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TETRAHEDRON: *ASYMMETRY*

Synthesis of enantiomerically pure 3-aminochroman derivatives

Stéphanie Usse,[a] Grégoire Pave,[a] Gérald Guillaumet[a] and Marie-Claude Viaud-Massuard[b,*]

[a]*Institut de Chimie Organique et Analytique, UMR CNRS 6005, Université d'Orléans, BP 6759, 45067 Orléans Cedex 2, France*
[b]*UFR Sciences Pharmaceutiques, Laboratoire de Chimie Organique, 31 avenue Monge, 37200 Tours, France*

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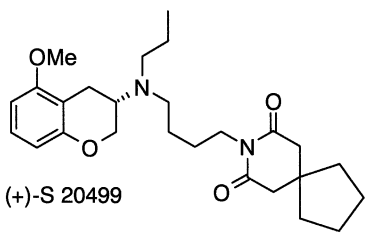
Abstract—Enantiomerically pure (3*R*)-amino-5-methoxy-3,4-dihydro-2*H*-1-benzopyran was successfully synthesised in nine steps starting from L-serine. The same synthetic pathway was used to prepare the (3*S*)-aminochroman derivative starting from D-serine. The enantiomeric purity of the final aminochroman derivatives was determined by capillary electrophoresis using β-cyclodextrin as the chiral selector. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

Serotonin (5-HT) is a neurotransmitter of the central nervous system and its receptors have a strong influence at the physiological and pathophysiological levels.[1,2] The dysfunction in serotoninergic systems has been linked to various behavioural problems involving memory, thermoregulation, sleep and sexual behaviour and it is also implicated in numerous neuropsychiatry disorders such as anxiety, depression, schizophrenia and Alzheimer's disease.[3–5] Due to the role of 5-HT_{1A} receptors in anxiety and depression behavioural disorders, the synthesis of 5-HT_{1A} agonists appears to be a very attractive goal. In our laboratory, previous work[6–8] has led to new therapeutic agents that demonstrate a good affinity and high selectivity for the 5-HT_{1A} receptors. Among them, the compound (+)-*S* **20499** (Fig. 1) has been taken to phase II in clinical trials.



(+)-S 20499

Figure 1.

To date, only a racemic synthesis of this 3-aminochroman derivative has been described. Each enantiomer was subsequently resolved using homochiral acetylvaline as the resolving agent.[9] The (*S*)-absolute configuration of the dextrogyre enantiomer was determined by X-ray crystallography. The difficulty of the resolution encouraged us to devise an asymmetric synthesis of this compound using D-serine as the starting material.

In view of the cost difference between D-serine and L-serine, we decided to optimise the synthesis of the (3*R*)-aminochroman derivative from the cheapest L-serine and then to transpose this synthesis to the preparation of the active (*S*)-enantiomer from D-serine. Federsel's publication,[10] which proposed a synthesis of enantiomerically pure 3-aminochroman derivatives similar to our own previously communicated results,[11] prompted us to publish them.

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 alkylation at position 2 of 1-methoxy-3-(methoxymethoxy)benzene[12] **1** with Garner's aldehyde **2**. Aldehyde **2** was prepared in three steps from L-serine.[13,14] Treatment of **1** with *n*-butyllithium in refluxing diethyl ether followed by the addition of aldehyde **2** at room temperature gave a diastereoisomeric mixture of alcohols **3** (ratio 7/3, as measured by NMR) in 70% yield (Scheme 2). This ratio agrees well with other similar additions described in the literature.[15]

* Corresponding author. Tel.: 33 247 36 72 27; fax: 33 247 36 72 29; e-mail: mcviaud@univ-tours.fr

