Synthesis of 3-Aminochroman Derivatives by Radical Cyclization

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Supporting information

All air- and moisture-sensitive reactions were carried out under an argon atmosphere. ^{1}H and ^{13}C NMR spectra were measured on spectrometers at 250.131 and 62.9 MHz, respectively. Chemical shifts (δ values) were reported in parts per million and coupling constants (*J* values) in Hz. Carbon multiplicities have been assigned by distortionless enhancement by polarization transfer (DEPT) experiments. Infrared spectra were recorded using NaCl film or KBr pellets techniques. Mass spectra (MS) were recorded on mass spectrometer by ion spray (IS). Melting points (mp) were determinated in open capillary tube and are uncorrected. Analytical thin-layer chromatography was performed on silica gel precoated plates. Flash chromatography was performed using silica gel 40-70 μm (230-400 mesh).

_N_-(_tert_-Butoxycarbonyl)-L-serine

Under an argon atmosphere, to a solution of L-serine (23 g, 0.22 mol) in 440 mL of an aqueous solution of NaOH 1M and 220 mL of dioxane at 0°C, was added di-*tert*-butyldicarbonate (57.4 g, 0.26 mol). The mixture was stirred for 12 h at rt. Dioxane was evaporated and the aqueous layer was washed with Et_2O. 440 mL of AcOEt was added. The aqueous layer was acidified to pH 2-3 with sulfurique acid 1M. The aqueous layer was extracted with AcOEt, dried over $MgSO_4$, filtered and concentrated, giving the expected carbamate as viscous colourless oil in 95 % yield.

IR (NaCl) : 3400-2400, 1732 cm^{-1}; $[\alpha]^{20}_{D}$ = +13.1 (*c* 10, 1N HCl); MS (IS) *m/z* 228 (M+1); ^{1}H NMR ($CDCl_3$) δ 1.46 (s, 9H), 2.10 (s, 1H), 3.84 (d, 2H, *J* = 12.7 Hz), 5.77 (s, 1H), 6.86 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 28.3, 57.5, 65.2, 80.4, 156.7, 171.2.

2-_tert_-Butoxycarbonylamino-3-hydroxy-propionic acid methyl ester

Under an argon atmosphere, to a solution of carbamate (41.7g, 0.2 mol) in 350 mL of DMF at 0 °C, were added dry K_2CO_3 (30.9 g, 0.22 mol) and methyl iodide (25.3 mL, 0.4 mol). The mixture was stirred 20 h at rt and then concentrated under reduce pressure. The crude was hydrolyzed, extracted with AcOEt and washed with brine. The organic layer was dried over $MgSO_4$, filtered and concentrated to furnish the expected ester as a yellow oil in 95 % yield.

IR (NaCl) : 3381, 1748, 1732 cm^{-1}; $[\alpha]^{20}_D$ = +22.0 (*c* 2, $CHCl_3$); MS (IS) *m/z* 220 (M+1), 242 (M+Na); ^1H NMR ($CDCl_3$) δ 1.42 (s, 9H), 3.26 (s, 1H), 3.76 (s, 3H), 3.88 (dd, 1H, *J* = 11.3, 3.7), 3.97 (dd, 1H, *J* = 11.3, 3.5 Hz), 4.30-4.42 (m, 1H), 5.71 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 28.1, 52.4, 55.6, 63.1, 80.0, 155.7, 171.4.

2,2-Dimethyl-oxazolidine-3,4-dicarboxylic acid 3-*tert*-butyl ester 4-methyl ester

Under an argon atmosphere, to a solution of ester (40.3 g, 0.18 mol) in 800 mL of dry toluene, 2,2-dimethoxypropane (56.5 mL, 0.46 mol) and *p*-toluenesulfonic acid (0.7 g, 3.7 mmol) were added. After 30 min. of stirring, 250 mL of toluene were distillated. 2,2-dimethoxypropane (22.6 mL, 0.18 mol) and *p*-toluenesulfonic acid (0.35 g, 1.84 mmol) were added. After 30 min. of stirring, the same operation was renewed. The mixture was stirred 20 h at reflux and concentrated. The crude was dissolved in AcOEt and washed by a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted by AcOEt, and the organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the expected ester as an orange oil in 92 % yield.

