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Stereoselective synthesis of (3*S*,4*R*)- and (3*R*,4*S*)-4-(*N*-substituted-amino)-2,2-dimethyl-6-nitrochroman-3-ols via the microwave assisted regioselective ring opening of epoxides in the presence of neutral alumina

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ABSTRACT

With the aim of discovering new molecules with potassium channel activating properties, we have designed and synthesized derivatives with structural similarity to cromakalim, an important molecule which shows specific affinity toward potassium channels, based on previous structure–activity investigations by applying different C-4 substitutions. This has been accomplished by using a stereoselective Jacobsen epoxidation and microwave assisted regioselective epoxide opening with neutral alumina as the key reactions.

1. Introduction

Potassium channels are exceptionally diverse both in variety and function. They play an important and complex role in the basic electrical and mechanical function of a wide variety of tissues, including smooth muscle, cardiac muscle, and glands. K_{ATP} channels have been shown to be involved in several physiological processes, such as hormone secretion, smooth muscle cell contractile activity, myocardial protection, and neurotransmitter release.[1]

Since the emergence of cromakalim **1**, the first benzopyran type potassium channel activator found to be a potent antihypertensive agent,[2] many other examples of this potentially important class of the agent have been disclosed. They include achiral EMD 52692 **2**, Ro 31-6930 **3**, chiral SDZ PCO 400 **4**, BRL 38227 **5**, **6**, and (−)-MJ-451 **7**. The pharmacological potency of these agents has extensively been studied and some potassium channel activators are currently under development for therapeutic applications in various diseases, especially in hypertension, asthma, and urinary incontinence (Fig. 1).[3–12]

We have synthesized analogues of cromakalim with the aim of obtaining compounds with increased relaxant activity on smooth muscle cells. The electron withdrawing cyano group of cromakalim, favorable to the myorelaxant activity,[13,14] was replaced with a nitro group and the hydroxyl group, which appears to be important for activity on smooth muscle cells[15,16] was also retained. The hydrogen bonding site at C-4 leading to the K_{ATP} channel opening properties of benzopyrans[13,17] has been variously substituted with the aim of discovering more efficient molecular structures and improving the structure–activity relationship. Moreover the stereogenic C-3 and C-4 centers have been synthesized stereospecifically.

2. Results and discussion

2.1. Retrosynthetic analysis of *N*-substituted (3*S*,4*R*)-4-amino-2,2-dimethyl-6-nitrochroman-3-ol 8

Our strategy involved the use of aminolysis of an epoxide as the key step for the construction of *N*-substituted (3*S*,4*R*)-4-amino-2,2-dimethyl-6-nitrochroman-3-ols **8**. The target compounds **8** could be obtained by the aminolysis of epoxide compound (1*aS*,7*bS*)-2,2-dimethyl-6-nitro-2,7*b*-dihydro-1*aH*-oxireno[2,3-*c*]chromene **9**, which could be prepared by the asymmetric epoxidation of 2,2-dimethyl-6-nitro-2*H*-chromene **10**. The retrosynthetic route is shown in Scheme 1.

2.2. Synthesis of chiral epoxides 9 and *ent*-9

Our synthesis started with the asymmetric epoxidation of 2,2-dimethyl-6-nitro-2*H*-chromene **10**[18] using (*S*,*S*)-Jacobsen's catalyst and following the earlier reported method to obtain (1*aS*,7*bS*)-2,2-

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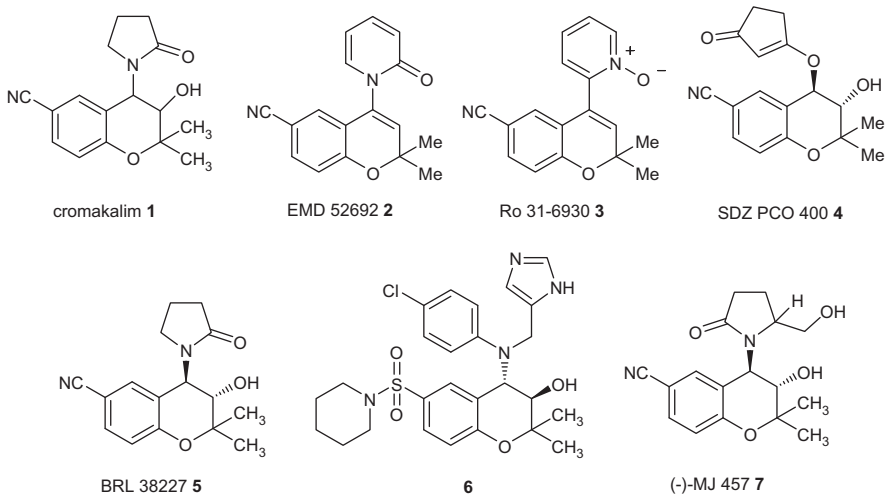
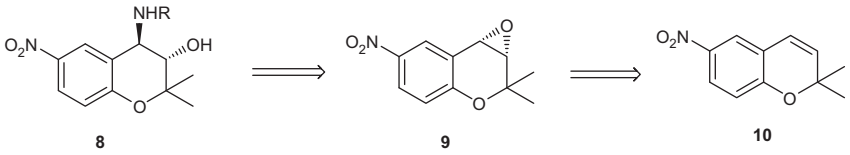


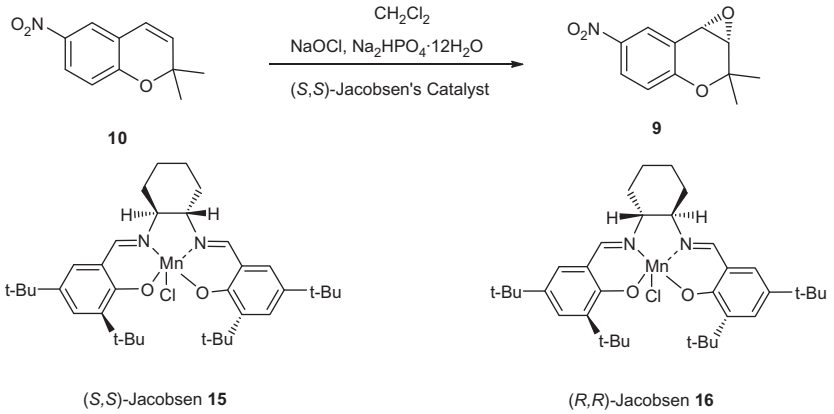
Figure 1. Chemical structures of potassium channel activators with a benzopyran ring.



Scheme 1. Retrosynthetic analysis of *N*-substituted (3*S*,4*R*)-4-amino-2,2-dimethyl-6-nitrochroman-3-ols **8**.

dimethyl-6-nitro-2,7*b*-dihydro-1*aH*-oxireno[2,3-*c*]chromene **9** as the chiral epoxide with a known enantiomeric purity (Scheme 2).[19] Its antipode was obtained by the use of (*R*,*R*)-Jacobsen's catalyst.

methods[24] have also been reported. More recently, Azizi et al. reported a method using water as solvent without any catalyst in 5–24 h.[25]



Scheme 2. Synthesis of (1a*S*,7b*S*)-2,2-dimethyl-6-nitro-2,7*b*-dihydro-1a*H*-oxireno[2,3-*c*]chromene **9**.

