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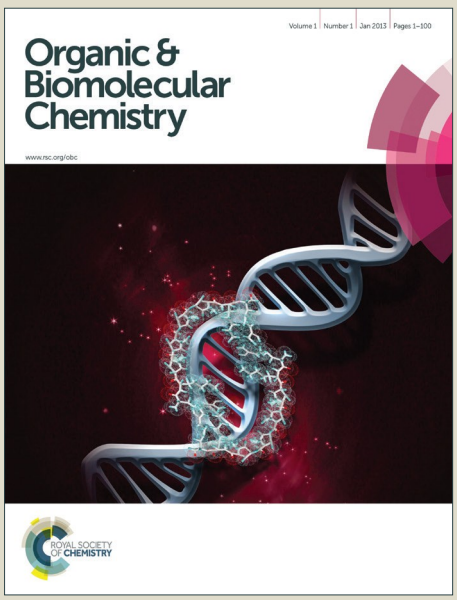

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Total Synthesis and Stereochemical Revision of Xiamenmycin A

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The relative and absolute configurations of xiamenmycin A, a benzopyran compound isolated from *Streptomyces xiamenensis* 318 with a highly potent anti-fibrotic activity, have been characterized through the total synthesis. The key steps include the construction of the 3-chromanol moiety *via* Sharpless epoxidation followed by regio- and diastereo-selective cyclization and introduction of the threonine moiety at a later stage *via* Pd-catalysed aminocarbonylation in a one-pot procedure. The stereochemical assignment of natural xiamenmycin A has been accordingly revised to be 2*R*, 3*S*, 3′*S*, 4′*R*.

Introduction

Fibrotic diseases, which can occur in a variety of organs such as pulmonary, liver, kidney and cardiovascular organs, are a serious threat to public health and life.[1] It has been estimated that approximately 45% of the mortalities in developed countries are related to the fibrotic diseases of various organs.[1] Therefore, more and more attention has been paid to finding small bioactive molecules that can be used to further dissect key pathways implicated in the pathogenesis of tissue fibrosis, and there remains a considerable need for continued research and drug discovery towards anti-fibrotic drugs.[2]

Xiamenmycin A (**1**), a benzopyran derivative with a prenylated side chain, has been isolated from mangrove-derived *Streptomyces xiamenensis* 318 in 2012.[3] Its structure was elucidated by NMR and mass spectrometric analyses. Based on the analysis of the spectroscopic data, Mosher's method, Marfey's reagent and NOE correlations, its absolute configuration was established as (2*S*, 3*S*, 3′*S*, 4′*R*) (Fig. 1).[3]

In our previous pharmacological studies, xiamenmycin A could significantly inhibit cell proliferation and the activation of primary human dermal fibroblasts as well as lung fibroblasts, by reducing the contractile ability of the fibroblasts, indicating that the compound may have an anti-fibrotic effect.[3] Xiamenmycin A attenuated hypertrophic scar formation by reducing $CD4^+$ lymphocyte and monocyte/macrophage retention in fibrotic foci and blocked fibroblast adhesion with monocytes and had no significant toxic effect on mice. Both *in vivo* and *in vitro* studies found that xiamenmycin A inhibited the mechanical stress-induced profibrotic effects by suppressing proliferation, activation, and fibroblast contraction as well as inactivating FAK, p38, and Rho guanosine triphosphatase signalling.[4] Furthermore, pharmacokinetic experiments showed that xiamenmycin A was rapidly absorbed into the blood and quickly eliminated in plasma.[5] Therefore, xiamenmycin A is becoming a promising drug candidate

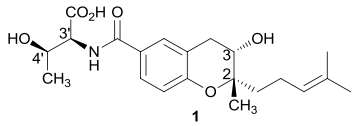

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Fig. 1 The proposed structure of xiamenmycin A **1**

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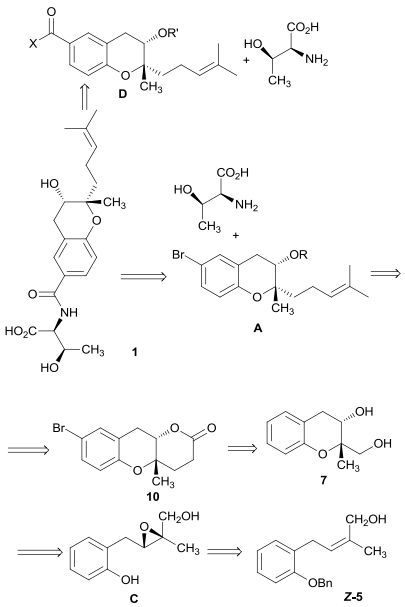
for treating excessive fibrotic diseases, and this has triggered our efforts to establish a flexible and efficient method for the asymmetric total synthesis of xiamenmycin A to supply samples for further pharmaceutical development.

Results and discussion

Although structure **1** might be expected to be obtained from the corresponding molecule **D** and threonine (Scheme 1), enantioselective synthesis of the deceptively simple molecule **D** with two adjacent *cis* stereocentres and a carboxyl group was difficult.[6] We felt that late stage introduction of the threonine moiety and the unsaturated side chain would make the synthesis more effective in terms of the number of steps. Specifically, our retrosynthetic analysis of **1** is shown in Scheme 1. We envisioned that the threonine moiety could be installed at a late stage *via* one-pot Pd-catalysed aminocarbonylation of the corresponding aryl bromide **A** with methyl threonine.[7, 8] The homoprenyl carbon chain might be elaborated from **10** *via* Wittig olefination. In addition, the key intermediate **10** in our strategy could later be amenable to analogue synthesis to probe biological activity, which in turn could be derived from allyl alcohol ***Z*-5** *via* Sharpless epoxidation and subsequent deprotection along with regio- and diastereo- selective cyclization.



Scheme 1 The retrosynthetic analysis of **1**

Our first work was to prepare the key intermediate diol **7** from commercially available 2-hydroxyphenylacetic acid **2** (Scheme 2). Protection of **2** with a benzyl group followed by reduction with DIBAL-H afforded the aldehyde **3** in 78% yield.[9] Horner-Wadsworth-Emmons olefination of aldehyde **3** with the Ando's reagent[10] provided **4** (*Z*/*E* 20/1). Reduction of *Z*-**4** with $LiAlH_4$ afforded allyl alcohol *Z*-**5**. Next, Sharpless epoxidation[11] of allyl alcohol *Z*-**5** with D-(-)-DIPT/titanium tetraisopropoxide/*t*-BuOOH gave the (2R, 3S)-epoxide **6a** as an oil but only in moderate ee (77% ee). Initial attempts to promote the enantiomeric purity of **6a** *via* reducing the reaction temperature and increasing the catalyst load were unsuccessful. However, the enantiomeric purity of **6a** could be improved to 94.5% by converting it to the corresponding 3, 5-dinitrobenzoate **6b** followed by recrystallization and hydrolysis.

After the removal of the benzyl group by hydrogenation, the acid catalytic cyclization[12] was carried out under various conditions (Table 1). An inseparable mixture of **7** and **7'** was obtained, and the best **7**/**7'** ratio, as determined by HPLC analysis, was approximately 7.36:1 when the reaction was performed in the presence of 5% BF_3-Et_2O in CH_2Cl_2 (entry 11).The pure isomer **7** could be obtained in 76% yield using the optimized conditions after it was treated with $NaIO_4$ and then purified by column chromatography. As expected, a pseudo-SN2 epoxide opening resulted in the *trans* orientation between 3-OH and 2-CH_3 in compound **7**,[13, 14] which was established on the basis of ^{1}H-NMR spectra and NOE analyses. The NOE correlation between the 4-H_{ax} (δ 3.05 ppm) and 2-CH_3 (δ 1.18 ppm) showed that the 2-CH_3 group was in an axial orientation. Moreover, analysis of the coupling constants of 3-H (δ 4.10 ppm, *pseudo* t, 3.6Hz) shows that 3-H was in an equatorial orientation (Fig. 3). Based on the above analysis, the absolute configurations at

