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Total Synthesis of the Neuroprotective Agent Cudraisoflavone J

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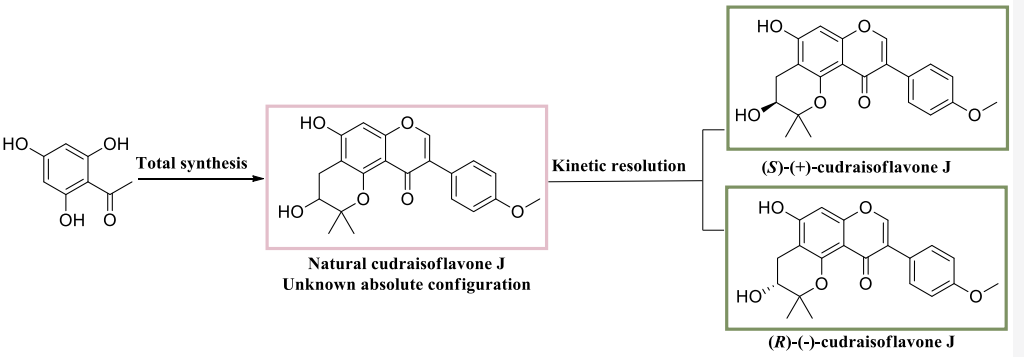

ABSTRACT: Cudraisoflavone J (**1**), isolated from *Cudrania tricuspidata*, is a potent neuroprotective compound with a chiral center. Herein, we report the first total synthesis of racemic cudraisoflavone J (**1**) using a Claisen rearrangement and a Suzuki coupling reaction as the key steps. Racemic secondary alcohol was kinetically resolved to give (+)- and (−)-cudraisoflavone J with up to 97 and 88% enantiomeric excess, respectively. The modified Mosher's method was used to elucidate the absolute configuration of naturally occurring cudraisoflavone J.

Cudrania tricuspidata (Carr.) Bur. ex Lavallee, which is a perennial plant of the family Moraceae, is widely used in east Asia as a traditional medicine or health supplement.[1] In China, *C. tricuspidata* has been used in the treatment of eczema, mumps, tuberculosis, contusions, and acute arthritis since ancient times.[2] In Korea, its edible fruits have been made into juices, jams, alcoholic beverages, dietary supplements, and other health products.[3,4] The immense medicinal and economic value of *C. tricuspidata* has encouraged numerous studies of its phytochemical and pharmacological activities.[5−7]

Flavonoids, including flavones, flavanones, and isoflavones, are considered to be the major bioactive constituents of *C. tricuspidata*, exhibiting notable anti-inflammatory,[8,9] antioxidative,[10] antitumor,[11] hepatoprotective,[12] neuroprotective,[13,14] and antiobesity[15,16] effects. In 2015, Lee and co-workers isolated a group of isoflavones from the fresh fruits of *C. tricuspidata* and found that they featured 3-hydroxy-2,2-dimethyldihydropyran groups substituted on their aromatic rings, as shown in Figure 1. Among these, cudraisoflavone J had the most potent activity against 6-hydroxydopamine (6-OHDA)-induced cell death in human neuroblastoma SH-SY5Y cells, with an EC_{50} value of 0.5 μM.[17] This suggested that cudraisoflavone J could be considered a candidate for further research into using it for therapeutic purposes to treat neurodegenerative diseases, such as Parkinson's disease. To the best of our knowledge, neither the total synthesis nor the

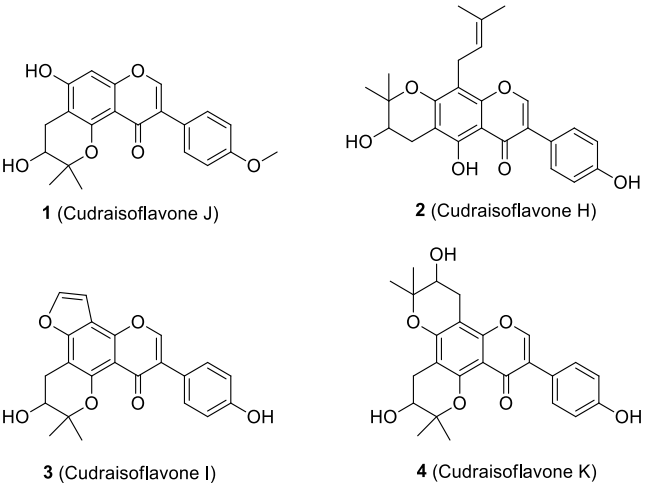

Figure 1. 3-Hydroxy-2,2-dimethyldihydropyran-containing natural products isolated from *C. tricuspidata*.

