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Tetrahedron: *Asymmetry* 15 (2004) 29–34
Tetrahedron: *Asymmetry*

The first asymmetric total synthesis of several 3,4-dihydroxy-2,2-dimethyl-chroman derivatives

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Received 15 July 2003; revised 9 October 2003; accepted 16 October 2003

Abstract—The stereoisomers of 3,4-dihydroxy-6-methoxy-2,2-dimethyl-chroman **1a–c** and 3,4,7-trihydroxy-6-acetyl-2,2-dimethyl-chroman **2a–c** were conveniently prepared for the first time via a synthesis in which Sharpless asymmetric dihydroxylation and Jacobsen's catalytic asymmetric epoxidation are the key steps.

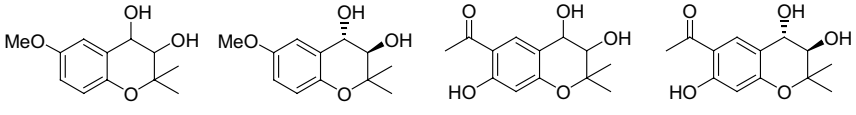
1. Introduction

3,4-Dihydroxy-2,2-dimethyl-chroman derivatives, which are of great interest because of their diverse physiological properties,[1] occur widely in plants. *cis* and *trans*-3,4-Dihydroxy-6-methoxy-2,2-dimethyl-chromans **1a–c** were isolated from the basidomycete *Panus rudis* Fr.[2] *cis* and *trans*-3,4,7-Trihydroxy-6-acetyl-2,2-dimethyl-chromans **2a–c** were isolated from *Helianthella quinquenervis*.[3] Among them, only **1c** was isolated as a non-racemic compound (Fig. 1). To the best of our knowledge, the total synthesis of the above nature products has not been reported. In order to study the relationship between structure and activity of these compounds, we describe herein their enantioselective total synthesis from the readily available hydroquinone **3** and resorcin **9** by use of the Sharpless AD reaction[4] and the Jacobsen's AE reaction[5] as a key step, respectively.

2. Results and discussion

2.1. Enantioselective synthesis of 1a, 1b, and 1c

As shown in Scheme 1, commercially available hydroquinone **3**, was reacted with 2-methyl-3-butene-2-ol in 80% HCOOH solution under reflux to give **4a** in moderate yield,[6] which was easily converted into the corresponding methyl ether **4b** in 90% yield. Oxidation of **4b** with pyridinium chlorochromate (PCC)[7] produced chromanone **5** in 90% yield. The key intermediate, chromane **7**, was obtained by reduction of **5** with $NaBH_4$ followed by dehydration with *p*-TsOH/THF.[8] Treatment of **7** with AD-mix-α and AD-mix-β[4a] stereoselectively afforded *cis*-diols **1a** $\{[\alpha]_D^{25} = +5.4$ (*c* 4.30, $CHCl_3)\}$ and **1b** $\{[\alpha]_D^{25} = -8.4$ (*c* 3.14, $CHCl_3)\}$, respectively. The absolute configurations of **1a** and **1b** were determined as (3*R*,4*R*) and (3*S*,4*S*).[4b] In addition, in the



1a (3*R*,4*R*)
1b (3*S*,4*S*)

1c (3*R*,4*S*)

2a (3*R*,4*R*)
2b (3*S*,4*S*)

2c (3*R*,4*S*)

Figure 1.

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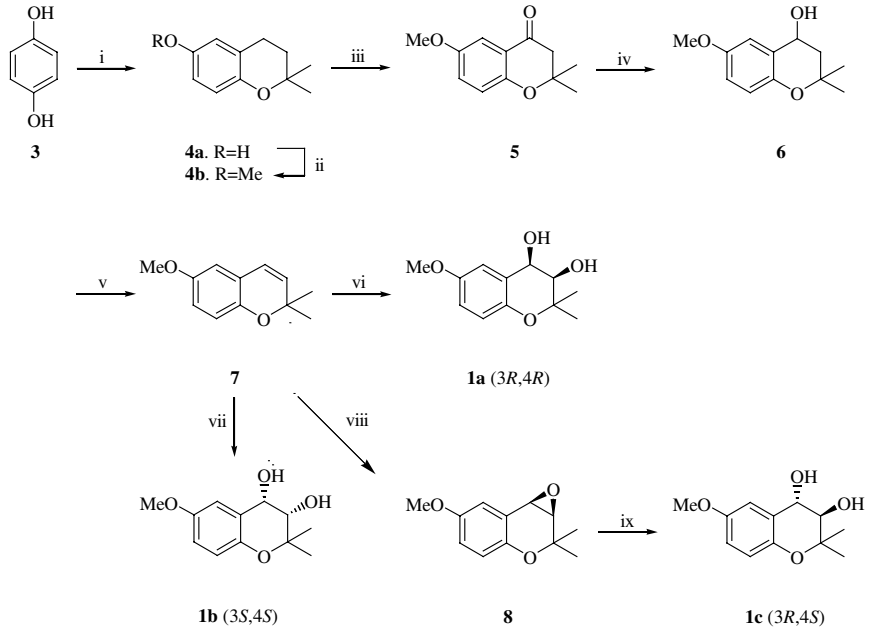
doi:10.1016/j.tetasy.2003.10.040