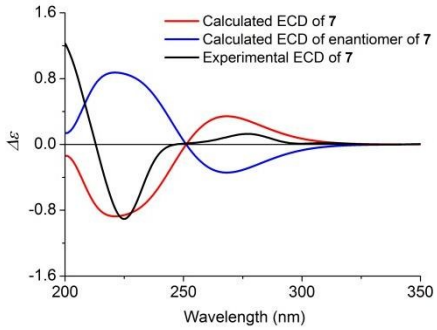


Fig. 2 The theoretical CD spectra and experimental CD spectra of **7**

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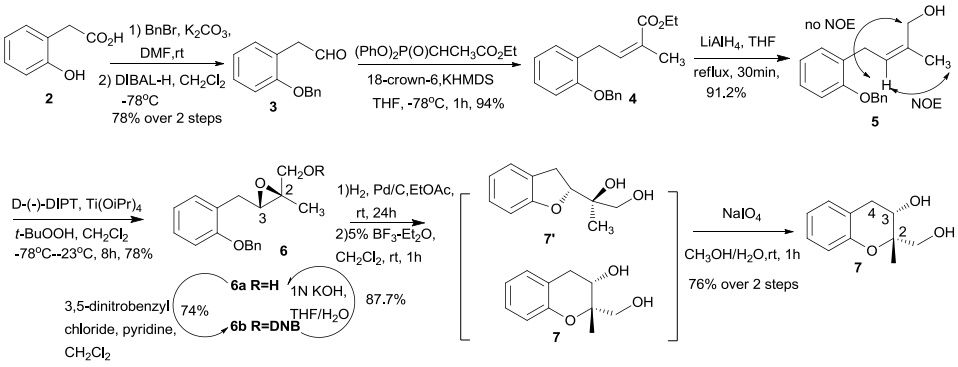
C-2 and C-3 in diol **7** were found to be *2S* and *3S*, which was also further confirmed by comparison of the experimental CD spectra with the spectra calculated for the *2S*, *3S* configuration using TDDFT method[15, 16] (Fig. 2).



Scheme 2 Synthesis of diol **7**.

Table 1 the optimization of the transformation of **6a** to **7** and **7'**[a]

Entry	Catalytic acid	solvent	Temp.	conv (%)	Ratio **7** :**7'**
1	2M HCl / Et_2O	CH_3CN	rt	70	5.8:1
2	10% TsOH	CH_2Cl_2	rt	93	2.42:1
3	20% TsOH	CH_2Cl_2	rt	90	2.38:1
4	10%TFA	CH_2Cl_2	rt	91	1.68:1
5	10% BF_3-Et_2O	CH_2Cl_2	rt	94	6.51:1
6	10% BF_3-Et_2O	CH_3CN	rt	82	9.19:1
7	10% BF_3-Et_2O	Toluene	rt	86	5.8:1
8	20% BF_3-Et_2O	CH_2Cl_2	rt	94	6.96:1
9	10% BF_3-Et_2O	CH_2Cl_2	reflux	94	6.47:1
10	5% BF_3-Et_2O	CH_2Cl_2	reflux	94	6.67:1
11	5% BF_3-Et_2O	CH_2Cl_2	rt	94	7.36:1

[a]General experimental conditions: 5 μmol of **6a**, 1 mL of solvent, 1h.

With diol **7** in hand, we next embarked on introducing the homoprenyl carbon chain and threonine moiety of xiamenmycin A **1** (Scheme 3). Selective oxidation[17] of the primary alcohol in diol **7** with BAIB in the presence of a catalytic amount of TEMPO followed by Wittig olefination with methyl 2-(triphenylphosphoranylidene) acetate produced **8**. Hydrogenation of **8** in HOAc would be carried out to give the lactone **9**. The bromine substitution reaction[18] of lactone **9** with $ZrCl_4$ and NBS gave lactone **10**. After reduction of lactone **10** with DIBAL-H, a Wittig reaction with isopropyltriphenylphosphonium iodide produced the chromanol **11** in THF. After esterification protection, Pd-catalysed fluorocarbonylation[7] with N-formylsaccharin and KF in the presence of Xantphos and the subsequent one-pot coupling[8] with L-threonine methyl ester hydrochloride was used to give amide **13**. Finally, a basic hydrolysis would give xiamenmycin A **1**. Comparison of the data of **1** with those of the natural product revealed that there were distinct differences in optical rotation and ^{13}C NMR spectra. The optical rotation of isolated xiamenmycin A was $[\alpha]_D^{22}$ = +39.5º (*c* 0.044, CH_3OH) and the optical rotation of

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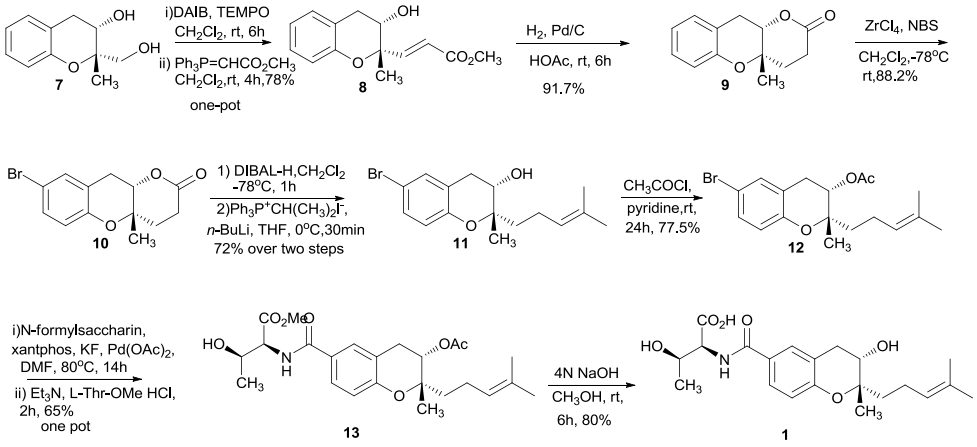
synthetic xiamenmycin A was $[\alpha]_D^{25}$ = +2.09º (*c* 0.438, CH_3OH). Specially, there were large deviations in the ^{13}C NMR spectra for the 2-position methyl carbon atom ($\Delta\delta$ = 3.3ppm) as well as the 2-position methylene carbon atom ($\Delta\delta$ = 4.9ppm). The results suggested that the stereo-structure of the proposed xiamenmycin A was incorrect.



Scheme 3 The synthesis of **1**

In our previous studies, the absolute configuration at C3 of xiamenmycin A was demonstrated by Mosher's method, and the absolute configuration at C2 of the natural product was determined through the relative configurations of C2 and C3 demonstrated by NOE correlations.[3] However, the assignment of the absolute configuration at C2 of this type of natural product still remained contentious. The relative configurations that were assigned for wittifurans,[19] yojironin D,[20] artopetelin F[21] and 8-benzoyl-2-(4-mehtylpenten-3-yl)chromane-3,5,7-triol[22] were based on NOE correlations. Moreover, the absolute configurations of myrsinoic acid,[23] and SMTP-0[24] were determined by the analysis of NOE cross peaks in addition to derivation with Mosher's reagent at 3-OH. In addition, to our knowledge, the first unambiguous total synthesis of the stereostructure of stachybotrin C was reported in 2013, and subsequently, the stereostructure was fully elucidated revising the stereoconfiguration of C2 to be *R*.[6] Therefore, the previous interpretation of the NOE correlations seems inadequate and misleading for the determination of the relative configuration of the pyran ring due to the partial chair conformation of the six-membered ring.

To fully elucidate the stereoconfiguration of C2, we further synthesized the epimer **24** of the proposed xiamenmycin A with an *R* configuration at C2 using the same intermediate **3** (Scheme 4). A Wittig reaction of **3** with 2-(triphenylphosphoranylidene) propanoate[25] produced *E*-**14**. After reduction, the allyl alcohol *E*-**15** was formed. A Sharpless epoxidation reaction was carried out with intermediate **15** and L-(+)-DET/titanium tetraisopropoxide/*t*-BuOOH in CH_2Cl_2 to yield the (2*S*, 3*S*)-epoxide **16** with 90.5% ee. Following a similar synthetic route, we successfully synthesized the C-2 epimer **24** of compound **1**.

The ^1H and ^{13}C NMR spectra as well as optical rotation of **24** were identical to those reported[3] for the previous isolated natural product. The HPLC analyses on a chiral phase column also confirmed that the retention time of compound **24** was the same as that of the isolated xiamenmycin A. Thus, the absolute configurations of the naturally occurred xiamenmycin A were revised to be 2*R*, 3*S*, 3'*S*, 4'*R* rather than 2*S*, 3*S*, 3'*S*, 4'*R* (Fig. 4).