2.3. Synthesis of the target compounds 8 by aminolysis of epoxide 9

The ring-opening addition reactions of 1,2-epoxides with ammonia or amines, and their synthetic equivalents, are one of the most widely used methods for β-amino alcohol synthesis.[20] It consists of heating an epoxide with an excess of amine at elevated temperatures.[21] Since some functional groups may be susceptible to high temperatures, various methods using promoters or catalysts in different organic solvents have been reported.[22] In addition, microwave irradiation,[23] and solvent-free condition

However, there are still some limitations to these methods; for example, deactivated amines fail to open these epoxides or still require high temperatures. Side products are often formed by this procedure and the reaction time is long. Furthermore, many of the catalysts used are corrosive, stoichiometric, moisture-sensitive or expensive, and hazardous organic solvents are often used.

Alumina was used in different reactions, such as carbonyl reductions and sulfonate ester elimination. Posner et al. introduced the epoxide ring opening by weak oxygen and nitrogen nucleophiles at an alumina surface.[26] However, the huge consumption of alumina limited this method. The promising reactivity of alu-

mina encouraged us to explore a new methodology. Herein we used the aminolysis of epoxides in *n*-butanol with alumina as the catalyst under microwave irradiation, to obtain a series of 4-(substituted-amino)-2,2-dimethyl-6-nitrochroman-3-ol **8**, with a short reaction time and high yields.

The aminolysis of epoxide **9** was catalyzed by activated, commercially available Woelm 50–200 neutral chromatographic alumina under microwave irradiation (Scheme 3). In order to find the best reaction conditions we first studied the solvent effect in the aminolysis of epoxide **9** with benzyl amine **11a** promoted by alumina. We examined the reactions in different non-dried undistilled solvents, without any precautions to exclude moisture.

Scheme 3. Microwave assisted aminolysis in the presence of neutral alumina.

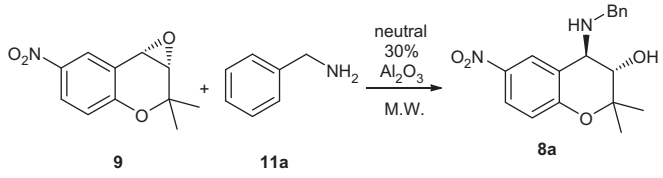
The results summarized in Table 1 show that the reaction in a high-polar solvent gave **8** in 54–92% yields. There was almost no reaction in dichloromethane, toluene, or acetonitrile. It is noteworthy that the yield and the time of the reaction were dependent on the nature of the solvent. This could probably be due to the boiling point of the solvent. The higher the temperature applied, the shorter the reaction time and the higher the yield (entry 7). From the above results we concluded that butan-1-ol gave the best results in the aminolysis of epoxides.

We next planned to evaluate the loading of the catalyst. The reaction was carried out at different mol % of catalyst in butan-1-ol. As shown in Table 2, the reaction time was reduced and the yield was increased when increasing the amount of alumina from 5 to 30 mol %. Keeping the reaction time the same led only to a slight deviation in yields when raising the catalyst above 30 mol % (entries 5–7). It should be noted that there was no product formation without any catalyst.

Finally, we investigated the scope and limitations of the reaction with respect to the amine. Thus, aromatic, linear, and cyclic amines were reacted with epoxide **9** in the presence of 30 mol % of alumina using undistilled non-dried butan-1-ol as the solvent at 117 °C under microwave irradiation. In general, the methodology worked well independent of the nature of the amine, to furnish the corresponding β-amino alcohol in good yields. As can be seen from Table 3, the process worked well for all types of amines including aromatic, linear, cyclic, and heterocyclic amines, giving moderate to excellent yields. Thus, anilines carrying highly deactivating groups such as *p*-nitroaniline (entry 6) gave very reasonable yields using a little more loading (10 mol % more) of catalyst. In the same way, secondary hindered amines such as dimethylamine (entry 7), morpholine (entry 8), and 1-(4-methoxyphenyl)piperazine (entry 9), gave products with very good yields in short reaction times.

Similarly, (3*R*,4*S*)-4-(substituted-amino)-2,2-dimethyl-6 nitrochroman-3-ol *ent*-**8** was prepared from the corresponding epoxide *ent*-**9** by following the same method (Table 4). The regioselective and stereoselective studies were carried out with (*R*)-1-phenylethanamine and (*S*)-1-phenylethanamine (Table 5). Of the similar kind of epoxy opening with amine[27] our reaction was completely regioselective since the only products isolated were those deriving from the attack of the amine to the C-4 posi-

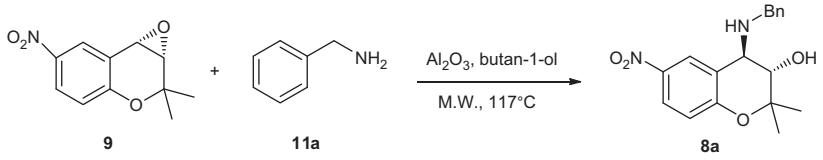
Table 1
Study of the solvent effect in the aminolysis of epoxide **9** promoted by activated alumina



Entry	Solvent	*T* (°C)	*t*[a] (h)	Yield[b] (%)
1	CH_2C1_2	40	12	N.R.
2	CH_3CN	81	12	N.R.
3	Toluene	110	12	N.R.
4	CH_3OH	64	48	54
5	C_2H_5OH	78	20	67
6	*iso*-Butanol	108	2	85
7	Butan-l-ol	118	1	92

N.R. = No Reaction.
[a] Reaction time (*t*) is the hold time after reaching the reaction temperature in 10 min.
[b] Yields refer to isolated pure compounds after column chromatography.

