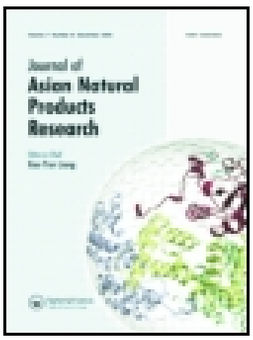

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Total synthesis of xiamenmycin C and all of its stereoisomers: stereochemical revision

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ABSTRACT
Xiamenmycin C, a potent anti-fibrotic natural product, and all of its stereoisomers have been synthesized and their structures were fully characterized. Based on this study, the originally proposed structure of xiamenmycin C has been accordingly revised to be 2R,3S.

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1. Introduction

A series of benzopyran derivatives with the benzopyran skeleton and a prenylated side chain, named xiamenmycins A–D (Figure 1), were isolated from mangrove-derived *Streptomyces xiamenensis* as potential drug candidates against excessive fibrotic diseases by Xu's group. Their absolute configurations were elucidated as (2S,3S) based on the analysis of the spectroscopic data, Mosher's method, Marfey's reagent, and NOESY correlation [1–4].

As promising drug candidates for treating excessive fibrotic diseases, xiamenmycins have triggered our efforts to establish a flexible and efficient approach to their synthesis. In our previous studies, the structure of xiamenmycin A has been revised [5]. As a continued program for biological research, a rapid access to all the isomers of 3-chromanol core of all the xiamenmycins is needed. Herein, we report the synthesis of the xiamenmmycin C, which possessed the related simple structure, and all of its stereoisomers.

2. Results and discussion

Our initial retrosynthetic analysis of xiamenmycin C (**1**) is outlined in Scheme 1. The amide moiety of xiamenmycin C could be synthesized from substituted methyl benzoate **6** via hydrolysis and amidation [6,7], while the key intermediate **6** might be formed through a highly regio- and diastereoselective oxidative cyclization [8] from **5**, which, in turn, could be accessed from organoboron **3** via Suzuki-Miyaura coupling [9,10].

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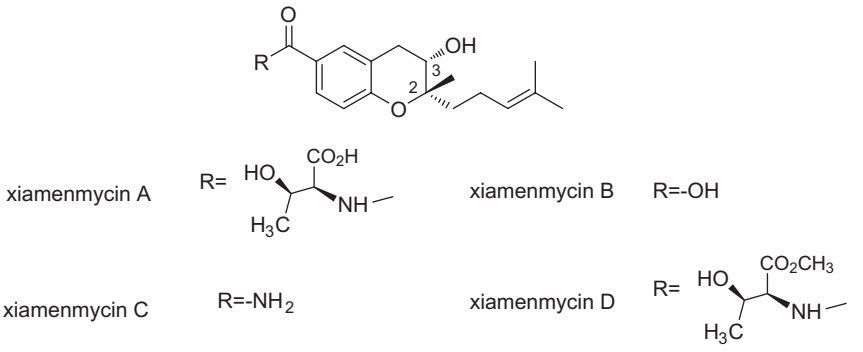


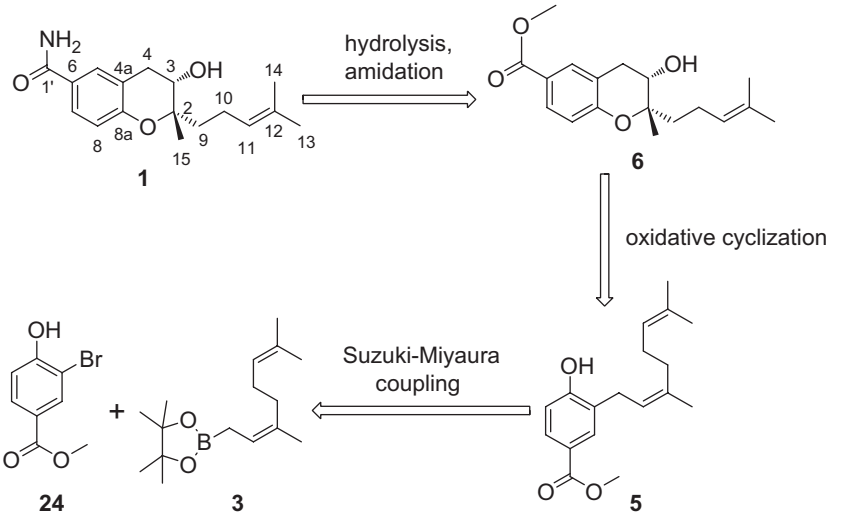
Figure 1. Structures of xiamenmycins A–D.

Our synthesis started with the commercially available neryl acetate **2**, which could be converted into the key intermediate benzoate *Z*-**5** in two steps. Thus, treatment of neryl acetate **2** with bis(pinacolato)diboron (B_2Pin_2) in the presence of catalytic amount of bis(1,5-cyclooctadiene)nickel(0) ($Ni(cod)_2$) and tricyclohexylphosphine (PCy_3) [9] afforded the organoboron **3,** which was subjected to the Suzuki-Miyaura coupling with MOM-protected methyl 3-bromo-4-hydroxybenzoate using [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) ($Pd(dppf)Cl_2$) [10] as catalyst to give the benzoate *Z*-**5** in good yield.