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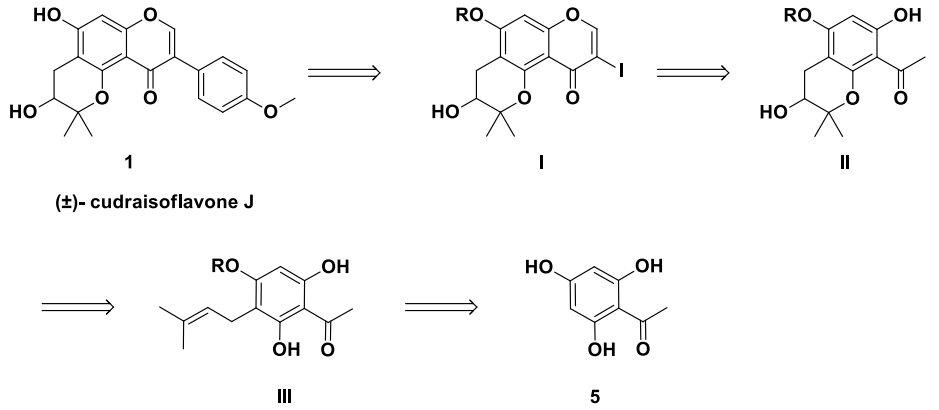
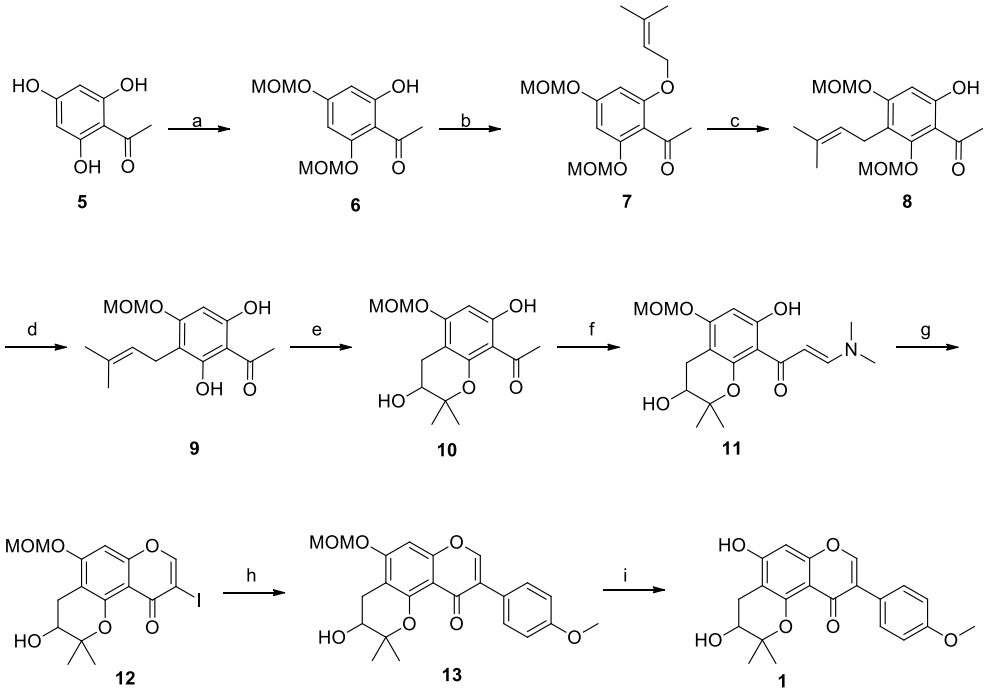
Scheme 1. Retrosynthetic Approach for (±)-Cudraisoflavone J (1)



Scheme 2. Total Synthesis of (±)-Cudraisoflavone J[a]



[a]Reagents and conditions: (a) MOMCl, DIPEA, DCM, 0 °C to room temperature (rt), 90%; (b) prenyl bromide, K_2CO_3, acetone, reflux, 60%; (c) *N*,*N*-diethylaniline, microwave, 89%; (d) 2 N HCl, DCM, MeOH, 93%; (e) *m*-CPBA, M-K10, DCM, 71%; (f) DMF-DMA, reflux, 83%; (g) I_2, MeOH, rt, 91%; (h) 4-methoxyphenylboronic acid, $Pd(OAc)_2$, K_2CO_3, PEG-400, 85%; and (i) 3 N HCl, DCM, MeOH, reflux, 73%.

synthetic approach for the absolute configuration of cudraisoflavone J has ever been reported. Considering this, we initiated a program to synthesize cudraisoflavone J and establish its absolute configuration. Herein, we report the first total synthesis of (±)-cudraisoflavone J (**1**) and both of its enantiomers.

RESULTS AND DISCUSSION

The retrosynthetic plan for (±)-cudraisoflavone J (**1**) is outlined in Scheme 1. The final isoflavone skeleton could be synthesized via a Suzuki coupling reaction between chromone I and commercially available 4-methoxyphenylboronic acid. The iodo/chromone intermediate I would be obtainable from chromane II by ring closure followed by iodination. The synthesis of key intermediate chromane II was envisioned from readily available 2′,4′,6′-trihydroxyacetophenone **5** via Claisen rearrangement and subsequent cyclization of III.

On the basis of our retrosynthetic analysis, our synthesis started with regioselective protection of the hydroxy groups of commercially available 2′,4′,6′-trihydroxyacetophenone (**5**) by treatment with methoxymethyl chloride (MOMCl) and *N*,*N*-diisopropylethylamine (DIPEA) in dry dichloromethane (DCM) to give compound **6** in 90% yield.[18] O-Prenylation of compound **6** K_2CO_3 as the base gave intermediate **7**, which underwent microwave-assisted *para*-Claisen rearrangement to produce compound **8** in 89% yield. The selective deprotection of compound **8** under acidic conditions (2 N HCl) afforded mono-MOM-protected compound **9**. Furthermore, treatment of compound **9** with *m*-chloroperoxybenzoic acid (*m*-CPBA) followed by *in situ* cyclization, catalyzed by montmorillonite K10 clay (M-K10), yielded key intermediate chromane **10**.[19] Condensation of compound **10** with *N*,*N*-dimethylformamide dimethyl acetal (DMF-DMA) gave the enaminoketone **11**, which underwent cyclization in the presence of I_2 to produce