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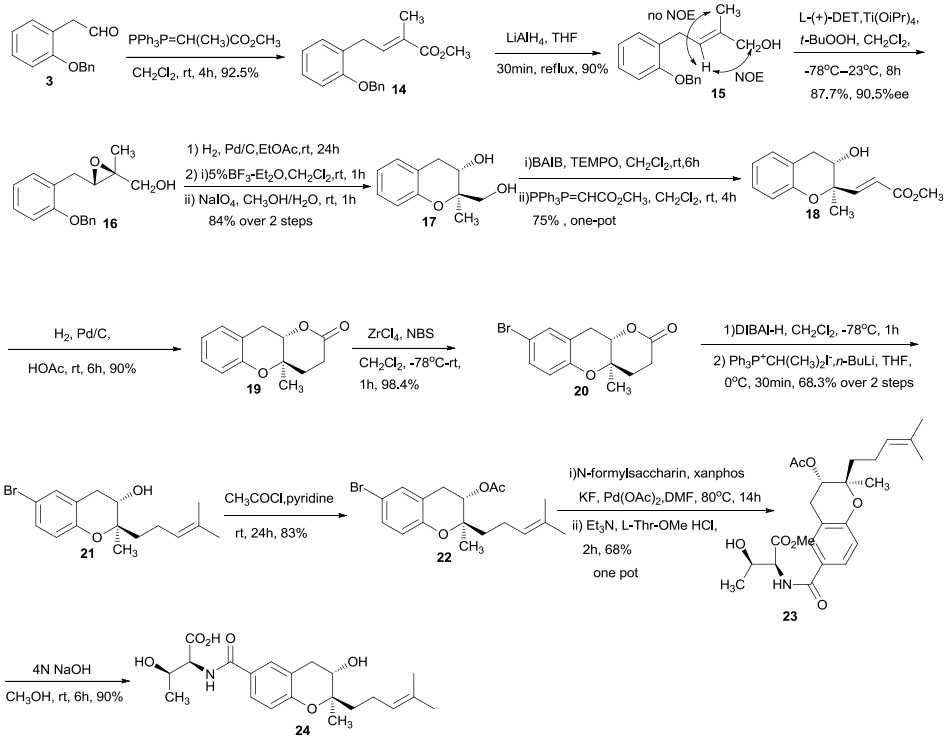

Scheme 4 The synthesis of the C-2 epimer **24** of compound **1**

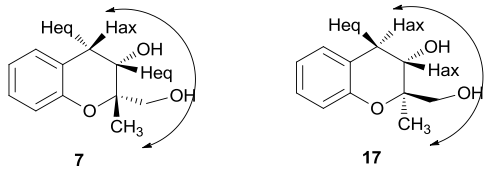

Fig. 3 Stereochemical structure of **7** and **17**

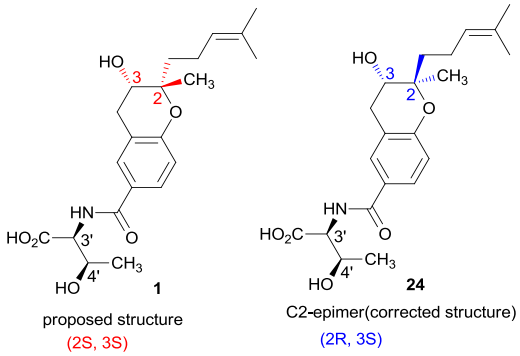

Fig. 4 The structure of the proposed xiamenmycin A **1** and the corrected xiamenmycin A **24**

Conclusions

In summary, the stereoconfiguration at C2 of xiamenmycin A was corrected through asymmetric total synthesis. Through the comparison of physicochemical properties of the synthetic counterpart with the natural isolated compound, we revised the stereoconfigurations of the proposed xiamenmycin A to be 2*R*, 3*S*, 3′*S*, 4′*R*. In addition, an asymmetric total synthesis of xiamenmycin A was achieved in 15 steps with an overall 11% yield from the commercially available 2-hydroxyphenylacetic acid. The strategy developed here can be used for the synthesis of various isomers and analogues of xiamenmycin A for finding new anti-fibrotic compounds.

Experimental

General

Solvents were dried according to standard procedures when needed. All reagents and solvents were purchased from commercial suppliers. Column chromatography was carried out on silica gel (160–200 mesh). Melting points were measured on a microscope melting point apparatus**.** IR spectra were recorded on a Thermo Nicolet 5700 FT-IR microscope Centaurμs spectrophotometer. NMR spectra were recorded on a 400 or 600 MHz NMR spectrometer. Chemical shifts are referenced to the residual solvent peak and reported in ppm (δ scale), and all coupling constant (*J*) values are given in Hz. The following multiplicity abbreviations are used: (s) singlet, (d) doublet, (t) triplet, (q) quartet, (m) multiplet, and (br) broad. ESI-HRMS data were measured on an orbitrap mass spectrometer.

(*Z*)-ethyl 4-(2-(benzyloxy)phenyl-2-methylbut-2-enoate (**4**). To a solution of ethyl 2-(diphenoxyphosphoryl) propanoate (650 mg, 1.95 mmol) and 18-crown-6 ether (1.22 g, 4.64 mmol) in dry THF (5 mL), 1 M KHMDS (1.85 mL, 1.85 mmol) was added under an argon atmosphere at -78°C, and then the mixture was stirred for 30 min. Afterwards, a solution of **3** (209 mg, 0.93 mmol) in dry THF was added and then the mixture was stirred for another 1 h. The reaction mixture was quenched by the addition of a saturated NH_4Cl solution and then stirred for 30 min at rt. The phase was separated, the aqueous phase was extracted with EtOAc (3 x 10 mL) and the combined organic layers were washed with brine (10 mL). The organic phase was dried over Na_2SO_4 and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (5% EtOAc in petroleum ether) to give **4** (270 mg, 94%) as a colourless oil. R_f 0.5 (5:1 petrol -EtOAc). ^{1}H NMR (400MHz, $CDCl_3$): δ 7.43-7.31 (m, 5H), 7.22-7.16 (m, 2H), 6.91 (d, *J*=8.0Hz, 2H), 6.09 (m, 1H), 5.09 (s, 2H),4.20 (q, *J*=7.2Hz, 2H), 3.88 (d, *J*=7.2Hz, 2H), 1.90 (s, 3H), 1.29 (t, *J*=7.2Hz, 2H). ^{13}C NMR (125MHz, $CDCl_3$) : δ168.1, 156.4, 140.8, 137.3, 130.1, 129.1, 128.4, 127.7, 127.4, 127.2, 127.0, 120.8, 111.7, 69.8, 60.1, 30.6, 20.6, 14.2. IR (film)ν_{max}/cm^{-1} 3064, 3032, 2978, 2929, 1711, 1600, 1588, 1493, 1453, 1378, 1240. HRMS (ESI): Calcd for $C_{20}H_{23}O_3$ $[M+H]^+$ 311.1640, found 311.1642.

(*Z*)-ethyl 4-(2-(benzyloxy)phenyl-2-methylbut-2-en-1-ol (**5**). To a solution of enoate **4** (3.75 g, 12.67 mmol) in dry THF (50 mL), $LiAlH_4$ (1.44 g, 37.89 mmol) was added in three separate portions at 0°C, and then the mixture was refluxed for 30 min. Upon completion, the reaction was quenched with saturated Na_2SO_4 and filtered. The residue was washed with EtOAc (2 x 50 mL), and the combined organic phase was washed with saturated brine (50 mL). The organic phase was dried over Na_2SO_4 and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (CH_2Cl_2) to give **5** (3.1 g, 91.2%) as a colourless oil. R_f 0.3 (5:1 petrol -EtOAc). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.43-7.34 (m, 5H), 7.16 (m, 2H), 6.92 (m, 2H), 5.45 (m, 1H), 5.08 (s, 2H), 4.13 (s, 2H), 3.43 (d, *J*=7.5Hz, 2H), 1.80 (s, 3H). ^{13}C NMR (125MHz, $CDCl_3$) : δ 156.3, 137.0, 134.9, 128.6, 128.0, 127.4, 127.2, 120.9, 111.7, 70.0, 61.5, 28.7, 21.4. IR (film)ν_{max}/cm^{-1} 3355, 3064, 3032, 2915, 2876, 1599, 1493, 1452, 1380, 1240. HRMS (ESI): Calcd for $C_{18}H_{21}O_2$ $[M+H]^+$ 269.1536, found 269.1527.