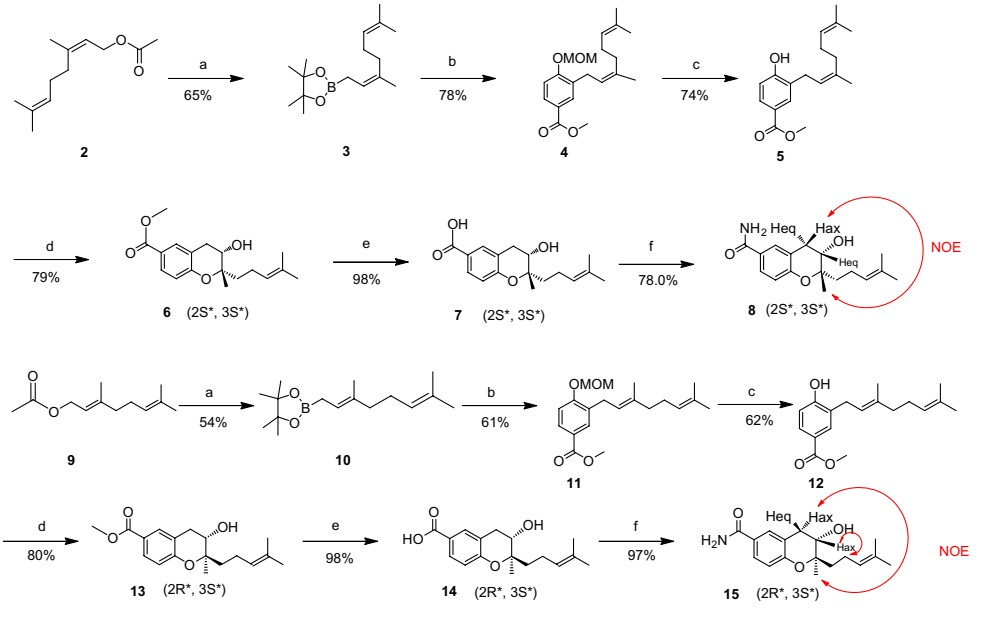
With benzoate *Z*-**5** in hand, we initially tried to establish a direct formation of the 3-chromanol through a vanadium-catalyzed asymmetric epoxidation of benzoate Z-**5** followed by regio- and diastereo-selective cyclization. Unfortunately, using bishydroxamic acid as a ligand [11], only low stereoselectivity was observed (ee = 14%). Based on this result, we had to first synthesize the racemic xiamenmycin C and then try to isolate each isomer [12]. For this purpose, followed a literature procedure [8,13,14], treatment of the Z-**5** with tert-Butyl hydroperoxide (t-BuOOH), vanadyl acetylacetonate ($VO(acac)_2$) in the presence of TFA, the required (±) **6** along with a small amount of the 5-exocyclization by-product **6a** (6:1) was achieved. Finally, after hydrolysis and subsequent amidation using Boc_2O/NH_4HCO_3 [6,7], compound (±) **8**, which has the originally proposed structure of xiamenmycin C, was obtained (Scheme 2).

As expected, a pseudo-SN2 epoxide opening resulted in the *trans* orientation between 3-OH and 2-CH_3 in compound (±) **8** [15,16], which is also confirmed by the NOE analyses. The coupling constants of 3-H ($J_{3\text{-}H}$ = 6.7, 5.2 Hz) showed that 3-H occupied the equatorial orientation (Scheme 2). Besides, it was found that 2-CH_3 was at the axial position because of the NOE correlation between the 4-Hax (δ 2.93) and 2-CH_3 (δ 1.22). Based on the above analysis, the relative configuration at C-2 and C-3 in (±) **8** were found to be (2S*,3S*). However, the comparison of NMR spectral data of compound (±) **8** with the reported natural xiamenmycin C showed that there were large deviations in the ^{13}C-NMR spectra for the 9-position carbon atom ($\Delta\delta$ = 4.9 ppm) and 15-position carbon atom ($\Delta\delta$ = 2.5 ppm) (Table 1). The results suggested that the stereochemistry of the proposed xiamenmycin C may be incorrect [1,5].

To fully elucidate the stereoconfiguration of C-2, we further synthesized the epimer (±) **15** with a similar method using *E*-geranyl acetate (**9**) as the starting material (Scheme 2). The structure of (±) **15** was determined by ^{1}H NMR and NOESY analyses, which showed



Scheme 1. Retrosynthetic analysis of xiamenmycin C.



Scheme 2. Synthesis of racemic xiamenmycin C. Reagents and conditions: (a) B_2Pin_2, $Ni(cod)_2$, PCy_3, AcOEt; (b) methyl 3-bromo-4-hydroxybenzoate, $Pd(dppf)Cl_2$, $CsCO_3$, 1,4-dioxane; (c) D-camphorsulfonic acid, MeOH; (d) $VO(acac)_2$, TBHP, TFA, DCM; (e) 4 N NaOH, CH_3OH; (f) Boc_2O, pyridine, NH_4HCO_3, 1,4-dioxane.

the 3-H and 2-CH_3 were in axial orientation. The ^1H and ^{13}C-NMR data of (±) **15** (2R*,3S*) were in accordance with those reported [1] for xiamenmycin C (Table 1).

After completing the total synthesis of originally proposed structure of xiamenmycin C (±) **8** and the revised xiamenmycin C (±) **15**, we found both racemates could be efficiently resolved by their (S)-O-methyl mandelic acid ester [17]. Reaction (±) **8** with (S)-O-methyl mandelic acid provided a pair of diastereomeric esters **16** (R_f = 0.4, 1:1 DCM/EtOAc) and

Table 1. Comparison of ^{1}H and ^{13}C NMR spectral data of compounds (±) **8**, (±) **15** and reported natural xiamenmycin C.