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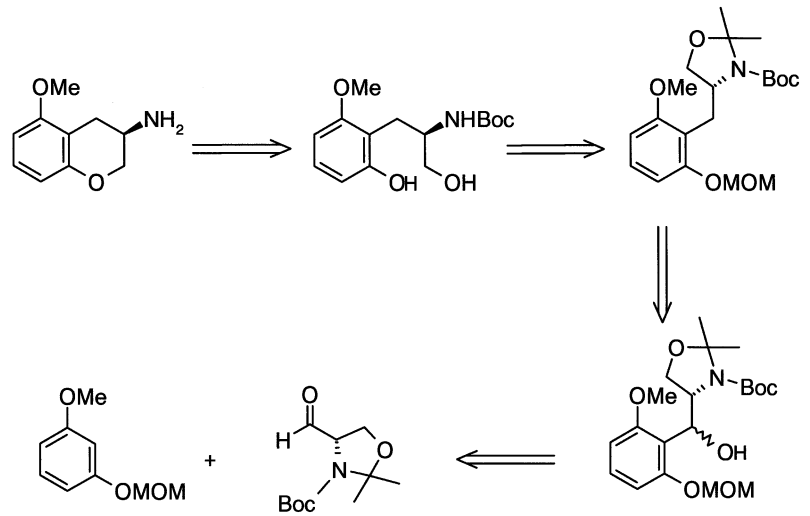
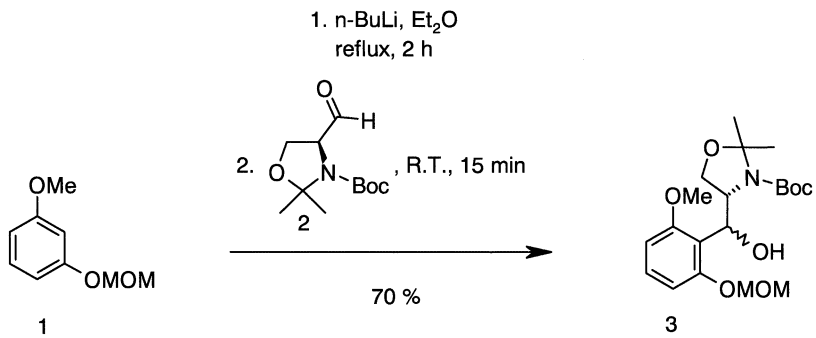


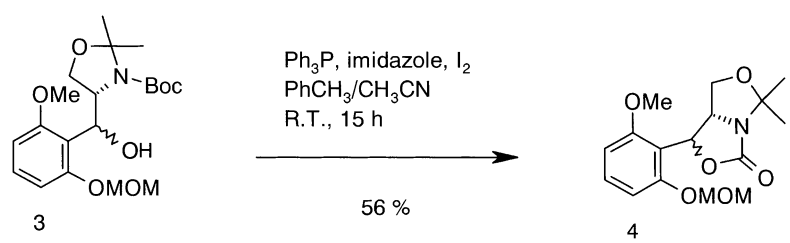
Scheme 1.



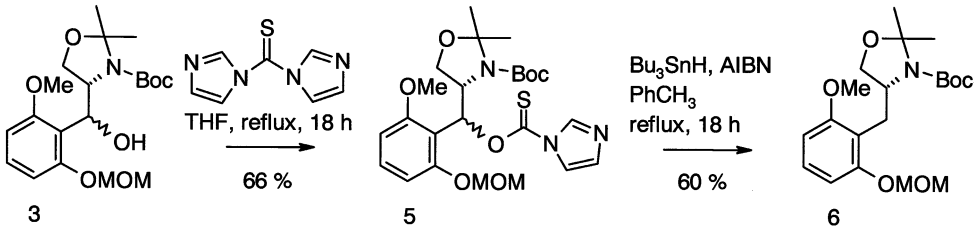
Scheme 2.

The next step, which involved removal of the hydroxyl group of **3**, proved to be difficult and several reduction procedures were examined. First, catalytic hydrogenation according to standard procedures afforded only returned starting material. The next approach involved the replacement of the hydroxyl group with iodide using Garreg's methodology[16] followed by reduction. Treatment of compounds **3** (Scheme 3) with triphenylphosphine, imidazole and iodide in a mixture of toluene and acetonitrile led to the unwanted formation of the oxazolidinones **4**. This cyclisation has been described in the literature.[17,18] The reduction of **3** was finally achieved using the Barton–McCombie reaction.[19] The diastereoisomeric mixture of thiocarbamate derivatives **5** (Scheme 4) was obtained in 66% yield by stirring **3** with *N*,*N*-thiocarbonyldiimidazole in refluxing tetrahydrofuran. The thiocarbamate moiety was then reduced using tributyltin hydride in the presence of AIBN in refluxing toluene (Scheme 4) to give the desired compound **6** in 60% yield.