((2R, 3S)-3-(2-(benzyloxy)benzyl)-2-methyloxiran-2-yl)methanol (**6**). To a suspension of 4A sieve powder (454 mg) and $Ti(O^iPr)_4$ (317 mg, 1.12 mmol) in dry CH_2Cl_2 (20 mL), a solution of D-(-)-DIPT (312 mg, 1.33 mmol) in dry CH_2Cl_2 (0.5 mL) was added dropwise under an argon atmosphere at -78°C. After 10 min, the solution of alcohol **5** (1 g, 3.73 mmol) in dry CH_2Cl_2 (1 mL) was added, and the mixture was stirred for 20 min at -78°C. After that, *t*-BuOOH (2.34 mL, 4 N in toluene) was added. The reaction mixture was stirred for 8 h at -20°C under an argon atmosphere. A solution of ferrous sulphate (2.34 g) and tartaric acid (936 mg) in water (10 mL) was added to the mixture, which was stirred for 10 min at 0°C and then for 30 min at rt. The aqueous portion was extracted with ether (3 x 20 mL),

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and the combined organic solution was washed with brine (20 mL). The organic phase was dried over Na_2SO_4 and evaporated in vacuo. The residue was dissolved in ether (20 mL), and a solution of NaOH (0.55 g) in brine (14 mL) was added, followed by stirring for 1 hr at 0°C. The aqueous phase was separated and extracted with ether (2 x 20 mL). The combined organic phase was washed with water (10 mL) and saturated brine (10 mL). The organic phase was dried over Na_2SO_4 and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (10% EtOAc in CH_2Cl_2) to give (-)-epoxide **6** (830 mg, 78%, 78%ee) as a colourless oil. R_f 0.3 (3:1 petrol -EtOAc). $[\alpha]_D^{27}$ = -4.4º (*c* 0.643, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41-7.34 (m, 5H), 7.22 (m, 2H), 6.96 (d, *J* = 6.0Hz, 2H), 5.11 (s, 2H), 3.69 (m, 2H), 3.12 (m, 1H), 3.01 (m, 2H), 1.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 156.4, 136.7, 128.5, 127.9, 127.4, 126.3, 121.1, 112.1, 70.3, 64.0, 63.9, 61.3, 29.1, 20.0. IR (film)ν_{max}/cm^{-1} 3434, 3064, 3033, 2972, 2931, 2876, 1741, 1601, 1589, 1495, 1453, 1380, 1242. HRMS (ESI): Calcd for $C_{18}H_{20}O_3Na$ $[M+H]^+$ 307.1305, found 307.1295.

((2R,3S)-3-(2-(benzyloxy)benzyl)-2-methyloxiran-2-yl)methyl 3,5-dinitrobenzonate (**6b**). To a solution of (-)-epoxide **6** (0.93 g, 3.27 mmol) in CH_2Cl_2 (20 mL), pyridine (3.6 mL) and 3,5-dinitrobenzyl chloride (1.065 g, 4.26 mmol) was added at 0-5°C, and then the mixture was stirred for 30 min at 0-5°C. Afterwards, the mixture was poured into ice-water. The organic layer was separated and the water layer was extracted with CH_2Cl_2. The combined organic layer was washed with water, a saturated $CuSO_4$ solution, water and brine, dried over Na_2SO_4 and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (1% EtOAc in petroleum) to give **6b** (1.2 g, 74%) as a white solid, which was recrystallized twice from toluene to give **6b** (800 mg). R_f 0.6 (5:1 petrol -EtOAc). m. p. 108-109°C; $[\alpha]_D^{25}$ = 0º (*c* 1.471, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) : δ 9.15 (complex, 2H), 7.43-7.29 (m, 5H), 7.21 (d, *J* = 7.6Hz, 1H), 7.17 (d, *J* = 7.6Hz, 1H), 6.91 (m, 2H), 5.11 (s, 2H), 4.54 (m, 2H), 3.26 (m, 1H), 3.11 (dd, J_1 = 5.2 Hz, J_2 = 10.8 Hz, 1H), 2.97 (dd, J_1 = 7.2 Hz, J_2 = 14.8 Hz, 1H), 1.45 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 162.1, 156.5, 148.6, 136.8, 133.4, 130.1, 129.4, 128.6, 128.1, 128.0, 127.3, 125.7, 122.5, 121.0, 111.8, 70.1, 68.1, 63.4, 58.4, 29.6, 20.3. IR (film)ν_{max}/ cm^{-1} 3110, 3062, 2989, 2965, 2902, 2857, 1736, 1628, 1549, 1495, 1451, 1381, 1346, 1278. HRMS (ESI): Calcd for $C_{25}H_{23}O_8N_2$ $[M+H]^+$ 479.1449, found 479.1440.

((2R, 3S)-3-(2-(benzyloxy)benzyl)-2-methyloxiran-2-yl)methanol (**6a**). To a solution of **6b** (500 mg, 1 mmol) in THF-CH_3OH (1:1, 10 mL), 1 N KOH (6 mL) was added at 0-5°C. The mixture was stirred for 15 min at 0-5°C and then poured into a saturated $NaHCO_3$ solution. The aqueous phase was extracted with CH_2Cl_2 and the combined organic layers was dried over Na_2SO_4 followed by evaporation *in vacuo*. The residue was purified by column chromatography on silica gel (10% EtOAc in CH_2Cl_2) to give **6a** (250 mg, 87.7%, 95% ee) as an oil. R_f 0.3 (3:1 petrol -EtOAc). $[\alpha]_D^{25}$ = -10º (*c* 1.14, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41-7.34 (m, 5H), 7.22 (m, 2H), 6.96 (d, *J* = 6.0Hz, 2H), 5.11 (s, 2H), 3.69 (m, 2H), 3.12 (m, 1H), 3.01 (m, 2H), 1.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 156.4, 136.7, 128.5, 127.9, 127.4, 126.3, 121.1, 112.1, 70.3, 64.0, 63.9, 61.3, 29.1, 20.0. IR (film)ν_{max}/cm^{-1} 3434, 3064, 3033, 2972, 2931, 2876, 1741, 1601, 1589, 1495, 1453, 1380, 1242. HRMS (ESI): Calcd for $C_{18}H_{20}O_3Na$ $[M+H]^+$ 307.1305, found 307.1295.

(2S, 3S)-2-(hydroxymethyl)-2-methylchroman-3-ol (**7**). To a solution of (-)-epoxide **6a** (1.37 g, 4.82 mmol) in EtOAc (20 mL), Pd/C (10% w/w, 69 mg) was added, and the suspension was stirred for 24 h under an atmosphere of H_2. Then, the reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was dissolved in dry CH_2Cl_2 (63.4 mL) without further purification, and a catalytic amount of BF_3-Et_2O (31.6 µL, 48% BF_3-Et_2O in CH_2Cl_2 v/v 1:9) was added under an argon atmosphere at rt. After the mixture was stirred for 1 h at rt, the reaction mixture was washed with water (20 mL) and saturated brine (20 mL). The organic phase was dried over Na_2SO_4 and evaporated *in vacuo*. The residue was dissolved in CH_3OH/H_2O (5 mL, v/v 10:1), and $NaIO_4$ (520 mg, 2.43 mmol) was added at rt. The mixture was stirred for 1 h. Afterwards, the reaction mixture was diluted with EtOAc (50 mL) and washed with water (15 mL) as well as saturated brine (15 mL). The organic phase was dried over Na_2SO_4 and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (10% EtOAc in CH_2Cl_2) to give diol **7** (600 mg, 64% over 2 step) as a colourless oil. R_f 0.3 (2:1 petrol -EtOAc). $[\alpha]_D^{26}$ = -1.8º (*c* 1.17, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) : δ 7.13 (dt, J_1 = 1.8Hz, J_2 = 7.8 Hz, 1H), 7.08 (d, *J* = 7.8 Hz, 1H), 6.90 (dt, J_1 = 1.2 Hz, J_2=7.8 Hz, 1H), 6.85 (d, *J* = 7.8 Hz, 1H), 4.10 (*pseudo* t, *J* = 3.6 Hz, 1H), 3.92 (d, *J* = 12.0 Hz, 1H), 3.86 (d, *J* = 11.4 Hz, 1H), 3.05 (dd, J_1 = 4.2 Hz, J_2 = 16.8 Hz, 1H), 2.80 (dd, J_1 = 3.6 Hz, J_2 = 16.8 Hz, 1H), 1.18 (s, 3H).. ^{13}C NMR (100 MHz, $CDCl_3$) : δ 152.3, 130.4, 127.7, 120.9, 118.4, 117.1, 76.5, 69.0, 68.8,

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41.0, 19.7. IR (film)ν_{max}/cm^{-1} 3390, 2978, 2935, 1612, 1584, 1489, 1457, 1237. HRMS (APCI): Calcd for $C_{11}H_{15}O_3$ $[M+H]^+$ 195.1016, found 195.1004.

