flow rate, 1.0 mL/min; column temperature, 25 °C; detection, 254 nm]. The retention times of **26**, **4**, and *N*-(9-fluorenylmethoxycarbonyl)-D-alanine were 6.0, 3.7, and 1.9 min, respectively. A small amount of the mixture was chromatographed on silica gel with $CHCl_3$/MeOH = 100/1 to give a pure **26** as an amorphous solid. ^{1}H NMR (200 MHz) δ 1.49 (d, 3H, J = 7), 4.20 (t, 1H, J = 7), 4.37 (d, 2H, J = 7), 5.27 (s, 2H), 6.00 (d, 1H, J = 7), 6.82 (d, 1H, J = 8), 7.14−7.5 (m, 11H), 7.59 (d, 2H, J = 7), 7.74 (d, 2H, J = 7), 7.87 (d, 1H, J = 3), 7.94 (d, 1H, J = 8), 9.40 (br s, 1H). MS *m*/*z*: 517 (MH^+).

Crude amorphous solid containing **26** thus obtained (ca. 40.1 g) was completely dissolved in a mixture of MeCN (100 mL) and 2-PrOH (15 mL, 0.20 mol) under warming. Sodium borohydride (5.7 g, 0.15 mol) was portionwise added to the solution, and then the mixture was heated to reflux for 5 h and cooled to ca. 5 °C. After careful addition of MeOH (100 mL), the mixture was raised to room temperature and then concentrated to dryness. The residue was dissolved in AcOEt (250 mL) and washed with water (100 mL) and dried over anhydrous $MgSO_4$. The reaction mixture was analyzed by HPLC (column, Shiseido capcell pak C_{18}; 4.6 mm i.d. × 150 mm; eluent, water containing 0.05% CF_3CO_2H/MeCN = 7/3; flow rate, 1.0 mL/min; column temperature, 25 °C; detection, 215 nm). The retention times of **28**, (*R*)-**7**, and **29** were 5.7, 9.4, and 7.3 min, respectively.

A solution of oxalic acid (4.5 g, 50 mmol) in AcOEt (45 mL) was added to the dry solution containing (*R*)-**7** at room temperature, and the mixture was stirred for 2 h. The resulting precipitate was collected by filtration, washed with AcOEt (100 mL), and dried to give 11.2 g (60% from **4**, 98% ee) of (*R*)-**7**·$(CO_2H)_2$, mp 206−208 °C. $[\alpha]^{25}_D$ −46.2° (*c* 1.0, DMF). ^{1}H NMR (DMSO-d_6, 200 MHz) δ 1.14 (d, 3H, J = 7), 2.80 (dd, 1H, J = 14, 8), 3.03 (dd, 1H, J = 14, 5), 3.42 (m, 1H), 5.26 (s, 2H), 5.94 (br, 4H), 6.75 (d, 1H, J = 8), 6.92 (t, 1H, J = 8), 7.11−7.22 (m, 2H), 7.32−7.48 (m, 3H), 7.51−7.62 (m, 2H), 11.11 (s, 1H). MS *m*/*z*: 281 (MH^+), 264. IR cm^{-1}; 3337, 1624, 1576, 1231. *Anal*. *Calcd* for $C_{18}H_{20}N_2O$·$C_2H_2O_4$·1/4H_2O; C: 64.07, H: 6.05, N: 7.47. Found; C: 64.11, H: 5.92, N: 7.39. Chiral HPLC [column, CHIRALCEL AD (Daicel Chemical Industries, Ltd., Japan); 4.6 mm i.d. × 250 mm; eluent, hexane/2-PrOH/Et_2NH = 90/10/0.2; flow rate, 1.0 mL/min; column temperature, 25 °C; detection, 254 nm]; the retention times of the free base of (*R*)-**7** and its enantiomer were 23.1 and 17.2 min, respectively.