	Natural xiamenmycin C[1]		Compound **15**		Compound **8**	
Position	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C
1	–	–	–	–	–	–
2	–	79.7 C	–	79.5 C		79.1 C
3	3.74,dd (7.4, 5.2)	66.3 CH	3.74, dt (7.8, 5.2)	66.0 CH	3.73, dt (6.7, 5.2)	67.1 CH
4	2.66,dd (17.3, 7.4)	31.3 CH_2	2.65, dd (16.6, 7.8)	30.9 CH_2	2.65, dd (16.9, 6.8)	30.6 CH_2
	2.93, dd (17.3, 5.2)	–	2.92, dd (16.6, 5.3)	–	2.93, dd (16.9, 5.2)	–
4a	–	120.4 C	–	120.2 C	–	120.0 C
5	7.63, d (1.8)	130.2 CH	7.62, s	130.0 CH	7.62, s	129.8 CH
6	–	126.3C	–	125.8 C	–	125.8 C
7	7.60, dd (8.4,1.8)	127.4 CH	7.58, d (8.0)	127.2 CH	7.58, d (8.5)	126.8 CH
8	6.74, d (8.4)	116.5 CH	6.73, d (8.4)	116.3 CH	6.72, d (8.0)	116.0 CH
8a	–	156.0C	–	155.8 C	–	155.4 C
9	1.59, m	38.0 CH_2	1.60–1.58, m	37.6 CH_2	1.68–1.64, m; 1.49–1.45, m	33.1 CH_2
10	2.10, m	21.6 CH_2	2.12–2.06, m	21.4	2.10–1.95, m	21.3 CH_2
11	5.10,t (7.3)	124.8 CH	5.10, t (7.3)	124.5 CH	5.07, t (7.5)	124.4 CH
12	–	131.3C	–	131.2 C	–	130.7 C
13	1.56, s	18.0 CH_3	1.55, s	17.7 CH_3	1.53, s	17.4 CH_3
14	1.63, s	25.9 CH_3	1.62, s	25.7 CH_3	1.61, s	25.4 CH_3
15	1.16, s	18.8 CH_3	1.15, s	18.7 CH_3	1.22, s	21.3 CH_3
1′	–	168.0 C	–	168.1 C	–	167.5C
CO-NH_2	8.38,brs	–	7.71, brs 7.07, brs	–	7.73, brs 7.09, brs	–

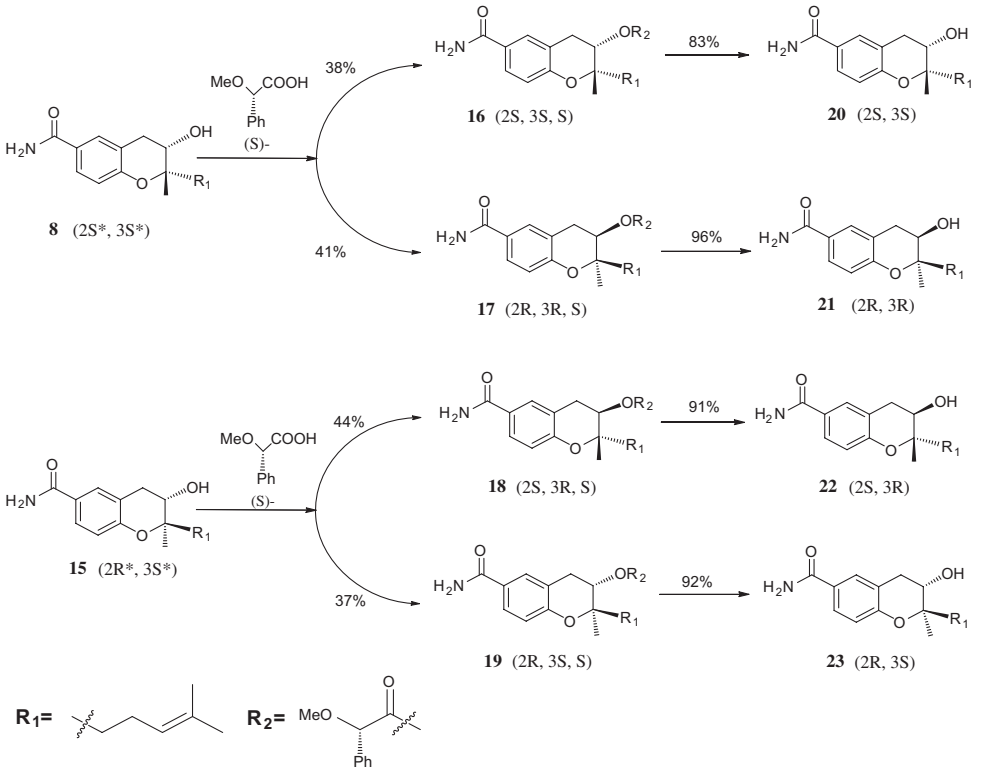
17 (R_f = 0.5, 1:1 DCM/EtOAc). After chromatography separation, each diastereomer was hydrolyzed using sodium methoxide [8] to afford (2S,3S)-**20** and (2R,3R)-**21**. Similarly, the stereoisomers (2S,3R)-**22**, (2R,3S)-**23** were obtained from (±) **15** (Scheme 3). Structures and stereochemistry of **20**, **21**, **22**, **23** were determined by ^{1}H, ^{13}C NMR spectra and NOE experiments, and comparison of the experimental CD spectra with the calculated spectra using TDDFT method [18,19] (Figure 2). The data of (2R,3S)-**23** were in agreement with those reported [1] for the natural product. Thus, the absolute configurations of xiamenmycin C were revised to be 2R,3S rather than 2*S*,3*S* (Figure 3).

In summary, we have accomplished the first total synthesis of xiamenmycin C and all of its stereoisomers in nine steps. Their stereoconfigurations were elucidated by ^{1}H-NMR spectra, ^{13}C NMR spectra, NOESY analyses, and calculated CD method. Furthermore, the stereoconfigurations of the initially proposed xiamenmycin C were revised to be 2R,3S through comparison of physicochemical properties of the synthetic stereoisomers with the isolated natural compound. The biological evaluation of xiamenmycin C and all of its stereoisomers is in progress.

3. Experimental

3.1. General experimental procedures

Melting points were measured on an MP-J3 micro-melting apparatus (Yanaco, Kyoto, Japan). Optical rotations were measured on PE341 (PerkinElmer, Fremont, CA, USA). NMR spectra were recorded on Mercury 400-plus (Varian, Palo Alto, CA, USA), Mercury 500-plus (Varian, Palo Alto, CA, USA) or else on a Varian Inova-600 NMR spectrometer (Varian, Palo Alto, CA, USA). HR-ESI-MS were obtained on orbitrap mass spectrometer (Thermo, Waltham, USA). ECD analysis was carried out using JASCO J-815 (JASCO, Tokyo, Japan).



Scheme 3. Synthesis of the xiamenmycin C and its stereoisomers.