(*E*)-methyl 3-((2S, 3S)-3-hydroxy-2-methylchroman-2-yl)acrylate (**8**). To a solution of **7** (300 mg, 1.55 mmol) in dry CH_2Cl_2 (25 mL), indobenzene diacetate (793 mg, 2.46 mmol) and 2,2,6,6-tetramethylpiperidine 1-oxyl (33 mg, 0.21 mmol) were added under an argon atmosphere, and then the mixture was stirred for 6 h at rt. Then, methyl 2-(triphenylphosphoranylidene) acetate (620 mg, 1.86 mmol) was added. The reaction mixture was stirred for 4 h and then evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (15% EtOAc in petroleum ether) to give **8** (300 mg, 78%) as a colorless oil. R_f 0.5 (3:1 petrol -EtOAc). $[\alpha]_D^{26}$ = +77.9º (*c* 0.737, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.13 (t, *J* = 7.2 Hz, 1H), 7.09 (d, *J* = 16 Hz, 1H), 7.01 (d, *J* = 7.2 Hz, 1H), 6.88 (m, 2H), 6.09 (d, *J* = 16 Hz, 1H) , 3.94 (dd, J_1 = 5.2 Hz, J_2 = 7.6Hz, 1H), 3.70 (s, 3H), 2.99 (dd, J_1 = 5.2 Hz, J_2 = 16.4 Hz, 1H), 2.69 (dd, J_1 = 7.6 Hz, J_2 = 16.4 Hz, 1H), 1.48 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 166.7, 152.1, 147.3, 129.8, 127.9, 121.4, 120.9, 119.0, 116.7, 78.9, 69.4, 51.6, 31.4, 23.8. IR (film)ν_{max}/cm^{-1} 3455, 2982, 2933, 2850, 1722, 1658, 1585, 1488, 1456, 1437, 1311. HRMS (ESI): Calcd for $C_{14}H_{17}O_4$ $[M+H]^+$ 249.1121, found 249.1115.

(4aS, 10aS)-4a-methyl-4, 4a, 10, 10a-tetrahydropyrano[3,2-b]chromen-2(3H)-one (**9**). To a solution of **8** (260 mg, 1.04 mmol) in HOAc (5 mL), Pd/C (10% w/w, 13 mg) was added, and the suspension was stirred for 6 h under an atmosphere of H_2. Then, the reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was diluted with EtOAc (20 mL) and washed with saturated $NaHCO_3$ (10 mL) as well as saturated brine (10 mL). The organic phase was dried over Na_2SO_4 and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (20% EtOAc in petroleum ether) to give **9** (210 mg, 91.7%) as a colourless oil. R_f 0.2 (3:1 petrol-EtOAc). $[\alpha]_D^{27}$ = -53.5º (*c* 0.934, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) : δ 7.13 (t, *J* = 7.5 Hz, 1H), 7.07 (d, *J* = 7.0 Hz, 1H), 6.90 (t, *J* = 7.5 Hz, 1H), 6.81 (d, *J* = 8.5 Hz, 1H),4.56 (m, 1H), 3.13 (dd, J_1 = 3.5 Hz, J_2 = 17.5 Hz, 1H), 3.01 (d, *J* = 17.5 Hz, 1H), 2.85 (m, 1H), 2.61 (m, 1H), 2.25 (m, 1H), 2.03 (m, 1H), 1.33 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) : δ 170.6, 152.1, 129.8, 127.8, 121.1, 117.2, 116.6, 76.6, 70.3, 32.3, 28.6, 26.4, 22.3. IR (film)ν_{max}/cm^{-1} 2978, 2938, 1739, 1585, 1490, 1360, 1296, 1230, 1200. HRMS (ESI): Calcd for $C_{13}H_{15}O_3$ $[M+H]^+$ 219.1016, found 219.1008.

(4aS, 10aS)-8-bromo-4a-methyl-4, 4a, 10, 10a-tetrahydropyrano[3,2-b]chromen-2(3H)-one (**10**). To a solution of **N-** bromosuccinimide (179.6 mg, 1.01 mmol) in dry CH_2Cl_2 (10 mL), $ZrCl_4$ (10.7mg, 0.05 mmol) was added under an argon atmosphere at -78°C, and then, the mixture was stirred for 15 min. Afterwards, lactone **9** (200 mg, 0.92 mmol) in dry CH_2Cl_2 (0.5 mL) was added, and the solution was warmed to room temperature slowly. The reaction mixture was stirred for 1 h at rt and then quenched with saturated $NaHCO_3$. The phases were separated, the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic layer was washed with brine (10 mL). The organic phase was dried over Na_2SO_4 and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (20% EtOAc in petroleum ether) to give **10** (240 mg, 88.2%) as a white solid. R_f 0.5 (2:1 petrol -EtOAc). m. p. 152-154°C; $[\alpha]_D^{27}$ = -119.8º (*c* 0.813, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.22 (m, 2H), 6.71 (d, *J* = 8.4 Hz, 1H), 4.55 (m, 1H), 3.11 (dd, J_1 = 4.0 Hz, J_2 = 18 Hz, 1H), 2.98 (d, *J* = 16.4 Hz, 1H), 2.82 (m, 1H), 2.62 (m, 1H), 2.23 (m, 1H), 2.06 (m, 1H), 1.31 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 170.2, 151.3, 132.3, 130.9, 119.1, 118.9, 113.2, 109.7, 75.9, 70.8, 32.3, 28.5, 26.3, 22.2. IR (film)ν_{max} /cm^{-1} 2996, 2938, 1733, 1571, 1475, 1250, 1223, 1200. HRMS (ESI): Calcd for $C_{13}H_{14}O_3Br$ $[M+H]^+$ 297.0121, found 297.0108.

(2S, 3S)-6-bromo-2-methyl-2-(4-methylpent-3-en-1-yl) chroman-3-ol (**11**). To a solution of lactone **10** (130 mg, 0.439 mmol) in dry CH_2Cl_2(10 mL), 1 M DIBAL-H **(**0.527 mL, 0.527 mmol) was added dropwise under argon atmosphere at -78°C. The reaction mixture was stirred for 1 h at -78°C and then quenched with a saturated potassium sodium tartrate solution (2 mL). The phases were separated, the aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL), and the combined organic layer was washed with brine (10 mL). The organic phase was dried over Na_2SO_4 and evaporated *in vacuo*. The organic phase was residue was used immediately without further purification because the resulting residue is unstable. To a solution of isopropyltriphenylphosphonium iodide (928.5 mg, 2.195 mmol) in dry THF (5 mL), 1.6 M n-BuLi (1.234 mL, 1.976 mmol) was added dropwise under an argon atmosphere at 0°C. After the mixture was stirred for 30 min, the colour of the solution turned to blood red. The residue mentioned above in dry THF (0.5 mL) was added at 0°C,

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and then the mixture was stirred for 30 min at 0°C. After saturated NH_4Cl (1 mL) was added at rt, the solution was extracted with EtOAc (3 x 6 mL). The combined organic phase was washed with saturated brine (3 mL), dried over Na_2SO_4 and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (20% EtOAc in petroleum ether) to give **11** (90 mg, 72% over 2 steps) as a colorless oil. R_f 0.6 (3:1 petrol -EtOAc). $[\alpha]_D^{27}$ = -14.6º (*c* 0.71, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.20 (m, 2H), 6.71 (d, *J* = 8.5 Hz, 1H), 5.13 (m, 1H), 3.86 (brs., 1H), 3.03 (dd, J_1 = 4.5 Hz, J_2 = 17.5 Hz, 1H), 2.77 (dd, J_1 = 4.5 Hz, J_2 = 17.5 Hz, 1H), 2.10 (m, 2H), 1.74 (m, 5H), 1.61 (s, 3H), 1.25 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ151.8, 132.5, 131.9, 130.5, 123.8, 121.3, 119.1, 112.5, 78.7, 68.1, 34.6, 30.8, 25.6, 21.8, 21.2, 17.6. IR (film)ν_{max} /cm^{-1} 3360, 2973, 2925, 1573, 1480, 1378, 1292, 1257, 1240. HRMS (ESI): Calcd for $C_{16}H_{22}O_2Br$ $[M+H]^+$ 325.0798, found 325.0800.

