Synthesis of a Chiral Spiranic Aminochroman Derivative from L-Proline

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Received July 7, 1999

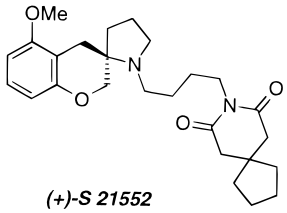
Introduction

Serotonin or 5-hydroxytryptamine (5-HT) is a neurotransmitter of the nervous central system[1,2] and has a strong influence at the physiological and pathophysiological levels. It has been linked to various behavioral problems involving memory, thermoregulation, sleep, and sexual behavior, and it is also implicated in numerous neuropsychiatry disorders such as anxiety, schizophrenia, or Alzheimer's disease.[3−5] At first, only four mains types of serotoninergic receptors were defined, i.e., the 5-HT_1, 5-HT_2, and 5-HT_3 in 1986[6] and 5-HT_4 in 1988.[7] Recently, three new classes of receptors, the 5-HT_5, 5-HT_6, and 5-HT_7,[8] were described. Among all of these classes, some have been subdivided such as 5-HT_1, which includes six subtypes such as the 5-HT_{1A} receptor.[7]

The synthesis of 5-HT_{1A} agonists appear to be very attractive due to their role in anxiety and depression behavioral disorders. In our laboratory, previous work[9,10] has led to new therapeutic agents that demonstrate very good affinity and high selectivity for the 5-HT_{1A} receptor. Among them, the compound **(+)-S 21552** (Chart 1) is a good candidate for a clinical development.[10]

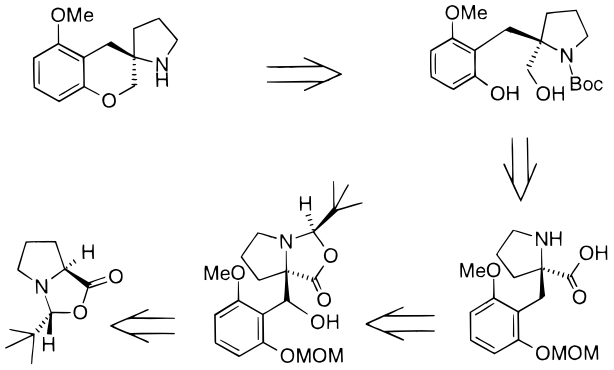
At the present time, only a racemic synthesis of this 3-aminochroman has been described. Each enantiomer could be resolved using optically pure 1,1′-binaphthyl-2,2′-diyl hydrogen phosphate as chiral agent for enantioselective resolution.[11] The high cost of resolving agent prompted us to devise a chiral synthesis of this aminochroman derivative using the commercially available L-proline.

Chart 1

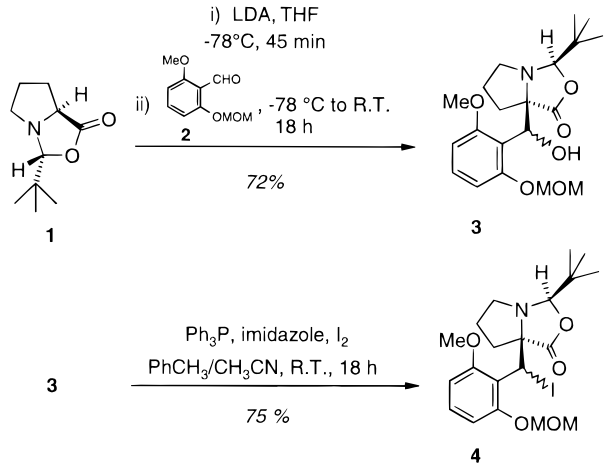


(+)-S 21552

Scheme 1



Scheme 2



Results and Discussion

The retrosynthetic pathway of this synthesis is illustrated in Scheme 1. The first reaction, which is the key step in our synthetic pathway, involves α-alkylation of oxazolidinone **1** with 2-methoxy-6-methoxymethoxybenzaldehyde **2**[12] using Seebach's methodology.[13]

Treatment of oxazolidinone **1**, prepared from L-proline,[13] with lithium diisopropylamide at −78 °C followed by the addition of the benzaldehyde **2** at same temperature gave a diastereosomeric mixture of alcohols **3** (ratio 3/1) in 72% yield (Scheme 2).

