Synthesis of 3-Dialkylaminochromans via Thallium(III)-Induced Cyclization of Allyl Aryl Ethers

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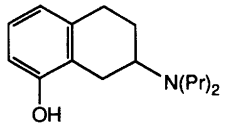
The sulfur-containing 3-alkylaminochromans, 5-methoxy-3-[*N*-(2-methylthioethyl)-propylamino]chroman (**15**), 5-hydroxy-3-[*N*-(2-methylthioethyl)propylamino]chroman (**5**) and 5-methoxy-8-methylthio-3-(dipropylamino)chroman (**6**), have been prepared from 8-bromo-5-methoxy-3-chromanol (**11**). This precursor was synthesized from 3-allyloxy-4-bromoanisole (**8**), by a thallium(III)-mediated ring-closure reaction. Compound **11** also served as starting material for the synthesis of 8-bromo-3-(dipropylamino)-5-methoxychroman (**7**).

The finding that 2-(dipropylamino)-8-hydroxytetralin (8-OH-DPAT) (**1**) and 2-(dipropylamino)-8-methoxytetralin (**2**) are potent and selective central 5-HT_{1A} (5-hydroxytryptamine or serotonin) receptor agonists[1,2] has initiated further interest in the synthesis and pharmacological evaluation of structural analogs. Serotonin is thought to be involved in a variety of functions in the CNS, including blood pressure regulation, depression and anxiety. 5-HT_{1A} receptor agonists could have a great clinical potential for the treatment of several dysfunctions in these areas.

While this work was in progress, the preparation and pharmacological evaluation of the isosteric chroman derivatives **3** and **4** were reported.[3–5] These chroman analogs of **1** and **2** are selective 5-HT_{1A} agonists with high potency. In compounds related to **1** and **2**, the introduction of a sulfur atom into the sidechain[6] or into the ring system[7] results in potent compounds with improved bioavailability. Based on these reports we decided to synthesize compounds **5** and **6**, sulfur analogs of **3** and **4**, respectively, and to evaluate them pharmacologically. The bromo derivative **7** was also included in the study, to be compared with both **6** and the debrominated methoxy compound **4**.

We desired 3-chromanones as intermediates. While there is extensive literature on 4-chromanones and their derivatives, considerably less work has been devoted to 3-chromanones.[8a–j] We chose the thallium(III)-mediated oxidative cyclization of easily accessible allyl aryl ethers to furnish 3-chromanols in one step, reported by Porter *et al.*,[9] despite the fact that the yields were only low to moderate. This approach has now been applied to our systems, to furnish 3-chromanones via subsequent oxidation.

We selected 3-allyloxy-4-bromoanisole (**8**) as the starting material. The bromine atom serves as a blocking group in the electrophilic ring closure reaction and the bromo function could, in principle, act as a handle for the introduction of a series of functionalities in the aromatic ring via metallation, including a methylthio group, as well as a hydroxy group. The latter is of potential interest with regard to metabolic studies.[10]



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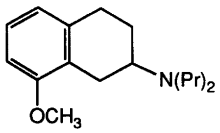

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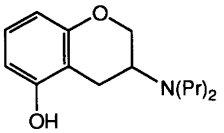
In an initial experiment, 3-allyloxyanisole was treated with thallium(III) sulfate in 1–1.25 M sulfuric acid at 55 °C for 18 h, to yield a mixture of **9** and its isomer **10** in low yield (Scheme 1). By starting from **8** (Scheme 2), we were able to isolate 8-bromo-5-methoxy-3-chromanol (**11**) in 24 % yield, in addition to a considerable amount of tar. The preparation of **12** by oxidation with chromium trioxide–pyridine in the presence of acetic anhydride[11] occurred smoothly in 81 % yield. Reductive amination of **12** with dipropylamine and sodium cyanoborohydride afforded the target compound, 8-bromo-3-(dipropylamino)-5-methoxychroman (**7**), in 75 % yield. Reductive amination/debromination of **12** was achieved by hydrogenation with Pd/C as catalyst to provide **4**. In order to introduce the methylthio group into the aromatic ring, the bromo compound **7** was treated with butyllithium followed by dimethyl disulfide to give **6**.