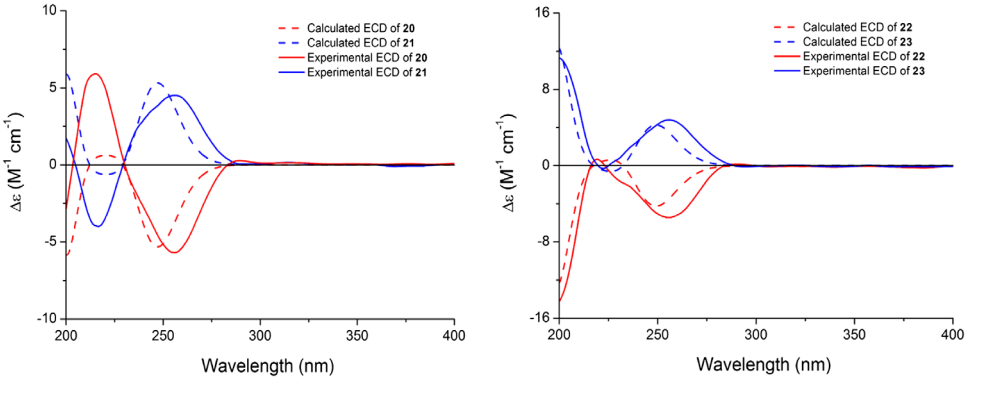


Figure 2. The theoretical CD spectra and experimental CD spectra of **20**, **21**, **22**, **23**.

Solvents were distilled under positive pressure of dry argon before use and dried by standard procedures. All reagents and solvents were purchased from commercial suppliers (Beijing, China). Column chromatography was carried out on silica gel (160–200 mesh). Reactions were monitored using thin-layer silica gel chromatography (TLC) using GF254 (Qingdao Marine Chemical Inc. Qingdao, China).

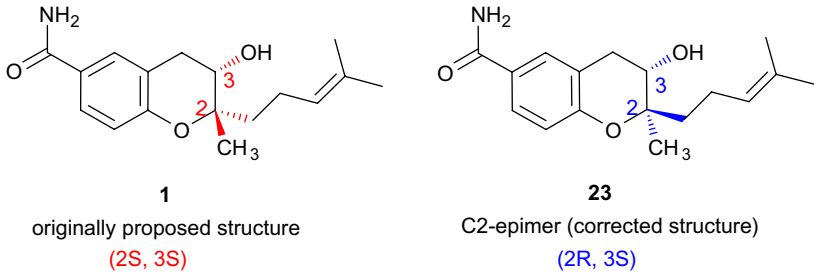


Figure 3. The structure of the proposed xiamenmycin C (**1**) and the corrected xiamenmycin C (**23**).

3.2. (Z)-2-(3,7-Dimethylocta-2,6-dien-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3)

To a solution of neryl acetate (12.60 g, 64.28 mmol) and bis(pinacolato)diboron (16.32 g, 64.28 mmol) in AcOEt (125 ml), bis(1,5-cyclooctadiene)nickel(0) (0.88 g, 3.21 mmol) and tricyclohexylphosphine (0.90 g, 3.21 mmol) were added carefully under argon atmosphere. The mixture was stirred at 60 °C for 10.5 h and then concentrated and purified by column chromatography using PE:AcOEt (200:1) to afford **3** (11 g, 65%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 5.62–5.10 (m, 1H), 4.36–4.23 (m, 1H), 2.06–2.03(m, 2H), 1.79–1.61 (m, 7H), 1.43–1.13 (complex, 18H).

3.3. (Z)-Methyl 3-(3,7-dimethylocta-2,6-dien-1-yl)-4-(methoxymethoxy) benzoate (4)

To a solution of **3** (1.65 g, 6.24 mmol) in 1,4-dioxane (50 ml) methyl 3-bromo-4-(methoxymethoxy)benzoate (1.14 g, 4.16 mmol), $CsCO_3$ (4.06 g, 12.47 mmol), Pd(dppf)Cl_2 (0.30 g, 0.42 mmol) was added under argon atmosphere. After being heated to reflux for 14 h, the reaction mixture was filtered by short column chromatography, and then concentrated under reduced pressure. The residue was purified by column chromatography using PE/DCM(3/1) as eluent affording **4** (1.07 g, 78%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.91–7.79 (m, 2H), 7.06 (d, J = 9.0 Hz, 1H), 5.31 (t, J = 7.4 Hz, 1H), 5.26 (s, 2H), 5.16–5.10 (m, 1H), 3.88 (s, 3H), 3.48 (s, 3H), 3.36 (d, J = 7.3 Hz, 2H), 2.18–2.09 (m, 4H), 1.74 (s, 3H), 1.67 (s, 3H), 1.60 (s, 3H).

3.4. (Z)-Methyl 3-(3,7-dimethylocta-2,6-dien-1-yl)-4-hydroxybenzoate (5)

To a solution of **4** (973 mg, 2.93 mmol) in MeOH (25 ml), CSA (136 mg, 0.59 mmol) was added, then the mixture was stirred at room temperature for one week before quenched with six drops of Et_3 N. The reaction mixture was extracted with CH_2Cl_2, washed with water and brine, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure. The residue was purified by column chromatography using PE:AcOEt (20:1) to afford **5** (625 mg, 74%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.82–7.81 (m, 2H), 6.82 (d, J = 8.9 Hz, 1H), 5.67 (s, 1H), 5.31 (t, J = 7.0 Hz, 1H), 5.14 (t, J = 6.9 Hz, 1H), 3.88 (s, 3H), 3.39 (d, J = 6.9 Hz, 2H), 2.22–2.20 (m, 2H), 2.16–2.14 (m, 2H), 1.78 (s, 3H), 1.69 (s, 3H), 1.62 (s, 3H).