Scheme 1. Reagents and conditions: (i) 2-methyl-3-butene-2-ol, 80% HCOOH, reflux, 4 h, 56%; (ii) MeI, K_2CO_3, acetone, rt, 24 h, 90%; (iii) PCC, CH_2Cl_2, reflux, 12 h, 90%; (iv) $NaBH_4$, MeOH, rt, 0.5 h, 95%; (v) *p*-TsOH, THF, reflux, 4 h, 90%; (vi) AD-mix-α, $MeSO_2NH_2$, *t*-BuOH, H_2O, 0 °C, rt, 18 h, 67%; (vii) AD-mix-β, $MeSO_2NH_2$, *t*-BuOH, H_2O, 0 °C, rt, 18 h, 65%; (viii) Jacobsen's (*R*,*R*)-(−)-salen-Mn(III), *m*-CPBA, NMO, CH_2Cl_2, −78 °C, rt, 2 h, 80%; (ix) $Ti(O^iPr)_4$, H_2O, THF, rt, 4 h, 93%.

presence of Jacobsen's (*R*,*R*)-(−)-salen-Mn(III) catalyst,[5b] epoxidation of the chromene **7** with the combination of *m*-chloroperbenzoic acid (*m*-CPBA) and *N*-methylmorphdine-*N*-oxide (NMO) under the anhydrous low temperature conditions (−78 °C) rapidly furnished the expected epoxide **8** with very high enantioselectivity (97% ee) in 80% yield. Finally, treatment of epoxide **8** with $Ti(O^iPr)_4$ and H_2O produced the desired *trans*-diol **1c** (3*R*,4*S*) as the only identifiable product resulting from the regioselective ring opening in 93% yield.[1] The improvement of stereoselectivity in opening the epoxide **8** could be understood by considering that the coordination of the epoxy-pyran with the metal center occurred in a bidentate manner, similar to that of Sharpless' selective epoxy alcohol opening.[9] The physical properties for **1c**[2] $[\alpha]_D^{25} = -31$ (*c* 3.2, acetone) agree with those described for the nature product $\{[\alpha]_D^{25} = -33$ (*c* 0.46, $CHCl_3)\}$, the absolute configuration of *trans*-diol **1c** was determined as (3*R*,4*S*).

2.2. Enantioselective synthesis of 2a, 2b, and 2c

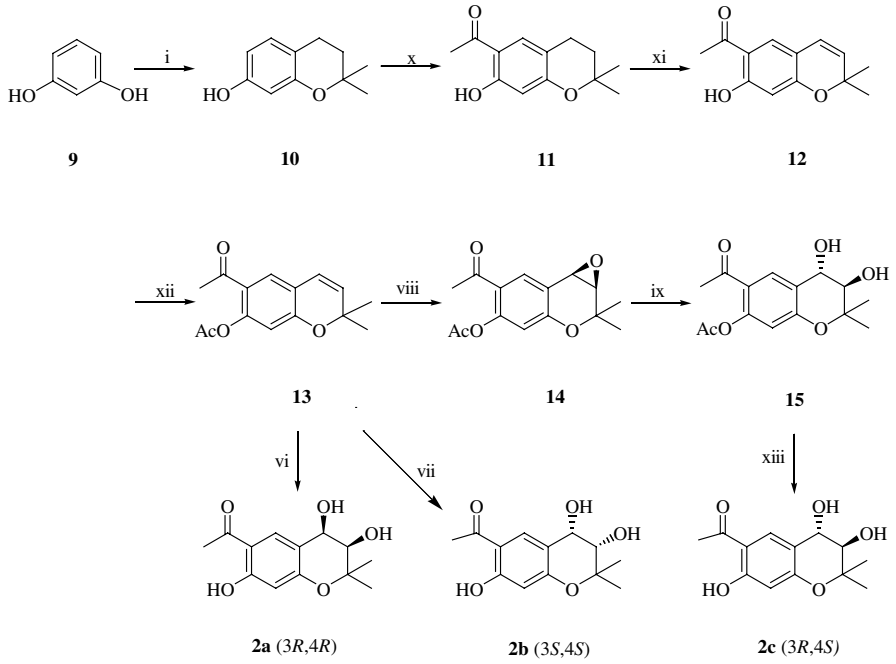
Adopting the same strategy as that of Scheme 1, the desired intermediate **10** can be easily obtained from resorcin **9** in 65% yield[6] (Scheme 2), and then compound **10** was acylated with acetyl chloride in the presence of aluminum chloride in methylene dichloride to produce expected compound **11**,[10] which was dehydrogenated by DDQ in refluxing benzene to give **12** in 95% yield.[6] After the acetalization of **12**, *cis*-diols **2a** (3*R*,4*R*) and **2b** (3*S*,4*S*) were obtained in one step by use of the Sharpless AD reaction.[4] In a similar manner to before, the epoxide **14**, which was prepared by the Jacobsen's AE reaction[5b] of the key intermediate **13**, produced compound **15**, which was hydrolyzed with K_2CO_3 in MeOH/H_2O to gave the *trans*-diol **2c** (3*R*,4*S*) in 90% yield.