IR (NaCl) :1759, 1711 cm^{-1}; $[\alpha]^{20}_D$ = –54.0 (*c* 1, $CHCl_3$); MS (IS) *m/z* 260 (M+1), 282 (M+Na); ^1H NMR (DMSO-d_6, 80°C) δ 1.40 (s, 9H), 1.46 and 1.56 (2s, 6H), 3.69 (s, 3H), 3.94 (dd, 1H, *J* = 9.1, 3.0 Hz), 4.17 (dd, 1H, *J* = 9.1, 7.1 Hz), 4.40 (dd, 1H, *J* = 7.1, 3.0 Hz); ^{13}C NMR (DMSO-d_6, 80°C) δ 27.7, 51.6, 58.6, 65.4, 79.4, 93.7, 151.1, 170.9.

4-Hydroxymethyl-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butylester 2

Under an argon atmosphere, to a suspension of $LiAlH_4$ (0.06 g, 1.54 mmol) in 5 mL of dry Et_2O, ester (0.4 g, 1.54 mmol) in 5 mL of dry Et_2O was added. The mixture was stirred 1h at reflux and allowed to reach room temperature. 3 mL of AcOEt were added and the mixture was hydrolyzed and filtered on a celite pad. The aqueous layer was extracted by AcOEt and the organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (eluent : petroleum ether/AcOEt, 3:1) to furnish the desired alcohol **2** as a yellow oil in 84 % yield.

IR (NaCl) : 3445, 1698 cm^{-1}; $[\alpha]^{20}_D$ = –23.6 (*c* 1.0, $CHCl_3$); MS (IS) m/z 232 (M+1), 254 (M+Na); ^1H NMR ($CDCl_3$) δ 1.49 (s, 9H), 1.55 (s, 6H), 3.60-4.22 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 24.1, 27.1, 28.3, 59.4, 64.8, 65.2, 81.0, 94.0, 153.9; Anal Calcd for $C_{11}H_{21}NO_4$: C, 57.12; H, 9.15; N, 6.06. Found C, 56.87; H, 9.20; N, 6.23.

General procedure for ethers 3 synthesis

Under an argon atmosphere, to a solution of phenol and diethylazodicarboxylate (1.2 eq.) in dry toluene, alcohol **2** (1 eq.) and triphenylphosphine (1.2 eq.) were added. The mixture was heated at 80 °C for 18h and allowed to reach room temperature. After evaporation under reduced pressure, the residue was purified by flash chromatography (eluent : petroleum ether/AcOEt, 9:1) to give the desired ether **3**.

4-(3-Acetyl-phenoxymethyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester 3a

Yield : 90 %; colourless oil; IR (NaCl) : 1693 cm^{-1}; $[\alpha]^{20}_D$ = –66.3 (*c* 1.0, $CHCl_3$); MS (IS) m/z 350 (M+1), 372 (M+Na); ^1H NMR (DMSO-d_6, 80 °C) δ 1.44 (s, 9H), 1.48 and 1.54 (2s, 6H), 2.56 (s, 3H), 3.91-4.24 (m, 5H), 7.24 (ddd, 1H, *J* = 8.1, 2.6, 1.0), 7.38-7.59 (m, 3H); ^{13}C NMR (DMSO-d_6, 80 °C) δ 27.1, 28.6, 56.2, 65.5, 67.8, 80.1, 114.5, 120.1, 121.5, 130.3, 139.2, 159.2, 197.9 ; Anal Calcd for $C_{19}H_{27}NO_5$: C, 35.31; H, 7.79; N, 4.01. Found C, 35.21; H, 7.82; N, 4.45.

4-(3-Methoxycarbonyl-phenoxymethyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester 3b

Yield : 70 %; yellow oil; IR (NaCl) : 1726, 1698 cm^{-1}; $[\alpha]^{20}_D$ = –60.1 (*c* 1.1, $CHCl_3$); MS (IS) m/z 388 (M+Na); ^{1}H NMR (DMSO-d_6, 80 °C) δ 1.43 (s, 9H), 1.47 and 1.53 (2s, 6H), 3.86 (s, 3H), 3.93-4.18 (m, 5H), 7.25 (ddd, 1H, *J* = 8.2, 2.4, 0.9 Hz), 7.43 (t, 1H, *J* = 8.2 Hz), 7.48-7.58 (m, 2H); ^{13}C NMR (DMSO-d_6, 80 °C) δ 26.3, 27.6, 51.3, 55.3, 64.5, 66.9, 79.2, 92.9, 114.8, 119.3, 121.4, 129.5, 132.0, 151.0, 158.1, 165.6; Anal Calcd for $C_{19}H_{27}NO_6$: C, 62.45; H, 7.45; N, 3.83. Found C, 65.01; H, 7.23; N, 3.93.