Preparation of *N*-(9-fluorenylmethoxycarbonyl)-D-alanyl chloride[18] (**22**): Oxalyl chloride (7.0 mL, 80 mmol) was portionwise to a suspension of *N*-(9-fluorenylmethoxycarbonyl)-D-alanine (23.35 g, 75 mmol) in a mixture of CH_2Cl_2 (240 mL) and *N*,*N*-dimethylformamide (DMF, 0.4 mL) at room temperature. The mixture was stirred at the same temperature for 1 h. After evaporation of the volatiles, the residual solid containing **22** was obtained. The residue was used in the next reaction without further purification.

(2*R*)-7-Benzyloxy-3-[2-(*tert*-butoxycarbonylamino)propyl]-1*H*-indole (30). After the mixture of (*R*)-**7**·$(CO_2H)_2$ (50.0 g, 135 mmol), K_2CO_3 (28.0 g, 0.20 mol), H_2O (500 mL), and AcOEt (250 mL) was stirred at room temperature for 2 h, di-*tert*-butyl dicarbonate (29.5 g, 135 mmol) was added portionwise under ice-cooling. The whole was warmed at room temperature and stirred for 3 h. The organic layer was separated, washed with brine, and dried over anhydrous $MgSO_4$. After evaporation of the solvent, hexane (150 mL) was added to the residue. The resulting precipitate was collected by filtration and dried to give 47.2 g (92%, 98.5% ee) of **30** as a white crystalline material, mp 94−95 °C. $[\alpha]^{25}_D$ −21.0° (*c* 1.0, MeOH). ^{1}H NMR (300 MHz) δ 1.11 (d, 3H, J = 6.6), 1.43 (s, 9H), 2.83 (dd, 1H, J = 14.5, 6.7), 2.94 (dd, 1H, J = 14.5, 5.1), 4.00 (m, 1H), 4.44 (m, 1H), 5.18 (s, 2H), 6.71 (d, 1H, J = 7.5), 6.97 (d, 1H, J = 2.2), 7.02 (t, 1H, J = 7.9), 7.20 (s, 1H), 7.24−7.51 (m, 5H), 8.30 (s, 1H). MS *m*/*z*: 381 (MH^+), 325, 281, 264. IR cm^{-1}; 3410, 3348, 2978, 1678, 1526, 1501, 1259, 11173. *Anal*. *Calcd* for $C_{23}H_{28}N_2O_3$; C: 72.61, H: 7.42, N: 7.36. Found; C: 72.50, H: 7.50, N: 7.42. Chiral HPLC [column, CHIRALCEL AD; 4.6 mm i.d. × 250 mm; eluent, hexane/2-PrOH = 70/30; flow rate, 0.8 mL/min; column temperature, 25 °C; detection, 254 nm]; the retention times of **30** and its enantiomer were 8.8 and 9.9 min, respectively.

(2*R*)-[3-[2-(*tert*-Butoxycarbonylamino)propyl]-1*H*-indol-7-yloxy]-*N*,*N*-diethylacetamide (32). A solution of **30** (750 g, 2.0 mol) in MeOH (3750 mL) was hydrogenated over 10% palladium on carbon (22.5 g) at ca. 35 °C at atmospheric pressure. After the calculated amount of the hydrogen was absorbed (ca. 1.5 h), the catalyst was removed by filtration. The filtrate was concentrated to dryness to give a residue containing (2*R*)-3-[2-(*tert*-butoxycarbonylamino)-propyl]-7-hydroxy-1*H*-indole (**31**). A mixture of **31**, K_2CO_3 (329 g, 2.4 mol), $ClCH_2CONEt_2$ (3256 g, 2.4 mol), KI (17.5 g, 0.105 mol), and acetone (4500 mL) was heated to reflux for 5 h and cooled to room temperature. After the insoluble materials were filtered off, the filtrate was concentrated to dryness. The residue was dissolved in $CHCl_3$ (5000 mL) and H_2O (2000 mL), and the organic layer was separated and dried over anhydrous $MgSO_4$. The solvent was evaporated, and the residual solid was triturated with a mixture of AcOEt (750 mL) and hexane (2250 mL) to afford 788 g (99%, >99% ee) of **32** as a white crystalline material, mp 124 °C. $[\alpha]^{25}_D$ −26.3° (*c* 1.0, MeOH). ^{1}H NMR (300 MHz) δ 1.10 (d, 3H, J = 6.6), 1.17 (t, 3H, J = 7.1), 1.22 (t, 3H, J = 7.1), 1.43 (s, 9H), 2.83 (dd, 1H, J = 13.9, 7.0), 2.94 (dd, 1H, J =