In summary, we have successfully achieved the highly enantioselective total synthesis of natural chromans **1a**–**c** and **2a**–**c** using the one-step construction of 2,2-dimethylchroman ring followed by an asymmetric dihydroxylation and epoxidation protocol as the key steps. Application of this sequence to the enantioselective synthesis of other kinds of more complex natural products incorporating the corresponding crucial chroman core structures is currently ongoing in our group.

3. Experimental

3.1. General

Melting points were measured on a Kofler apparatus and were uncorrected. The ^1H and ^{13}C NMR data were recorded in $CDCl_3$ or DMSO-d_6 solution with Bruker AM-200, AM-300 or AM-400 MHz spectrometer. The chemical shifts are reported in ppm relative to TMS. Optical rotations were determined on a JASCO J-20C polarimeter with 0.2 dm tube. Mass spectra were measured with EI (70 eV) technique. Chiral analysis was performed on Varian Dynamax SD-300 using chiralcel column CDMPC (150×4.6 mm ∅) with hexane/isopropyl alcohol as eluent. Column chromatographs were generally performed on silica gel (200–300 mesh) eluting with petroleum ether and ethyl acetate.



Scheme 2. Reagents and conditions: (i) 2-methyl-3-butene-2-ol, 80% HCOOH, reflux, 4 h, 65%; (x) CH_3COCl, $AlCl_3$, CH_2Cl_2, −10 °C, rt, 2 h, 60%; (xi) DDQ, benzene, reflux, 4 h, 95%; (xii) Ac_2O, pyridine, CH_2Cl_2, rt, 18 h, 90%; (vi) AD-mix-α, $MeSO_2NH_2$, *t*-BuOH, H_2O, 0 °C, rt, 18 h, 60%; (vii) AD-mix-β, $MeSO_2NH_2$, *t*-BuOH, H_2O, 0 °C, rt, 18 h, 62%; (viii) Jacobsen's (*R*,*R*)-(−)-salen-Mn(III), *m*-CPBA, NMO, CH_2Cl_2, −78 °C, rt, 2 h, 74%; (ix) $Ti(O^iPr)_4$, H_2O, THF, rt, 4 h, 90%; (xiii) K_2CO_3, $MeOH/H_2O$, rt, 0.5 h, 90%.

3.2. 6-Hydroxy-2,2-dimethyl-chroman, 4a

To a solution of **3** (5.50 g, 50.00 mmol) in 80% HCOOH was added 2-methyl-3-butene-2-ol (2.60 mL, 24.80 mmol). The mixture was heated under refluxing for 4 h. After being cooled, the solution was poured into water (300 mL) and neutralized with $NaHCO_3$ to pH 7–8. The aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic extracts were dried with anhydrous Na_2SO_4 and the solvent was evaporated in vacuo. The crude products were purified by column chromatography using petroleum ether and ethyl acetate (20:1, v/v) to afford **4a** (2.47 g, 56%) as white needle crystals. Mp 73–74 °C. ^1H NMR (200 MHz, $CDCl_3$): δ 1.29 (s, 6H, CH_3), 1.74 (t, 2H, $J = 6.8$ Hz, 3-H), 2.70 (t, 2H, $J = 6.8$ Hz, 4-H), 4.42 (s, 1H, Ar–OH), 6.53–6.65 (m, 3H, Ar-H). MS (EI): m/z 178 (M^+, 46), 163 (17), 123 (100), 94 (20), 77 (10).