(2S, 3S)-6-bromo-2-methyl-2-(4-methylpent-3-en-1-yl) chroman-3-yl acetate (**12**). To a solution of chroman **11** (80 mg, 0.246 mmol) in pyridine (1 mL), acetyl chloride(28 µL, 0.369 mmol) was added at 0°C, and the suspension was stirred for 24 h at rt. Then, the reaction mixture was diluted with EtOAc (10 mL) and washed with 1 M HCl (5 mL), water (5 mL) and saturated brine (5 mL). The organic phase was dried over Na_2SO_4 and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (5% EtOAc in petroleum ether) to give **12** (70 mg, 77.5%) as a colourless oil. R_f 0.5 (10:1 petrol -EtOAc). $[\alpha]_D^{27}$ = +29.9º (*c* 0.62, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.21 (d, *J* = 8.8 Hz, 1H), 7.16 (s, 1H), 6.72 (d, *J* = 8.8 Hz, 1H), 5.08 (m, 1H), 5.03 (m, 1H), 3.09 (dd, J_1 = 5.2 Hz, J_2 = 17.6 Hz, 1H), 2.77 (dd, J_1 = 4.8 Hz, J_2 = 18.0 Hz, 1H), 2.05 (m, 5H), 1.67 (m, 5H), 1.59 (s, 3H), 1.26 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 170.2, 151.6, 131.9, 130.4, 123.5, 120.5, 118.9, 112.2, 76.6, 69.5, 35.1, 27.8, 25.5, 21.6, 21.2, 20.9, 17.4. IR (film)ν_{max} /cm^{-1} 2973, 2929, 1740, 1481, 1375, 1243. HRMS (ESI): Calcd for $C_{18}H_{24}O_3Br$ $[M+H]^+$ 367.0903, found 367.0898.

(2S, 3R)-methyl 2-((2S, 3S)-3-acetoxy-2-methyl-2-(4-methylpent-3-en-1-yl) chroman-6-carboxamido)-3-hydroxybutanoate (**13**). To a solution of **12** (70 mg, 0.19 mmol) in dry DMF (2 mL), N-formylsaccharin (48.3 mg, 0.229 mmol), Xantphos (5 mg, 0.0086 mmol), KF (27.7 mg, 0.476 mmol) and $Pd(OAc)_2$ (1.28 mg, 0.0057 mmol) was added under an argon atmosphere, and then the mixture was stirred for 14h at 80°C and cooled to rt. Afterwards, Et_3N (93 µL, 0.667 mmol) and L-threonine methyl ester hydrochloride (48.5 mg, 0.286 mmol) were added, and then, the mixture was stirred for 2 h at rt. EtOAc (10 mL) and water (10 mL) were added, and the phases were separated. The aqueous phase was extracted with EtOAc (10 mL), and the combined organic layer was washed with brine (10 mL). The organic phase was dried over Na_2SO_4 and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (20% EtOAc in petroleum ether) to give **13** (55 mg, 65%) as a colourless oil. R_f 0.2 (1:1 petrol -EtOAc). $[\alpha]_D^{28}$ = +29.4º (*c* 0.605, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (m, 2H), 7.16 (s, 1H), 6.88 (d, *J* = 8.4 Hz, 1H), 6.74 (d, *J* = 8.8 Hz, 1H), 5.09 (m, 2H), 4.81 (m, 1H), 4.45 (m, 1H), 3.80 (s, 3H), 3.15 (m, 1H), 2.86 (m, 1H), 2.05 (m, 5H), 1.68 (m, 5H), 1.60 (s, 3H), 1.28 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 171.9, 170.5, 167.4, 156.0, 132.3, 129.5, 126.8, 123.5, 118.6, 117.3, 77.8, 69.6, 68.3, 57.5, 52.6, 35.5, 28.0, 25.7, 21.7, 21.5, 21.1, 20.1, 17.6. IR (film)ν_{max} /cm^{-1} 3382, 2974, 2928, 1742, 1643, 1581, 1491, 1376, 1245. HRMS (ESI): Calcd for $C_{24}H_{34}O_7N$ $[M+H]^+$ 448.2330, found 448.2324.

(2S,3R)-3-hydroxy-2((2S,3S)-3-hydroxy-2-methyl-2-(4-methylpent-3-enyl)chroman-6-carboxamino)butanoic acid (1). To a solution of **13** (14 mg, 0.031 mmol) in CH_3OH (1 mL), 4 M aq. NaOH (38 µL, 0.152 mmol) was added, and the mixture was stirred for 6 h at rt. The pH of the mixture was adjusted to 7 with 1 M aq. HCl, and then, EtOAc (15 mL) was added. The mixture was washed with water (5 mL) and saturated brine (5 mL). Then, it was dried over Na_2SO_4 and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (5% CH_3OH in CH_2Cl_2) to give **1** (10 mg, 80%) as a white solid. R_f 0.3 (5:1 CH_2Cl_2-CH_3OH). m. p. 105-107°C; $[\alpha]_D^{25}$ = +2.09º (*c* 0.438, CH_3OH). ^{1}H NMR (600 MHz, DMSO) : δ7.75 (d, J = 8.4 Hz, 1H), 7.65 (s, 1H), 7.61 (d, J = 8.4 Hz, 1H), 6.78 (d, *J* = 8.4 Hz, 1H), 5.13 (d, J = 4.2 Hz, 1H), 5.08 (t, J = 7.2 Hz, 1H), 4.38 (dd, J_1 = 3.6 Hz, J_2 = 8.4 Hz, 1H), 4.17 (m, 1H), 3.74 (br., 1H), 2.96 (dd, J_1 = 5.4 Hz, J_2 = 16.8 Hz, 1H), 2.69 (dd, J_1 = 7.2 Hz, J_2 = 16.8 Hz, 1H), 2.05 (m, 2H), 1.69-1.61 (complex, 4H), 1.59-1.45 (complex, 4H), 1.23 (s, 3H), 1.11 (d, J = 6.6 Hz, 3H). ^{1}H NMR (600 MHz, DMSO+D_2O): 7.62 (s, 1H), 7.59 (d, J=9.0Hz, 1H), 6.77 (d, *J*=8.4Hz, 1H), 5.05 (t, J = 7.2 Hz, 1H), 4.37 (m, 1H), 4.16 (m, 1H), 3.73 (br., 1H), 2.95 (dd, J_1 = 5.4 Hz, J_2 = 16.8 Hz, 1H), 2.66 (dd, J_1 = 7.2 Hz, J_2 = 16.8 Hz, 1H), 2.02 (m, 2H), 1.64-1.59 (complex, 4H), 1.55-1.45 (complex, 4H), 1.21 (s, 3H), 1.10 (d, J = 6.6 Hz, 3H). ^{13}C NMR (150 MHz, DMSO): δ 172.3, 166.3, 155.6, 130.7, 129.5, 126.7, 125.5, 124.4, 120.3, 116.2, 79.2, 67.2, 66.6,

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58.5, 33.1, 30.6, 25.4, 22.0, 21.3, 20.5, 17.4. IR (film)ν_{max}/cm^{-1} 3369, 2925, 2855, 1726, 1640, 1611, 1538, 1491, 1262. HRMS (ESI): Calcd for $C_{21}H_{30}O_6N$ $[M+H]^+$ 392.2068, found 392.2063.

(*E*)-methyl 4-(2-(benzyloxy)phenyl-2-methylbut-2-enoate (**14**). To a solution of 2-(triphenylphosphoranylidene) propanoate (6.8 g, 19.6 mmol) in dry CH_2Cl_2 (5 mL), **3** (2.95 g, 13 mmol) was added under an an argon atmosphere at rt, and then, the mixture was refluxed for 4 h. The reaction mixture was evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (50% CH_2Cl_2 in petroleum ether) to give **14** (3.57 g, 92.5%) as a colourless oil. R_f 0.5 (5:1 petrol-EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41-7.38 (m, 5H), 7.22-7.14 (m, 2H), 6.93 (m, 3H), 5.09 (s, 2H), 3.72 (s, 3H), 3.55 (d, *J* = 7.2 Hz, 2H), 1.88 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ168.6, 156.4, 140.5, 137.0, 129.8, 128.5, 127.8, 127.8, 127.7, 127.3, 120.8, 111.6, 69.9, 51.6, 29.7, 12.4. IR (film)ν_{max}/cm^{-1} 3063, 3032, 2949, 2865, 1714, 1600, 1494, 1453, 1245. HRMS (ESI): Calcd for $C_{19}H_{21}O_3$ $[M+H]^+$ 297.1485, found 297.1475.