In order to avoid aziridine formation during the final ring closure, the MOM ether and isopropylidene protective groups would need to be cleaved while conserving the *tert*-butoxycarbonyl amine protection. Several standard procedures were examined, as depicted in Scheme 5. The use of *p*-toluenesulfonic acid in methanol[20] or in refluxing acetic acid[21] led to the alcohol **7**, with the MOM ether still intact, in 82 and 54% yields, respectively. The hydrolysis was accomplished in



Scheme 3.



Scheme 4.

good yield and with the desired selectivity by treatment of **6** with *tert*-butyldimethylsilyl bromide in methylene chloride at −30°C[22] to furnish the desired diol **8** in 64% yield.

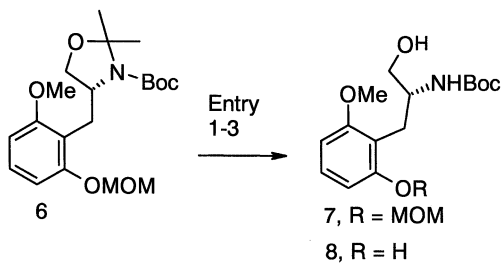
Scheme 6 illustrates the synthesis of derivative **10**, which was obtained in two steps from **8**. Ring closure of **8** under Mitsunobu conditions[23] using triphenylphosphine and diethyl azodicarboxylate at 80°C in toluene provided the benzopyran **9** in 74% yield. The *tert*-butoxycarbonyl group was removed with trifluoroacetic acid in methylene chloride to give the desired aminochroman **10** in 78% yield. The final step, leading to the (+)-*S* **20499** analogue, involves *N*,*N*-dialkylation of amine **10**, a sequence which has already been described in the literature.[6]

(3*S*)-3-Amino-5-methoxy-3,4-dihydro-2*H*-1-benzopyran **11** was prepared according to the same synthetic pathway starting from D-serine (Scheme 7). All compounds were fully characterized (IR, ^{1}H, ^{13}C NMR, mass and specific rotation) and physical data are identical to those described for their enantiomers.

The enantiomeric purities of aminochromans **10** and **11** were determined by capillary electrophoresis using β-cylcodextrin as the chiral selector.[24] In each case, we obtained the desired enantiomer with an e.e. of >99.5%.

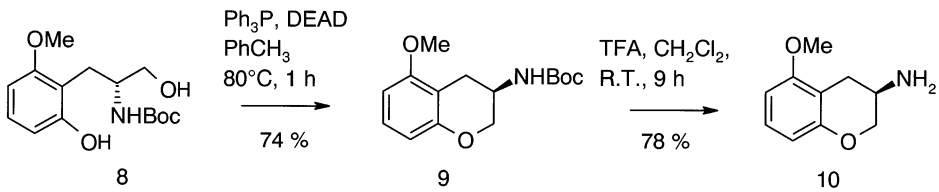
3. Conclusion

In conclusion, the synthesis of (3*R*)-3-amino-5-methoxy-3,4-dihydro-2*H*-1-benzopyran was accomplished starting with the (*S*)-Garner's aldehyde prepared from naturally occurring L-serine. The synthesis was completed in six steps with an overall yield of 10%. The (*S*)-enantiomer was synthesised using an analogous route starting from (*R*)-Garner's aldehyde with a similar overall yield. The key step in our synthe-