3.5. (2S*,3S*)-Methyl 3-hydroxy-2-methyl-2-(4-methylpent-3-en-1-yl)chroman-6-carboxylate (6) and (R*)-methyl 2-((R*)-2-hydroxy-6-methylhept-5-en-2-yl)-2,3-dihydrobenzofuran-5-carboxylate (6a)

To a solution of **5** (700 g, 2.43 mmol) in DCM (10 ml), $VO(acac)_2$ (10 mg, 0.037 mmol) was added under argon atmosphere, and the mixture was stirred at room temperature. After 5 min, TBHP (4 N, 0.79 ml) and TFA (36 µl, 0.49 mmol) were added. The solution was stirred at 40 °C for 3 h. The solvents were removed under reduced pressure, diluted with CH_2Cl_2, then washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduce pressure. The residue was purified by column chromatography using PE/AcOEt (20/1) as eluent affording **6** (584 mg, 79%) and **6a** (97 mg, 13%) as a colorless oil.

Compound **6**: ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.80 (s, 2H), 6.85 (d, J = 6.4 Hz, 1H), 5.13 (s, 1H), 3.90 (s, 1H), 3.87 (s, 3H), 3.08(d, J = 16 Hz, 1H), 2.85(d, J = 16 Hz, 1H), 2.14–2.10 (m, 2H), 1.78–1.70 (m, 3H), 1.68 (s, 3H), 1.66–1.63 (m, 1H), 1.60 (s, 3H), 1.57–1.55 (m, 1H), 1.29 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 167.0, 157.0, 132.3, 132.0, 129.5, 123.8, 122.3, 118.9, 117.2, 79.5, 77.3, 77.0, 76.8, 68.3, 51.8, 34.7, 30.8, 25.6, 21.8, 21.6, 17.6. HR-ESI-MS: *m/z* 305.1742 $[M+H]^+$ (calcd for $C_{18}H_{25}O_4$, 305.1747). Compound **6a**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.86 (d, J = 8.7 Hz, 2H), 6.78 (d, J = 8.7 Hz, 1H), 5.15 (t, J = 7.3 Hz, 1H), 4.75 (t, J = 9.1 Hz, 1H), 3.87 (s, 3H), 3.24–3.23 (m, 1H), 3.16–3.12 (m, 1H), 2.15–2.13 (m, 2H), 1.76–1.71 (m, 1H), 1.69 (s, 3H), 1.64 (s, 3H), 1.62–1.58 (m, 1H), 1.17 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.9, 163.6, 132.1, 131.0, 129.9, 127.6, 126.7, 124.0, 122.8, 108.9, 89.5, 77.2, 77.0, 76.8, 73.6, 51.8, 38.9, 29.9, 25.7, 22.3, 21.1, 17.7. HR-ESI-MS: *m/z* 305.1744 $[M+H]^+$ (calcd for $C_{18}H_{25}O_4$, 305.1747).

3.6. (2S*,3S*)-3-Hydroxy-2-methyl-2-(4-methylpent-3-en-1-yl)chroman-6-carboxylic acid (7)

To a solution of **6** (254 mg, 0.84 mmol) in MeOH (25 ml), aqueous NaOH (4 N, 1.0 ml) was added dropwise. The mixture was stirred at room temperature for 36 h. The solvents were removed under reduced pressure, diluted with water, and washed with EtOAc. The pH was adjusted to 1~2, and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure affording **7** (237 mg, 98%) as a white solid.

m. p. 145–148 °C. ^{1}H NMR (400 MHz, acetone-d_6) δ (ppm): 7.76 (s, 2H), 6.80 (d, J = 8.4 Hz, 1H), 5.14–5.10 (m, 1H), 3.94–3.91(m, 1H), 3.10–3.05 (m, 1H), 2.84–2.79 (m, 1H), 2.18–2.09 (m, 2H), 1.82–1.76 (m, 1H), 1.63 (s, 3H), 1.59 (s, 1H), 1.56 (s, 3H), 1.34 (s, 3H). ^{13}C NMR (150 MHz, acetone-d_6) δ (ppm): 167.3, 158.1, 132.9, 131.7, 129.8, 125.1, 122.8, 121.1, 117.4, 80.3, 68.6, 34.1, 31.4, 25.6, 22.4, 22.3, 17.4. HR-ESI-MS: *m/z* 291.1588 $[M+H]^+$ (calcd for $C_{17}H_{23}O_4$, 291.1591).

3.7. (2S*,3S*)-3-Hydroxy-2-methyl-2-(4-methylpent-3-en-1-yl)chroman-6-carboxamide (8)

To a solution of **7** (200 mg, 0.69 mmol) in 1,4-dioxane (20 ml), azabenzene (0.50 ml) and di-tert-butyl dicarbonate (2556 mg, 11.70 mmol) were added, then the mixture was stirred at room temperature for 15 min, and ammonium bicarbonate (927 mg, 11.70 mg) was added.

The solution was stirred at room temperature for 3 h, then quenched with saturated aqueous $NaHCO_3$ (50 ml), extracted with EtOAc and dried over anhydrous Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography using DCM/ AcOEt (5/1) as eluent affording **8** (155 mg, 78%) as a white solid.

m. p. 150–151 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 7.73 (s, 1H), 7.62 (s, 1H), 7.58 (d, J = 8.5 Hz, 1H), 7.09 (s, 1H), 6.72 (d, J = 8.0 Hz, 1H), 5.13 (d, J = 5.0 Hz, 1H), 5.07 (t, J = 7.5 Hz, 1H), 3.73 (dt, J = 6.7, 5.2 Hz, 1H), 2.93 (dd, J = 16.9, 5.2 Hz, 1H), 2.64 (dd, J = 16.9, 6.8 Hz, 1H), 2.10–1.95 (m, 2H), 1.68–1.64 (m, 1H), 1.61 (s, 3H), 1.53 (s, 3H), 1.49–1.45 (m, 1H), 1.22 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 167.5, 155.4, 130.7, 129.8, 126.8, 125.8, 124.4, 120.0, 116.0, 79.1, 67.1, 33.1, 30.6, 25.4, 22.0, 21.3, 17.4. HR-ESI-MS: m/z 293.1389 $[M+H]^+$ (calcd for $C_{17}H_{17}ON_4$, 293.1397).

3.8. (E)-2-(3,7-Dimethylocta-2,6-dien-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (10)

10 (9.13 g, 54%) was prepared from geranyl acetate (12.60 g, 64.28 mmol) following the procedure described for **3**.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.64–5.61 (m, 2H), 2.37–1.93 (m, 5H), 1.86–1.54 (m, 6H), 1.52–1.31 (m, 4H), 1.27–1.19 (m, 12H).