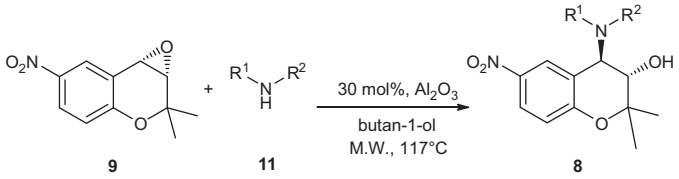
Table 2
Aminolysis of epoxide **9** with different loadings of activated Al_2O_3



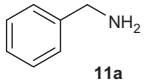
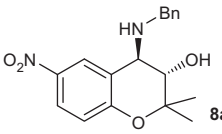
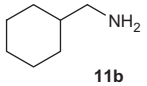
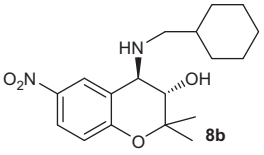
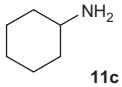
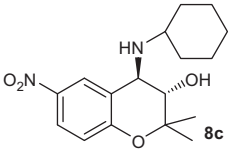
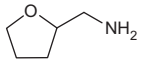
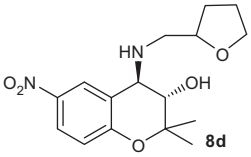
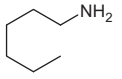
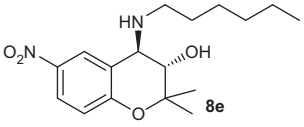
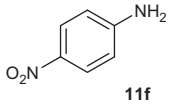
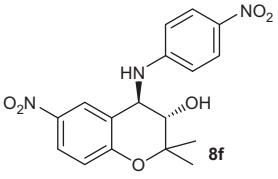
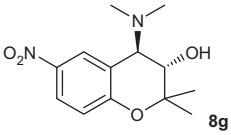
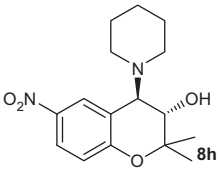
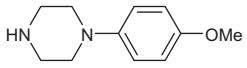
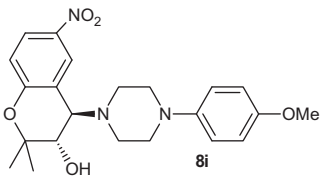
Entry	Catalyst (mol %)	*t*[a] (h)	Yield[b] (%)
1	5	12	69
2	10	8	78
3	20	4	82
4	30	1	92
5	50	1	94
6	100	1	87
7	0	12	N.R.

N.R. = No Reaction.
[a] Reaction time (*t*) is the hold time after reaching the reaction temperature in 10 min.
[b] Yields refer to isolated pure compounds after column chromatography.

Table 3
Microwave assisted alumina-catalyzed aminolysis of epoxide **9**

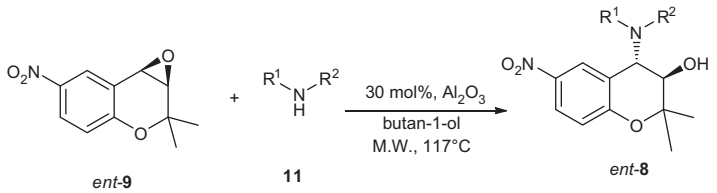


9 **11** **8**

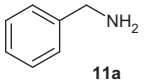
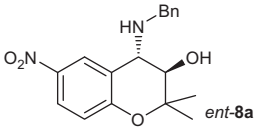
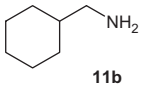
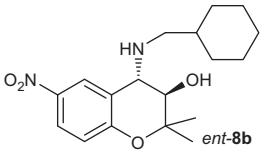
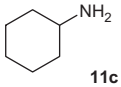
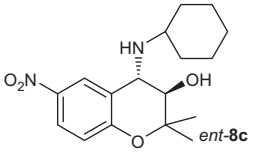
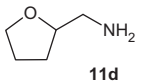
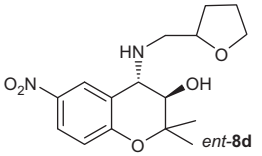
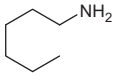
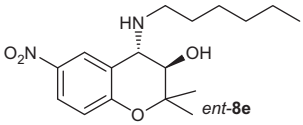
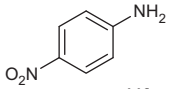
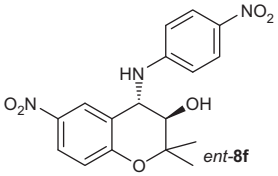
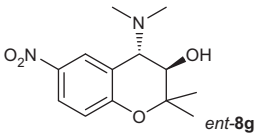
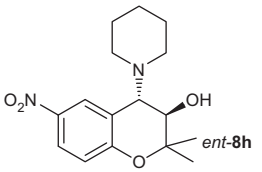
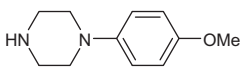
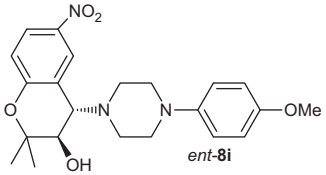
Entry	Amine, **11**	Amino alcohol, **8**	t[a] (h)	Yield[b] (%)
1	 **11a**	 **8a**	1	92
2	 **11b**	 **8b**	1	86
3	 **11c**	 **8c**	1.5	81
4	 **11d**	 **8d**	2	90
5	 **11e**	 **8e**	1	95
6	 **11f**	 **8f**	3	65[c]
7	 **11g**	 **8g**	2	76
8	 **11h**	 **8h**	3	80
9	 **11i**	 **8i**	0.2	94

[a] Reaction time (t) is the hold time after reaching the reaction temperature in 10 min.
[b] Yields refer to isolated pure compounds after column chromatography.
[c] 10 mol % more catalyst used.

Table 4
Microwave assisted alumina-catalyzed aminolysis of epoxide *ent*-**9**

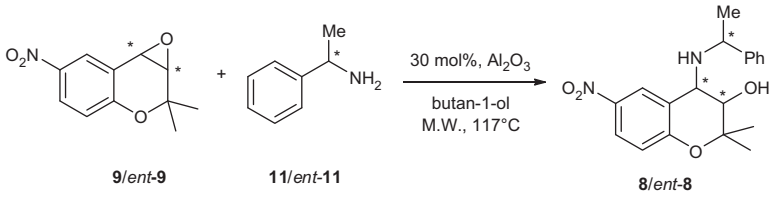


ent-**9** + **11** → *ent*-**8**

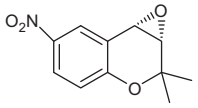
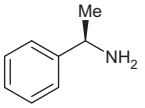
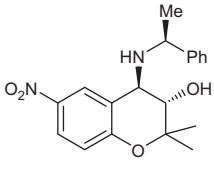
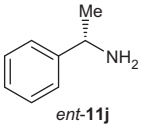
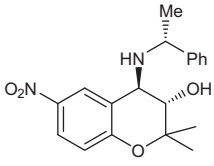
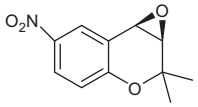
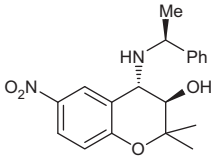
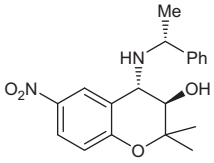
Entry	Amine, **11**	Amino alcohol, *ent*-**8**	t[a] (h)	Yield[b] (%)
1	 **11a**	 *ent*-**8a**	1	92
2	 **11b**	 *ent*-**8b**	1	86
3	 **11c**	 *ent*-**8c**	1.5	81
4	 **11d**	 *ent*-**8d**	2	90
5	 **11e**	 *ent*-**8e**	1	95
6	 **11f**	 *ent*-**8f**	3	65[c]
7	 **11g**	 *ent*-**8g**	2	76
8	 **11h**	 *ent*-**8h**	3	80
9	 **11i**	 *ent*-**8i**	0.2	94

[a] Reaction time (t) is the hold time after reaching the reaction temperature in 10 min.
[b] Yields refer to isolated pure compounds after column chromatography.
[c] 10 mol % more catalyst.