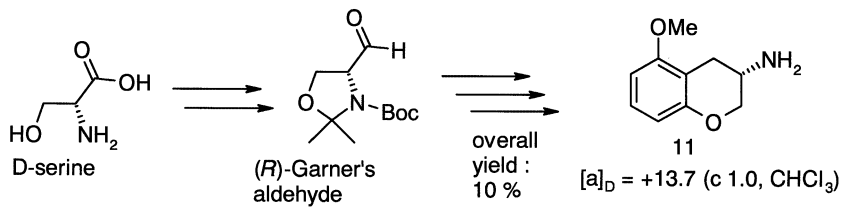


Entry	Conditions	R	Yield (%)	Product
1	APTS, MeOH R.T., 24 h	MOM	82	7
2	AcOH, reflux, 3 h	MOM	54	7
3	TMSBr, CH_2Cl_2 -30°C, 2 h	H	64	8

Scheme 5.



Scheme 6.



Scheme 7.

sis was the alkylation at position 2 of 1-methoxy-3-(methoxymethoxy)benzene **1** with Garner's aldehyde. The benzopyran targets **10** and **11** were obtained from the synthesis in enantiomerically pure form with e.e.s of >99.5%.

4. Experimental

All air- and moisture-sensitive reactions were carried out under an argon atmosphere. Anhydrous solvents (Et_2O and THF) were freshly distilled from sodium/benzophenone under nitrogen prior to use. ^1H and ^{13}C NMR spectra were obtained with a Bruker instrument Avance DPX250 at 250.131 and 62.9 MHz, respectively. Chemical shifts (δ values) are reported in parts per million and coupling constants (J) in Hz. Carbon multiplicities were assigned by distortionless enhancement by polarisation transfer (DEPT) experiments. Infrared spectra were recorded using NaCl film or KBr pellets techniques on a Perkin–Elmer spectrometer FT PARAGON 1000PC. Mass spectra (MS) were recorded on a Perkin–Elmer mass spectrometer SCIEX API 300 by ion spray (IS). Melting points (mp) were determined in open capillary tubes 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). Garner's aldehyde was prepared according to a methodology described in the literature.[14]

4.1. *tert*-Butyl (4*S*)-4-[hydroxy(2-methoxy-6-(methoxymethoxy)phenyl)methyl]-2,2-di-methyl-1,3-oxazolidine-3-carboxylate 3

Under an argon atmosphere, 1-methoxy-3-(methoxymethoxy)benzene **1** (1.13 g, 6.72 mmol) was dissolved in anhydrous Et_2O and *n*-butyllithium (1.6 M solution in hexane, 5.0 mL, 8.06 mmol) was slowly added. The mixture was stirred under reflux for 2 h and a solution of aldehyde **2** (1.70 g, 7.39 mmol) in anhydrous Et_2O (2 mL) was added. After stirring under reflux for 15 min the mixture was cooled to room temperature, hydrolysed and extracted with EtOAc. The organic layers were dried over $MgSO_4$, concentrated, and purified by flash chromatography (eluent: petroleum ether/EtOAc, 8/2) to give a mixture of the desired alcohols **3** as a colourless oil (1.87 g, 70%). IR (NaCl): ν cm^{-1} 3543 (OH), 1704 (C=O). ^1H NMR (DMSO-d_6, 80°C): δ ppm major isomer 1.11 (s, 9H), 1.48 (s, 6H), 3.41 (s, 3H), 3.76 (s, 3H), 3.65–3.90 (m, 2H), 4.21–4.42 (m, 2H), 5.14 (d, 1H, $J=4.3$ Hz), 5.18 (s, 2H), 6.59–6.77 (m, 2H), 7.14 (t, 1H, $J=8.2$ Hz); minor isomer 1.11 (s, 9H), 1.48 (s, 6H), 3.42 (s, 3H), 3.80 (s, 3H), 3.65–3.90 (m, 2H), 4.21–4.42 (m, 2H), 5.14 (d, 1H, $J=4.3$ Hz), 5.18 (s, 2H), 6.59–6.77 (m, 2H), 7.20 (t, 1H, $J=8.2$ Hz). ^{13}C NMR (DMSO-d_6, 80°C): δ ppm major isomer 28.0 ($3CH_3$), 28.6 ($2CH_3$), 55.9 ($2CH_3$), 60.3 (CH), 65.1 (CH), 66.3 (CH_2), 78.6 (C), 93.7 (C), 95.3 (CH_2), 105.7 (CH), 108.0 (CH), 119.5 (C), 128.7 (CH), 151.9 (C), 156.1 (C), 157.0 (C); minor isomer 28.0 ($3CH_3$), 28.6 ($2CH_3$), 56.1 ($2CH_3$), 60.3 (CH), 65.1 (CH), 66.3 (CH_2), 78.6 (C), 93.7 (C), 95.2 (CH_2), 106.2 (CH), 108.2 (CH), 119.5 (C), 129.4 (CH), 151.9 (C), 156.1 (C), 157.0 (C). MS (IS): $m/z=398$ (M+1). Anal. calcd for $C_{20}H_{31}NO_7$: C, 60.44; H, 7.86; N, 3.52. Found: C, 60.19; H, 7.98; N, 3.50%.