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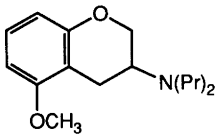

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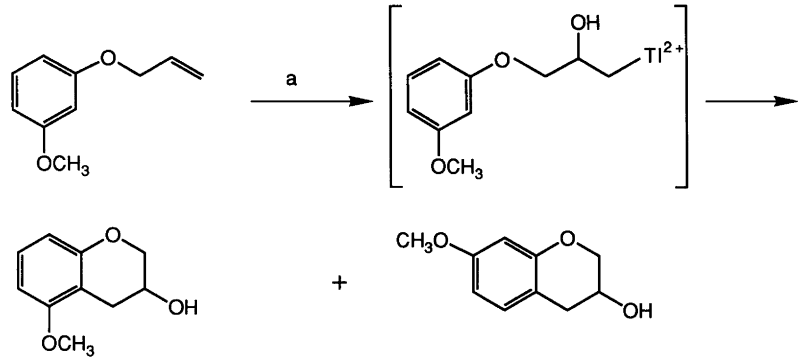
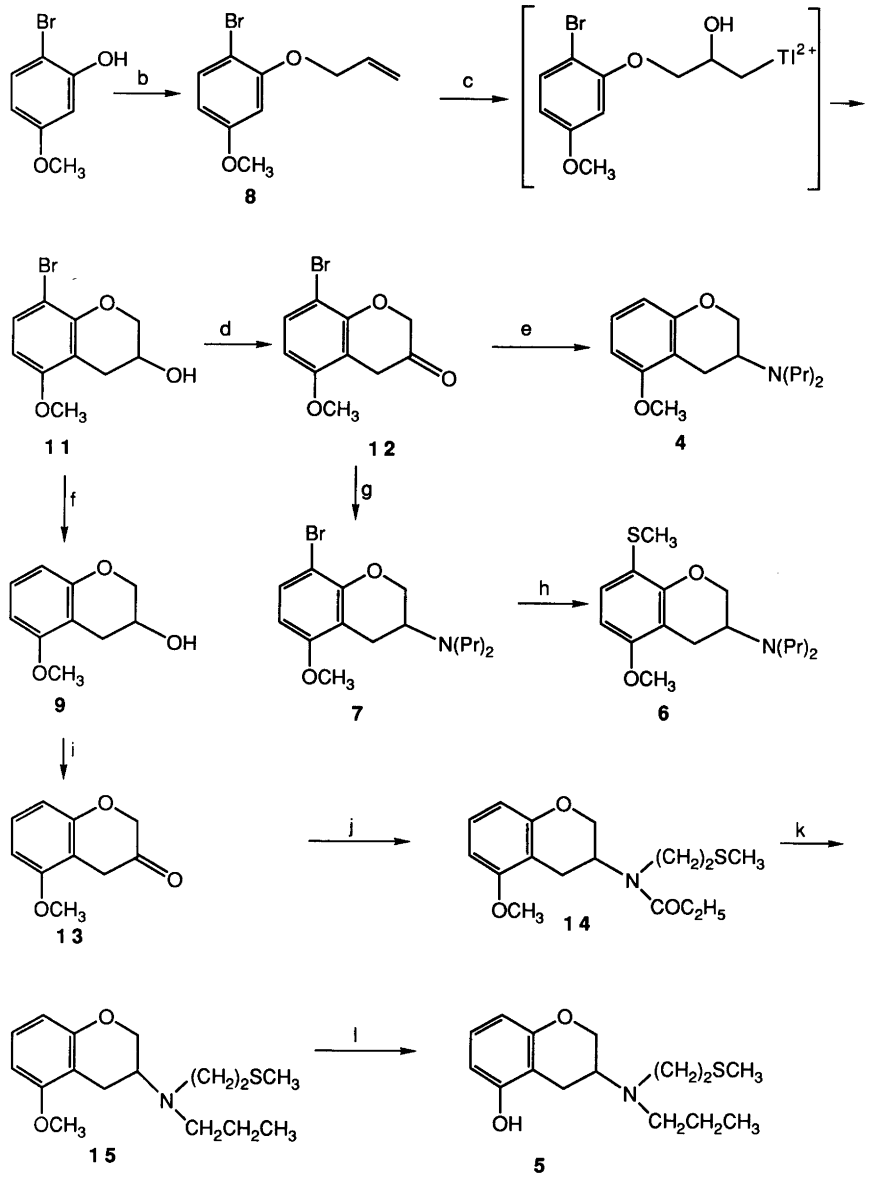


Scheme 1.