The next step in our sequence focused on deoxygenation of the hydroxyl group of **3**. Our first attempt used the Barton−McCombie reaction,[14] which met with failure.

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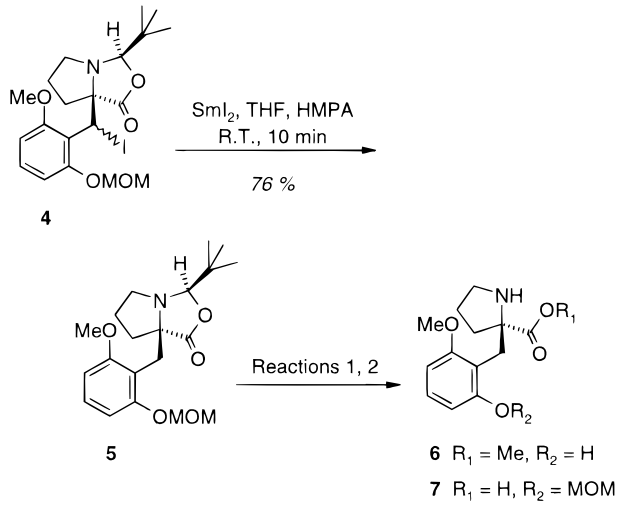
10.1021/jo991089y CCC: $19.00
Published on Web 01/10/2000

Scheme 3



Reactions	Conditions	Yield (%)	Compound
1	Amberlyst, HCl 6N MeOH, R.T., 18 h	69	**6**
2	SiO_2, MeOH/H_2O refluxed, 62 h	97	**7**

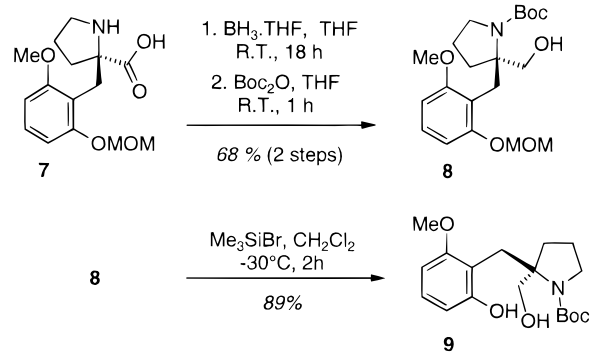
The next approach involved replacement of the hydroxyl group with iodide followed by reduction. The introduction of iodide (Scheme 2) was achieved using Garreg's methodology[15] by reacting compound **3** with triphenylphosphine, imidazole, and iodine in a mixture toluene/acetonitrile at room temperature to furnish **4** in 75% yield. Compound **4** was shown to be a diastereomeric mixture.

The removal of iodine proved to be very difficult, and a number of reduction procedures were examined. Several standard procedures using zinc in acetic acid or lithium aluminum hydride in diethyl ether were unsuccessful, and both led to degradation products. Likewise, catalytic hydrogenation of **4** using Pd/C in methyl alcohol quantitatively cleaved the MOM group and led to replacement of the iodo substituent with a methoxy group. To avoid the formation of this compound, the hydrogenation was carried out in dioxane but only degradation products were obtained. Finally, the reduction of the organic halide **4** was accomplished using samarium(II) iodide[16] in tetrahydrofuran in the presence of hexamethylphosphoramide (Scheme 3) to afford the desired compound **5** in 76% yield.

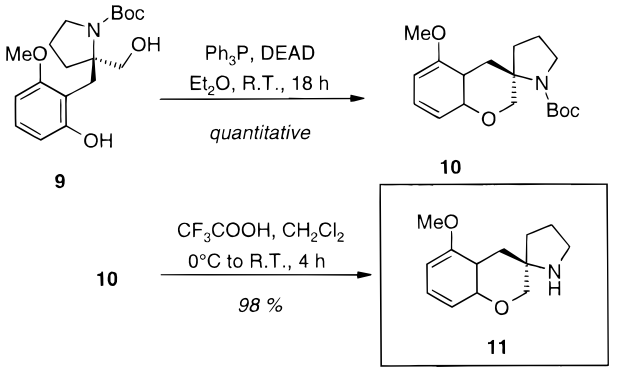
We explored several chemical procedures to hydrolyze the oxazolidinone moiety of **5** and found that Amberlyst XN-1010 in a mixture of hydrochloric acid and methyl alcohol (Scheme 3) was one of the more promising. This reaction mixture led to the corresponding methyl ester **6**, as the main product, in 69% yield.