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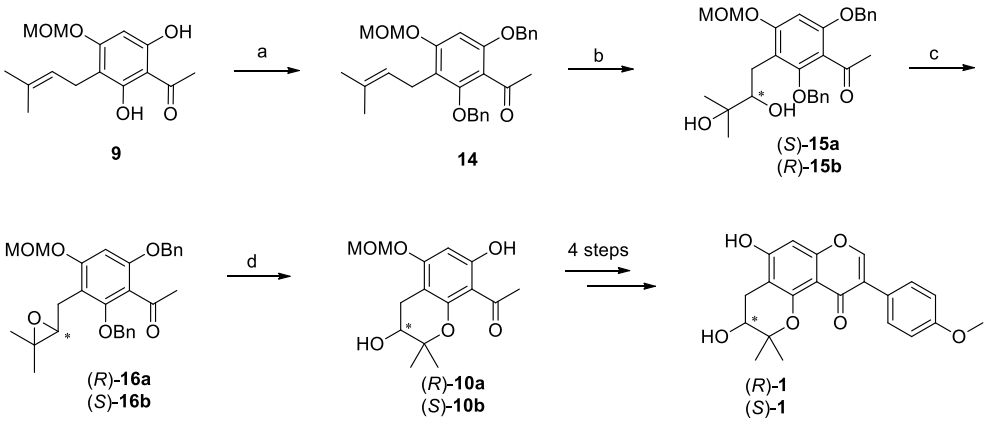
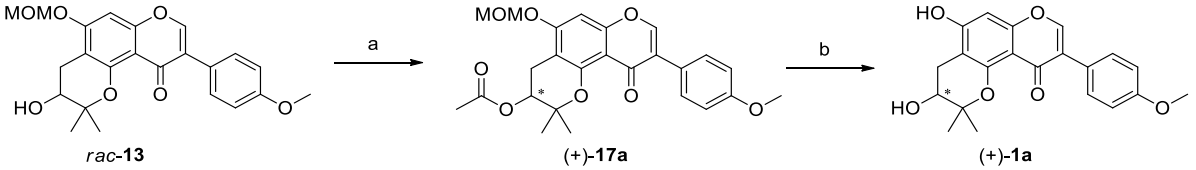
Scheme 3. Stereo Selective Synthesis of Cudraisoflavone J[a]



[a]Reagents and conditions: (a) benzyl bromide, K_2CO_3, DMF, rt; (b) AD-mix α, methanesulfonamide, *t*-BuOH−H_2O for compound **15a**; AD-mix β, methanesulfonamide, *t*-BuOH−H_2O for compound **15b**; (c) (i) methanesulfonyl chloride, pyridine, (ii) K_2CO_3, MeOH; and (d) 10% Pd/C, H_2. EtOAc, M-K10.

Table 1. Enantioselective O-Acetylation of *rac*-13 under Enzymatic Kinetic Resolution Conditions[a]



catalyst	solvent	conversion (%)	specific rotation[b]	ee_{17} (%)[c]	ee_1 (%)[c]
Novozym 435	TBME	<1			
Novozym 435	EtOAc	<1			
Amano PS	THF	12	+47.6	99	97

[a]Conditions: (a) *rac*-**13** (100 mg), catalyst (100 mg), vinyl acetate (1 mL), rt, 72 h; (b) K_2CO_3 (4 equiv), 3 M HCl, MeOH, reflux. [b]Specific rotations were recorded on a JACO P-2200 digital polarimeter. [c]The ee was determined by chiral-phase HPLC using a Chiralpak IG-3 (4.6 × 150, 3) column.

chromone **12** as a white solid. The Suzuki coupling reaction between chromone **12** and 4-methoxyphenylboronic acid gave the protected compound **13**.[20] Lastly, MOM deprotection under acidic conditions (3 N HCl) produced the desired natural compound (±)-cudraisoflavone J (**1**) in 15% overall yield (Scheme 2). The ^1H and ^{13}C nuclear magnetic resonance (NMR) data of synthetic compound **1** were shown to be in accordance with those reported for the natural compound.

After completion of the synthesis of (±)-cudraisoflavone J, we turned our attention to the asymmetric syntheses of (*R*)- and (*S*)-cudraisoflavone J. Initially, we attempted to conduct stereoselective synthesis of cudraisoflavone J featuring Sharpless asymmetric dihydroxylation as the key step (Scheme 3). As we planned, benzyl-protected prenylated compound **14** was prepared from compound **9**, and then the Sharpless asymmetric dihydroxylation of compound **14** using commercially available catalyst AD-mix α or β yielded diols (*S*)-**15a** or (*R*)-**15b**, respectively.[21,22] The selective mesylation of the secondary alcohol of diols followed by treatment with K_2CO_3 in methanol produced the desired epoxide **16**. The debenzylation of compound **16** followed by *in situ* opening of epoxidation under acidic conditions provided the key intermediate **10**, which can be converted to cudraisoflavone J in four steps, as mentioned in Scheme 2. However, in practice, Sharpless asymmetric dihydroxylation of compound **14** produced relatively poor enantiomeric excess (ee) values (57% for **15a** and 67% for **15b**), and we obtained (*S*)- and (*R*)-**1** with 59 and 56% ee, respectively (see the Supporting Information). The resulting selectivity in Sharpless asymmetric dihydroxylation for our compound **14** drove us to find other solutions.

Enzymatic/non-enymatic kinetic resolution (KR) of racemic mixtures is a convenient and efficient method to access enantiomerically pure alcohol and amine derivatives, owing to its high performance in terms of activity and selectivity.[23,24] Thus, we shifted our focus to KR and tested different enzymatic/non-enzymatic catalysts in asymmetric acylation of *rac*-**13**.