4-(3-Formyl-phenoxymethyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester 3c

Yield : 27 %; colourless oil; IR (NaCl) : 1704, 1694 cm^{-1}; $[\alpha]^{20}_D$ = –71.7 (*c* 1.0, $CHCl_3$); MS (IS) m/z 358 (M+Na); ^{1}H NMR ($CDCl_3$) δ 1.43 (s, 9H), 1.45-1.70 (m, 6H), 3.85-4.40 (m, 5H), 7.16-7.30 (m, 1H), 7.37-7.55 (m, 3H), 9.98 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 24.2, 27.5, 28.4, 56.0, 65.1, 66.3, 80.7, 93.6, 113.4, 121.7, 123.4, 130.0, 137.8, 152.3, 159.0, 192.1; Anal Calcd for $C_{18}H_{25}NO_5$: C, 64.46; H, 7.51; N, 4.18. Found C, 64.23; H, 7.48; N, 4.36.

General procedure for alcohols 4 synthesis

To a solution of ether **3** in MeOH at rt, *p*-toluenesulfonic acid (0.4 eq.) was added. The mixture was stirred for 18 h and hydrolyzed by a saturated aqueous solution of $NaHCO_3$ until pH 9. After removing MeOH under reduced pressure, the aqueous layer was extracted by AcOEt. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (eluent : petroleum ether/AcOEt, 6:4) to furnish alcohol **4**.

[2-(3-Acetyl-phenoxy)-1-hydroxymethyl-ethyl]-carbamic acid *tert*-butyl ester 4a

Yield : 81 %; colourless oil; IR (NaCl) : 3730-3070, 1682 cm^{-1}; $[\alpha]^{20}_D$ = –26.0 (*c* 1.0, $CHCl_3$); MS (IS) m/z 310.5 (M+1), 332.5 (M+Na); ^{1}H NMR (DMSO-d_6, 80 °C) δ 1.44 (s, 9H), 2.57 (s, 3H), 3.72-4.23 (m, 5H), 5.02 (s, 1H), 7.11 (dd, 1H, *J* = 8.0, 1.8 Hz), 7.36 (t, 1H, *J* = 8.0 Hz), 7.45-7.58 (m, 2H); ^{13}C NMR (DMSO-d_6, 80 °C) δ 26.7, 28.3, 51.3, 62.3, 67.2, 80.0, 113.4, 119.8, 121.5, 129.7, 138.4, 159.2, 158.6, 197.9; Anal Calcd for $C_{16}H_{23}NO_5$: C, 62.12; H, 7.49; N, 4.53. Found C, 61.93; H, 7.33; N, 4.68.

3-(2-*tert*-Butoxycarbonylamino-3-hydroxy-propoxy)-benzoic acid methyl ester 4b

Yield : 66 %; yellow oil; IR (NaCl) : 3672-3132, 1714, 1694 cm^{-1}; $[\alpha]^{20}_D$ = –23.0 (*c* 1.0, $CHCl_3$); MS (IS) m/z 326 (M+1), 348 (M+Na); ^{1}H NMR (DMSO-d_6, 80 °C) δ 1.40 (s, 9H), 3.48-3.54 (m, 2H), 3.76-3.87 (m, 1H), 3.86 (s, 3H), 3.99-4.15 (m, 2H), 4.55 (t, 1H, *J* = 5.5 Hz), 6.38 (brs, 1H), 7.22 (ddd, 1H, *J* = 8.2, 2.7, 0.9 Hz), 7.42 (t, 1H, *J* = 8.2 Hz), 7.47-7.56 (m, 2H); ^{13}C NMR (DMSO-d_6, 80 °C) δ 27.8, 51.6, 51.7, 60.2, 67.2, 77.5, 114.7, 119.4, 121.1, 129.4, 130.8, 154.8, 158.4, 165.7; Anal Calcd for $C_{16}H_{23}NO_6$: C, 59.07; H, 7.13; N, 4.30. Found C, 59.23; H, 7.02; N, 4.45.