Table 5
Aminolysis of epoxide, **9** with (*R*)-1-phenylethanamine and (*S*)-1-phenylethanamine



9/*ent*-**9** **11**/*ent*-**11** **8**/*ent*-**8**

Entry	Epoxide	Amine	Product	t^a (h)	Yield[b] (%)
1	 **9**	 **11j**	 **8j**	1.2	72
2	**9**	 *ent*-**11j**	 **8k**	1.2	71
3	 ***ent*-9**	**11j**	 *ent*-**8k**	1	85
4	*ent*-**9**	*ent*-**11j**	 *ent*-**8j**	1	80

[a] Reaction time (t) is the hold time after reaching the reaction temperature in 10 min.
[b] Yields refer to isolated pure compounds after column chromatography.

tion of the pyran ring.[28] This selectivity could be explained by the fact that an unsaturated aryl group helps to promote the positively charged C-4 carbon atom of the epoxide ring in the presence of a nucleophilic reagent, owing to its high degree of resonance stabilization[29] and the effect of two methyl groups at the C-2 position, which enhanced the steric hindrance of the C-3 position greatly. Due to the configuration of the substrate, the amine only attacked the opposite side of the epoxide, which resulted in the enantiomerically pure products. The relative stereochemistry was also determined based on the coupling constants of the peaks (C*H*NHPh; d, J = 9.6 Hz) and (C*H*OH; d, J = 9.6 Hz) in their ^{1}H NMR spectra.

3. Conclusion

On the basis of our investigation of the structure–activity relationship, we have designed and synthesized a series of potential antihypertensive agents by applying different C-4 substitutions with the aim of discovering more efficient molecular structures and improving the structure–activity relationship. The C-3 and C-4 positions were functionalized stereoselectively using an asymmetric Jacobsen epoxidation and microwave assisted regioselective epoxide opening.

A practical and efficient epoxide ring opening method was introduced for the preparation of (3*S*,4*R*)-4-(*N*-substituted-amino)-2,2-dimethyl-6-nitro chroman-3-ol **8** and (3*R*,4*S*)-4-(*N*-substituted-amino)-2,2-dimethyl-6-nitrochroman-3-ol *ent*-**8** in *n*-butanol by microwave irradiation. This method offers high yields, very short reaction time, uses a simple procedure, and environmentally friendly conditions with commercially available alumina as the catalyst, compared with the existing methods.

4. Experimental

4.1. General

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and were uncorrected. Optical rotations were measured with a Rudolph AUTOPOL IV digital polarimeter. Nuclear magnetic resonance (^{1}H and ^{13}C NMR spectra) were recorded in $CDCl_3$ (400 MHz for ^{1}H and 100 MHz for ^{13}C, respectively) with TMS as the internal reference on a Bruker Advance 400 FT spectrometer. Chemicals shifts are reported in parts per million. Mass spectra (MS) were measured by the EI method. Silica gel (Merck D-6100, 70–230 mesh, ASTM) was used for flash column chromatography. All reactions were monitored by TLC using 0.25 mm silica gel plates (Merck 60F-254) with or without a UV indicator. All other reagents were commercially available (Acros, Aldrich) and used without further purification. All microwave-assisted reactions were carried out on KMIC-1.5KW creator from Korea Microwave Instrument Company. The microwave-assisted

reaction time is the hold time at the final temperature after reaching it in 10 min (RAMP).

4.2. Experimental procedures

4.2.1. Typical procedure for the aminolysis of epoxide under microwave irradiation in the presence of neutral alumina

To a solution of epoxide, **9** (0.44 g, 2 mmol) in *n*-butan-1-ol (10 mL) were added amine (0.43 g, 4 mmol) and Al_2O_3 (61.0 mg, 0.6 mmol). The resulting mixture was placed into a microwave oven (KMIC-1.5 kW) at 117 °C and irradiated for the period listed in Table 3. The solvent was evaporated under reduced pressure. The crude product was purified by short column chromatography using ethyl acetate as the eluting solvent to afford the pure compound.

4.2.1.1. (3*S*,4*R*)-4-(Benzylamino)-2,2-dimethyl-6-nitrochroman-3-ol 8a. A light-yellow solid, mp 93–94 °C; $[\alpha]_D^{20} = +67.7$ (*c* 1.0, CH_2Cl_2); IR (KBr) ν/cm^{-1}: 3529, 3342, 3075, 2981, 1586, 1513, 1476, 1327, 1270, 1122, 1069, 936, 836, 742, 692; ^1H NMR (400 MHz, $CDCl_3$) δ 1.29 (s, 3H), 1.60 (s, 3H), 3.71–3.91 (m, 4H), 6.93 (d, *J* = 8.4 Hz, 1H), 7.31–7.42 (m, 5H), 8.11 (d, *J* = 8.4 Hz, 1H), 8.40 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.16, 26.95, 48.70, 56.52, 71.13, 80.15, 118.13, 123.49, 123.85, 124.88, 127.59, 128.25, 128.84, 139.83, 141.52, 159.35; MS (EI) *m/z*: 257 (M^+-71, 70%), 91 (100).

4.2.1.2. (3*S*,4*R*)-4-(Cyclohexylmethylamino)-2,2-dimethyl-6-nitrochroman-3-ol 8b. A light-yellow solid, mp 88–89 °C; $[\alpha]_D^{20} = +134.5$ (*c* 1.0, CH_2Cl_2); IR (KBr) ν/cm^{-1}: 3327, 3075, 2928, 2852, 1590, 1513, 1476, 1270, 1122, 1069, 940, 840, 795, 753; ^1H NMR (400 MHz, $CDCl_3$) δ 0.93–1.03 (m, 2H), 1.21–1.32 (m, 6H), 1.42–1.48 (m, 1H), 1.59 (s, 3H), 1.70–1.85 (m, 5H), 2.40–2.55 (m, 2H), 3.62 (d, *J* = 6.0 Hz, 1H), 3.78 (d, *J* = 6.0 Hz, 1H), 6.89 (d, *J* = 8.8 Hz, 1H), 8.07 (dd, *J* = 8.8, 2.8 Hz, 1H), 8.26 (d, *J* = 1.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.18, 26.04, 26.63, 27.02, 31.35, 31.45, 39.12, 50.87, 56.64, 70.77, 80.07, 117.95, 123.76, 124.86, 141.35, 159.31; MS (EI) *m/z*: 263 (M^+-71, 100%), 219 (3), 180 (44), 167 (13).