3.3. 6-Methoxy-2,2-dimethyl-chroman, 4b

To a solution of **4a** (2.14 g, 12.00 mmol) in acetone (20 mL) were added anhydrous K_2CO_3 (5.00 g, 36.00 mmol) and 1 mL MeI (2.00 g, 12.00 mmol), and the mixture was stirred at room temperature for 24 h. On completion of the reaction, acetone was distilled off and water was added to the residue. It was then extracted with ether, and the organic extracts were washed with water, dried with anhydrous Na_2SO_4, and the solvent was evaporated. The residue was flash chromatographed using petroleum ether and ethyl acetate (50:1, v/v) to give the compound **4b** as a colorless oil (2.07 g, 90%). ^1H NMR (200 MHz, $CDCl_3$): δ 1.30 (s, 6H, CH_3), 1.79 (t, 2H, $J = 6.8$ Hz, 3-H), 2.76 (t, 2H, $J = 6.8$ Hz, 4-H), 3.73 (s, 3H, OCH_3), 6.61–6.72 (m, 3H, Ar-H). MS (EI): m/z 192 (M^+, 37), 177 (8), 137 (100), 108 (28), 91 (13), 77 (32).

3.4. 6-Methoxy-2,2-dimethyl-4-chromanone, 5

To a solution of compound **4b** (2.00 g, 10.40 mmol) in methylene dichloride (20 mL) was added pyridinium chlorochromate (PCC) (2.24 g, 10.40 mmol) and the reaction mixture was heated under refluxing for 12 h. The reaction mixture was cooled to room temperature and 10 mL of ether was added, then, the product filtered through neutral Al_2O_3. The residue was washed with 100 mL of ether and the eluate was then passed through the column using petroleum ether and ethyl acetate (15:1, v/v) to afford **5** (1.93 g, 90%) as white needle crystals. Mp 72–74 °C. ^1H NMR (200 MHz, $CDCl_3$): δ 1.49 (s, 6H, CH_3), 2.73 (s, 2H, 3-H), 3.82 (s, 3H, OCH_3), 6.86–7.32 (m, 3H, Ar-H). MS (EI): m/z 206 (M^+, 34), 191 (100), 151 (69), 135 (15), 122 (15), 107 (32), 79 (35).

3.5. 6-Methoxy-2,2-dimethyl-4-chromanol, 6

To a solution of **5** (1.92 g, 9.30 mmol) in methanol (15 mL) was added $NaBH_4$ (0.35 g, 9.30 mmol), and the mixture stirred for 0.5 h. Then water was added, the mixture was extracted with EtOAc, and the combined organic layer was washed with brine and then dried with

anhydrous Na_2SO_4. Evaporation of the solvent gave the crude product **6** (1.84 g). The alcohol **6** was used directly in the next step.

3.6. 6-Methoxy-2,2-dimethyl-3-chromene, 7

To a solution of *p*-TsOH (catalytic amount) in THF (10 mL) was added alcohol **6** (1.79 g, 8.60 mmol), and the mixture was refluxed for 4 h under N_2. Then 10% NaOH (10 mL) was added, and the mixture was extracted with CH_2Cl_2. The organic phase was washed with 10% NaOH (3 × 10 mL), brine, and water and dried with anhydrous Na_2SO_4. The crude product was purified by column chromatography using petroleum ether and ethyl acetate (50:1, v/v) to give compound **7** as colorless oil (1.36 g, 90%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.43 (s, 6H, CH_3), 3.77 (s, 3H, OCH_3), 5.67 (d, 1H, $J = 9.8$ Hz, 3-H), 6.32 (d, 1H, $J = 9.8$ Hz, 4-H), 6.56–6.76 (m, 3H, Ar-H). MS (EI): m/z 190 (M^+, 14), 175 (100), 160 (10), 132 (22), 91 (9), 77 (14).

3.7. (3*R*,4*R*)-3,4-Dihydroxy-6-methoxy-2,2-dimethyl-chroman, 1a

To a stirred solution of *t*-BuOH (5 mL) and H_2O (5 mL), AD-mix-α (1.40 g) and $MeSO_2NH_2$ (95 mg) were added, the mixture was stirred at room temperature until both phases were clear, and then cooled to 0 °C. Compound **7** (0.19 g, 1.00 mmol) was added immediately. The mixture was stirred vigorously at 0 °C until TLC revealed the absence of **7**. The reaction was quenched at 0 °C by addition of Na_2SO_3 (1.50 g), then warmed to room temperature and stirred for 0.5 h. The reaction mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic layer was washed with a 2 N KOH solution, water, dried with anhydrous Na_2SO_4. The solvent was distilled off, and the residue was flash chromatographed using petroleum ether and ethyl acetate (5:1, v/v) to afford the diol **1a** (0.15 g, 67%, ee 70%) as colorless needles. Mp 142–144 °C. $[\alpha]_D^{25} = +5.4$ (*c* 4.30, $CHCl_3$). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.15 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 3.52 (dd, 1H, $J = 4.3$, 4.2 Hz, 3-H), 3.67 (s, 3H, OCH_3), 4.62 (m, 1H, 4-H), 4.77 (d, 1H, $J = 4.6$ Hz, 3-OH), 5.11 (d, 1H, $J = 7.6$ Hz, 4-OH), 6.57–6.94 (m, 3H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 24.2, 24.5, 55.3, 64.2, 70.3, 77.2, 112.7, 114.4, 116.3, 124.5, 146.4, 152.7. MS (EI): m/z 224 (M^+, 19), 152 (100), 137 (47), 125 (25), 95 (15), 80 (23). HRMS calcd for $C_{12}H_{16}O_4Na$ (M+Na): 247.0941. Found $(M+Na)^+$: 247.0941.