Among the enzymes, lipases are extensively investigated as catalysts for enantioselective acylation of racemic secondary and primary alcohols.[25] We employed Novozym 435 and lipase from *Pseudomonas cepecia* (Amano PS) as the catalyst and vinyl acetate as the acyl source in the KR of *rac*-**13** and found that the reaction did not proceed at all with Novozym 435. Amano PS performed excellent enantioselective acylation to give (+)-**17a** at 99% ee (Table 1). However, the conversion of the reaction was only 12%. Even after repeating the reaction 3 times, we could not obtain enantio-rich alcohol (−)-**13**. More recently, Maguire and co-workers reported that enzymatic dynamic kinetic enantioselective acylations (DKEA) of 2-chromanols bearing substituents on the aromatic ring lead to poor conversion, mainly as a result of steric interactions with the enzyme active site.[26] On the basis of this report, we hypothesized that it would be hard to achieve DKEA of *rac*-**13**

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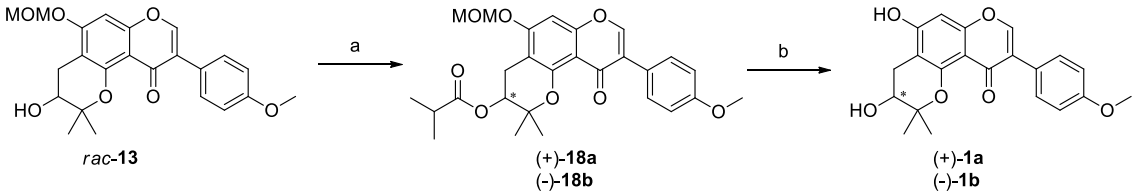
Table 2. Enantioselective O-Acetylation of *rac*-13 under Non-enzymatic Kinetic Resolution Conditions[a]



catalyst	product	conversion (%)	specific rotation[b]	ee_{18} (%)[c]	ee_1 (%)[c]
(*S*)-BTM	**18a**	26	+45.4	81	78
(*R*)-BTM	**18b**	23	−46.8	88	88

[a]Conditions: (a) *rac*-**13** (1 equiv), catalyst (1 equiv), isobutyric anhydride (1 equiv), DCM, rt, 2 h; (b) K_2CO_3 (4 equiv), 3 M HCl, MeOH, reflux. [b]Specific rotations were ordered on a JACO P-2200 digital polarimeter. [c]The ee was determined by chiral-phase HPLC using a Chiralpak IG-3 (4.6 × 150, 3) column.

with enzymes. Hence, we subsequently conducted the kinetic resolution with a non-enzymatic catalyst, chiral benzotetramisole (BTM).[27,28] To our delight, (+)- and (−)-acylated compound **18** was produced by (*S*)/(*R*)-BTM separately (Table 2). In comparison to Amano PS, BTM provides better KR conversion but worse ee. Lastly, deprotection of acetyl (under basic conditions) and MOM (under acidic conditions) groups of compounds **17a** and **18b** produced (+)-**1a** (97% ee) and (−)-**1b** (88% ee), respectively.

The absolute configurations of C-2″ in compounds **1a** and **1b** were confirmed by Mosher's method using MTPA esters.[29] The $\Delta\delta^{SR}$ values between the *S*- and *R*-MTPA esters of compound **1a** at 2″-OH were positive for H-4″/5″ and negative for H-1″/2″, which suggested the 2″*S* configuration. Similarly, the 2″*R* configuration of compound **1b** was also confirmed by Mosher's method using MTPA esters (Figure 2).

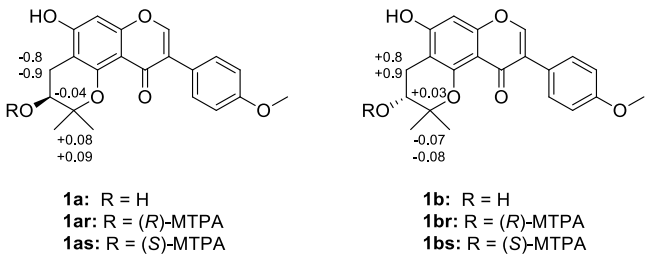


Figure 2. Values of Δ_{S-R} for Mosher's MTPA esters of compounds **1a** and **1b** in pyridine-d_5.

According to Lee and his co-workers, the specific rotation value of the natural cudraisoflavone J was $[\alpha]_D^{22}$ −4.9 (*c* 0.01, MeOH).[17] We recorded the specific rotation value of (*S*)-cudraisoflavone J {$[\alpha]_D^{22}$ +58.9 (*c* 0.01, MeOH)} and (*R*)-cudraisoflavone J {$[\alpha]_D^{22}$ −55.4 (*c* 0.01, MeOH)}. On the basis of this, we assume that naturally occurring cudraisoflavone J was scalemic, with a slightly higher proportion of the (*S*) enantiomer.

In conclusion, the first total synthesis of (±)-cudraisoflavone J was achieved in 15% overall yield via a nine-step sequence involving Claisen rearrangement and Suzuki coupling reactions. In addition, we have successfully obtained both of its enantiomers by kinetic resolution, using enzymatic and non-enzymatic catalysts. Furthermore, this synthetic methodology is well-suited to the development of new structural analogues.