3.9. (E)-Methyl 3-(3,7-dimethylocta-2,6-dien-1-yl)-4-(methoxymethoxy)benzoate (11)

11 (811 mg, 61%) was prepared from **10** (1.58 g, 6.0 mmol) following the procedure described for **4**.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.85 (d, 2H), 7.07 (d, J = 9.2 Hz, 1H), 5.33–5.29 (m, 1H), 5.26 (s, 2H), 5.10 (s, 1H), 3.88 (s, 3H), 3.48 (s, 3H), 3.36 (d, J = 7.3 Hz, 2H), 2.09–2.03 (m, 4H), 1.73 (s, 3H), 1.66 (s, 3H), 1.59 (s, 3H).

3.10. (E)-Methyl 3-(3,7-dimethylocta-2,6-dien-1-yl)-4-hydroxybenzoate (12)

12 (320 mg, 62%) was prepared from **11** (660 mg, 1.99 mmol) following the procedure described for **5**.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.91–7.74 (m, 2H), 6.84 (d, J = 8.1 Hz, 1H), 6.13 (s, 1H), 5.32 (t, J = 7.1 Hz, 1H), 5.07 (d, J = 6.0 Hz, 1H), 3.88 (s, 3H), 3.40 (d, J = 7.1 Hz, 2H), 2.15–2.09 (m, 4H), 1.77 (s, 3H), 1.68 (s, 3H), 1.61 (s, 3H).

3.11. (2R*,3S*)-Methyl 3-hydroxy-2-methyl-2-(4-methylpent-3-en-1-yl)chroman-6-carboxylate (13)

13 (800 mg, 80%) was prepared from **12** (1 g, 3.47 mmol) following the procedure described for **6**.

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.80 (d, J = 6.9 Hz, 2H), 6.84 (d, J = 8.9 Hz, 1H), 5.09–5.07 (m, 1H), 3.92–3.89 (m, 1H), 3.87 (s, 3H), 3.08 (dd, J = 16.7, 4.6 Hz, 1H), 2.82 (dd, J = 16.7, 6.0 Hz, 1H), 2.17–2.11 (m, 2H), 1.76–1.74 (m, 1H), 1.68 (s, 3H), 1.64–1.60 (m, 1H), 1.58 (s, 3H), 1.34 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 166.9, 157.1, 132.3,

132.2, 129.5, 123.7, 122.4, 118.9, 117.2, 79.7, 67.8, 51.8, 37.3, 30.9, 25.6, 21.6, 19.2, 17.6. HR-ESI-MS: *m/z* 305.1733 $[M+H]^+$ (calcd for $C_{18}H_{25}O_4$, 305.1747).

3.12. (2R*,3S*)-3-Hydroxy-2-methyl-2-(4-methylpent-3-en-1-yl)chroman-6-carboxylic acid (14)

14 (46 mg, 98%) was prepared from **13** (49 mg, 0.16 mmol) following the procedure described for **7**.

m. p. 146–148 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.87 (d, J = 7.2 Hz, 2H), 6.87 (d, J = 8.6 Hz, 1H), 5.10–5.07 (m, 1H), 3.93 (t, J = 5.6 Hz, 1H), 3.10 (dd, J = 16.9, 5.1 Hz, 1H), 2.85 (dd, J = 16.9, 6.1 Hz, 1H), 2.18–2.11 (m, 2H), 1.67 (s, 3H), 1.64–1.62 (m, 2H), 1.59 (s, 3H), 1.36 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 200.6, 171.3, 157.9, 132.9, 132.4, 130.2, 123.6, 121.4, 119.0, 117.4, 79.8, 67.7, 37.3, 30.9, 25.7, 21.6, 19.2, 17.6. HR-ESI-MS: *m/z* 291.1574 $[M+H]^+$ (calcd for $C_{17}H_{23}O_4$, 291.1591).

3.13. (2R*,3S*)-3-Hydroxy-2-methyl-2-(4-methylpent-3-en-1-yl)chroman-6-carboxamide (15)

15 (48 mg, 97%) was prepared from **14** (50 mg, 0.17 mmol) following the procedure described for **8**.

m. p. 123–125 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.71 (s, 1H), 7.62 (s, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.07 (s, 1H), 6.73 (d, J = 8.4 Hz, 1H), 5.16 (d, J = 4.9 Hz, 1H), 5.10 (t, J = 7.3 Hz, 1H), 3.74 (dt, J = 7.8, 5.2 Hz,1H), 2.92 (dd, J = 16.6, 5.3 Hz, 1H), 2.65 (dd, J = 16.6, 7.8 Hz, 1H), 2.12–2.06 (m, 2H), 1.62 (s, 3H), 1.60–1.58 (m, 2H), 1.55 (s, 3H), 1.15 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 168.1, 155.8, 131.2, 130.0, 127.2, 125.8, 124.5, 120.2, 116.3, 79.5, 66.0, 37.6, 30.9, 25.7, 21.4, 18.7, 17.7. HR-ESI-MS: *m/z* 290.1735 $[M+H]^+$ (calcd for $C_{17}H_{24}O_3$ N, 290.1751).

3.14. (S)-(2S,3S)-6-Carbamoyl-2-methyl-2-(4-methylpent-3-en-1-yl)chroman-3-yl 2-methoxy-2-phenylacetate (16) and (S)-(2R,3R)-6-carbamoyl-2-methyl-2-(4-Methyl-pent-3-en-1-yl)chroman-3-yl 2-methoxy-2-phenylacetate (17)

To a solution of **8** (76 mg, 0.26 mmol) in dry dichloromethane (8 ml), (S)-methoxyphenylacetic acid (48 mg, 0.29 mmol), dicyclohexylcarbodiimide (70 mg, 0.34 mmol) and 4-(dimethylamino)pyridine (4 mg, 0.0057 mmol) were added, and the mixture was stirred at room temperature for 1 h. Then, the reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography using DCM/AcOEt (20/1) as eluent affording **16** (44 mg, 38%) and **17** (47 mg, 41%) as colorless oils.