Scheme 2. Reagents: a, Tl_2O_3/H_2SO_4, 8 % **9** and 22 % **10**; b, allyl bromide, K_2CO_3, 93 %; c, Tl_2O_3/H_2SO_4, 24 %; d, pyridine/CrO_3, acetic anhydride, 81 %; e, dipropylamine, *p*-toluenesulfonic acid, H_2, Pd/C, 77 %; f, H_2, Pd/C, 90 %; g, dipropylamine, *p*-toluenesulfonic acid, $NaBH_3CN$, 75 %; h, BuLi $(CH_3S)_2$, 67 %; i, pyridine/CrO_3, acetic anhydride, 62 %; j, ascorbic acid, acetic acid, 2-methylthioethylamine, $NaBH_3CN$, propionyl chloride, $(Et)_3N$, 64 %; k, $LiAlH_4$, 99 %; l, HBr (48 %), 58 %.

For the preparation of compounds possessing sulfur in the amine alkyl sidechain, we used 5-methoxy-3-chromanone (**13**) as the starting material, obtained via debromination of **11** by catalytic hydrogenation followed by oxidation with chromium trioxide–pyridine. The introduction of the methylthioethyl sidechain was accomplished by reductive amination in acetic acid with cystamine, compound **13** and sodium cyanoborohydride, in the presence of traces of ascorbic acid. In the absence of ascorbic acid the yield of **14** was considerably lower. The secondary amine formed was treated with propionyl chloride at room temperature to furnish **14**. Reduction of **14** with lithium aluminium hydride provided 5-methoxy-3-[*N*-(2-methylthioethyl)propylamino]chroman (**15**). Cleavage of the aromatic methyl ether bond in **15** to give **5** was performed with 48 % aqueous HBr at 120 °C.

Compounds **5–7** were tested in an *in vivo* pharmacological model[12] for their effects on central monoamine receptors. Compound **5**, with a sulfur atom in the sidechain, proved to be an agonist, with effects at central 5-HT_{1A} receptors, but with somewhat decreased potency compared with **1** and **3**. The bioavailability of **5** was not improved, compared with **1**.

The most interesting pharmacological finding was the effect of the substituents in position 8. Both compounds **6** and **7** showed a different pharmacological profile than that of **2** and **4**. Unexpectedly, compound **7** is a potent dopamine (DA) receptor agonist with only weak serotonergic effects. Compound **7** also exhibited good bioavailability. Compound **6** showed mixed dopaminergic and serotonergic effects.

The method reported here gives access to a variety of substituted 3-aminochromans possessing interesting properties for further pharmacological evaluation.

Experimental section

Melting points (uncorrected) were determined with a melting point microscope (Reichert Termovar). ^{1}H NMR spectra were recorded with Bruker 500 MHz and Varian EM-390 instruments (Me_3Si). GLC was performed with a Hewlett-Packard 5830A instrument with a flame-ionization detector. A fused silica column (11 m, 0.22 mm i.d.) coated with cross-linked SE-54 (film thickness 0.3 μm, gas He, gas velocity 40 cm s^{-1} was used throughout. GLC/MS spectra were recorded on an HP 5970 mass selective detector working at 70 eV and interfaced with an HP 5700A gas chromatograph with a fused silica column (see above). High resolution MS spectra were recorded with a ZAB-HF mass spectrometer (VG-analytical) working in the EI mode (60 eV) or with positive FAB-ionization with direct inlet. The elemental analyses for new crystalline substances (C, H, N) were to within 0.4 % of the theoretical values. For purity tests, TLC was performed on fluorescent silica gel plates developed in at least two different systems. For all the compounds, only one spot (visualized by UV light and I_2 vapour) was obtained.