4.2. (7a*S*)-1-[2-Methoxy-6-(methoxymethoxy)phenyl]-5,5-dimethyldihydro-1*H*-[1,3]-oxazolo-[3,4-*c*][1,3]oxazol-3-one 4

Under an argon atmosphere, the mixture of diastereoisomeric alcohols **3** (110 mg, 0.28 mmol) was dissolved in a mixture of toluene (2 mL) and acetonitrile (1 mL). The mixture was cooled to 0°C, and Ph_3P (220 mg, 0.84 mmol), imidazole (114 mg, 1.68 mmol) and iodine (213 mg, 0.84 mmol) were added. The mixture was allowed to warm to room temperature and stirred for 15 h. After evaporation, the residue was hydrolysed 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, 4/1) to give **4** as a colourless oil (50 mg, 56%). IR (NaCl): ν cm^{-1} 1758 (C=O). ^1H NMR ($CDCl_3$): δ ppm major isomer 1.48 (s, 3H), 1.79 (s, 3H), 3.47 (s, 3H), 3.74 (t, 1H, $J=8.2$ Hz), 3.83 (s, 3H), 4.12 (dd, 1H, $J=8.2$ Hz, $J'=6.3$ Hz), 4.40–4.52 (m, 1H), 5.20 (s, 2H), 5.89 (d, 1H, $J=5.9$ Hz), 6.61 (d, 1H, $J=8.4$ Hz), 6.77 (d, 1H, $J=8.4$ Hz), 7.28 (t, 1H, $J=8.4$ Hz). ^{13}C NMR ($CDCl_3$): δ ppm major isomer 23.3 (CH_3), 27.5 (CH_3), 55.9 (CH_3), 56.3 (CH_3), 63.7 (CH), 69.1 (CH_2), 72.0 (CH), 94.4 (CH_2), 94.6 (C), 104.9 (CH), 107.1 (CH), 113.8 (C), 130.9 (CH), 156.6 (C), 157.5 (C), 158.8 (C). MS (IS): $m/z=324$ (M+1). Anal. calcd for $C_{16}H_{21}NO_6$: C, 59.43; H, 6.55; N, 4.33. Found: C, 59.20; H, 6.41; N, 4.69%.

4.3. *tert*-Butyl (4*S*)-4-{[(1*H*-imidazol-1-ylthiocarbonyl)-oxy](2-methoxy-6-methoxymethoxy)phenyl)-methyl}-2,2-dimethyl-1,3-oxazolidine-3-carboxylate 5