3.8. (3*S*,4*S*)-3,4-Dihydroxy-6-methoxy-2,2-dimethyl-chroman, 1b

As similar procedure as preparation of compound **1a**, treatment of compound **7** (0.19 g, 1.00 mmol) with AD-mix-β (1.40 g) and $Me_2SO_2NH_2$ (95 mg) at 0 °C in *t*-BuOH/H_2O afforded **1b** using petroleum ether and ethyl acetate (5:1, v/v) as colorless needles (0.15 g, 65%). Mp 142–144 °C. $[\alpha]_D^{25} = -8.4$ (*c* 3.14, $CHCl_3$, ee 70%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.15 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 3.52 (dd, 1H, $J = 4.8$, 3.9 Hz, 3-H), 3.67 (s, 3H, OCH_3), 4.62 (m, 1H, 4-H), 4.74 (d, 1H, $J = 4.5$ Hz, 3-OH), 5.09 (d, 1H, $J = 7.5$ Hz, 4-OH), 6.56–6.94 (m, 3H, Ar-H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 29.7, 30.0, 60.7, 69.6, 75.7, 82.6, 118.1, 119.9, 121.8, 129.9, 151.8, 158.1. MS (EI): m/z 224 (M^+, 9), 152 (42), 137 (21), 125 (12), 95 (51), 80 (100). HRMS calcd for $C_{12}H_{16}O_4Na$ (M+Na): 247.0941. Found $(M+Na)^+$: 247.0940.

3.9. 6-Methoxy-3,4-epoxy-2,2-dimethyl-chroman, 8

To a solution of **7** (0.70 g, 4.00 mmol) in CH_2Cl_2 was added Jacobsen's (*R*,*R*)-(−)-salen-Mn(III) catalyst (12.60 mg, 0.20 mmol) and NMO (2.34 g, 20.00 mmol). The solution was cooled to −78 °C. Then *m*-CPBA (1.38 g, 8.00 mmol) in two roughly equal portions was added. The reaction was monitored by TLC, upon consumption of the olefin, the reaction was quenched by the addition of a solution of dimethyl sulfide (1.15 g, 18.50 mmol) in CH_2Cl_2 (3 mL) precooled to −78 °C. A solution of 2 N NaOH (10 mL) was then added and the organic layer was separated, washed with distilled water, and dried with anhydrous Na_2SO_4. After solvent removal, the crude product was purified by flash chromatography on silica gel using petroleum ether and ethyl acetate (15:1, v/v) to afford **8** as white needles (0.66 g, 80%). Mp 90–92 °C. $[\alpha]_D^{25} = +13$ (*c* 5.00, $CDCl_3$, ee >97%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.39 (s, 6H, CH_3), 3.54 (d, 1H, $J = 4.4$ Hz, 3-H), 3.81 (s, 3H, OCH_3), 3.96 (d, 1H, $J = 4.4$ Hz, 4-H), 6.63–6.94 (m, 3H, Ar-H). MS (EI): m/z 206 (M^+, 78), 191 (8), 178 (50), 163 (100), 135 (27), 108 (15), 91 (14), 77 (23).

3.10. (3*R*,4*S*)-3,4-Dihydroxy-6-methoxy-2,2-dimethyl-chroman, 1c

To a solution of **8** (0.62 g, 3.00 mmol) in dry THF (10 mL) was added $Ti(O^iPr)_4$ (1.46 mL, 4.95 mmol) at 0 °C under argon atmosphere. After 5 min, H_2O (1 mL) was added and the mixture was stirred at room temperature for 4 h. Then the reaction mixture was diluted with Et_2O (60 mL), and 5% H_2SO_4 (10 mL) was added. The aqueous phase was extracted with EtOAc (3 × 30 mL). The combined organic extracts were dried with anhydrous Na_2SO_4, and the solvent was evaporated. The crude product was purified by column chromatography using petroleum ether and ethyl acetate (5:1, v/v) to afford **1c** (0.62 g, 93%) as colorless needles. Mp 77–78 °C. $[\alpha]_D^{25} = -31$ (*c* 3.2, acetone) {lit.[2] $[\alpha]_D^{25} = -33$ (*c* 0.46 in $CHCl_3$)}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.06 (s, 3H, CH_3), 1.31 (s, 3H, CH_3), 3.33 (dd, 1H, $J = 8.0$, 5.2 Hz, 3-H), 3.67 (s, 3H, OCH_3), 4.27 (m, 1H, $J = 8.0$, 6.8 Hz, 4-H), 5.42 (d, 1H, $J = 4.8$ Hz, 3-OH), 5.48 (d, 1H, $J = 6.4$ Hz, 4-OH), 6.58–6.90 (m, 3H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 19.0, 26.8, 55.3, 68.2, 74.8, 78.1, 112.4, 114.8, 116.7, 126.3, 145.8, 153.0. MS (EI): m/z 224 (M^+, 15), 152 (71), 137 (27), 125 (15), 43 (100). HRMS calcd for $C_{12}H_{16}O_4Na$ (M+Na): 247.0941. Found $(M+Na)^+$: 247.0941.