EXPERIMENTAL SECTION

General Experimental Procedures. All of the commercial chemicals were of reagent grade and were used without further purification. All reactions were carried out under an atmosphere of dried argon, in flame-dried glassware. Melting points were measured on the Thermo Scientific 9200 apparatus. Optical rotations were recorded on a JASCO P-2200 digital polarimeter. Infrared (IR) spectra were recorded on a FTIR Nicolet iS5 spectrometer (Thermo Fisher Scientific, Madison, WI, U.S.A.). Proton nuclear magnetic resonance (^{1}H NMR) spectra were determined on a Varian (400 MHz) spectrometer (Varian Medical Systems, Inc., Palo Alto, CA, U.S.A.). Multiplicity is indicated by the following abbreviations: singlet (s), doublet (d), doublet of doublet (dd), triplet (t), quartet (q), multiplet (m), and broad (b). The values of the chemical shifts are expressed in δ values (ppm), and the coupling constants (J) are reported in hertz. ^{13}C NMR spectra were recorded on a Varian (100 MHz) spectrometer. Chemical shifts are provided in parts per million (ppm) downfield from tetramethylsilane (internal standard) with coupling constants in hertz. Mass spectra were recorded using high-resolution mass spectrometry (HRMS, ESI−MS), obtained on a G2 QTOF mass spectrometer (Waters Corporation, Milford, MA, U.S.A.). Products were purified by column or flash column chromatography (Biotage, Sweden) using silica gel 60 (230−400 mesh Kieselgel 60). Additionally, thin-layer chromatography on 0.25 mm silica plates (E. Merck, silica gel 60 F254) was used to monitor reactions. Spots were detected by viewing under ultraviolet (UV) light and colorized with charring after dipping in anisaldehyde or basic $KMnO_4$ solution. The optical purity of the synthesized compounds was established by chiral high-performance liquid chromatography (HPLC) analysis: Chiralpak IG-3 (4.6 × 150, 3), hexane/EtOH/MeOH = 85:10:5, 1.5 mL/min, and λ = 280 nm.

*1-(2-Hydroxy-4,6-bis(methoxymethoxy)phenyl)ethanone (**6**).* A solution of 1-(2,4,6-trihydroxyphenyl)ethanone (1.0 g, 5.95 mmol) in DCM (20 mL) was cooled to 0 °C, and DIPEA (2.6 mL, 14.88 mmol) was slowly added. After 20 min, MOMCl (1.0 mL, 13.69 mmol) was added dropwise. The mixture was maintained at 0 °C for 20 min and then brought to room temperature. After 5 h, the reaction mixture was quenched with H_2O (20.0 mL) and then extracted with DCM (3 × 30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (gradient, *n*-hexane/EtOAc = 19:1−9:1) to obtain compound **6** (1.37 g, 90%) as a white solid. Melting point (mp) = 48−50 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.73 (s, 1H), 6.27 (d, J = 2.4 Hz, 1H), 6.25 (d, J = 2.4 Hz, 1H), 5.26 (s, 2H), 5.17 (s, 2H), 3.52 (s, 3H), 3.47 (s, 3H), 2.66 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.16, 166.76, 163.40, 160.31, 106.85, 97.05, 94.43, 93.95, 56.66, 56.39, 32.97. HRMS (ESI): m/z calculated for $C_{12}H_{17}O_6$ $[M + H]^+$, 257.1025; found, 257.1019.

*1-(2,4-Bis(methoxymethoxy)-6-((3-methylbut-2-en-1-yl)oxy)-phenyl)ethanone (**7**).* To a solution of compound **6** (210.0 mg, 0.64 mmol) and K_2CO_3 (265.0 mg, 1.92 mmol) in acetone (10 mL) was added prenyl bromide (0.11 mL, 0.96 mmol), and it was refluxed for

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21.5 h under N_2. The reaction mixture was cooled to room temperature, filtered with EtOAc, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 9:1) to produce *O*-prenyl compound **7** (185.1 mg, 60%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.43 (d, J = 1.2 Hz, 1H), 6.30 (d, J = 1.2 Hz, 1H), 5.39 (t, J = 6.6 Hz, 1H), 5.15 (s, 2H), 5.14 (s, 2H), 4.49 (d, J = 6.8 Hz, 2H), 3.47 (s, 3H), 3.45 (s, 3H), 2.47 (s, 3H), 1.75 (s, 3H), 1.70 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.75, 159.51, 157.22, 155.21, 137.91, 119.33, 116.32, 95.99, 95.05, 94.79, 94.46, 65.63, 56.32, 56.16, 32.53, 25.74, 18.24. HRMS (ESI): m/z calculated for $C_{17}H_{25}O_6$ $[M + H]^+$, 325.1651; found, 325.1647.

*1-(6-Hydroxy-2,4-bis(methoxymethoxy)-3-(3-methylbut-2-en-1-yl)phenyl)ethanone (**8**).* A solution of compound **7** (180.1 mg, 0.55 mmol) in *N*,*N*-diethylaniline (2 mL) was placed in a vessel suited for microwave irradiation and irradiated at 210 °C for 1.0 h. The mixture was washed with aqueous 10% HCl (5 mL), H_2O, and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 19:1) to produce the target compound **8** (160.0 mg, 89%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.95 (s, 1H), 6.47 (s, 1H), 5.22 (s, 2H), 5.15 (t, J = 5.8 Hz, 1H), 4.96 (s, 2H), 3.52 (s, 3H), 3.46 (s, 3H), 3.31 (d, J = 6.0 Hz, 2H), 2.70 (s, 3H), 1.77 (s, 3H), 1.69 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.88, 163.47, 161.57, 157.12, 131.62, 122.97, 116.17, 110.97, 101.38, 98.81, 93.85, 58.35, 56.31, 31.42, 25.69, 23.08, 17.87. HRMS (ESI): m/z calculated for $C_{17}H_{25}O_6$ $[M + H]^+$, 325.1651; found, 325.1646.