Finally, the best procedure for the hydrolysis of chiral oxazolidinone **5** employed a suspension of silica gel in a mixture of methyl alcohol and water according to the conditions described by Johnson et al.[17] but instead under reflux as depicted in Scheme 3. The amino acid **7** was obtained in 97% yield.

Scheme 4



Scheme 5



The strategy we followed to complete the synthesis is outlined in Scheme 4. Acid **7** was used as starting material. The carboxylic acid function was first reduced to the corresponding primary alcohol with borane−tetrahydrofuran complex[18] in tetrahydrofuran at room temperature. To avoid the formation of aziridine, the amino group was protected using di-*tert*-butyl dicarbonate in anhydrous tetrahydrofuran at room temperature to provide the expected compound **8** in 71% overall yield. Cleavage of methoxymethoxy group occurred in methyl alcohol either with hydrochloric acid or with Amberlyst to give compound **9** in low or moderate yield, whereas bromotrimethylsilane[19] in methylene chloride at −30 °C provided **9** in very good yield.

Scheme 5 illustrates the synthesis of final derivative **11**, which was obtained in two steps from **9** in 98% yield. Ring closure of **9** by the Mitsunobu reaction[20] using triphenylphosphine and diethyl azodicarboxylate in anhydrous diethyl ether at room temperature provided a quantitative yield of the pyran **10**, which in turn was hydrolyzed with trifluoroacetic acid in methylene chloride to furnish **11** in 98% yield.

The enantiomeric purity of the aminochroman **11** was determined by capillary electrophoresis using anionic sulfated-β-cyclodextrins as chiral selector.[21] An alternative route used chiral high-performance liquid chromatography (Chiralpak). In these two cases, we obtained the desired enantiomer with an enantiomeric excess of 99.7%.

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In conclusion, the synthesis of (2*R*)-5′-methoxy-3′,4′-dihydrospiro[pyrrolidine-2,3′(2′*H*)-benzopyran] was accomplished starting with the naturally occurring L-proline. It took 10 steps with an overall yield of approximately 18%. The key step of the synthetic sequence concerned the alkylation of the L-proline derivative **1** according to Seebach's strategy. This synthetic sequence proved to be highly stereoselective, and the final compound **11** was obtained with an enantiomeric excess of 99.7%.

Experimental Section

All air- and moisture-sensitive reactions were carried out under an argon atmosphere. Anhydrous solvents (diethyl ether and tetrahydrofuran) were freshly distilled from sodium/benzophenone under nitrogen prior to use. ^{1}H and ^{13}C NMR spectra were recorded at 250.131 and 62.9 MHz, respectively. Carbon multiplicities have been assigned by distortionless enhancement by polarization transfer (DEPT) experiments. Infrared spectra were recorded using NaCl film or KBr pellet techniques. Mass spectra (MS) were recorded by ion spray (IS). Melting points were determined in open capillary tube and are uncorrected. Analytical thin-layer chromatography was performed on Merck $60F_{254}$ silica gel precoated plates. Flash chromatography was performed using silica gel Merck 40−70 μm (230−400 mesh). For the diastereoisomers of **4** only, signals are different in the NMR spectra for each isomer.