(*E*)-ethyl 4-(2-(benzyloxy)phenyl-2-methylbut-2-en-1-ol (**15**). **15** (3.1 g) was prepared from **14** (3.75 g, 12.7 mmol) following the procedure described for **5** in 90% yield. R_f 0.3 (5:1 petrol-EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44-7.33 (m, 5H), 7.16 (m, 2H), 6.91 (m, 2H), 5.61 (m, 1H), 5.09 (s, 2H), 4.02 (s, 3H), 3.43 (d, *J* = 7.2 Hz, 2H), 1.72 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) : δ 156.4, 137.3, 135.4, 129.6, 128.5, 127.8, 127.2, 127.1, 124.4, 120.8, 111.6, 69.7, 69.0, 28.5, 13.7. IR (film)ν_{max}/cm^{-1} 3351, 3063, 3032, 2916, 2863, 1599, 1589, 1494, 1452, 1381, 1241. HRMS (ESI): Calcd for $C_{18}H_{21}O_2$ $[M+H]^+$ 269.1536, found 269.1528

((2S, 3S)-3-(2-(benzyloxy) benzyl)-2-methyloxiran-2-yl)methanol (**16**). To a suspension of 4A sieve powder (906 mg) and Ti(O^{i}Pr)$_4$ (646 mg, 2.24mmol) in dry CH_2Cl_2 (45 mL), a solution of L-(+)-DET (628 mg, 2.69 mmol) in dry CH_2Cl_2 (1 mL) was added dropwise under an argon atmosphere at -78°C. After 10 min, the solution of the alcohol **15** (2 g, 7.46 mmol) in dry CH_2Cl_2 (1 mL) was added and the mixture was stirred for 20 min at -78°C. Afterwards, *t*-BuOOH (4.68 mL, 4 N in toluene) was added. The reaction mixture was stirred for 8 h at -20°C under an argon atmosphere. A solution of ferrous sulphate (4.68 g) and tartaric acid (1.87 g) in water (15 mL) was added to the mixture, and it was stirred for 10 min at 0°C, followed by stirring for 30 min at rt. The aqueous phase was extracted with ether (3 x 20 mL), and the combined organic solution was washed with brine (20 mL). The organic phase was dried over Na_2SO_4 and evaporated *in vacuo*. The residue was dissolved in ether (20 mL) and a solution of NaOH (1.1 g) in brine (28 mL) was added followed by stirring for 1 h at 0°C. The aqueous phase was separated and extracted with ether (2 x 20 mL). The combined organic phase was washed with water (10 mL) and saturated brine (10 mL). The organic phase was dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by column chromatography on silica gel (10% EtOAc in CH_2Cl_2) to give (-)-epoxide **16** (1.86 g, 87.7%, 90.5%ee) as a colourless oil. R_f 0.3 (3:1 petrol -EtOAc). $[\alpha]_D^{28}$ = -21.2º (*c* 0.839, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.42-7.33 (m, 5H), 7.22 (m, 2H), 6.94 (m, 2H), 5.09 (s, 2H), 3.65 (dd, J_1 = 4.8 Hz, J_2 = 12.4 Hz, 1H), 3.54 (m, 1H), 3.35 (m, 1H), 2.98 (m, 2H), 1.34 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) : δ 156.5, 137.0, 128.5, 127.9, 127.8, 127.3, 126.3, 120.9, 111.6, 67.0, 65.3, 61.4, 59.6, 29.1, 14.3. IR (film)ν_{max} /cm^{-1} IR (film)ν_{max}/cm^{-1} 3435, 3063, 3033, 2928, 2868, 1741, 1601, 1589, 1495, 1453, 1383, 1242. HRMS (ESI): Calcd for $C_{18}H_{20}O_3Na$ $[M+H]^+$ 307.1305, found 307.1297.

(2R, 3S)-2-(hydroxymethyl)-2-methylchroman-3-ol (**17**). **17** (373 mg) was prepared from **16** (650 mg, 2.29 mmol) following the procedure described for **7** in 84% yield. R_f 0.3 (2:1 petrol-EtOAc). $[\alpha]_D^{22}$ = +25.1º (*c* 0.395, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.12 (t, *J* = 7.8 Hz, 1H), 7.07 (d, *J* = 7.8 Hz, 1H), 6.88 (t, *J* = 7.8 Hz, 1H), 6.81 (d, *J* = 7.8 Hz, 1H), 4.25 (dd, J_1 = 6.0 Hz, J_2 = 10.2 Hz, 1H), 3.83 (d, *J* = 10 Hz, 1H), 3.75 (d, *J* = 10 Hz, 1H), 3.01 (dd, J_1 = 6.0 Hz, J_2 = 16.2 Hz, 1H), 2.81 (dd, J_1 = 10.2 Hz, J_2 = 16.2 Hz, 1H), 1.19 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) : δ 152.4, 129.7, 127.8, 120.8, 120.0, 117.1, 78.8, 67.4, 65.6, 30.8, 14.6. IR (film)ν_{max} /cm^{-1} 3348, 2981, 2930, 1612, 1584, 1486, 1457, 1232. HRMS (APCI): Calcd for $C_{11}H_{14}O_3Na$ $[M+Na]^+$ 217.0835, found 217.0842.

(*E*)-methyl 3-((2R, 3S)-3-hydroxy-2-methylchroman-2-yl)acrylate (**18**). **18** (287 mg) was prepared from **17** (300 mg, 1.55mmol) following the procedure described for **8** in 75% yield. R_f 0.5 (3:1 petrol-EtOAc). $[\alpha]_D^{25}$ = -75º (*c* 0.902, CH_3OH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16 (t, *J* = 7.6 Hz, 1H), 7.03 (d, *J* = 7.2 Hz, 1H), 6.98-6.88 (m, 3H), 6.01 (d, *J* = 16.0 Hz, 1H) , 3.95 (brs., 1H), 3.70 (s, 3H), 2.95 (dd, J_1 = 4.0 Hz, J_2 = 15.2 Hz, 1H), 2.81 (dd, J_1 = 4.0 Hz, J_2 = 16.8 Hz, 1H), 1.50 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 166.7, 152.2, 148.5, 130.3, 128.0, 121.1, 120.3, 118.0, 116.7, 78.9, 67.6, 51.7, 31.5, 21.8. IR (film)ν_{max}/cm^{-1} 3445, 3024, 2986, 2949, 2846, 1723, 1658, 1585,

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1489, 1457, 1436, 1311. HRMS (ESI): Calcd for $C_{14}H_{17}O_4$ $[M+H]^+$ 249.1121, found 249.1115.

(4aR, 10aS)-4a-methyl-4, 4a, 10, 10a-tetrahydropyrano[3,2-b]chromen-2(3H)-one (**19**). **19** (158 mg) was prepared from **18** (200 mg, 0.81 mmol) following the procedure described for **9** in 90% yield. R_f 0.2 (3:1 petrol-EtOAc). $[\alpha]_D^{25}$ = -4.0º (*c* 0.63, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.18-7.11 (m, 2H), 6.93 (t, *J* = 7.2 Hz, 1H), 6.84 (d, *J* = 8.0 Hz, 1H), 4.52 (dd, J_1 = 6.4 Hz, J_2 = 11.2 Hz, 1H), 3.12 (dd, J_1 = 6.0 Hz, J_2 = 16.0 Hz, 1H), 2.87 (m, 2H), 2.73 (m, 1H), 2.20 (m, 2H), 1.29 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 169.9, 151.9, 129.8, 128.1, 121.1, 118.6, 117.1, 76.0, 71.9, 32.8, 28.2, 27.9, 16.2. IR (film)ν_{max} /cm^{-1} 2976, 2916, 1733, 1609, 1581, 1490, 1458, 1305, 1251. HRMS (ESI): Calcd for $C_{13}H_{15}O_3$ $[M+H]^+$ 219.1016, found 219.1006.