[2-(3-Formyl-phenoxy)-1-hydroxymethyl-ethyl]-carbamic acid tert-butyl ester 4c

Yield : 38 %; colourless oil; IR (NaCl) : 3708-3084, 1705, 1694 cm^{-1}; $[\alpha]^{20}_D$ = –27.3 (*c* 0.6, $CHCl_3$); MS (IS) m/z 296 (M+1), 318 (M+Na); ^{1}H NMR ($CDCl_3$) δ 1.46 (s, 9H), 2.24 (brs, 1H), 3.75-4.27 (m, 5H), 5.14 (brs, 1H), 7.16-7.23 (m, 1H), 7.38-7.58 (m, 3H), 9.97 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 28.3, 51.3, 62.4, 67.3, 80.1, 113.2, 121.6, 123.8, 130.2, 137.8, 155.9, 159.0, 192.0; Anal Calcd for $C_{15}H_{21}NO_5$: C, 61.60; H, 7.17; N, 4.74. Found C, 62.03; H, 7.23; N, 4.93.

General procedure for compounds 5a-c synthesis

Under an argon atmosphere, alcohol **4** was dissolved in a mixture of toluene and acetonitrile (2/1). The mixture was cooled to 0 °C, and triphenylphosphine (2 eq.), imidazole (3 eq.) and iodine (2 eq.) were added. The mixture was allowed to room temperature and stirred during 4 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/AcOEt, 8:2) to give **5**.

[2-(3-Acetyl-phenoxy)-1-iodomethyl-ethyl]-carbamic acid *tert*-butyl ester 5a

Yield : 79 %; yellow solid; IR (NaCl) : 3378, 1683 cm^{-1}; $[\alpha]^{20}_D$ = –46.6 (*c* 1.0, $CHCl_3$); mp = 101 °C; MS (IS) m/z 420 (M+1), 442 (M+Na); ^{1}H NMR ($CDCl_3$) δ 1.47 (s, 9H), 2.60 (s, 3H), 3.40-3.60 (m, 2H), 3.90-4.35 (m, 3H), 5.02 (s, 1H), 7.13 (ddd, 1H, *J* = 7.9, 2.5, 0.9 Hz), 7.39 (t, 1H, *J* = 7.9 Hz), 7.47-7.61 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 7.6, 26.7, 28.3, 50.0, 68.8, 80.3, 113.1, 119.8, 121.8, 129.7, 138.4, 154.8, 158.6, 197.9; Anal Calcd for $C_{16}H_{22}INO_4$: C, 45.84; H, 5.29; N, 3.34. Found C, 45.23; H, 5.32; N, 3.23.

3-(2-*tert*-Butoxycarbonylamino-3-iodo-propoxy)-benzoic acid methyl ester 5b

Yield : 73 %; white solid; IR (NaCl) : 3494-3138, 1731, 1694 cm^{-1}; $[\alpha]^{20}_D$ = –42.0 (*c* 1.0, $CHCl_3$); mp = 97 °C; MS (IS) m/z 436 (M+1), 458 (M+Na); ^{1}H NMR (DMSO-d_6, 80 °C) δ 1.40 (s, 9H), 3.32 (dd, 1H, *J* = 10.0, 7.3 Hz), 3.45 (dd, 1H, *J* = 10.0, 5.2 Hz), 3.84 (s, 3H), 3.86-4.18 (m, 3H,), 6.83 (brs, 1H), 7.39-7.57 (m, 4H); ^{13}C NMR (DMSO-d_6, 80 °C) δ 7.6, 24.1, 51.4, 52.4, 68.8, 80.3, 115.6, 120.3, 122.3, 130.3, 131.7, 158.9, 159.1, 165.7; Anal Calcd for $C_{16}H_{22}INO_5$: C, 44.15; H, 5.09; N, 3.22. Found C, 44.02; H, 5.11; N, 3.33.