(3*R*,7a*R*)-3-(*tert*-Butyl)-7a-[1-hydroxy-1-[2-methoxy-6-methoxymethoxyphenyl]methyl]perhydropyrrolo[1,2-*c*]-[1,3]oxazol-1-one (3). Under an argon atmosphere, a solution of 1.2 g (6.6 mmol) of oxazolone (**1**)[13] in anhydrous THF (30 mL) was cooled to −78 °C, and then 4.3 mL (17.7 mmol) of LDA, 2 M solution in hexane, was slowly added. After 45 min, 1.73 g (8.5 mmol) of aldehyde **2** was added. The mixture was stirred during 40 min at −78 °C and then allowed to warm to room temperature and stirred during 18 h. After evaporation, the crude product was hydrolyzed by 25 mL of saturated NH_4Cl solution and extracted with EtOAc. The organic layers were dried over $MgSO_4$, concentrated, and purified by flash chromatography (eluent: petroleum ether/EtOAc, 9/1) to give a mixture of the desired alcohols **3** (1.78 g, 72%) as a white solid. IR (KBr): ν cm^{-1} 3522−3242 (O−H), 1773 (C═O). NMR ^{1}H ($CDCl_3$): δ ppm 0.77 (s, 9H), 1.69−2.05 (m, 3H), 2.39−2.61 (m, 1H), 2.68−2.91 (m, 1H), 2.98−3.16 (m, 1H), 3.49 (s, 3H), 3.84 (s, 3H), 4.13 (s, 1H), 4.71 (d, 1H, J = 9.3 Hz), 5.16 (s, 2H), 5.47 (d, 1H, J = 9.3 Hz), 6.59 (d, 1H, J = 8.5 Hz), 6.81 (d, 1H, J = 8.5 Hz), 7.17 (t, 1H, J = 8.5 Hz). NMR ^{13}C ($CDCl_3$): δ ppm 24.1 ($3CH_3$), 24.9 (CH_2), 33.6 (CH_2), 35.9 (C), 55.5 (CH_3), 56.2 (CH_3), 57.0 (CH_2), 72.5 (CH), 78.2 (C), 95.2 (CH_2), 103.8 (CH), 104.9 (CH), 107.7 (CH), 116.4 (C), 129.3 (CH), 155.4 (C), 158.8 (C), 175.4 (C). MS (IS): m/z = 380 (M + 1). Anal. Calcd for $C_{20}H_{29}NO_6$: C, 63.31, H, 7.70, N, 3.69. Found: C, 63.13, H, 7.81, N, 3.53.

(3*R*,7a*R*)-3-(*tert*-Butyl)-7a-[1-iodo-1-[2-methoxy-6-methoxymethoxyphenyl]methyl]perhydropyrrolo[1,2-*c*][1,3]-oxazol-1-one (4). Under an argon atmosphere, 840 mg (2.21 mmol) of alcohols **3** was dissolved in a mixture of toluene (10 mL) and acetonitrile (5 mL). The mixture was cooled to 0 °C, and 1.7 g (6.48 mmol) of Ph_3P, 890 mg (13.07 mmol) of imidazole and 1.7 g (6.70 mmol) of iodine were added. The mixture was allowed to room temperature and stirred during 18 h. After evaporation, the residue was hydrolyzed and extracted with CH_2Cl_2. The organic layers were combined and dried over $MgSO_4$, concentrated, and purified by flash chromatography (eluent: petroleum ether/EtOAc, 9/1) to give desired iodine compounds **4** (810 mg, 75%) as a yellow solid. IR (KBr): ν cm^{-1} 1781 (C═O). NMR ^{1}H ($CDCl_3$): δ ppm major isomer, 0.96 (s, 9H), 1.46−1.72 (m, 1H), 1.75−1.91 (m, 1H), 2.11−2.27 (m, 1H), 2.51−2.68 (m, 1H), 2.68−2.81 (m, 1H), 3.18−3.34 (m, 1H), 3.46 (s, 3H), 3.88 (s, 3H), 4.12 (s, 1H), 5.14 (s, 2H), 6.32 (s, 1H), 6.56 (d, 1H, J = 8.5 Hz), 6.66 (d, 1H, J = 8.5 Hz), 7.19 (t, 1H, J = 8.5 Hz); minor isomer, 0.96 (s, 9H), 1.46−1.72 (m, 1H), 1.75−1.91 (m, 1H), 2.11−2.27 (m, 1H), 2.51−2.68 (m, 1H), 2.68−2.81 (m, 1H), 3.18−3.34 (m, 1H), 3.58 (s, 3H), 3.77 (s, 3H), 4.12 (s, 1H), 5.14 (s, 2H), 6.32 (s, 1H), 6.47 (d, 1H, J = 8.5 Hz), 6.77 (d, 1H, J = 8.5 Hz), 7.18 (t, 1H, J = 8.5 Hz). NMR ^{13}C ($CDCl_3$): δ ppm major isomer, 24.3 ($3CH_3$), 25.4 (CH_2), 30.1 (CH), 36.0 (C), 37.6 (CH_2), 54.7 (CH_3), 56.1 (CH_3), 57.7 (CH_2), 75.9 (C), 94.4 (CH_2), 104.3 (CH), 105.3 (CH), 106.0 (CH), 116.7 (C), 129.6 (CH), 154.4 (C), 159.7 (C), 171.3 (C); minor isomer, 24.3 ($3CH_3$), 25.4 (CH_2), 29.9 (CH), 36.0 (C), 37.7 (CH_2), 55.9 (CH_3), 56.7 (CH_3), 57.7 (CH_2), 75.9 (C), 94.0 (CH_2), 104.0 (CH), 104.3 (CH), 107.2 (CH), 116.4 (C), 129.6 (CH), 156.8 (C), 157.8 (C), 171.3 (C). MS (IS): m/z = 490 (M + 1). Anal. Calcd for $C_{20}H_{28}INO_5$: C, 49.09, H, 5.77, N, 2.86. Found: C, 49.29, H, 5.61, N, 2.65.