4.2.1.3. (3*S*,4*R*)-4-(Cyclohexylamino)-2,2-dimethyl-6-nitrochroman-3-ol 8c. A light-yellow solid, mp 164–165 °C; $[\alpha]_D^{20} = +32.3$ (*c* 1.0, CH_2Cl_2); IR (KBr) ν/cm^{-1}: 3312, 3079, 2935, 2856, 1582, 1509, 1472, 1376, 1323, 1263, 1216, 1118, 1069, 932, 803, 750; ^1H NMR (400 MHz, $CDCl_3$) δ 1.14–1.43 (m, 8H), 1.56 (s, 3H), 1.65–1.69 (m, 1H), 1.77–1.84 (m, 2H), 2.00–2.03 (m, 2H), 2.88–2.93 (m, 1H), 3.37 (d, *J* = 10.0 Hz, 1H), 3.69 (d, *J* = 10.0 Hz, 1H), 6.84 (d, *J* = 8.8 Hz, 1H), 8.03 (dd, *J* = 9.2, 2.8 Hz, 1H), 8.27 (d, *J* = 2.8, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.63, 24.71, 25.06, 25.90, 27.06, 35.04, 35.08, 54.84, 55.87, 73.64, 80.30, 117.65, 123.30, 124.62, 126.25, 141.39, 158.79; MS (EI) *m/z*: 249 (M^+-71, 100%), 231 (8), 219 (30), 205 (18), 193 (11), 180 (8), 167 (23), 55 (9).

4.2.1.4. (3*S*,4*R*)-2,2-Dimethyl-6-nitro-4-((tetrahydrofuran-2-yl)methylamino)chroman-3-ol 8d. A light-yellow solid, mp 145–146 °C; $[\alpha]_D^{20} = +121.6$ (*c* 1.0, CH_2Cl_2); IR (KBr) ν/cm^{-1}: 3331, 3083, 2977, 2874, 1586, 1509, 1482, 1331, 1267, 1077, 940, 818, 753; ^1H NMR (400 MHz, $CDCl_3$) δ 1.26 (s, 3H), 1.53–1.61 (m, 4H), 1.89–2.03 (m, 3H), 2.56–2.91 (m, 2H), 3.57–3.63 (m, 1H), 3.78–3.86 (m, 2H), 3.89–4.08 (m, 2H), 6.84 (dd, *J* = 8.8, 3.2 Hz, 1H), 8.03 (d, *J* = 8.8 Hz, 1H), 8.38 (dd, *J* = 2.8, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.10, 25.82, 26.99, 28.88, 48.90, 56.74, 68.05, 71.87, 79.50, 80.31, 117.77, 124.12, 124.57, 124.69, 141.48, 159.23; MS (EI) *m/z*: 251 (M^+-71, 100%), 222 (17), 207 (8), 180 (56), 164 (10), 152 (6), 84 (7), 71 (36), 59 (8).

4.2.1.5. (3*S*,4*R*)-4-(Hexylamino)-2,2-dimethyl-6-nitrochroman-3-ol 8e. A yellow oil; $[\alpha]_D^{20} = +101.5$ (*c* 1.0, CH_2Cl_2); IR (KBr) ν/cm^{-1}: 3525, 3083, 2928, 2863, 1726, 1582, 1517, 1472, 1331, 1270, 1133, 1069, 940, 833, 746, 688; ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, *J* = 6.8 Hz, 3H), 1.26–1.38 (m, 9H), 1.51–1.57 (m, 5H), 2.53–2.59 (m, 1H), 2.66–2.73 (m, 1H), 3.60 (d, *J* = 6.0 Hz, 1H), 3.76 (d, *J* = 6.0 Hz, 1H), 6.87 (d, *J* = 9.2 Hz, 1H), 8.05 (dd, J = 9.2, 2.8 Hz, 1H), 8.26–8.27 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.11, 19.14, 22.67, 28.93, 27.00, 30.96, 31.73, 44.34, 56.58, 70.84, 80.10, 117.98, 123.85, 123.70, 124.70, 141.37, 159.30; MS (EI) *m/z*: 251 (M^+-71, 100%), 221 (47), 207 (9), 193 (20), 180 (19), 167 (7).

4.2.1.6. (3*S*,4*R*)-2,2-Dimethyl-6-nitro-4-(4-nitrophenylamino) chroman-3-ol 8f. A yellow solid, mp 166–168 °C; $[\alpha]_D^{20} = +102.8$ (*c* 1.0, CH_2Cl_2); IR (KBr) ν/cm^{-1}: 3529, 3342, 3075, 2981, 1586, 1513, 1476, 1327, 1270, 1122, 1069, 936, 836, 742, 692; ^1H NMR (400 MHz, $CDCl_3$) δ 1.48 (s, 3H), 2.13 (s, 3H), 5.22 (d, *J* = 10.0 Hz, 1H), 5.55 (s, 1H), 6.60–6.61 (dd, *J* = 2.4, 0.8 Hz, 1H), 6.75 (d, *J* = 8.8 Hz, 1H), 6.97–7.01 (m, 1H), 7.40–7.43 (dd, *J* = 8.8, 1.2 Hz, 2H) 8.04 (d, *J* = 2.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.58, 25.98, 71.70, 78.63, 84.95, 121.73, 122.42, 128.44, 132.11, 139.06, 148.29, 148.98, 154.24, 160.13, 167.51; MS (EI) *m/z*: 288 (M^+-71, 100%), 238 (46), 238 (11), 222 (23), 204 (13), 137 (56).

4.2.1.7. (3*S*,4*R*)-4-(Dimethylamino)-2,2-dimethyl-6-nitrochroman-3-ol 8g. A light-yellow solid, mp 111–113 °C; $[\alpha]_D^{20} = +55.9$ (*c* 1.0, CH_2Cl_2); IR (KBr) ν/cm^{-1}: 3437, 2969, 2928, 2874, 2813, 1586, 1521, 1472, 1331, 1267, 1091, 1057, 928, 836, 750, 685; ^1H NMR (400 MHz, $CDCl_3$) δ 1.18 (s, 6H), 1.27 (s, 3H), 1.57 (s, 3H), 3.49 (d, *J* = 6.0 Hz, 1H), 3.83 (d, *J* = 6.0 Hz, 1H), 6.87 (d, *J* = 8.8 Hz, 1H), 8.04–8.06 (dd, *J* = 8.8, 1.6 Hz, 1H), 8.20 (dd, *J* = 2.8, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.50, 19.08, 27.21, 60.65, 70.58, 80.15, 118.16, 122.87, 124.05, 124.55, 140.85, 159.81; MS (EI) *m/z*: 223 (M^+-43, 96%), 205 (100), 193 (97), 177 (19), 165 (13), 147 (15), 119 (8), 70 (8).