3.11. 7-Hydroxy-2,2-dimethyl-chroman, 10

To a solution of **9** (5.50 g, 50.00 mmol) in 80% HCOOH was added 2-methyl-3-butene-2-ol (2.60 mL, 24.80 mmol). The mixture was heated under refluxing for 4 h. After being cooled, the solution was poured into water (300 mL) and neutralized with $NaHCO_3$ to pH 7–8. The aqueous phase was extracted with EtOAc (3×50 mL). The combined organic extracts were dried with anhydrous Na_2SO_4 and the solvent was evaporated. The crude product was purified by column chromatography using petroleum ether and ethyl acetate (15:1, v/v) to afford **10** (2.49 g, 65%) as white needles. Mp 62–64 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.32 (s, 6H, CH_3), 1.77 (t, 2H, $J = 6.8$ Hz, 3-H), 2.72 (t, 2H, $J = 6.8$ Hz, 4-H), 6.56–6.65 (m, 3H, Ar-H). MS (EI): m/z 178 (M^+, 28), 163 (15), 123 (100), 94 (7), 77 (6).

3.12. 6-Acetyl-7-hydroxy-2,2-dimethyl-chroman, 11

To a solution of **11** (2.40 g, 13.50 mmol) in CH_2Cl_2 (30 mL), acetyl chloride (0.96 mL, 13.50 mmol) was added dropwise to keep the reaction temperature below −5 °C. Then anhydrous $AlCl_3$ (1.80 g, 13.50 mmol) was added portionwise. After stirring for 2 h, the mixture was poured into ice-water and extracted with CH_2Cl_2. The combined organic layer was successively washed with saturated $NaHCO_3$ and brine, then dried with anhydrous Na_2SO_4. After column chromatography purification using petroleum ether and ethyl acetate (10:1, v/v), the compound **11** (1.78 g, 60%) was obtained as colorless needles. Mp 116–117 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.33 (s, 6H, CH_3), 1.80 (t, 2H, $J = 6.8$ Hz, 3-H), 2.51 (s, 3H, CH_3CO), 2.71 (t, 2H, $J = 6.8$ Hz, 4-H), 6.28 (s, 1H, Ar-H), 7.41 (s, 1H, Ar-H), 12.32 (s, 1H, Ar–OH). MS (EI): m/z 220 (M^+, 19), 205 (15), 165 (100), 147 (13), 77 (7), 43 (55).

3.13. 6-Acetyl-7-hydroxy-2,2-dimethyl-3-chromene, 12

The compound **11** (1.76 g, 8.00 mmol) and DDQ (1.76 g, 7.75 mmol) were refluxed in benzene (20 mL) for 4 h. After the mixture was cooled and filtered, the filtrate was evaporated to dryness. The resulting yellow solid was chromatographed over silica gel using petroleum ether and ethyl acetate (10:1, v/v) to give pure **12** (1.66 g, 95%) as yellow needles from hexane. Mp 74–76 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.44 (s, 6H, CH_3), 2.55 (s, 3H, CH_3CO), 5.59 (d, 1H, $J = 9.8$ Hz, 3-H), 6.27 (d, 1H, $J = 9.8$ Hz, 4-H), 6.34 (s, 1H, Ar-H), 7.32 (s, 1H, Ar-H), 12.71 (s, 1H, Ar–OH). MS (EI): m/z 218 (M^+, 7), 203 (62), 185 (13), 178 (25), 163 (15), 123 (100), 77 (11), 43 (40).