(3*R*,7a*R*)-3-*tert*-Butyl-7a-[2-methoxy-6-(methoxymethoxy)-benzyl]perhydropyrrolo[1,2-*c*][1,3]oxazol-1-one (5). Under an argon atmosphere, 1 mL of HMPA and 1.1 mL of 2-propanol were added to 500 mg (1.02 mmol) of iodo derivatives **4** dissolved in anhydrous THF (5 mL). The mixture was degassed during 30 min, and 26 mL (2.55 mmol) of samarium iodide, 0.1 M solution in THF, was added. After 5 min, the solvent was removed under vacuum, and the residue was purified by flash chromatography (eluent: petroleum ether/EtOAc, 9/1) to give desired compound **5** (564 mg, 76%) as a white solid. Mp: 61−62 °C. IR (KBr): ν cm^{-1} 1767 (C═O). NMR ^{1}H ($CDCl_3$): δ ppm 0.85 (s, 9H), 1.64−1.95 (m, 3H), 2.08−2.22 (m, 1H), 2.64−2.76 (m, 1H), 2.95−3.08 (m, 1H), 3.15 (d, 1H, J = 13.3 Hz), 3.22 (d, 1H, J = 13.3 Hz), 3.47 (s, 3H), 3.78 (s, 3H), 4.18 (s, 1H), 5.14 (s, 2H), 6.54 (d, 1H, J = 8.2 Hz), 6.75 (d, 1H, J = 8.2 Hz), 7.13 (t, 1H, J = 8.2 Hz). NMR ^{13}C ($CDCl_3$): δ ppm 23.6 ($3CH_3$), 24.9 (CH_2), 29.6 (CH_2), 35.7 (CH_2), 36.1 (C), 55.2 (CH_3), 56.0 (CH_3), 57.8 (CH_2), 72.6 (C), 94.7 (CH_2), 104.9 (CH), 105.5 (CH), 106.6 (CH), 114.4 (C), 128.0 (CH), 157.1 (C), 159.2 (C), 177.5 (C). MS (IS): m/z = 364 (M + 1). $[\alpha]^{20}_D$ = −5 (c 1.1, $CHCl_3$). Anal. Calcd for $C_{20}H_{29}NO_5$: C, 66.09; H, 8.04; N, 3.85. Found: C, 66.22; H, 7.85; N, 3.67.

Methyl (2*R*)-2-(2-Hydroxy-6-methoxybenzyl)pyrrolidine-2-carboxylate (6). Under an argon atmosphere, 130 mg of Amberlyst XN-1010 and 1 mL of HCl 6 N were added to 130 mg (0.358 mmol) of oxazolidinone (**5**) dissolved in MeOH (6 mL). The mixture was stirred during 48 h at room temperature and neutralized with saturated $NaHCO_3$ solution. After hydrolysis, Amberlyst was filtered off and the mixture washed with CH_2Cl_2. After extraction of the aqueous layer with CH_2Cl_2, the organic layers were dried over $MgSO_4$ and evaporated to give crude ester **6** (66 mg, 69%) as a yellow oil. IR (NaCl): ν cm^{-1} 3500−3000 (NH, OH), 1732 (C═O). NMR ^{1}H ($CDCl_3$): δ ppm 1.41−1.73 (m, 2H), 1.82−2.00 (m, 1H), 2.02−2.20 (m, 1H), 2.75−2.91 (m, 1H), 2.91−3.02 (m, 1H), 3.08 (d, 1H, J = 13.9 Hz), 3.30 (d, 1H, J = 13.9 Hz), 3.78 (s, 3H), 3.79 (s, 3H), 4.29 (s, 1H), 6.39 (d, 1H, J = 8.2 Hz), 6.54 (d, 1H, J = 8.2 Hz), 7.06 (t, 1H, J = 8.2 Hz), 10.68 (s, 1H). NMR ^{13}C ($CDCl_3$): δ ppm 26.3 (CH_2), 33.5 (CH_2), 34.0 (CH_2), 46.4 (CH_2), 52.7 (CH_3), 55.5 (CH_3), 70.7 (C), 101.6 (CH), 111.0 (CH), 112.2 (C), 128.3 (CH), 158.7 (2C), 176.8 (C). MS (IS): m/z = 266 (M + 1).