5-Methoxy-3-chromanol (**9**)[13] and *7-methoxy-3-chromanol* (**10**). To a mixture of H_2SO_4 (50 ml) and water (58 ml) at room temperature, was added Tl_2O_3 (20.4 g, 44.7 mmol). After 30 min of stirring, more water (350 ml) was added. The temperature was raised to 60 °C, 3-allyloxyanisole (14.6 g, 90.0 mmol) was added and the mixture was then stirred for 16 h. Another portion of Tl_2O_3 (10.2 g, 22.3 mmol), that had been stirred for 30 min at 20 °C in H_2SO_4 (25 ml) and water (30 ml), was finally added. Stirring was continued for an additional 12 h at 60 °C. The reaction was cooled and extracted with chloroform and the organic layer was washed with water and dried ($MgSO_4$). The solvent was evaporated and the crude product was chromatographed (SiO_2) with ether as the eluant. Compound **10** was eluted first as a pure product according to GLC analyses. The fractions enriched with **9** were further chromatographed (SiO_2) with light petroleum–ether (1:1) as the eluant, affording pure **9** and **10**. The yields of **9** and **10** were 1.16 g (8 %) and 3.19 g (22 %), respectively. An analytical sample of **10** was obtained after recrystallization from a mixture of light petroleum and ether.

The use of thallium(III) nitrate, chloride or tetrafluoroborate to perform the ring-closure reaction did not improve the yields, and the isomer distribution was not altered.

5-Methoxy-3-chromanol (**9**).[13] M.p. 96–98 °C. ^{1}H NMR ($CDCl_3$): δ 2.1–2.4 (s, br, 1 H), 2.7–2.8 (dd, 1 H), 2.8–2.9 (dd, 1 H), 3.8 (s, 3 H), 4.0–4.1 (s, br, 2 H), 4.2–4.3 (m, 1 H), 6.4 (d, 1 H), 6.5 (d, 1 H), 7.0–7.1 (t, 1 H). ^{13}C NMR: δ 28.40, 55.44, 62.98, 69.30, 102.53, 108.58, 109.31, 127.26, 154.60, 158.49. MS: 180 (93, *M*), 136 (100), 106 (44), 137 (23), 108 (22).

Compound **9** was alternatively synthesized from **11** (400 mg, 1.54 mmol) in 90% yield by catalytic hydrogenation (Pd/C, 355 kPa) in ethanol/5 M NaOH (1000:1) for 16 h.

7-Methoxy-3-chromanol (**10**). M.p. 62–64 °C. ^{1}H NMR ($CDCl_3$): δ 1.95–2.0 (s, br, 1 H), 2.65–2.75 (dd, 1 H), 2.25–3.10 (dd, 1 H), 3.7 (s, 3 H), 4.0–4.1 (m, 2 H), 4.15–4.25 (m, 1 H), 6.4 (d, 1 H), 6.5 (dd, 1 H), 6.95 (d, 1 H). ^{13}C NMR: δ 32.94, 51.31, 63.40, 69.75, 101.52, 108.10, 111.23, 130.86, 154.49, 159.34. MS: 180 (78, *M*), 137 (79), 136 (100), 108 (61), 78 (28). Anal. $C_{10}H_{12}O_3$: C, H.

3-Allyloxy-4-bromoanisole (**8**). To a solution of 4-bromo-3-hydroxyanisole[14] (14.49 g, 59.3 mmol) in CH_3CN (200 ml), were added dry potassium carbonate (20 g) and allyl bromide (8.0 ml, 92.4 mmol). The reaction mixture was stirred and refluxed for 1 h and then cooled to room temperature, filtered and evaporated. The residue was dissolved in ether and extracted with water. The organic layer was separated and dried (Na_2SO_4). Evaporation of the solvent afforded 16.0 g (93 %) of **8** as an oil. MS: 244/242 (40/40, *M*), 163 (100), 149 (97), 135 (62). High resolution MS with EI ionization showed M^+ at 241.994 (Calc. 241.994). ^{1}H NMR ($CDCl_3$): δ 3.8 (s, 3 H), 4.6–4.7 (m, 2 H), 5.3–5.5 (m,

2 H), 6.0–6.2 (m, 1 H), 6.4 (dd, 1 H), 6.5 (d, 1 H), 7.4 (d, 1 H). ^{13}C NMR: δ 55.87, 69.38, 101.71, 103.38, 106.59, 118.12, 132.84, 133.51, 155.90, 160.36.