(4aR, 10aS)-8-bromo-4a-methyl-4, 4a, 10, 10a-tetrahydropyrano[3,2-b]chromen-2(3H)-one (**20**). **20** (400 mg) was prepared from **19** (300 mg, 1.38mmol) following the procedure described for **10** in 98.4% yield. R_f 0.5 (2:1 petrol-EtOAc). $[\alpha]_D^{25}$ = +4.5º (*c* 0.662, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.26 (br., 2H), 6.73 (d, *J* = 6.8 Hz, 1H), 4.48 (m, 1H), 3.08 (m, 1H), 2.89 (m, 2H), 2.72 (m, 1H), 222-2.15 (m, 2H), 1.26 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 169.6, 151.1, 132.2, 131.1, 120.8, 119.0, 113.2, 75.4, 72.2, 32.6, 27.9, 27.8, 16.1. IR (film)ν_{max} /cm^{-1} 2981, 2931, 1873, 1725, 1572, 1479, 1246, 1225. HRMS (ESI): Calcd for $C_{13}H_{14}O_3Br$ $[M+H]^+$ 297.0121, found 297.0111.

(2R, 3S)-6-bromo-2-methyl-2-(4-methylpent-3-en-1-yl) chroman-3-ol (**21**). **21** (209 mg) was prepared from **20** (280 mg, 0.95 mmol) following the procedure described for **11** in 68.3% yield. R_f 0.6 (3:1 petrol -EtOAc). $[\alpha]_D^{25}$ = +11.8º (*c* 0.509, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.21-7.18 (m, 2H), 6.71 (d, *J* = 8.4 Hz, 1H), 5.07 (m, 1H), 3.86 (t, *J* = 5.4 Hz, 1H), 3.02 (dd, J_1 = 4.8 Hz, J_2 = 16.8 Hz, 1H), 2.76 (dd, J_1 = 6.0 Hz, J_2 = 16.8 Hz, 1H), 2.11 (m, 2H), 1.66 (s, 3H), 1.60 (m, 5H), 1.32 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ152.0, 132.5, 132.2, 130.6, 123.7, 121.3, 119.1, 112.5, 79.0, 67.8, 37.0, 31.0, 25.6, 21.6, 19.2, 17.6. IR (film)ν_{max} /cm^{-1} 3382, 2972, 2925, 1574, 1479, 1378, 1291, 1260. HRMS (ESI): Calcd for $C_{16}H_{22}O_2Br$ $[M+H]^+$ 325.0798, found 325.0784.

(2R, 3S)-6-bromo-2-methyl-2-(4-methylpent-3-en-1-yl) chroman-3-yl acetate (**22**). **22** (75 mg) was prepared from **21** (80 mg, 0.25 mmol) following the procedure described for **12** in 83% yield. R_f 0.5 (10:1 petrol-EtOAc). $[\alpha]_D^{25}$ = +63.5º (*c* 0.495, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) : δ 7.24 (d, *J* = 8.5 Hz, 1H), 7.20 (s, 1H), 6.78 (d, *J* = 8.5 Hz, 1H), 5.09 (m, 2H), 3.15 (dd, J_1 = 5.0 Hz, J_2 = 17.5 Hz, 1H), 2.79 (dd, J_1 = 5.0 Hz, J_2 = 17.5 Hz, 1H), 2.14 (m, 5H), 1.70 (s, 3H), 1.61 (m, 5H), 1.34 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) : δ 170.5, 151.9, 132.3, 132.1, 130.6, 123.4, 120.6, 119.1, 112.4, 69.3, 36.9, 28.0, 25.7, 21.6, 21.1, 20.0, 17.6. IR (film)ν_{max} /cm^{-1} 2971, 2923, 1744, 1480, 1376, 1235. HRMS (ESI): Calcd for $C_{18}H_{24}O_3Br$ $[M+H]^+$ 367.0903, found 367.0903.

(2S, 3R)-methyl 2-((2R, 3S)-3-acetoxy-2-methyl-2-(4-methylpent-3-en-1-yl) chroman-6-carboxamido)-3-hydroxybutanoate (**23**). **23** (35 mg) was prepared from **22** (42 mg, 0.114mmol) following the procedure described for **13** in 68% yield. R_f 0.2 (1:1 petrol-EtOAc). $[\alpha]_D^{26}$ = +74.5º (*c* 0.52, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.62 (dd, J_1 = 2.4 Hz, J_2 = 8.4 Hz, 1H), 7.60 (s, 1H), 6.87 (d, *J* = 8.4 Hz, 1H), 6.80 (d, *J* = 8.4 Hz, 1H), 5.11 (t, J = 4.8 Hz, 1H), 5.04 (m, 1H), 4.81 (dd, J_1 = 2.4 Hz, J_2 = 9.0 Hz,, 1H), 4.44 (m, 1H), 3.80 (s, 3H), 3.16 (dd, J_1 = 4.8 Hz, J_2 = 17.4 Hz,, 1H), 2.83 (dd, J_1 = 4.8 Hz, J_2 = 17.4 Hz,, 1H), 2.10 (m, 2H), 2.07 (s, 3H), 1.66 (s, 3H), 1.60 (m, 5H), 1.33 (s, 3H), 1.26 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) : δ 171.8, 170.5, 167.2, 156.1, 132.4, 129.5, 126.9, 125.8, 123.3, 118.6, 117.3, 77.9, 69.4, 68.3, 57.5, 52.7, 37.1, 28.1, 25.7, 21.6, 21.1, 20.1, 20.1, 17.6. IR (film)ν_{max} /cm^{-1} 3434, 3391, 2969, 2934, 1750, 1638, 1613, 1546, 1494, 1377, 1251. HRMS (ESI): Calcd for $C_{24}H_{34}O_7N$ $[M+H]^+$ 448.2330, found 448.2334.

(2S, 3R)-3-hydroxy-2((2R,3S)-3-hydroxy-2-methyl-2-(4-methylpent-3-en-1-yl) chroman-6-carboxamino)butanoic acid (24). 24 (15 mg) was prepared from **23** (20 mg, 0.045 mmol) following the procedure described for **1** in 90% yield. R_f 0.3 (5:1 CH_2Cl_2-CH_3OH). $[\alpha]_D^{16}$ = +38.7º (*c* 0.124, CH_3OH). ^{1}H NMR (600 MHz, DMSO): δ7.77 (d, J = 8.4 Hz, 1H), 7.65 (s, 1H), 7.61 (d, J = 8.4 Hz, 1H), 6.79 (d, *J* = 8.4 Hz, 1H), 5.19 (br., 1H), 5.10 (t, J = 6.6 Hz, 1H), 4.38 (dd, J_1 = 3.6 Hz, J_2 = 8.4 Hz, 1H), 4.17 (m, 1H), 3.74 (t, J = 5.4 Hz, 1H), 2.96 (dd, J_1 = 5.4Hz, J_2 = 16.8 Hz, 1H), 2.69 (dd, J_1 = 7.8Hz, J_2 = 16.8 Hz, 1H), 2.09 (m, 2H), 1.62 (s, 3H), 1.59 (m, 2H), 1.55 (s, 3H), 1.16 (s, 3H), 1.11 (d, J = 6.6 Hz, 3H). ^{1}H NMR (600 MHz, DMSO+D_2O): 7.61 (s, 1H), 7.58 (d, J = 8.4 Hz, 1H), 6.76 (d, *J* = 8.4 Hz, 1H), 5.05 (br., 1H), 4.36 (d, J = 3.0 Hz, 1H), 4.17 (m, 1H), 3.72 (pesu t, J = 6.0Hz, 1H), 2.94 (dd, J_1 = 4.8 Hz, J_2 = 16.8 Hz, 1H), 2.67 (dd, J_1 = 7.8 Hz, J_2 = 16.8 Hz, 1H), 2.05 (m, 2H),

1.58 (s, 3H), 1.54 (t, J = 8.4 Hz, 2H), 1.50 (s, 3H), 1.15 (s, 3H), 1.09 (d, J = 6.6 Hz, 3H). ^{13}C NMR (150 MHz, DMSO): δ 172.3, 166.2, 155.7, 130.8, 129.4, 126.8, 125.5, 124.3, 120.2, 116.2, 79.3, 66.6, 65.9, 58.5, 37.5, 30.8, 25.4, 21.1, 20.5, 18.3, 17.4. IR (film)ν_{max}/cm^{-1} 3359, 2958, 2920, 2852, 1723, 1641, 1611, 1578, 1536, 1490, 1443. HRMS (ESI): Calcd for $C_{21}H_{30}O_6N$ $[M+H]^+$ 392.2068, found 392.2057.

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