Compound **16**: $[\alpha]_D^{20}$ +4.2 (*c* 0.5, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.58–7.56 (m, 2H), 7.38–7.36 (m, 2H), 7.34–7.32 (m, 3H), 6.86–6.84 (m, 1H), 5.05 (t, J = 4.8 Hz, 1H), 4.70 (s, 1H), 4.66 (t, J = 7.2 Hz, 1H), 3.36 (s, 3H), 3.12 (dd, J = 17.4, 4.8 Hz, 1H), 2.87 (dd, J = 17.4, 4.7 Hz, 1H), 1.66 (m, 2H), 1.61 (s, 3H), 1.48 (s, 3H), 1.34–1.32 (m, 2H), 1.08 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 170.0, 168.9, 156.1, 135.9, 131.6, 129.8, 128.9, 128.7, 127.3, 127.1, 125.4, 123.4, 118.3, 117.3, 82.2, 77.8, 70.2, 57.1, 34.8, 28.0, 25.6, 21.5, 21.4, 17.5. HR-ESI-MS: *m/z* 438.2258 $[M+H]^+$ (calcd for $C_{26}H_{32}O_5$ N, 438.2275). Compound **17**: $[\alpha]_D^{20}$ +59.3 (*c* 1.0, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.56 (dd, 1H, J = 8.4, 1.8 Hz),

7.26–7.23 (m, 3H), 7.18–7.15 (m, 2H), 6.84 (d, J = 8.4 Hz, 1H), 5.11 (t, J = 4.4, 1.0 Hz, 1H), 5.05 (m, 1H), 4.73 (s, 1H), 3.36 (s, 3H), 2.94 (dd, J = 17.4, 4.4 Hz, 1H), 2.47 (dd, J = 17.4, 4.2 Hz, 1H), 2.10–2.06 (m, 2H), 1.72–1.68 (m, 2H), 1.68 (s, 3H), 1.61 (s, 3H), 1.59 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 170.1, 168.7, 155.9, 135.6, 132.2, 129.6, 128.6, 128.4, 127.1, 126.6, 125.2, 123.5, 117.9, 117.1, 82.2, 77.7, 70.2, 57.3, 35.6, 27.5, 25.7, 21.8, 21.6, 17.6. HR-ESI-MS: m/z 438.2262 $[M+H]^+$ (calcd for $C_{26}H_{32}O_5$ N, 438.2275).

3.15. (S)-(2S,3R)-6-Carbamoyl-2-methyl-2-(4-methylpent-3-en-1-yl)chroman-3-yl 2-methoxy-2-phenylacetate (18) and (S)-(2R,3S)-6-carbamoyl-2-methyl-2-(4-methylpent-3-en-1-yl)chroman-3-yl 2-methoxy-2-phenylacetate (19)

18 (30 mg, 44%) and **19** (25 mg, 37%) were prepared from **15** (45 mg, 0.16 mmol) following the procedure described for **16**.

Compound **18**: $[\alpha]_D^{20}$ +13.6 (c 0.5, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.56 (d, J = 8.5 Hz, 1H), 7.30 (s, 1H), 7.26 (s, 3H), 7.23–7.21 (m, 2H), 7.21–7.19 (m, 1H), 6.84 (d, J = 8.5 Hz, 1H), 5.81 (s, 2H), 5.12 (t, J = 4.7 Hz, 1H), 5.01–4.96 (m, 1H), 4.76 (s, 1H), 3.39 (s, 3H), 2.98 (dd, J = 17.2, 4.3 Hz, 1H), 2.45 (dd, J = 17.2, 4.8 Hz, 1H), 2.11–2.04 (m, 3H), 1.68 (s, 2H), 1.64 (s, 3H), 1.54 (s, 3H), 1.53–1.46 (m, 2H), 1.32 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 170.1, 168.7, 156.0, 135.7, 132.4, 129.6, 128.6, 128.5, 127.1, 126.7, 125.2, 123.2, 118.0, 117.1, 82.2, 77.7, 77.2, 77.0, 76.8, 70.1, 57.3, 37.1, 29.7, 27.5, 25.6, 21.5, 20.2, 17. 6. HR-ESI-MS: m/z 438.2264 $[M+H]^+$ (calcd for $C_{26}H_{32}O_5$ N, 438.2275). Compound **19**: $[\alpha]_D^{20}$ +74.2 (c 0.5, MeOH); ^{1}H NMR (500 MHz, acetone-d_6) δ (ppm): 7.71 (d, J = 8.0 Hz, 1H), 7.68 (s, 1H), 7.39–7.41 (m, 2H), 7.36–7.34 (m, 3H), 7.26 (s, 1H), 6.81 (d, J = 8 Hz, 1H), 6.42 (s, 1H), 5.10–5.07 (m, 1H), 4.91–4.88 (m, 1H), 4.85 (s, 1H), 3.36 (s, 3H), 3.20 (dd, J = 5.5 Hz, 1H), 2.87–2.85 (m, 1H), 2.03–1.93 (m, 1H), 1.59 (s, 3H), 1.49 (s, 3H), 1.41–1.34 (m, 2H), 1.05 (s, 3H). ^{13}C NMR (150 MHz, acetone-d_6) δ (ppm): 170.4, 168.3, 156.2, 137.7, 132.0, 129.3, 129.2, 128.1, 128.1, 127.5, 124.4, 119.0, 117.3, 82.9, 78.3, 70.4, 70.4, 57.3, 37.5, 28.6, 25.6, 21.9, 19.7, 17.5. HR-ESI-MS: m/z 438.2263 $[M+H]^+$ (calcd for $C_{26}H_{32}O_5$ N: 438.2275).