8-Bromo-5-methoxy-3-chromanol (**11**). To a mixture of H_2SO_4 (6.9 ml) and water (6.1 ml) at room temperature, was added Tl_2O_3 (2.38 g, 5.22 mmol). The mixture was stirred for 30 min and water (37 ml) was added. The temperature was then raised to 60 °C and **8** (2.16 g, 8.89 mmol) was added. The mixture was stirred at 60 °C for 4.5 h. Another portion of Tl_2O_3 (1.0 g, 2.19 mmol), that had been stirred for 30 min at 20 °C in H_2SO_4 (2.6 ml) and water (3 ml), was finally added. Stirring of the reaction mixture was continued for an additional 17 h at 60 °C. After being cooled the mixture was extracted with $CHCl_3$. The organic layer was washed with water, dried ($MgSO_4$) and evaporated. The crude product was chromatographed (SiO_2) with ether as the eluant and 552 mg (24 %) of **11** was isolated. An analytical sample of **11** was obtained after recrystallization from a mixture of light petroleum and ether, m.p. 115–117 °C.

^{1}H NMR ($CDCl_3$): δ 2.0–2.1 (s, br, 1 H), 2.7–2.8 (dd, 1 H), 2.9–3.0 (dd, 1 H), 4.1 (s, 3 H), 4.8–5.0 (m, 3 H), 6.4 (d, 1 H), 7.3 (d, 1 H). ^{13}C NMR: δ 28.65, 55.64, 62.64, 70.08, 101.85, 103.79, 110.34, 130.49, 150.75, 157.70. MS: 260/258 (100/100, *M*), 216 (93), 214 (91), 185 (50). Anal. $C_{10}H_{11}BrO_3$: C, H.

8-Bromo-5-methoxy-3-chromanone (**12**). Dry pyridine (0.7 ml, 8.7 mmol) in CH_2Cl_2 (120 ml, dried over P_2O_5) was treated with CrO_3 (435 mg, 4.35 mmol). The mixture was stirred for 15 min and a solution of **11** (293 mg, 1.13 mmol) in dry CH_2Cl_2 (10 ml) was added immediately followed by acetic anhydride (0.41 ml, 4.35 mmol). Stirring was continued for an additional 10 min. The mixture was filtered through a short silica column (13 g, SiO_2) under vacuum. Fast filtration was essential to avoid decomposition. The column was washed with CH_2Cl_2 and evaporation of the solvent gave 237 mg (81 %) of **12**. An analytical sample of **12** was obtained after recrystallization from a mixture of light petroleum and ether, m.p. 97–100 °C. Attempts to use Moffat oxidation,[15] pyridinium chlorochromate oxidation[16] or silica/chromium trioxide oxidation[17] were unsuccessful.

^{1}H NMR ($CDCl_3$): δ 3.55 (s, 2 H), 3.80 (s, 3 H), 4.45 (s, 2 H), 6.5 (d, 1 H), 7.4 (d, 1 H). MS: 258/256 (64/57, *M*), 134 (100), 76 (11), 50 (11). Anal. $C_{10}H_9BrO_3$: C, H.

8-Bromo-3-(dipropylamino)-5-methoxychroman (**7**). To a solution of **12** (550 mg, 2.14 mmol) in benzene (40 ml), dipropylamine (1.8 ml, 13.2 mmol) and *p*-toluenesulfonic acid monohydrate (41 mg, 0.32 mmol) were added. The solution was refluxed for 5 h with a Dean–Stark apparatus under a nitrogen atmosphere. After the reaction had been cooled to room temperature, a solution of $NaBH_3CN$ (2.0 g, 32 mmol) in methanol (50 ml) was added and stirring was continued overnight. Water (50 ml) and 2 M NaOH (5 ml) were added. The solution was extracted with CH_2Cl_2. The organic layer was separated, washed with water and dried (Na_2SO_4). The solvent was evaporated and the residue chromatographed (SiO_2) with light petroleum ether (3:1) as the eluant, yielding 550 mg (75 %) of **7** as an oil.