4.2.1.8. (3*S*,4*R*)-2,2-dimethyl-6-nitro-4-(piperidin-1-yl)chroman-3-ol 8h. A light-yellow solid, mp 120–121 °C; $[\alpha]_D^{20} = +145.6$ (*c* 1.0, CH_2Cl_2); IR (KBr) ν/cm^{-1}: 3486, 3437, 2935, 2809, 1582, 1513, 1472, 1335, 1270, 1118, 1069, 1034, 924, 833, 753, 688; ^1H NMR (400 MHz, $CDCl_3$) δ 1.24 (s, 3H), 1.55–1.62 (m, 9H), 2.77–2.96 (m, 5H), 3.66–3.73 (m, 2H), 6.85 (d, *J* = 8.0 Hz, 1H), 8.02–8.05 (dd, *J* = 8.0, 2.8 Hz, 1H), 8.37–8.38 (dd, *J* = 2.8, 0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 18.75, 24.69, 26.91, 27.35, 64.15, 70.26, 79.90, 117.91, 122.99, 124.45, 124.80, 141.12, 159.46; MS (EI) m/z: 234 (M^+-72, 100%), 217 (49), 200 (30), 187 (11), 82 (9).

4.2.1.9. (3*S*,4*R*)-4-(4-(4-Methoxyphenyl)piperazin-1-yl)-2,2-dimethyl-6-nitrochroman-3-ol 8i. A light-yellow solid, mp 181–182 °C; $[\alpha]_D^{20} = +167.8$ (*c* 1.0, CH_2Cl_2); IR (KBr) ν/cm^{-1}: 3336, 3073, 3038, 2979, 2948, 2930, 2896, 2833, 1613, 1584, 1509, 1463, 1407, 1370, 1348, 1333, 1292, 1270, 1251, 1220, 1178, 1165, 1137, 1062, 1033, 1016, 993, 945, 927, 914, 827, 747, 712, 691; ^1H NMR (400 MHz, $CDCl_3$) δ 1.24 (s, 3H), 1.50 (s, 3H), 2.86 (s, 1H), 3.00–3.06 (m, 4H), 3.11–3.13 (m, 4H), 3.78 (s, 3H), 3.81–3.85 (m, 2H), 6.84–6.94 (m, 5H), 8.04 (dd, *J* = 9.2, 2.0 Hz, 1H), 8.48 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.64, 26.79, 49.94, 52.15, 55.61, 63.09, 70.25, 79.99, 114.46, 118.08, 118.73, 122.84, 124.71, 124.97, 141.45, 145.65, 154.08, 159.48; MS (EI) *m/z*: 413 (M^+, 43%), 342 (10), 191 (21), 162 (100), 148 (22), 134 (21), 120 (16), 56 (10).

4.2.1.10. (3*S*,4*R*)-2,2-Dimethyl-6-nitro-4-((*S*)-1-phenylethyl amino)chroman-3-ol 8j. An off-white solid, mp 125–126 °C; $[\alpha]_D^{20} = +51.5$ (*c* 1.0, CH_2Cl_2); IR (KBr) ν/cm^{-1}: 3513, 3345, 3072, 3030, 2973, 2932, 2867, 1582, 1509, 1331, 1270, 1126, 1065, 981, 943, 905, 829, 750; ^1H NMR (400 MHz, $CDCl_3$) δ 1.08 (s, 3H), 1.48 (s, 3H), 1.60 (d, *J* = 6.8 Hz, 3H), 3.39 (d, *J* = 9.6 Hz, 1H), 3.54 (d, *J* = 9.6 Hz, 1H), 4.36–4.41 (q, *J* = 6.8 Hz, 1H), 6.84 (d, *J* = 9.2 Hz, 1H), 7.33 (m, 1H), 7.38–7.43 (m, 4H), 8.05–8.07 (dd, *J* = 9.2, 2.4 Hz, 1H), 8.34–8.35 (dd, *J* = 2.4, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.27, 24.80, 26.85, 55.25, 58.34, 73.79, 80.22, 117.78, 123.38, 124.81, 126.89, 127.94, 129.12, 141.33, 158.71; MS (EI) *m/z*: 271 (M^+-71, 59%), 166 (19), 105 (100), 79 (9).

4.2.1.11. (3*S*,4*R*)-2,2-Dimethyl-6-nitro-4-((*R*)-1-phenylethyl amino)chroman-3-ol 8k. An off-white solid, mp 122–124 °C; $[\alpha]_D^{20} = +91.2$ (*c* 1.0, CH_2Cl_2); IR (KBr) ν/cm^{-1}: 3490, 3345, 3072, 2985, 2920, 2863, 1582, 1513, 1472, 1331, 1274, 1130, 1061, 985, 947, 913, 829, 756, 696; ^1H NMR (400 MHz, $CDCl_3$) δ 1.24 (s, 3H), 1.46–1.49 (m, 6H), 3.39 (d, *J* = 9.6 Hz, 1H), 3.75 (d, *J* = 9.6 Hz, 1H), 4.11–4.16 (q, *J* = 6.8 Hz, 1H), 6.85 (d, *J* = 9.2 Hz, 1H), 7.31 (m, 1H), 7.39–7.47 (m, 4H), 8.04–8.07 (dd, *J* = 8.8, 2.8 Hz, 1H), 8.34–8.35 (dd, *J* = 2.8, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.47, 25.27, 26.75, 55.64, 55.80, 73.25, 80.12, 117.82, 124.10, 124.70, 126.50, 127.66, 129.05, 141.42, 145.91, 159.02; MS (EI) *m/z*: 271 (M^+-71, 55%), 166 (15), 105 (100), 79 (9).

4.2.1.12. (3*R*,4*S*)-4-(Benzylamino)-2,2-dimethyl-6-nitrochroman-3-ol *ent*-8a. A light-yellow solid, mp 103–104 °C; $[\alpha]_D^{20} = -67.5$ (*c* 1.0, CH_2Cl_2); IR (KBr) ν/cm^{-1}: 3527, 3340, 3075, 2976, 1582, 1510, 1471, 1320, 1265, 1117, 1063, 939, 843, 746, 690; ^1H NMR (400 MHz, $CDCl_3$) δ 1.29 (s, 3H), 1.60 (s, 3H), 3.72–3.92 (m, 4H), 6.94 (d, *J* = 8.4 Hz, 1H), 7.33–7.43 (m, 5H), 8.12 (d, *J* = 8.4 Hz, 1H), 8.40 (s, 1H); $^{13}C^{13}C$ NMR (100 MHz, $CDCl_3$) δ 19.26, 27.03, 48.62, 56.57, 71.19, 80.21, 118.20, 123.48, 123.85, 124.98, 127.79, 128.32, 128.95, 139.89, 141.46, 159.53; MS (EI) *m/z*: 257 (M^+-71, 72%), 91 (100).