(2*R*)-2-[2-Methoxy-6-(methoxymethoxy)benzyl]pyrrolidine-2-carboxylic Acid (7). To a solution of 578 mg (1.59 mmol) of oxazolidinone **5** in a mixture MeOH/H_2O (6/1, 7 mL) was added 720 mg of silica gel 200−400 mesh, 60 Å. The mixture was heated during 62 h, and solvents were evaporated. The purification was made by flash chromatography (eluent: CH_2Cl_2/MeOH, 95/5 and 8/2) to give desired compound **7** (454 mg, 97%) as a white foam. Mp: 175−176 °C. IR (KBr): ν cm^{-1} 3660−3040 (NH, OH), 1622 (C═O). NMR ^{1}H ($CDCl_3$): δ ppm 1.54−1.71 (m, 1H), 1.75−2.03 (m, 2H), 2.36−2.53 (m, 1H), 2.79−2.97 (m, 1H), 3.26 (d, 1H, J = 14.5 Hz), 3.47 (s, 1H), 3.49 (s, 3H), 3.55−3.69 (m, 1H), 3.81 (d, 1H, J = 14.5 Hz), 3.92 (s, 3H), 5.27 (d, 1H, J = 6.9 Hz), 5.34 (d, 1H, J = 6.9 Hz), 6.66 (d, 1H, J = 8.3 Hz), 6.86 (d, 1H, J = 8.3 Hz), 7.26 (t, 1H, J = 8.3 Hz), 7.53 (br s, 1H). NMR ^{13}C ($CDCl_3$): δ ppm 24.1 (CH_2), 28.3 (CH_2), 32.9 (CH_2), 46.7 (CH_2), 56.1 (CH_3), 56.3 (CH_3), 74.8 (C), 94.6 (CH_2), 104.8 (CH), 107.3 (CH), 113.0 (C), 128.9 (CH), 156.5 (C), 158.3 (C), 174.3 (C). MS (IS): m/z = 296 (M + 1). $[\alpha]^{20}_D$ = −43 (c 1.0, $CHCl_3$). Anal. Calcd for $C_{15}H_{21}NO_5$: C, 61.00; H, 7.17; N, 4.74. Found: C, 61.29; H, 7.33; N, 4.59.

***tert*-Butyl (2*R*)-2-(Hydroxymethyl)-2-[2-methoxy-6-(methoxymethoxy)benzyl]pyrrolidine-1-carboxylate (8).** Under an argon atmosphere, 3.1 mL (3.08 mmol) of BH_3·THF, 1 M in THF, was slowly added to a suspension of 454 mg (1.54 mmol) of amino acid **7** in anhydrous THF (8 mL). The mixture was stirred during 18 h at room temperature, and 2.7 mL of MeOH was added. After evaporation, the residue was hydrolyzed by

2.7 mL of a solution of 20% KOH and extracted with CH_2Cl_2. The organic layers were dried over $MgSO_4$ and concentrated. The crude amino alcohol was engaged in the next step without further purification. IR (NaCl): ν cm^{-1} 3686−3050 (NH, OH). NMR ^1H ($CDCl_3$): δ ppm 1.55−1.80 (m, 4H), 2.80−3.02 (m, 2H), 2.88 (d, 1H, J = 13.7 Hz), 2.97 (d, 1H, J = 13.7 Hz), 3.19 (br s, 2H), 3.26 (d, 1H, J = 10.9 Hz), 3.32 (d, 1H, J = 10.9 Hz), 3.49 (s, 3H), 3.83 (s, 3H), 5.19 (s, 2H), 6.60 (d, 1H, J = 8.2 Hz), 6.78 (d, 1H, J = 8.2 Hz), 7.15 (t, 1H, J = 8.2 Hz). NMR ^{13}C ($CDCl_3$): δ ppm 25.8 (CH_2), 29.8 (CH_2), 33.1 (CH_2), 46.3 (CH_2), 55.6 (CH_3), 56.3 (CH_3), 67.0 (C), 67.3 (CH_2), 94.8 (CH_2), 104.6 (CH), 107.1 (CH), 115.6 (C), 127.7 (CH), 156.5 (C), 158.6 (C). MS (IS): m/z = 282 (M + 1).