^{1}H NMR ($CDCl_3$): δ 0.6–0.9 (t, 6 H), 1.1–1.6 (m, 4 H), 2.5–3.3 (m, 8 H), 3.75 (s, 3 H), 4.2–4.5 (m, 1 H), 6.25–6.35 (d, 1 H), 7.2–7.4 (d, 1 H). MS: 343/341 (10/10, *M*), 314 (91), 312 (100), 241 (80).

The amine was converted into its hydrochloride with HCl-saturated ethanol. Evaporation and recrystallization from a mixture of ethanol and ether gave **7** · HCl, m.p. 180–182 °C. Anal. $C_{16}H_{25}BrNO_2Cl$: C, H, N.

3-(Dipropylamino)-5-methoxychroman (**4**).[3] To a solution of **12** (125 mg, 0.49 mmol) in benzene (20 ml), dipropylamine (0.5 ml, 3.7 mmol) and *p*-toluenesulfonic acid monohydrate (10 mg, 0.08 mmol) were added. The solution was refluxed for 5 h in a Dean–Stark apparatus under a nitrogen atmosphere. The reaction mixture was transferred to a Parr flask, absolute EtOH was added (50 ml) and the pH was adjusted to 11 with 2 M NaOH. The product was hydrogenated overnight with Pd/C as the catalyst at 355 kPa. The catalyst was filtered off and the solvent was evaporated. The residual oil was dissolved in CH_2Cl_2 and washed with 5 % aqueous Na_2CO_3. The phases were separated and the organic layer was dried (Na_2SO_4) to yield 99 mg (77 %) of **4** as an oil with physical data in accordance with those reported in the literature.[3]

3-(Dipropylamino)-5-methoxy-8-methylthiochroman (**6**). A solution of **7** (174 mg, 0.51 mmol) in dry ether was treated with 1.6 M butyllithium in hexane (0.6 ml, 0.96 mmol) at 0 °C for 30 min under a dry argon atmosphere. Dry, distilled dimethyl disulfide was added (0.2 ml, 2.3 mmol) and the reaction mixture was stirred for 2 h at 0 °C. The mixture was allowed to reach room temperature, water was added and the phases were separated. The organic layer was washed with water, separated and dried (Na_2SO_4). The solvent was evaporated and the remaining oil chromatographed (SiO_2) with light petroleum ether (3:1) as the eluant, yielding 105 mg (67 %) of **6** as an oil. ^{1}H NMR ($CDCl_3$): δ 0.7–1.1 (t, 6 H), 1.2–1.7 (m, 4 H), 2.4 (s, 3 H), 2.45–3.40 (m, 8 H), 3.9 (s, 3 H), 4.4–4.6 (m, 1 H), 6.45–6.55 (d, 1 H), 7.15–7.30 (d, 1 H). MS: 309 (41, *M*), 280 (99), 209 (100), 162 (26), 281 (19).

The amine was converted into its hydrochloride with HCl-saturated ethanol. Evaporation and recrystallization from a mixture of light petroleum and ether gave **6** · HCl, m.p. 138–140 °C. Anal. $C_{17}H_{28}NO_2SCl \times C_2H_5OH$: C, H, N. Ethanol incorporation of the hydrochloride of **6** was verified by ^{1}H NMR spectroscopy.

5-Methoxy-3-chromanone (**13**).[8h,j] 5-Methoxy-3-chromanone **13** was obtained from the oxidation of **9** (445 mg, 2.5 mmol), by analogy with the synthesis of **12**, in 62 % yield. MS: 178 (100, *M*), 177 (83), 135 (20), 91 (18), 43 (22).