4.2.1.13. (3*R*,4*S*)-4-(Cyclohexylmethylamino)-2,2-dimethyl-6-nitrochroman-3-ol *ent*-8b. A light-yellow solid, mp 92–93 °C; $[\alpha]_D^{20} = -134.9$ (*c* 1.0, CH_2Cl_2); IR (KBr) ν/cm^{-1}: 3327, 3073, 2925, 2850, 1586, 1523, 1472, 1269, 1127, 1052, 944, 847, 802, 758; ^1H NMR (400 MHz, $CDCl_3$) δ 0.92–1.03 (m, 2H), 1.20–1.31 (m, 6H), 1.40–1.47 (m, 1H), 1.55 (s, 3H), 1.68–1.83 (m, 5H), 2.43–2.57 (m, 2H), 3.65 (d, *J* = 6.0 Hz, 1H), 3.78 (d, *J* = 6.0 Hz, 1H), 6.89 (d, *J* = 8.8 Hz, 1H), 8.08 (dd, *J* = 8.8, 2.8 Hz, 1H), 8.27 (d, *J* = 1.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.25, 26.16, 26.73, 27.13, 31.47, 31.45, 39.10, 50.81, 56.62, 70.87, 80.15, 118.00, 123.79, 124.91, 141.43, 159.31; MS (EI) *m/z*: 263 (M^+-71, 100%), 219 (5), 180 (42), 167 (13).

4.2.1.14. (3*R*,4*S*)-4-(Cyclohexylamino)-2,2-dimethyl-6-nitrochroman-3-ol *ent*-8c. A light-yellow solid, mp 174–175 °C; $[\alpha]_D^{20} = -32.1$ (*c* 1.0, CH_2Cl_2); IR (KBr) ν/cm^{-1}: 3312, 3078, 2936, 2852, 1580, 1506, 1470, 1379, 1326, 1264, 1218, 1120, 1060, 938, 809, 756; ^1H NMR (400 MHz, $CDCl_3$) δ 1.15–1.43 (m, 8H), 1.56 (s, 3H), 1.66–1.71 (m, 1H), 1.78–1.86 (m, 2H), 2.01–2.04 (m, 2H), 2.86–2.93 (m, 1H), 3.36 (d, *J* = 10.0 Hz, 1H), 3.68 (d, *J* = 10.0 Hz, 1H), 6.84 (d, *J* = 8.8 Hz, 1H), 8.04 (dd, *J* = 9.2, 2.8 Hz, 1H), 8.26 (d, *J* = 2.8, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.73, 24.79, 25.09, 25.92, 27.26, 35.18, 35.21, 54.74, 55.79, 73.60, 80.20, 117.66, 123.33, 124.66, 126.24, 141.37, 158.86; MS (EI) *m/z*: 249 (M^+-71, 100%), 231 (10), 219 (38), 205 (18), 193 (13), 180 (7), 167 (22), 55 (11).

4.2.1.15. (3*R*,4*S*)-2,2-Dimethyl-6-nitro-4-((tetrahydrofuran-2-yl)methylamino)chroman-3-ol *ent*-8d. A light-yellow solid, mp 147–148 °C; $[\alpha]_D^{20} = -121.8$ (*c* 1.0, CH_2Cl_2); IR (KBr) ν/cm^{-1}: 3334, 3083, 2979, 2878, 1586, 1502, 1468, 1334, 1268, 1079, 932, 818, 752; ^1H NMR (400 MHz, $CDCl_3$) δ 1.27 (s, 3H), 1.53–1.61 (m, 4H), 1.89–2.02 (m, 3H), 2.57–2.92 (m, 2H), 3.56–3.63 (m, 1H), 3.77–3.85 (m, 2H), 3.89–4.08 (m, 2H), 6.80 (dd, *J* = 8.8, 3.2 Hz, 1H), 8.01 (d, *J* = 8.8 Hz, 1H), 8.35 (dd, *J* = 2.8, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.21, 25.92, 26.99, 28.97, 48.99, 56.94, 68.19, 71.89, 79.64, 80.43, 117.98, 124.22, 124.64, 124.75, 141.40, 159.22; MS (EI) *m/z*: 251 (M^+-71, 100%), 222 (17), 207 (11), 180 (55), 164 (8), 152 (6), 84 (7), 71 (38), 59 (7).

4.2.1.16. (3*R*,4*S*)-4-(Hexylamino)-2,2-dimethyl-6-nitrochroman-3-ol *ent*-8e. A yellow oil; $[\alpha]_D^{20} = -100.5$ (*c* 1.0, CH_2Cl_2); IR (KBr) ν/cm^{-1}: 3525, 3083, 2933, 2863, 1729, 1588, 1514, 1470, 1334, 1273, 1137, 1064, 940, 832, 744, 689; ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, *J* = 6.8 Hz, 3H), 1.27–1.38 (m, 9H), 1.52–1.59 (m, 5H), 2.55–2.61 (m, 1H), 2.66–2.74 (m, 1H), 3.61 (d, *J* = 6.0 Hz, 1H), 3.77 (d, *J* = 6.0 Hz, 1H), 6.88 (d, *J* = 9.2 Hz, 1H), 8.07 (dd, J = 9.2, 2.8 Hz, 1H), 8.26–8.28 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.19, 19.17, 22.57, 29.10, 27.05, 31.13, 31.81, 44.39, 56.57, 70.85, 80.12, 118.07, 123.97, 123.77, 124.74, 141.39, 159.34; MS (EI) *m/z*: 251 (M^+-71, 100%), 221 (45), 207 (9), 193 (25), 180 (20), 167 (7).

4.2.1.17. (3*R*,4*S*)-2,2-Dimethyl-6-nitro-4-(4-nitrophenyl amino)chroman-3-ol *ent*-8f. A light-yellow solid, mp 171–172 °C; $[\alpha]_D^{20} = -102.1$ (*c* 1.0, CH_2Cl_2);); IR (KBr) ν/cm^{-1}: 3528, 3340, 3076, 2985, 1588, 1503, 1468, 1320, 1263, 1121, 1063, 935, 833, 745, 698; ^1H NMR (400 MHz, $CDCl_3$) δ 1.48 (s, 3H), 2.13 (s, 3H), 5.20 (d, *J* = 10.0 Hz, 1H), 5.54 (s, 1H), 6.63–6.64 (dd, *J* = 2.4, 0.8 Hz, 1H), 6.76 (d, *J* = 8.8 Hz, 1H), 6.98–7.02 (m, 1H), 7.41–7.44 (dd, *J* = 8.8, 1.2 Hz, 2H), 8.04 (d, *J* = 2.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.65, 26.06, 71.79, 78.73, 84.98, 121.91, 122.62, 128.59, 132.25, 139.09, 148.32, 149.03, 154.27, 160.16, 167.56; MS (EI) *m/z*: 288 (M^+-71, 100%), 238 (46), 238 (11), 222 (23), 204 (13), 137 (56).