Under an argon atmosphere, *N*,*N*-thiocarbonyldiimidazole (540 mg, 3.02 mmol) was added to a solution of the mixture of alcohols **3** (480 mg, 1.21 mmol) in anhydrous THF (12 mL). The mixture was heated for 18 h. *N*,*N*-Thiocarbonyldiimidazole (540 mg, 3.02 mmol) was added and the mixture was stirred under reflux for a further 8 h. After concentration, the residue was hydrolysed and extracted with CH_2Cl_2. The organic layers were dried over $MgSO_4$, concentrated and purified by flash chromatography (eluent: petroleum ether/EtOAc, 4/1 and 3/2) to give the desired thiocarbamate compounds **5** as a yellow oil (402 mg, 66%). IR (NaCl): ν cm^{-1} 1697 (C=O), 1055 (C=S). ^1H NMR (DMSO-d_6, 80°C): δ ppm major isomer 1.17 (s, 9H), 1.39 (s, 6H), 3.47 (s, 3H), 3.83 (s, 3H), 3.90–4.15 (m, 2H), 4.55–4.71 (m, 1H), 5.21 (s, 2H), 5.78 (d, 1H, $J=8.5$ Hz), 6.66 (d, 1H, $J=8.5$ Hz), 6.71 (d, 1H, $J=8.5$ Hz), 7.07–7.08 (m, 1H), 7.18 (t, 1H, $J=8.5$ Hz), 7.62–7.63 (m, 1H), 8.28 (s, 1H). ^{13}C NMR (DMSO-d_6, 80°C): δ ppm major isomer 27.2 ($2CH_3$), 28.0 ($3CH_3$), 56.3 (CH_3), 59.5 (CH_3), 66.1 (CH_2), 79.3 (CH), 94.4 (CH_2), 95.0 (C), 95.3 (CH), 105.6 (CH), 107.3 (CH), 116.1 (C),

116.7 (CH), 129.5 (CH), 131.0 (CH), 135.9 (CH), 151.8 (C), 158.7 (2C), 166.8 (C). MS (IS): $m/z=508$ (M+1). Anal. calcd for $C_{24}H_{33}N_3O_7S$: C, 56.79; H, 6.55; N, 8.28. Found: C, 57.01; H, 6.36; N, 7.95%.

4.4. *tert*-Butyl (4*R*)-4-[2-methoxy-6-(methoxymethoxy)-benzyl]-2,2-dimethyl-1,3-oxazolidine-3-carboxylate 6

Under an argon atmosphere, a solution of compounds **5** (564 mg, 1.11 mmol) in anhydrous toluene (3 mL) was slowly added to a refluxing mixture of tributyltin hydride (0.6 mL, 2.22 mmol) in anhydrous toluene (5 mL) in the presence of AIBN. The mixture was heated for 18 h and hydrolysed. The tributyltin salts were filtered off and washed with CH_2Cl_2. After extraction of the aqueous layer with CH_2Cl_2, the organic layers were dried over $MgSO_4$, concentrated and purified by flash chromatography (eluent: petroleum ether/EtOAc, 95/5) to furnish the desired compound **6** (253 mg, 60%) as a colourless oil. IR (NaCl): ν cm^{-1} 1699 (C=O). ^1H NMR ($CDCl_3$): δ ppm 1.44 (s, 9H), 1.48 (s, 6H), 2.85–3.05 (m, 1H), 3.13 (dd, 1H, $J=12.5$ Hz, $J'=5.7$ Hz), 3.48 (s, 3H), 3.81 (s, 3H), 3.65–3.95 (m, 2H), 4.10–4.35 (m, 1H), 5.19 (s, 2H), 6.56 (d, 1H, $J=8.3$ Hz), 6.75 (d, 1H, $J=8.3$ Hz), 7.13 (t, 1H, $J=8.3$ Hz). ^{13}C NMR ($CDCl_3$): δ ppm 17.5 (CH_2), 26.8 (CH_3), 27.8 (CH_3), 28.4 ($3CH_3$), 55.4 (CH_3), 56.1 (CH_3), 56.4 (CH), 66.8 (CH_2), 79.6 (C), 94.1 (C), 94.3 (CH_2), 104.2 (CH), 106.7 (CH), 115.1 (C), 127.5 (CH), 152.1 (C), 156.6 (C), 158.9 (C). MS (IS): $m/z=382$ (M+1). $[\alpha]_D^{20}=+19.7$ (c 1.0, $CHCl_3$). Anal. calcd for $C_{20}H_{31}NO_6$: C, 62.97; H, 8.19; N, 3.67. Found: C, 63.19; H, 7.94; N, 3.56%.