[2-(3-Formyl-phenoxy)-1-iodomethyl-ethyl]-carbamic acid *tert*-butyl ester 5c

Yield : 37 %; yellow oil; IR (NaCl) : 3371, 1994, 1682 cm^{-1}; $[\alpha]^{20}_D$ = –38.8 (*c* 1.2, $CHCl_3$); MS (IS) m/z 406 (M+1), 428 (M+Na); ^{1}H NMR ($CDCl_3$) δ 1.46 (s, 9H), 3.40-3.60 (m, 2H), 3.90-4.35 (m, 3H), 5.00 (brs, 1H), 7.15-7.23 (m, 1H), 7.37-7.55 (m, 3H), 9.98 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 7.6, 28.3, 49.8, 68.6, 80.3, 113.1, 121.7, 124.1, 130.2, 137.8, 154.8, 158.7, 192.0; Anal Calcd for $C_{15}H_{20}INO_4$: C, 44.46; H,4.97; N, 3.46. Found C, 44.38; H, 4.89; N, 3.51.

[2-(3-Acetyl-phenoxy)-1-chloromethyl-ethyl]-carbamic acid *tert*-butyl ester 5d

Under an argon atmosphere, to a solution of alcohol **4** (0.5 g, 1.6 mmol) in 10 mL of acetonitrile, triphenylphosphine (0.85 g, 3.2 mmol) and carbone tetrachloride (0.31 mL, 3.2 mmol) were added at rt. The mixture was stirred for 18 h and evaporated. Purification was carried out by flash chromatography (eluent : petroleum ether/AcOEt 9:1) to furnish compound **5d** as a white solid in 45 % yield.

IR (KBr) : 3474-3224, 1687 cm^{-1}; $[\alpha]^{20}_D$ = –38.8 (*c* 1.0, $CHCl_3$); mp = 99 °C; MS (IS) m/z 350 (M+Na, ^{35}Cl), 352 (M+Na, ^{37}Cl); ^{1}H NMR (DMSO-d_6, 80 °C) δ 1.41 (s, 9H), 2.56 (s, 3H), 3.08 (brs, 1H), 3.68-3.83 (m, 2H), 4.04-4.15 (m, 3H), 7.23 (ddd, 1H, *J* = 7.9, 2.4, 0.9 Hz), 7.44 (t, 1H, *J* = 7.9 Hz), 7.46-7.59 (m, 2H); ^{13}C NMR (DMSO-d_6, 80 °C) δ 26.2, 27.8, 43.9, 51.3, 67.3, 78.0, 113.5, 119.4, 120.7, 129.4, 138.2, 154.7, 158.1, 197.0; Anal Calcd for $C_{16}H_{22}ClNO_4$: C, 58.62; H, 6.76; N, 4.27. Found C, 58.51; H, 6.68; N, 4.31.

General procedure for xanthates 5e-f synthesis

Under an argon atmosphere, to a solution of iodo derivative **5a** or **5b** in acetonitrile, ethylxanthic acid potassium salt (1.1 eq.) was added at rt. The mixture was stirred for 18h and

concentrated under reduced pressure. The residue was hydrolyzed and extracted with dichloromethane. The organic layer was dried over $MgSO_4$, filtered, concentrated under reduced pressure and purified by flash chromatography (eluent petroleum ether/AcOEt, 9:1) to give xantate **5e** or **5f**.

Dithiocarbonic acid S-[3-(3-acetyl-phenoxy)-2-*tert*-butoxycarbonylamino-propyl] ester O-ethyl ester 5e

Yield : 98 %, yellow solid; IR (NaCl) : 3566-3196, 1714, 1647 cm^{-1}; $[\alpha]^{20}_D$ = –32.2 (*c* 1.0, $CHCl_3$); MS (IS) m/z 414 (M+1), 436 (M+Na); ^{1}H NMR ($CDCl_3$) δ 1.42 (t, 3H, *J* = 7.0 Hz), 1.45 (s, 9H), 2.60 (s, 3H), 3.45-3.54 (m, 2H), 4.08 (dd, 1H, *J* = 9.4, 4.6 Hz), 4.20 (dd, 1H, *J* = 9.4, 3.3 Hz), 4.25-4.38 (m, 1H), 4.64 (q, 2H, *J* = 7.0 Hz), 5.03 (brs, 1H), 7.11 (ddd, 1H, *J* = 7.9, 2.4, 0.9 Hz), 7.38 (t, 1H, *J* = 7.9 Hz), 7.48 (brs, 1H), 7.56 (d, 2H, *J* = 7.9 Hz); ^{13}C NMR ($CDCl_3$) δ 13.9, 26.9, 28.4, 37.3, 59.5, 68.7, 70.6, 80.1, 113.5, 119.9, 121.7, 129.8, 138.7, 155.2, 158.7, 197.9; Anal Calcd for $C_{19}H_{27}NO_5S_2$: C, 55.18; H, 6.58; N, 3.39. Found C, 54.98; H, 6.56; N, 3.45.