Under an argon atmosphere, 386 mg of the crude amino alcohol was dissolved in anhydrous THF (7 mL), and 350 μL (1.50 mmol) of di-*tert*-butyl dicarbonate was added. The mixture was stirred at room temperature during 1 h, hydrolyzed, and extracted with CH_2Cl_2. The organic layers were dried over $MgSO_4$, concentrated, and purified by flash chromatography (eluent: petroleum ether/EtOAc, 8/2) to lead to carbamate **8** (400 mg, 68% overall yield for two steps) as a colorless oil. IR (NaCl): ν cm^{-1} 3710−3130 (OH), 1674 (C═O). NMR ^1H ($CDCl_3$): δ ppm 1.40−1.75 (m, 2H), 1.49 (s, 9H), 1.75−2.10 (m, 2H), 2.98−3.27 (m, 4H), 3.48 (s, 3H), 3.40−3.72 (m, 2H), 3.72−4.00 (m, 4H), 5.17 (s, 2H), 6.56 (d, 1H, J = 8.2 Hz), 6.76 (d, 1H, J = 8.2 Hz), 7.13 (t, 1H, J = 8.2 Hz). NMR ^{13}C ($CDCl_3$): δ ppm 21.7 (CH_2), 26.3 (CH_2), 28.7 ($3CH_3$), 33.9 (CH_2), 48.7 (CH_2), 55.7 (CH_3), 56.1 (CH_3), 68.5 (C), 71.1 (CH_2), 79.3 (C), 94.8 (CH_2), 104.4 (CH), 107.1 (CH), 116.6 (C), 127.5 (CH), 155.8 (C), 157.0 (C), 159.2 (C). MS (IS): m/z = 382 (M + 1). $[\alpha]^{20}_D$ = +63 (c 1.1, $CHCl_3$). Anal. Calcd for $C_{20}H_{31}NO_6$: C, 62.97; H, 8.19; N, 3.67. Found: C, 62.77; H, 8.01; N, 3.43.

***tert*-Butyl (2*R*)-2-(2-Hydroxy-6-methoxybenzyl)-2-(hydroxymethyl)pyrrolidine-1-carboxylate (9).** Under an argon atmosphere, 100 mg (0.26 mmol) of carbamate **8** was dissolved in CH_2Cl_2 (4 mL). The mixture was cooled to −30 °C, and 140 μL (1.05 mmol) of bromotrimethylsilane was added. The solution was stirred during 2 h at −30 °C and then hydrolyzed. The mixture was allowed to room temperature and the aqueous layer was extracted with CH_2Cl_2. The organic layers were dried over $MgSO_4$, and after concentration, the residue was purified by flash chromatography (eluent: petroleum ether/EtOAc, 9/1) to give diol **9** (78 mg, 89%) as a white solid. Mp: 133−134 °C. IR (KBr): ν cm^{-1} 3740−3000 (OH), 1646 (C═O). NMR ^1H ($CDCl_3$ + D_2O): δ ppm 1.09−1.34 (m, 1H), 1.48 (s, 9H), 1.66−1.87 (m, 2H), 2.12−2.38 (m, 1H), 2.97 (d, 1H, J = 14.1 Hz), 3.34 (d, 1H, J = 14.1 Hz), 3.27−3.43 (m, 1H), 3.46 (d, 1H, J = 12.5 Hz), 3.62 (d, 1H, J = 12.5 Hz), 3.57−3.73 (m, 1H), 6.42 (d, 1H, J = 8.2 Hz), 6.58 (d, 1H, J = 8.2 Hz), 7.10 (t, 1H, J = 8.2 Hz). NMR ^{13}C ($CDCl_3$): δ ppm 21.4 (CH_2), 24.7 (CH_2), 28.4 ($3CH_3$), 33.2 (CH_2), 48.9 (CH_2), 55.2 (CH_3), 67.6 (CH_2), 69.3 (C), 80.9 (C), 101.6 (CH), 110.9 (CH), 112.1 (C), 128.1 (CH), 156.9 (C), 158.0 (C), 159.4 (C). MS (IS): m/z = 338 (M + 1). $[\alpha]^{20}_D$ = −21 (c 1.1, $CHCl_3$). Anal. Calcd for $C_{18}H_{27}NO_5$: C, 64.07; H, 8.06; N, 4.15. Found: C, 64.26; H, 8.29; N, 3.99.