*1-(2,6-Dihydroxy-4-(methoxymethoxy)-3-(3-methylbut-2-en-1-yl)phenyl)ethanone (**9**).* Compound **8** (2.70 g, 10.0 mmol) in MeOH (50 mL) was cooled to 0 °C. Then, 2 N HCl (10 mL) was added dropwise. After addition, the reaction mixture was warmed to 40 °C and stirred for 3 h. The reaction was quenched with $NaHCO_3$ (aqueous) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (*n*-hexane/EtOAc = 8:1) to produce compound **9** (2.16 g, 93%) as an off-white solid. mp = 112−114 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.18 (s, 1H), 5.20 (s, 2H), 5.18 (s, 1H), 3.47 (s, 3H), 3.35 (d, J = 7.2 Hz, 2H), 2.67 (s, 3H), 1.83 (s, 3H), 1.76 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 203.98, 161.39, 160.89, 160.60, 134.11, 121.92, 107.97, 105.86, 93.94, 93.90, 56.27, 32.99, 25.83, 21.63, 17.82. HRMS (ESI): m/z 281.1389 calculated for $C_{15}H_{21}O_5$ $[M + H]^+$, 281.1385.

*1-(3,7-Dihydroxy-5-(methoxymethoxy)-2,2-dimethylchroman-8-yl)ethanone (**10**).* To a solution of compound **9** (2.16 g, 7.69 mmol) in anhydrous DCM (30.0 mL) was added 75% *m*-CPBA (1.80 g, 7.80 mmol) at 0 °C, and the mixture was stirred for 20 min at room temperature. After complete consumption of compound **9** (TLC), montmorillonite K10 (2.1 g) was added and the mixture was further stirred for 30 min at room temperature. The mixture was filtered and washed with EtOAc. The organic layer was washed with saturated Na_2CO_3 (aqueous), H_2O, and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 2:1) to produce compound **10** (1.61 g, 71%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.71 (s, 1H), 6.23 (s, 1H), 5.20 (s, 2H), 3.81 (q, J = 5.9 Hz, 1H), 3.48 (s, 3H), 2.86 (dd, J = 17.1 and 5.2 Hz, 1H), 2.65 (s, 3H), 2.62 (dd, J = 16.0 and 4.0 Hz, merged, 1H), 1.82 (d, J = 7.2 Hz, 1H), 1.42 (s, 3H), 1.39 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.41, 165.23, 161.20, 155.39, 106.48, 99.36, 94.64, 94.04, 78.36, 68.43, 56.45, 33.27, 25.91, 24.86, 21.91. HRMS (ESI): m/z calculated for $C_{15}H_{21}O_6$ $[M + H]^+$, 297.1338; found, 297.1325.

*(E)-1-(3,7-Dihydroxy-5-(methoxymethoxy)-2,2-dimethylchroman-8-yl)-3-(dimethylamino)prop-2-en-1-one (**11**).* Compound **10** (1.3 g, 4.39 mmol) was dissolved in DMF, and the solution was warmed to 75 °C in an oil bath. DMF-DMA (0.7 mL, 5.26 mmol) was then added dropwise to the flask. The mixture was stirred for 4.5 h and then cooled to room temperature. The reaction was quenched with H_2O, and the mixture was extracted with EtOAc (3 × 10 mL). The extracts were washed with H_2O, dried, filtered, and concentrated under reduced pressure to give a thick yellow oil that was purified by silica gel column chromatography (*n*-hexane/EtOAc = 3:2) to give cubic yellow crystals (1.27 g, 83%). mp = 154−156 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, J = 12.4 Hz, 1H), 6.44 (d, J = 12.4 Hz, 1H), 6.22 (s, 1H), 5.18 (s, 2H), 3.80 (q, J = 6.1 Hz, 1H), 3.47 (s,3H), 3.16 (s, 3H), 2.92 (s, 3H), 2.88 (dd, J = 17.2 and 5.6 Hz, 1H), 2.64 (dd, J = 17.0 and 5.4 Hz, 1H), 1.75 (d, J = 8.0 Hz, 1H), 1.43 (s, 3H), 1.38 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.09, 165.68, 159.12, 154.15, 154.01, 105.92, 98.69, 97.42, 95.22, 94.02, 77.66, 68.70, 56.33, 45.09, 37.25, 26.30, 24.85, 22.12. HRMS (ESI): m/z calculated for $C_{18}H_{26}O_6$ $[M + H]^+$, 352.1760; found, 352.1754.

*3-Hydroxy-9-iodo-5-(methoxymethoxy)-2,2-dimethyl-3,4-dihydropyrano[2,3-f]chromen-10(2H)-one (**12**).* A mixture of compound **11** (170.0 mg, 0.48 mmol) in MeOH (5 mL) was stirred at room temperature for 10.5 h and then concentrated *in vacuo* to give a reddish black residue. To remove residual I_2, the residue was treated with saturated aqueous $Na_2S_2O_3$ until the mixture became clear. The mixture was then extracted with DCM, and the resulting off-white solid was purified by silica gel chromatography (*n*-hexane/EtOAc = 3:2) to give a white solid (107.1 mg, 91%). mp = 134−136 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (s, 1H), 6.65 (s, 1H), 5.26 (s, 2H), 3.86 (q, J = 8.0 Hz, 1H), 3.50 (s, 3H), 2.92 (dd, J = 17.5 and 5.2 Hz, 1H), 2.71 (dd, J = 17.5 and 5.6 Hz, 1H), 2.22 (d, J = 7.0 Hz, 1H), 1.44 (s, 3H), 1.41 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.25, 159.35, 157.90, 155.39, 153.67, 106.55, 94.40, 93.60, 89.69, 78.36, 68.35, 56.60, 44.29, 26.36, 24.73, 21.47. HRMS (ESI): m/z calculated for $C_{16}H_{18}IO_6$ $[M + H]^+$, 433.0148; found, 433.0141.