3-(2-*tert*-Butoxycarbonylamino-3-ethoxythiocarbonylsulfanyl-propoxy)-benzoic acid methyl ester 5f

Yield : 88 %; colourless oil; IR (NaCl) : 3480-3182, 1727 cm^{-1}; $[\alpha]^{20}_D$ = –26.4 (*c* 1.0, $CHCl_3$); MS (IS) m/z 430 (M+1), 452 (M+Na); ^{1}H NMR ($CDCl_3$) δ 1.42 (t, 3H, *J* = 6.9), 1.45 (s, 9H), 3.49-3.55 (m, 2H), 3.91 (s, 3H), 4.07 (dd, 1H, *J* = 9.4, 4.4), 4.19 (dd, 1H, *J* = 9.4, 3.4), 4.25-4.37 (m, 1H), 4.64 (q, 2H, *J* = 6.9), 5.08 (brs, 1H), 7.11 (ddd, 1H, *J* = 8.1, 2.5, 0.9), 7.35 (t, 1H, *J* = 8.1), 7.55 (brs, 1H), 7.66 (d, 1H, *J* = 8.1); ^{13}C NMR ($CDCl_3$) δ 13.8, 28.4, 37.3, 49.4, 52.3, 68.8, 70.5, 80.0, 115.0, 119.7, 122.7, 129.6, 131.6, 155.2, 158.4, 166.8, 214.0; Anal Calcd for $C_{19}H_{27}NO_6S_2$: C, 53.13; H, 6.34; N, 3.26. Found C, 53.22; H, 6.29; N, 3.45.

General procedure for radical reaction starting from xantate derivatives

Under an argon atmosphere, lauroyl peroxide (1.5 eq.) was added portion-wise to a degassed solution of xanthate **5** in chlorobenzene at reflux over 3h (0.25 eq./0.5h). The reaction mixture was cooled to room temperature and the solvent removed under reduced pressure. The crude was purified by flash chromatography (eluent : petroleum ether/AcOEt, 85:15 to 7:3) to furnish 3-aminochromans **6** (69 %), **7** (20 %) and reduced compound **8** (< 5%)

(3*S*)-(5-Acetyl-chroman-3-yl)-carbamic acid *tert*-butyl ester 6

Colourless oil; IR (KBr) : 3370, 1685 cm^{-1}; $[\alpha]^{20}_D$ = –54.5 (*c* 1.0, $CHCl_3$); mp = 78 °C; MS (IS) m/z 292 (M+1), 314 (M+Na); ^{1}H NMR ($CDCl_3$) δ 1.44 (s, 9H), 2.57 (s, 3H), 2.97 (dd, 1H, *J* = 17.9, 5.0 Hz), 3.32 (dd, 1H, *J* = 17.9, 5.6 Hz), 3.92-4.25 (m, 3H), 4.72 (s, 1H), 7.02 (dd, 1H, *J* = 8.0, 1.2 Hz), 7.21 (t, 1H, *J* = 8.0 Hz), 7.36 (dd, 1H, *J* = 8.0, 1.2 Hz); ^{13}C NMR ($CDCl_3$) δ 28.3, 29.5, 30.6, 43.2, 68.0, 79.9, 119.8, 121.0, 122.8, 127.1, 138.5, 154.7, 155.1, 200.9; Anal Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.27; N, 4.81. Found C, 66.03; H, 7.33; N, 4.98.

(3*R*)-(7-Acetyl-chroman-3-yl)-carbamic acid *tert*-butyl ester 7

White solid; IR (KBr) : 3352, 1685 cm^{-1}; $[\alpha]^{20}_D$ = –55.6 (*c* 1.0, $CHCl_3$); mp = 105 °C; MS (IS) m/z 292 (M+1), 314 (M+Na); ^{1}H NMR ($CDCl_3$) δ 1.43 (s, 9H), 2.54 (s, 3H), 2.80 (dd, 1H, *J* = 17.3, 3.9 Hz), 3.12 (dd, 1H, *J* = 17.3, 3.9 Hz), 4.05-4.25 (m, 3H), 5.07 (brs, 1H), 7.12 (d, 1H, *J* = 7.9 Hz), 7.41 (d, 1H, *J* = 1.6 Hz), 7.48 (dd, 1H, *J* = 7.9, 1.6 Hz); ^{13}C NMR ($CDCl_3$) δ 28.4, 29.7, 31.5, 43.2, 68.7, 79.9, 117.0, 120.9, 125.2, 130.8, 155.3, 154.1, 197.7; Anal Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.27; N, 4.81. Found C, 65.68; H, 7.45; N, 4.97.