(2*R*)-1-*tert*-Butoxycarbonyl-5′-methoxy-3′,4′-dihydrospiro-[pyrrolidine-2,3′(2′*H*)-benzopyran] (10). Under an argon atmosphere, 126 mg (0.48 mmol) of Ph_3P and 75 μL (0.48 mmol) of diethyl azodicarboxylate were added to a solution of 135 mg (0.40 mmol) of diol **9** in anhydrous Et_2O (4 mL). The mixture was stirred during 18 h at room temperature, and after evaporation, the residue was purified by flash chromatography (eluent: petroleum ether/EtOAc, 98/2 then 95/5) to give desired compound **10** (128 mg, quantitative) as a white solid. Mp: 100−101 °C. IR (KBr): ν cm^{-1} 1681 (C═O). NMR ^1H (DMSO-d_6 at 80 °C): δ ppm 1.40 (s, 9H), 1.55−1.68 (m, 1H), 1.77 (q, 2H, J = 6.7 Hz), 1,87−2.02 (m, 1H), 2.40−2.55 (m, 1H), 3.26−3.56 (m, 3H), 3.70−3.82 (m, 1H), 3.76 (s, 3H), 4.40 (d, 1H, J = 9.9 Hz), 6.42 (d, 1H, J = 8.2 Hz), 6.51 (d, 1H, J = 8.2 Hz), 7.03 (t, 1H, J = 8.2 Hz). NMR ^{13}C (DMSO-d_6 at 80 °C): δ ppm 20.6 (CH_2), 27.7 ($3CH_3$), 28.6 (CH_2), 35.6 (CH_2), 47.7 (CH_2), 55.0 (CH_3), 58.4 (C), 69.0 (CH_2), 78.4 (C), 102.3 (CH), 108.5 (CH), 109.8 (C), 126.4 (CH), 152.6 (C), 153.7 (C), 157.6 (C). MS (IS): m/z = 320 (M + 1). $[\alpha]^{20}_D$ = −21 (c 1.0, $CHCl_3$). Anal. Calcd for $C_{18}H_{25}NO_4$: C, 67.69; H, 7.89; N, 4.38. Found: C, 67.90; H, 7.69; N, 4.53.

(2*R*)-5′-Methoxy-3′,4′-dihydrospiro[pyrrolidine-2,3′(2′*H*)-benzopyran] (11). Under an argon atmosphere, 280 μL (3.3 mmol) of trifluoroacetic acid dissolved in CH_2Cl_2 (2 mL) was transferred to a cold solution of 110 mg (0.33 mmol) of protected amine **10** in CH_2Cl_2 (2 mL). The mixture was allowed to warm to room temperature, stirred for 4 h, and hydrolyzed by a saturated $NaHCO_3$ solution. After extraction of the aqueous layer with CH_2Cl_2, the organic layers were dried over $MgSO_4$, concentrated, and then purified by flash chromatography (eluent: CH_2Cl_2/MeOH, 9/1) to give desired amine **11** (70 mg, 98%) as a yellow oil. IR (NaCl): ν cm^{-1} 3330 (NH). NMR ^1H ($CDCl_3$): δ ppm 1.53−1.98 (m, 4H), 2.36 (s, 1H), 2.67 (s, 2H), 2.92−3.19 (m, 2H), 3.80 (s, 3H), 3.82 (s, 2H), 6.42 (d, 1H, J = 8.2 Hz), 6.50 (d, 1H, J = 8.2 Hz), 7.06 (t, 1H, J = 8.2 Hz). NMR ^{13}C ($CDCl_3$): δ ppm 25.7 (CH_2), 33.4 (CH_2), 34.8 (CH_2), 46.3 (CH_2), 55.5 (CH_3), 57.4 (C), 72.3 (CH_2), 102.1 (CH), 109.3 (CH), 110.4 (C), 127.2 (CH), 154.8 (C), 158.3 (C). MS (IS): m/z = 220 (M + 1). $[\alpha]^{20}_D$ = +10 (c 0.9, $CHCl_3$). Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.81; N, 6.39. Found: C, 70.97; H, 8.03; N, 6.21.

JO991089Y