14.3, 5.1), 3.34 (q, 2H, $J = 7.1$), 3.44 (q, 2H, $J = 7.1$), 3.99 (br, 1H), 4.45 (br, 1H), 4.80 (s, 2H), 6.67 (d, 1H, $J = 7.7$), 6.99 (t, 1H, $J = 7.9$), 7.10 (s, 1H), 7.30 (d, 1H, $J = 7.9$), 9.41 (s, 1H). MS *m*/*z*: 404 (MH^+), 304, 287. IR cm^{-1}; 3556, 3300, 2980, 1699, 1649, 1638, 1522, 1485, 1448, 1171. *Anal*. *Calcd* for $C_{22}H_{33}N_3O_4$; C: 65.48, H: 8.24, N: 10.41. Found; C: 65.24, H: 8.20, N: 10.62. Chiral HPLC [column, CHIRALCEL AD; 4.6 mm i.d. × 250 mm; eluent, hexane/2-PrOH = 50/50; flow rate, 0.8 mL/min; column temperature, 25 °C; detection, 254 nm]; the retention times of **32** and its enantiomer were 6.6 and 8.0 min, respectively.

(2*R*)-[3-(2-Aminopropyl)-1*H*-indol-7-yloxy]-*N*,*N*-diethylacetamide (3). A mixture of **32** (475 g, 1.2 mol), oxalic acid (318.7 g, 3.5 mol), and MeCN (2850 mL) was heated to reflux for 4 h and cooled to ca. 5 °C. The resulting precipitate was collected by filtration and washed with MeCN. The precipitate was completely dissolved in a mixture of 10% aqueous K_2CO_3 (2000 mL) and $CHCl_3$ (4800 mL). The organic layer was separated and dried over anhydrous $MgSO_4$. The solvent was evaporated, and the residue was triturated with diisopropyl ether to give 282 g (79%, >99% ee) of **3** as a white crystalline material, mp 133 °C. $[\alpha]^{25}_D$ −46.3° (*c* 1.0, MeOH). ^{1}H NMR (300 MHz) δ 1.16 (d, 3H, $J = 6.6$), 1.17 (t, 3H, $J = 7.1$), 1.22 (t, 3H, $J = 7.1$), 1.40−2.00 (br, 2H), 2.64 (dd, 1H, $J = 14.1, 8.2$), 2.86 (dd, 1H, $J = 14.1, 5.0$), 3.18 (m, 1H), 3.35 (q, 2H, $J = 7.1$), 3.44 (q, 2H, $J = 7.1$), 4.80 (s, 2H), 6.68 (d, 1H, $J = 7.5$), 6.99 (t, 1H, $J = 7.9$), 7.05 (s, 1H), 7.28 (d, 1H, $J = 8.0$ Hz), 9.42 (s, 1H). MS *m*/*z*: 304 (MH^+), 287. IR cm^{-1}; 3294, 2972, 1641, 1577, 1439, 1231. *Anal. Calcd* for $C_{17}H_{25}N_3O_2$; C: 67.30, H: 8.31, N: 13.85. Found; C: 67.29, H: 8.45, N: 13.72. Chiral HPLC [column, CHIRALCEL AD; 4.6 mm i.d. × 250 mm; eluent, hexane/2-PrOH/Et_2NH = 85/15/0.8; flow rate, 1.0 mL/min; column temperature, 25 °C; detection, 254 nm]; the retention times of **3** and its enantiomer were 19.9 and 18.0 min, respectively.

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