*3-Hydroxy-5-(methoxymethoxy)-9-(4-methoxyphenyl)-2,2-dimethyl-3,4-dihydropyrano[2,3-f]chromen-10(2H)-one (**13**).* A mixture of aryl **12** (1.0 g, 2.31 mmol), 4-methyphenylboronic acid (527.8 mg, 3.47 mmol), $Pd(OAc)_2$ (10.4 mg, 2 mol %), K_2CO_3 (480.1 mg, 3.47 mmol), and PEG-400 (8.0 g) was stirred at 45 °C for the indicated time until complete consumption of the starting material, as monitored by gas chromatography (GC). The mixture was added to brine (15 mL) and extracted 4 times with Et_2O (4 × 15 mL). The solvent was concentrated *in vacuo*, and the crude product was purified by silica gel column chromatography (*n*-hexane/EtOAc = 1:1) to produce compound **13** (808.1 mg, 85%) as a white solid. mp = 156−158 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (s, 1H), 7.46 (d, J = 8.4 Hz, 2H), 6.93 (d, J = 8.4 Hz, 2H), 6.67 (s, 1H), 5.27 (s, 2H), 3.86 (q, J = 6.0 Hz, 1H), 3.82 (s, 3H), 3.51 (s, 3H), 2.93 (dd, J = 17.4 and 5.2 Hz, 1H), 2.72 (dd, J = 17.5 and 5.5 Hz, 1H), 2.13 (d, J = 7.4 Hz, 1H), 1.44 (s, 3H), 1.40 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.37, 159.34, 158.93, 158.05, 154.15, 150.08, 130.51, 125.91, 124.44, 113.67, 105.93, 94.31, 93.78, 78.08, 68.43, 56.49, 55.30, 26.43, 24.67, 21.47. HRMS (ESI): m/z calculated for $C_{23}H_{25}O_7$ $[M + H]^+$, 413.16; found, 413.1592.

*3,5-Dihydroxy-9-(4-methoxyphenyl)-2,2-dimethyl-3,4-dihydropyrano[2,3-f]chromen-10(2H)-one (**1**).* To a solution of compound **13** (195.5 mg, 0.47 mmol) in anhydrous MeOH (3.0 mL) was added 3 N HCl (3.0 mL), and it was refluxed for 40 min under N_2. The mixture was cooled to room temperature, quenched with water, and extracted 3 times with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 1:1) to produce the target compound (127.4 mg, 73%) as an off-white solid. mp = 300−302 °C. $[\alpha]_D^{22}$ +5.4 (*c* 0.01, MeOH). IR (neat) ν_{max} (cm^{-1}): 3138.50 (>OH), 1738.40 (>C═O). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.10 (s, 1H), 7.46 (d, J = 8.3 Hz, 2H), 7.00 (d, J = 8.4 Hz, 2H), 6.45 (s, 1H), 5.21 (d, J = 4.6 Hz, 1H), 3.82 (s, 3H), 3.69 (q, J = 6.7 Hz, 1H), 2.81 (dd, J = 17.2 and 5.5 Hz, 1H), 2.45 (dd, J = 16.8 and 7.3 Hz, 1H), 1.34 (s, 3H), 1.23 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.99, 160.31, 159.14, 157.61, 154.59, 150.78, 130.75, 125.15, 124.69, 113.77, 108.01, 105.48, 93.98, 78.04, 67.27, 55.53, 26.48, 25.86, 20.91. HRMS (ESI): m/z calculated for $C_{21}H_{21}O_6$ $[M + H]^+$, 369.1338; found, 369.1333.

General procedure for lipase-mediated enantioselective acylation of *rac*-**13**: to a solution of *rac*-**13** (100 mg) was added lipase (100 mg). The suspension was stirred at room temperature. After a few minutes, vinyl acetate (1 mL) was added and the reaction mixture was stirred

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on a magnetic stirrer and monitored by TLC. After about 50% conversion, the lipase was filtered off, the solvent was evaporated, and the resulting gum was purified by silica gel column chromatography (*n*-hexane/EtOAc = 2:1) to give the desired product.

*(S)-5-(Methoxymethoxy)-9-(4-methoxyphenyl)-2,2-dimethyl-10-oxo-2,3,4,10-tetrahydropyrano[2,3-f]chromen-3-yl acetate (**17a**) (98.0% ee).* White solid. 12% yield. mp = 136−138 °C. $[\alpha]_D^{22}$ +47.6 (*c* 0.01, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (s, 1H), 7.46 (d, *J* = 8.6 Hz, 2H), 6.93 (d, *J* = 8.7 Hz, 2H), 6.67 (s, 1H), 5.29−5.24 (m, 2H), 5.06 (t, *J* = 5.3 Hz, 1H), 3.82 (s, 3H), 3.51 (s, 3H), 3.03 (dd, *J* = 17.8 and 5.5 Hz, 1H), 2.72 (dd, *J* = 17.8 and 5.1 Hz, 1H), 2.08 (s, 3H), 1.42 (s, 3H), 1.40 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.21, 170.60, 159.39, 158.68, 158.15, 154.16, 150.02, 130.56, 126.01, 124.48, 113.70, 110.31, 104.99, 94.42, 93.81, 76.12, 69.86, 56.56, 55.33, 24.68, 23.70, 22.49, 21.15. HRMS (ESI): *m*/*z* calculated for $C_{25}H_{27}O_8$ $[M + H]^+$, 455.1706; found, 455.1698.

General procedure for BTM-mediated enantioselective acylation of *rac*-**13**: catalyst (0.1 equiv) and compound **13** (1.0 equiv) were dissolved in DCM. Isobutyric anhydride (1.1 equiv) was added, and the reaction was capped and stirred under argon. The reaction was monitored via TLC. When the reaction was deemed complete, MeOH was added and the reaction was stirred for another 30 min. The solvent was removed under vacuum, and the residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 2:1) to give the desired product.