5-Methoxy-3-[N-(2-methylthioethyl)propionamido]chroman (**14**). To a solution of ascorbic acid (400 mg, 2.27 mmol) and acetic acid (400 mg, 6.99 mmol) in absolute ethanol (10 ml) was added **13** (250 mg, 1.40 mmol), followed by 2-methylthioethylamine (0.6 ml, 6.41 mmol). The solution was stirred with 4 Å molecular sieves for 1 h 15 min. Methanol (25 ml) was added followed by $NaBH_3CN$ (1.5 g, 23.8 mmol) dissolved in methanol (10 ml). After 30 min of stirring, water was added (50 ml) and the pH adjustment with 2 M NaOH to 11. The mixture was extracted with CH_2Cl_2. The phases were separated and the organic layer washed with water, dried (Na_2SO_4) and evaporated. The crude product was immediately propionylated with propionyl chloride (0.5 ml, 5.72 mmol) in CH_2Cl_2 (20 ml) and triethylamine (1 ml, 7.2 mmol). The reaction mixture was stirred for 30 min, washed with 5 % aqueous Na_2CO_3 solution, 1 M HCl and water. The organic layer was separated and dried ($MgSO_4$). The solvent was evaporated and the crude product chromatographed (SiO_2) with light petroleum ether (1:1) as the eluant, yielding 276 mg (64 %) of **14** as an oil.

^{1}H NMR ($CDCl_3$): δ 1.1–1.3 (t, 3 H), 1.90–3.05 (m, 9 H), 3.30–3.65 (m, 2 H), 3.85 (s, 3 H), 4.05–4.40 (t, br, 2 H), 4.5–4.8 (s, br, 1 H), 6.4–6.7 (dd, 2 H), 7.05–7.3 (t, 1 H). MS: 310 (0.2, *M*), 192 (22), 163 (50), 162 (100), 161 (54). High resolution MS with FAB ionization showed M^++H at 311.141 (Calc. 311.157).

5-Methoxy-3-[N-(2-methylthioethyl)propylamino]chroman (**15**). A solution of **14** (207 mg, 0.70 mmol) in dry ether (10 ml) was cooled with ice and $LiAlH_4$ (250 mg, 6.59 mmol) was added. The mixture was stirred at 0 °C for 40 min. The usual work-up gave 195 mg (99 %) of **15** as an oil.

^{1}H NMR ($CDCl_3$): δ 0.80–0.95 (t, 3 H), 1.40–1.55 (m, 2 H), 2.10 (s, 3 H), 2.45–3.20 (m, 8 H), 3.70–3.90 (m, 2 H), 3.90 (2, 3 H), 4.2–4.3 (m, 1 H), 6.40–6.55 (dd, 2 H), 7.0–7.1 (t, 1 H). MS: 295 (0.1, *M*), 235 (15), 234 (98), 164 (10), 163 (100). High resolution MS with FAB ionization showed M^+ +H at 296.165 (Calc. 296.168).

5-Hydroxy-3-[N-(2-methylthioethyl)propylamino]chroman (**5**). A solution of **15** (166 mg, 0.56 mmol) in 48 % aqueous HBr was heated at 120 °C for 30 min under a nitrogen atmosphere. The hydrobromic acid was evaporated and the residue was evaporated several times with absolute EtOH. Water was added and the pH adjusted to 11 with 10 % Na_2CO_3 solution. The aqueous solution was extracted with CH_2Cl_2. The organic layer was separated, dried and the solvent was evaporated. The crude product was chromatographed (SiO_2) with light petroleum ether (3:1) as the eluant, to yield 85 mg (54 %) of **5** as an oil.

^{1}H NMR ($CDCl_3$): δ 0.85–1.0 (t, 3 H), 1.4–1.8 (m, 2 H), 2.1 (s, 3 H), 2.45–3.15 (m, 9 H), 3.8–4.1 (m, br, 2 H), 4.25–4.35 (m, 1 H), 6.2–6.5 (d, 2 H), 6.9–7.0 (t, 1 H).

The amine was converted into its hydrochloride with HCl-saturated ethanol. Evaporation and recrystallization from a mixture of ethanol and ether gave **5** · HCl, m.p. 125–130 °C. Anal. $C_{15}H_{24}NO_2SCl \times C_2H_5OH$: C, H, N. Ethanol incorporation of the hydrochloride of **5** was verified by ^{1}H NMR spectroscopy.

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