4.5. *tert*-Butyl (1*R*)-2-hydroxy-1-[2-methoxy-6-(methoxymethoxy)benzyl]ethylcarbamate 7

4.5.1. Method A. Under an argon atmosphere, APTS·H_2O (5 mg, 0.026 mmol) was added to a mixture of compound **6** (100 mg, 0.26 mmol) in anhydrous MeOH (2 mL). The mixture was stirred for 24 h at room temperature and neutralised with a saturated $NaHCO_3$ solution. After evaporation of MeOH, the aqueous layer was extracted with EtOAc, and the organic layers were dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (eluent: petroleum ether/EtOAc, 3/2) to give compound **7** as a white solid (73 mg, 82%).

4.5.2. Method B. A solution of compound **6** (54 mg, 0.14 mmol) in acetic acid (2 mL) was heated for 3 h and then cooled to room temperature. After evaporation of the acetic acid, the residue was dissolved in AcOEt and the organic layer was washed several times with an Na_2CO_3 solution (2 M). The organic layer was dried over $MgSO_4$, concentrated and purified by flash chromatography (eluent: petroleum ether/EtOAc, 6/4) to give compound **7** (26 mg, 54%) as a white solid. Mp 69–70°C. IR (KBr): ν cm^{-1} 3695–3060 (NH, OH), 1681 (C=O). ^1H NMR ($CDCl_3$): δ ppm 1.36 (s, 9H), 2.73–3.00 (m, 2H), 3.21 (s, 1H), 3.35–3.65 (m, 2H), 3.46 (s, 3H), 3.66–3.95 (m, 1H), 3.80 (s, 3H), 5.18 (s, 2H), 5.37 (s, 1H), 6.56 (d, 1H, $J=8.3$ Hz), 6.75 (d, 1H, $J=8.3$ Hz), 7.12 (t, 1H, $J=8.3$ Hz). ^{13}C NMR ($CDCl_3$): δ ppm 24.6 (CH_2), 28.3 ($3CH_3$), 52.8 (CH), 55.6 (CH_3), 56.2 (CH_3), 65.6 (CH_2), 79.1 (C), 94.6 (CH_2), 104.4 (CH), 106.9 (CH), 114.9 (C), 127.8 (CH), 156.1 (C), 156.5 (C), 158.3 (C). MS (IS): $m/z=342.5$ (M+1), 364.5 (M+Na). $[\alpha]_D^{20}=+13.9$ (c 1.0, $CHCl_3$). Anal. calcd for $C_{17}H_{27}NO_6$: C, 59.81; H, 7.97; N, 4.10. Found: C, 60.07; H, 7.73; N, 3.87%.

4.6. *tert*-Butyl (1*R*)-2-hydroxy-1-(2-hydroxy-6-methoxybenzyl)ethylcarbamate 8

Under an argon atmosphere, compound **6** (50 mg, 0.13 mmol) was dissolved in anhydrous CH_2Cl_2 (2 mL). The mixture was cooled to −30°C and bromotrimethylsilane (52 μL, 0.39 mmol) was added. The solution was stirred for 2 h at −30°C and then hydrolysed by a saturated $NaHCO_3$ solution. The mixture was allowed to warm 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, 7/3 and 6/4) to give the desired compound **8** (25 mg, 64%) as a colourless oil. IR (NaCl): ν cm^{-1} 3700–3046 (NH, OH), 1693 (C=O). ^1H NMR ($CDCl_3$): δ ppm 1.45 (s, 9H), 2.80–3.08 (m, 2H), 3.45–3.80 (m, 4H), 3.82 (s, 3H), 5.45 (d, 1H, $J=7.3$ Hz), 6.45 (d, 1H, $J=8.0$ Hz), 6.57 (d, 1H, $J=8.0$ Hz), 7.07 (t, 1H, $J=8.0$ Hz), 8.14 (s, 1H). ^{13}C NMR ($CDCl_3$): δ ppm 24.4 (CH_2), 28.3 ($3CH_3$), 52.5 (CH), 55.6 (CH_3), 63.3 (CH_2), 79.9 (C), 102.4 (CH), 109.7 (CH), 112.2 (C), 127.9 (CH), 156.4 (C), 156.7 (C), 158.4 (C). MS (IS): $m/z=298$ (M+1). $[\alpha]_D^{20}=+11.2$ (c 1.0, $CHCl_3$). Anal. calcd for $C_{15}H_{23}NO_5$: C, 60.59; H, 7.80; N, 4.71. Found: C, 60.91; H, 7.47; N, 4.52%.