3.16. (2S,3S)-3-Hydroxy-2-methyl-2-(4-methylpent-3-en-1-yl)chroman-6-carboxamide (20)

To a solution of **16** (20 mg, 0.046 mmol) in MeOH (2 ml), a solution of MeONa in MeOH (25% w/w, 16 µL, 0.069 mmol) was added at 0 °C, and the mixture was stirred at room temperature for 3 h. The reaction mixture was quenched with HCl (2 N, 1 ml), and the product was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure. Then, the crude material was purified by column chromatography using DCM/MeOH (20/1) as eluent affording **20** (11 mg, 83%) as a colorless solid.

Compound **20**: m. p. 41–43 °C. $[\alpha]_D^{20}$ −16.99 (c 0.206, MeOH); ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 7.72 (s, 1H), 7.62 (s, 1H), 7.59 (dd, J = 8.5, 2.0 Hz, 1H), 7.07 (s, 1H), 6.72 (d, J = 8.5 Hz, 1H), 5.11 (d, J = 4.8 Hz, 1H), 5.08 (t, J = 7.8 Hz, 1H), 3.73 (dd, J = 11.5, 5.1 Hz, 1H), 2.93 (dd, J = 16.8, 5.0 Hz, 1H), 2.65 (dd, J = 16.9, 6.8 Hz, 1H), 2.12–1.89 (m, 2H), 1.66–1.62 (m, 1H), 1.61 (s, 3H), 1.52 (s, 3H), 1.50–1.46 (m, 1H), 1.23 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 167.5, 155.3, 130.7, 129.8, 126.8, 125.8, 124.4, 120.0, 116.0,

79.1, 67.2, 33.0, 30.6, 25.4, 22.0, 21.3, 17.4. HR-ESI-MS: *m/z* 290.1740 $[M+H]^+$ (calcd for $C_{17}H_{24}O_3N$, 290.1751).

3.17. (2R,3R)-3-Hydroxy-2-methyl-2-(4-methylpent-3-en-1-yl)chroman-6-carboxamide (21)

21 (26 mg, 96%) was prepared from **17** (40 mg, 0.092 mmol) following the procedure described for **20**.

Compound **21**: m. p. 158–160 °C. $[\alpha]_D^{20}$ +19.81 (*c* 0.369, MeOH); ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 7.74 (s, 1H), 7.63 (d, *J* = 2.2 Hz, 1H), 7.60 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.09 (s, 1H), 6.74 (d, *J* = 8.5 Hz, 1H), 5.13 (d, *J* = 4.8 Hz, 1H), 5.09 (t, *J* = 7.1 Hz, 1H), 3.74 (dt, J = 6.7, 5.1 Hz,1H), 2.95 (dd, *J* = 16.9, 5.1 Hz, 1H), 2.66 (dd, *J* = 16.9, 6.8 Hz, 1H), 2.08–2.00 (m, 2H), 1.69–1.64 (m, 1H), 1.62 (s, 3H), 1.51 (s, 3H), 1.52–1.47 (m, 1H), 1.24 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 167.6, 155.3, 130.7, 129.8, 126.8, 125.8, 124.4, 120.0, 116.0, 79.1, 67.2, 33.1, 30.6, 25.4, 22.0, 21.3, 17.4. HR-ESI-MS: *m/z* 290.1741 $[M+H]^+$ (calcd for $C_{17}H_{24}O_3N$, 290.1751).

3.18. (2S,3R)-3-Hydroxy-2-methyl-2-(4-methylpent-3-en-1-yl)chroman-6-carboxamide (22)

22 (15 mg, 91%) was prepared from **18** (25 mg, 0.057 mmol) following the procedure described for **20**.

Compound **22**: m. p. 117–119 °C. $[\alpha]_D^{20}$ −11.18 (*c* 0.93, MeOH); ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 7.73 (s, 1H), 7.63 (d, *J* = 2.2 Hz, 1H), 7.60 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.09 (s, 1H), 6.74 (d, *J* = 8.5 Hz, 1H), 5.18 (d, *J* = 5.0 Hz, 1H), 5.11 (t, *J* = 7.1 Hz, 1H), 3.75 (dt, *J* = 7.8, 5.2 Hz, 1H), 2.93 (dd, *J* = 16.6, 5.2 Hz, 1H), 2.67 (dd, *J* = 16.6, 7.8 Hz, 1H), 2.12–2.08 (m, 2H), 1.64 (s, 3H), 1.60–1.58 (m, 2H), 1.56 (s, 3H), 1.16 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 167.5, 155.5, 130.8, 129.7, 126.9, 125.8, 124.3, 119.9, 116.0, 79.2, 65.8, 37.5, 30.8, 25.4, 21.1, 18.3, 17.4. HR-ESI-MS: *m/z* 290.1739 $[M+H]^+$ (calcd for $C_{17}H_{24}O_3N$, 290.1751).

3.19. (2R,3S)-3-hydroxy-2-methyl-2-(4-methylpent-3-en-1-yl)chroman-6-carboxamide (23)

23 (10 mg, 92%) was prepared from **19** (16 mg, 0.036 mmol) following the procedure described for **20**.

Compound **23**: m. p. 47–49 °C. $[\alpha]_D^{20}$ +10.43 (*c* 0.23, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.72 (s, 1H), 7.63 (d, *J* = 2.0 Hz, 1H), 7.58 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.07 (s, 1H), 6.73 (d, *J* = 8.4 Hz, 1H), 5.17–5.15 (m, 1H), 5.09 (t, *J* = 7.1 Hz, 1H), 3.73 (dt, *J* = 7.7, 5.4 Hz,1H), 2.92 (dd, *J* = 16.6, 5.2 Hz, 1H), 2.65 (dd, *J* = 16.6, 7.8 Hz, 1H), 2.12–2.04 (m, 2H), 1.62 (s, 3H), 1.60–1.58 (m, 2H), 1.55 (s, 3H), 1.15 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 167.5, 155.5, 130.9, 129.8, 126.9, 125.7, 124.3, 119.9, 116.0, 79.3, 65.8, 37.5, 30.8, 25.5, 21.2, 18.4, 17.5. HR-ESI-MS: *m/z* 290.1738 $[M+H]^+$ (calcd for $C_{17}H_{24}O_3N$, 290.1751).

Disclosure statement

No potential conflict of interest was reported by the authors.

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