4.2.1.18. (3*R*,4*S*)-4-(Dimethylamino)-2,2-dimethyl-6-nitrochroman-3-ol *ent*-8g. A light-yellow solid, mp 115–116 °C; $[\alpha]_D^{20} = -55.9$ (*c* 1.0, CH_2Cl_2); IR (KBr) ν/cm^{-1}: 3437, 2969, 2928, 2874, 2813, 1585, 1528, 1472, 1331, 1267, 1091, 1057, 928, 836, 756, 685; ^1H NMR (400 MHz, $CDCl_3$) δ 1.19 (s, 6H), 1.28 (s, 3H), 1.58 (s, 3H), 3.51 (d, *J* = 6.0 Hz, 1H), 3.84 (d, *J* = 6.0 Hz, 1H), 6.87 (d, *J* = 8.8 Hz, 1H), 8.04–8.06 (dd, *J* = 8.8, 1.6 Hz, 1H), 8.19 (dd, *J* = 2.8, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.50, 19.08, 27.12, 60.83, 70.48, 80.21, 118.16, 122.86, 124.03, 124.59, 140.84, 159.83; MS (EI) *m/z*: 223 (M^+-43, 97%), 205 (100), 193 (94), 177 (19), 165 (20), 147 (15), 119 (10), 70 (6).

4.2.1.19. (3*R*,4*S*)-2,2-Dimethyl-6-nitro-4-(piperidin-1-yl)chroman-3-ol *ent*-8h. A light-yellow solid, mp 122–123 °C; $[\alpha]_D^{20} = -146.2$ (*c* 1.0, CH_2Cl_2); IR (KBr) ν/cm^{-1}: 3486, 3437, 2934, 2808, 1582, 1513, 1472, 1337, 1275, 1120, 1069, 1037, 922, 835, 751, 687; ^1H NMR (400 MHz, $CDCl_3$) δ 1.25 (s, 3H), 1.59–1.66 (m, 9H), 2.79–2.98 (m, 5H), 3.67–3.74 (m, 2H), 6.88 (d, *J* = 8.0 Hz, 1H), 8.03–8.06 (dd, *J* = 8.0, 2.8 Hz, 1H), 8.37–8.38 (dd, *J* = 2.8, 0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 18.55, 24.47, 26.80, 27.18, 64.02, 70.17, 79.79, 117.93, 122.95, 124.25, 124.80, 141.15, 159.49; MS (EI) m/z: 234 (M^+-72, 100%), 217 (47), 200 (35), 187 (13), 82 (10).

4.2.1.20. (3*R*,4*S*)-4-(4-(4-Methoxyphenyl)piperazin-1-yl)-2,2-dimethyl-6-nitrochroman-3-ol *ent*-8i. An off-white solid, mp 183–184 °C; $[\alpha]_D^{20} = -170.2$ (*c* 1.0, CH_2Cl_2); IR (KBr) ν/cm^{-1}:

3390, 3074, 3039, 2978, 2948, 2895, 2948, 2833, 1614, 1585, 1510, 1463, 1406, 1379, 1370, 1348, 1334, 1270, 1251, 1221, 1179, 1166, 1137, 1077, 1063, 1034, 1016, 993, 945, 927, 914, 827, 747, 729, 712, 692, 633; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (s, 3H), 1.49 (s, 3H), 2.86 (s, 1H), 3.02–3.06 (m, 4H), 3.11–3.13 (m, 4H), 3.78 (s, 3H), 3.81–3.85 (m, 2H), 6.84–6.94 (m, 5H), 8.04 (dd, J = 8.8, 2.8 Hz, 1H), 8.48 (d, J = 2.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.63, 26.81, 49.94, 52.15, 55.61, 63.10, 70.26, 80.02, 114.48, 118.09, 118.73, 122.84, 124.71, 124.96, 141.44, 145.65, 154.10, 159.48; MS (EI) *m/z*: 413 (M^+, 32%), 355 (8), 341 (7), 327 (8), 281 (47), 267 (7), 253 (18), 207 (100), 191 (24), 162 (62), 152 (15), 135 (22), 120 (12), 96 (11), 73 (10), 59 (10), 44 (31).

4.2.1.21. (3*R*,4*S*)-2,2-Dimethyl-6-nitro-4-((*S*)-1-phenylethyl amino)chroman-3-ol *ent*-8k. An off-white solid, mp 124–125 °C; $[\alpha]_D^{20} = -91.3$ (*c* 1.0, CH_2Cl_2); IR (KBr) ν/cm^{-1}: 3486, 3344, 3072, 2985, 2920, 2863, 1582, 1513, 1472, 1327, 1274, 1130, 1061, 980, 943, 913, 829, 756, 693; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (s, 3H), 1.45 (s, 3H), 1.48 (d, J = 6.8 Hz, 3H), 3.39 (d, J = 9.6 Hz, 1H), 3.76 (d, J = 9.6 Hz, 1H), 4.12–4.17 (q, J = 6.8 Hz, 1H), 6.85 (d, J = 9.2 Hz, 1H), 7.29–7.34 (m, 1H), 7.39–7.47 (m, 4H), 8.05–8.08 (dd, J = 8.8, 2.8 Hz, 1H), 8.34–8.35 (dd, J = 2.8, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.40, 25.12, 26.75, 55.75, 55.92, 73.10, 80.11, 117.86, 124.07, 124.76, 126.54, 127.75, 129.08, 141.43, 159.00; MS (EI) *m/z*: 271 (M^+-71, 59%), 166 (19), 105 (100), 79 (9).

4.2.1.22. (3*R*,4*S*)-2,2-Dimethyl-6-nitro-4-((*R*)-1-phenylethyl amino)chroman-3-ol *ent*-8j. A light-yellow solid, mp 129–130 °C; $[\alpha]_D^{20} = -51.6$ (*c* 1.0, CH_2Cl_2); IR (KBr) ν/cm^{-1}: 3510, 3345, 3072, 3030, 2977, 2935, 2870, 1582, 1509, 1334, 1274, 1126, 1065, 980, 943, 905, 829, 752; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (s, 3H), 1.48 (s, 3H), 1.62 (d, J = 6.8 Hz, 3H), 3.43 (d, J = 9.6 Hz, 1H), 3.57 (d, J = 9.6 Hz, 1H), 4.38–4.32 (q, J = 6.8 Hz, 1H), 6.84 (d, J = 9.2 Hz, 1H), 7.30–7.40 (m, 1H), 7.42–7.44 (m, 4H), 8.06–8.09 (dd, J = 8.8, 2.8 Hz, 1H), 8.34–8.35 (dd, J = 2.8, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.18, 24.63, 26.83, 55.35, 58.41, 73.57, 73.59, 80.21, 117.86, 123.42, 124.92, 126.94, 128.06, 129.17, 141.34, 158.71; MS (EI) *m/z*: 271 (M^+-71, 57%), 166 (17), 105 (100), 79 (15).

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