3.14. 6-Acetyl-7-acetoxy-2,2-dimethyl-3-chromene, 13

A mixture of **12** (1.64 g, 7.50 mmol), acetic anhydride (2.1 mL, 22.50 mmol), and pyridine (catalytic amount) in CH_2Cl_2 was stirred 18 h at room temperature. The reaction mixture was poured into water and extracted with ethyl acetate (3×30 mL). The combined organic layer was successively washed with saturated $NaHCO_3$ and brine, dried with anhydrous Na_2SO_4. The solvent was distilled off, and the residue was flash chromatographed using petroleum ether and ethyl acetate (8:1, v/v) to afford **13** (1.76 g, 90%) as white solid. Mp 79–81 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.45 (s, 6H, CH_3), 2.34 (s, 3H, O–$COCH_3$), 2.50 (s, 3H, CH_3CO), 5.66 (d, 1H, $J = 9.8$ Hz, 3-H), 6.33 (d, 1H, $J = 9.8$ Hz, 4-H), 6.48 (s, 1H, Ar-H), 7.50 (s, 1H, Ar-H). MS (EI): m/z 260 (M^+, 4), 218 (12), 203 (100), 185 (7), 77 (5), 43 (32).

3.15. (3*R*,4*R*)-6-Acetyl-3,4,7-trihydroxy-2,2-dimethyl-chroman, 2a

As similar procedure as preparation of compound **1a**, treatment of compound **13** (0.26 g, 1.00 mmol) with AD-mix-α (1.40 g) and $Me_2SO_2NH_2$ (95 mg) at 0 °C in *t*-BuOH/H_2O afforded **2a** using petroleum ether and ethyl acetate (2:1, v/v) as white needles (0.15 g, 60%). Mp 219–221 °C. $[\alpha]_D^{25} = +27$ (*c* 0.33, acetone, ee 70%). ^{1}H NMR (400 MHz, acetone-d_6): δ 1.30 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 2.25 (s, 3H, CH_3CO), 3.77 (dd, 1H, $J = 4.4$, 4.4 Hz, 3-H), 4.12 (d, 1H, $J = 4.6$ Hz, 3-OH), 4.30 (d, 1H, $J = 7.6$ Hz, 4-OH), 4.81 (m, 1H, 4-H), 6.15 (s, 1H, Ar-H), 7.98 (s, 1H, Ar-H), 12.45 (s, 1H, Ar–OH). ^{13}C NMR (100 MHz, acetone-d_6): δ 24.8 (2C), 26.3, 64.9, 71.7, 80.1, 103.8, 115.1, 116.8, 133.6, 161.0, 164.5. MS (EI): m/z 252 (M^+, 5), 181 (48), 165 (15), 95 (4), 57 (32), 43 (100). HRMS calcd for $C_{13}H_{17}O_5$ (M+H): 253.1071. Found $(M+H)^+$: 253.1072.

3.16. (3*S*,4*S*)-6-Acetyl-3,4,7-trihydroxy-2,2-dimethyl-chroman, 2b

As similar procedure as preparation of compound **1a**, treatment of compound **13** (0.26 g, 1.00 mmol) with AD-mix-β (1.40 g) and $Me_2SO_2NH_2$ (95 mg) at 0 °C in *t*-BuOH/H_2O afforded **2b** using petroleum ether and ethyl acetate (2:1, v/v) as colorless needles (0.16 g, 62%). Mp 219–220 °C. $[\alpha]_D^{25} = -37$ (*c* 0.67, acetone, ee 70%). ^{1}H NMR (400 MHz, $CDCl_3$+3 drop DMSO-d_6): δ 1.29 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 2.84 (s, 3H, CH_3CO), 3.72 (dd, 1H, $J = 4.5$, 4.2 Hz, 3-H), 4.36 (d, 1H, $J = 4.8$ Hz, 3-OH), 4.47 (d, 1H, $J = 8.1$ Hz, 4-OH), 4.76 (m, $J = 4.2$ Hz, 4-H), 6.26 (s, 1H, Ar-H), 7.96 (s, 1H, Ar-H), 12.41 (s, 1H, Ar–OH). ^{13}C NMR (100 MHz, $CDCl_3$+3 drop DMSO-d_6): δ 24.1 (2C), 25.7, 63.9, 64.2, 71.0, 79.5, 103.1, 110.0, 114.5, 133.0, 160.4, 163.9. MS (EI): m/z 252 (M^+, 10), 181 (68), 165 (20), 95 (31), 57 (49), 43 (100). HRMS calcd for $C_{13}H_{17}O_5$ (M+H): 253.1071. Found $(M+H)^+$: 253.1070.