(2*S*)-[2-(3-Acetyl-phenoxy)-1-methyl-ethyl]-carbamic acid *tert*-butyl ester 8
Colourless oil; IR (NaCl) : 3353, 1683 cm^{-1}; $[\alpha]^{20}_D$ = –42.0 (*c* 1.0, $CHCl_3$); MS (IS) m/z 294 (M+1), 316 (M+Na); ^{1}H NMR ($CDCl_3$) δ 1.30 (d, 3H, *J* = 6.6 Hz,), 1.45 (s, 9H), 3.00 (s, 3H), 3.93-4.18 (m, 3H), 4.76 (brs, 1H), 7.16 (ddd, 1H, *J* = 8.2, 2.5, 0.9 Hz), 7.37 (t, 1H, *J* = 8.2 Hz), 7.47-7.58 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 17.7, 26.5, 28.2, 45.6, 70.9, 79.3, 113.1, 119.6, 121.1, 129.4, 138.3, 155.0, 158.7, 197.7; Anal Calcd for $C_{16}H_{23}NO_4$: C, 66.51; H, 7.90; N, 4.77. Found C, 66.89; H, 7.84; N, 4.89.

General procedure for 3-aminochromans synthesis
Under an argon atmosphere, trifluoroacetic acid (12 eq.) dissolved in CH_2Cl_2 was transferred to a cold solution of protected amine **6** or **9** in CH_2Cl_2. The mixture was allowed to warm to room temperature, stirred for 5 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 $MgSO_4$, filtered, concentrated and purified by flash chromatography (eluent : CH_2Cl_2/MeOH, 9:1) to give desired amine **(S)-12** or **1c**.

(3*S*)-1-(3-Amino-chroman-5-yl)-ethanone (*S*)-12
Yield : 76 %, colourless oil; IR (NaCl) : 3550-3125, 1681 cm^{-1}; $[\alpha]^{20}_D$ = +39.8 (*c* 1.0, $CHCl_3$); MS (IS) m/z 192 (M+1); ^{1}H NMR ($CDCl_3$) δ 1.49 (brs, 2H), 2.56 (s, 3H), 2.77-2.88 (m, 1H), 3.26-3.38 (m, 2H), 3.83 (dd, 1H, *J* = 10.3, 6.7 Hz), 4.12-4.18 (m, 1H), 7.00 (dd, 1H, *J* = 7.9, 1.2 Hz), 7.19 (t, 1H, *J* = 7.9 Hz), 7.35 (dd, 1H, *J* = 7.9, 1.2 Hz); ^{13}C NMR ($CDCl_3$) δ 29.7, 33.9, 44.0, 71.0, 120.8, 122.6, 126.9, 138.6, 154.8, 201.3; Anal Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found C, 69.25; H, 6.91; N, 7.44.

(3*S*)-3-Amino-chroman-5-carboxylic acid methyl ester 1c
Yield : 88 %, colourless oil; IR (NaCl) : 3550-3025, 1719 cm^{-1}; $[\alpha]^{20}_D$ = +23.0 (*c* 1.0, $CHCl_3$); MS (IS) m/z 208 (M+1); ^{1}H NMR ($CDCl_3$) δ 2.92 (dd, 1H, *J* = 19.1 Hz), 3.09 (brs, 2H), 3.35-3.43 (m, 2H), 3.89 (s, 3H), 3.85-3.91 (m, 1H), 4.12-4.17 (m, 1H), 7.02 (d, 1H, *J* = 8.0 Hz), 7.16 (t, 1H, *J* = 8.0 Hz), 7.53 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$) δ 36.9, 50.9, 51.8, 72.4, 110.8, 121.2, 124.5, 127.9, 134.8, 134.8, 168.9; Anal Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found C, 63.71; H, 6.27; N, 6.89.