4.7. *tert*-Butyl (3*R*)-5-methoxy-3,4-dihydro-2*H*-chromen-3-yl-carbamate 9

Under an argon atmosphere, Ph_3P (39 mg, 0.15 mmol) and diethyl azodicarboxylate (24 μL, 0.15 mmol) were added to a solution of diol **8** (36 mg, 0.12 mmol) in anhydrous toluene (2 mL). The mixture was heated for 1 h and allowed to reach room temperature. After evaporation, the residue was purified by flash chromatography (eluent: petroleum ether/EtOAc, 9/1) to give the desired compound **9** (25 mg, 74%) as a colourless oil. IR (NaCl): ν cm^{-1} 3354 (NH), 1698 (C=O). ^1H NMR ($CDCl_3$): δ ppm 1.44 (s, 9H), 2.55–2.75 (m, 1H), 2.88 (dd, 1H, $J=17.5$ Hz, $J'=5.4$ Hz), 3.80 (s, 3H), 4.07 (bs, 2H), 4.10–4.25 (m, 1H), 4.83 (s, 1H), 6.45 (d, 1H, $J=8.2$ Hz), 6.50 (d, 1H, $J=8.2$ Hz), 7.08 (t, 1H, $J=8.2$ Hz). ^{13}C NMR ($CDCl_3$): δ ppm 26.1 (CH_2), 28.3 ($3CH_3$), 42.8 (CH), 55.4 (CH_3), 68.0 (CH_2), 79.5 (C), 102.4 (CH), 109.3 (CH), 108.6 (C), 127.3 (CH), 154.7 (C), 155.2 (C), 158.4 (C). MS (IS): $m/z=280$ (M+1). $[\alpha]_D^{20}=+25.8$ (c 1.0, $CHCl_3$). Anal. calcd for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.86; H, 7.44; N, 5.32%.

4.8. (3*R*)-3-Amino-5-methoxy-3,4-dihydro-2*H*-1-benzopyran 10

Under an argon atmosphere, a solution of trifluoroacetic acid (194 μL, 2.5 mmol) in CH_2Cl_2 (1 mL) was transferred to a cold solution of protected amine **9** (60 mg, 0.21 mmol) in CH_2Cl_2 (2 mL). The mixture was allowed to warm to room temperature, stirred for 9 h and hydrolysed 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 the desired amine **10** as a colourless oil (30 mg, 78%). IR (NaCl): ν cm^{-1} 3690–3050 (NH_2). ^1H NMR ($CDCl_3$): δ ppm 2.16 (s, 2H), 2.44 (dd, 1H, $J=16.9$ Hz, $J'=6.6$ Hz), 2.97 (dd, 1H, $J=16.9$ Hz, $J'=5.2$ Hz), 3.30–3.45 (m, 1H), 3.75–3.95 (m, 1H), 3.81 (s, 3H), 4.05–4.18 (m, 1H), 6.44 (d, 1H, $J=8.2$ Hz), 6.50 (d, 1H, $J=8.2$ Hz), 7.07 (t, 1H, $J=8.2$ Hz). ^{13}C NMR ($CDCl_3$): δ ppm 29.3 (CH_2), 43.8 (CH), 55.4 (CH_3), 71.0 (CH_2), 102.1 (CH), 109.2 (CH), 109.4 (C), 127.1 (CH), 154.7 (C), 158.3 (C). MS (IS): $m/z=$ 180 (M+1). $[\alpha]_D^{20}=-13.7$ (c 1.0, $CHCl_3$). Anal. calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.81. Found: C, 67.13; H, 7.12; N, 8.03%.

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