3.17. 6-Acetyl-3,4-epoxy-7-acetoxy-2,2-dimethyl-chroman, 14

To a solution of **7** (0.78 g, 3.00 mmol) in CH_2Cl_2 were added Jacobsen's (*R*,*R*)-(−)-salen-Mn(III) catalyst (9.50 mg, 0.15 mmol) and NMO (1.76 g, 15.00 mmol). The solution was cooled to −78 °C. Then *m*-CPBA

(1.05 g, 6.00 mmol) in two roughly equal portions was added. The reaction was monitored by TLC, upon consumption of the olefin, the reaction was quenched by the addition of a solution of dimethyl sulfide (0.86 g, 13.80 mmol) in CH_2Cl_2 (3 mL) precooled to −78 °C. A solution of 2 M NaOH (10 mL) was then added, and the organic layer was separated, washed with distilled water, and dried with anhydrous Na_2SO_4. After solvent removal, the crude product was purified by flash chromatography on silica gel using petroleum ether and ethyl acetate (5:1, v/v) to afford **8** (0.61 g, 74%). $[\alpha]_D^{25} = +62$ (*c* 1.00, acetone, ee >97%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.31 (s, 3H, CH_3), 1.59 (s, 3H, CH_3), 2.35 (s, 3H, O–$COCH_3$), 2.53 (s, 3H, CH_3CO), 3.52 (d, 1H, $J = 4.4$ Hz, 3-H), 3.95 (d, 1H, $J = 4.4$ Hz, 4-H), 6.55 (s, 1H, Ar-H), 7.89 (s, 1H, Ar-H). MS (EI): *m*/*z* 276 (M^+, 6), 234 (13), 191 (11), 178 (55), 163 (12), 43 (100).

3.18. 6-Acetyl-3,4-dihydroxy-7-acetoxy-2,2-dimethylchroman, 15

To a solution of **14** (0.58 g, 2.10 mmol) in dry THF (10 mL) was added $Ti(O^iPr)_4$ (1.00 mL, 3.50 mmol) at 0 °C under argon atmosphere. After 5 min, H_2O (1 mL) was added and the mixture was stirred at room temperature. After 4 h, the reaction mixture was diluted with Et_2O (60 mL), and 5% H_2SO_4 (10 mL) was added. The aqueous phase was extracted with EtOAc (3 × 30 mL). The combined organic extracts were dried with anhydrous Na_2SO_4 and the solvent was evaporated. The crude product was purified by column chromatography using petroleum ether and ethyl acetate (2:1, v/v) to afford **15** (0.55 g, 90%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.16 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 2.24 (s, 3H, O–$COCH_3$), 2.49 (s, 3H, CH_3CO), 3.40 (m, 1H, 3-H), 4.37 (dd, 1H, $J = 8.4$, 6.2 Hz, 4-H), 5.61 (d, 1H, $J = 5.2$ Hz, 3-OH), 5.73 (d, 1H, $J = 6.2$ Hz, 4-OH), 6.52 (s, 1H, Ar-H), 8.00 (s, 1H, Ar-H). MS (EI): *m*/*z* 294 (M^+, 2), 252 (5), 181 (44), 165 (12), 77 (12), 57 (46), 43 (100).

3.19. (3*R*,4*S*)-6-Acetyl-3,4,7-trihydroxy-2,2-dimethylchroman, 2c

To a solution of **15** (0.53 g, 1.80 mmol) in MeOH/H_2O (v/v, 9:1) was added K_2CO_3 (0.52 g, 3.77 mmol), and the mixture was stirred at room temperature. The methanol in the reaction mixture was evaporated in vacuo, and 2 N HCl (2 mL) was added. The mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic layer was washed with brine, and then dried with anhydrous Na_2SO_4. The solvent was distilled off, and the residue was flash chromatographed using petroleum ether and ethyl acetate (2:1, v/v) as eluent. Colorless crystals of **2c** (0.41 g, 90%) was obtained. Mp 171–173 °C. $[\alpha]_D^{25} = -104$ (*c* 1.4, acetone, lit.[3] $[\alpha]_D^{25} = -6$). ^{1}H NMR (400 MHz, $CDCl_3$+3 drop DMSO-d_6): δ 1.24 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 2.58 (s, 3H, CH_3CO), 3.49 (dd, 1H, $J = 8.7$, 4.4 Hz, 3-H), 4.46 (m, 1H, $J = 8.7$, 5.2 Hz, 4-H), 5.18 (d, 1H, $J = 4.4$ Hz, 3-OH), 5.27 (d, 1H, $J = 5.2$ Hz, 4-OH), 6.20 (s, 1H, Ar-H), 7.95 (s, 1H, Ar-H), 12.39 (s, 1H, Ar–OH). ^{13}C NMR (100 MHz, $CDCl_3$+3 drop DMSO-d_6): δ 19.1, 25.8, 26.3, 67.4, 74.8, 79.7, 102.9, 113.8, 116.8, 131.4, 159.0, 162.8, 202.2. MS (EI): *m*/*z* 252 (M^+, 13), 181 (100), 165 (31), 69 (28), 57 (29), 43 (87). HRMS calcd for $C_{13}H_{17}O_5$ (M+H): 253.1071. Found $(M+H)^+$: 253.1072.

Acknowledgements

We are grateful to the National Science Foundation of China (no. 20172023), GanSu Science Foundation (no. YS031-A21-001) and Doctoral Research Foundation of Lanzhou University (no. 5715220101) for financial support.

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