*(S)-5-(Methoxymethoxy)-9-(4-methoxyphenyl)-2,2-dimethyl-10-oxo-2,3,4,10-tetrahydropyrano[2,3-f]chromen-3-yl isobutyrate (**18a**) (81% ee).* (*S*)-BTM was employed as the catalyst. White solid. 26% yield. mp = 129−131 °C. $[\alpha]_D^{22}$ +45.4 (*c* 0.01, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (s, 1H), 7.46 (d, *J* = 8.9 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 6.67 (s, 1H), 5.27 (s, 2H), 5.03 (t, *J* = 5.9 Hz, 1H), 3.82 (s, 3H), 3.50 (s, 3H), 3.05 (dd, *J* = 17.6 and 5.6 Hz, 1H), 2.65 (dd, *J* = 17.6 and 6.1 Hz, 1H), 2.60−2.53 (m, 1H), 1.43 (s, 3H), 1.40 (s, 3H), 1.18 (d, *J* = 7.0 Hz, 3H), 1.14 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.55, 175.19, 159.39, 158.60, 158.14, 154.16, 150.00, 130.57, 126.01, 124.49, 113.70, 105.25, 94.34, 93.80, 76.24, 69.75, 56.50, 55.33, 34.04, 25.04, 23.64, 21.90, 19.01, 18.86. HRMS (ESI): *m*/*z* calculated for $C_{27}H_{31}O_8$ $[M + H]^+$, 483.2019; found, 483.2023.

*(R)-5-(Methoxymethoxy)-9-(4-methoxyphenyl)-2,2-dimethyl-10-oxo-2,3,4,10-tetrahydropyrano[2,3-f]chromen-3-yl isobutyrate (**18b**) (88% ee).* (*R*)-BTM was employed as the catalyst. White solid. 23% yield. mp = 125−127 °C. $[\alpha]_D^{22}$ −46.8 (*c* 0.01, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (s, 1H), 7.46 (d, *J* = 8.9 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 6.67 (s, 1H), 5.27 (s, 2H), 5.03 (t, *J* = 5.9 Hz, 1H), 3.82 (s, 3H), 3.50 (s, 3H), 3.05 (dd, *J* = 17.6 and 5.6 Hz, 1H), 2.65 (dd, *J* = 17.6 and 6.1 Hz, 1H), 2.60−2.53 (m, 1H), 1.43 (s, 3H), 1.40 (s, 3H), 1.18 (d, *J* = 7.0 Hz, 3H), 1.14 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.55, 175.18, 159.39, 158.59, 158.14, 154.17, 150.00, 130.57, 126.01, 124.49, 113.70, 110.30, 105.25, 94.34, 93.80, 76.23, 69.75, 56.50, 55.33, 34.04, 25.04, 23.64, 21.90, 19.01, 18.86. HRMS (ESI): *m*/*z* calculated for $C_{27}H_{31}O_8$ $[M + H]^+$, 483.2019; found, 483.2012.

*(S)-3,5-Dihydroxy-9-(4-methoxyphenyl)-2,2-dimethyl-3,4-dihydropyrano[2,3-f]chromen-10(2H)-one (**1a**) (97% ee).* In a 25 mL flask, a solution of compound **17a** (45.9 mg, 0.10 mmol) in MeOH (4 mL) was added to K_2CO_3 (55.8 mg, 0.40 mmol) and the reaction mixture was stirred overnight. After the Ac group was smoothly removed, 3 M HCl (3 mL) was added and the solution was refluxed for 30 min, during which the MOM group was easily cleaved. Then, MeOH was evaporated, and the residue was diluted with EtOAc, washed with saturated $NaHCO_3$, H_2O, and brine, dried, and concentrated. The crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc = 1:1) to furnish compound **1a** (24.0 mg, 65%) as an off-white amorphous powder. mp = 298−301 °C. $[\alpha]_D^{22}$ +58.9 (*c* 0.01, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.05 (s, 1H), 7.41 (d, *J* = 8.4 Hz, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 6.40 (s, 1H), 5.16 (d, *J* = 4.4 Hz, 1H), 3.78 (s, 3H), 3.64 (q, *J* = 5.7 Hz, 1H), 2.76 (dd, *J* = 17.2 and 5.6 Hz, 1H), 2.40 (dd, *J* = 17.2 and 7.2 Hz, 1H), 1.30 (s, 3H), 1.18 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.99, 160.30, 159.14, 157.61, 154.59, 150.77, 130.75, 125.15, 124.70, 113.76, 108.02, 105.48, 93.98, 78.04, 67.28, 55.53, 26.49, 25.86, 20.91. The other spectra are the same as those of compound **1**.

*(R)-3,5-Dihydroxy-9-(4-methoxyphenyl)-2,2-dimethyl-3,4-dihydropyrano[2,3-f]chromen-10(2H)-one (**1b**) (88% ee).* mp 297−299 °C. $[\alpha]_D^{22}$ −55.4 (*c* 0.01, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.05 (s, 1H), 7.41 (d, *J* = 8.4 Hz, 2H), 6.95 (d, *J* = 8.4 Hz, 2H), 6.41 (s, 1H), 5.17 (d, *J* = 4.8 Hz, 1H), 3.78 (s, 3H), 3.64 (q, *J* = 5.6 Hz, 1H), 2.77 (dd, *J* = 17.0 and 5.4 Hz, 1H), 2.41 (dd, *J* = 17.2 and 7.2 Hz, 1H), 1.30 (s, 3H), 1.19 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.98, 160.33, 159.14, 157.61, 154.58, 150.77, 130.75, 125.15, 124.69, 113.77, 108.00, 105.48, 93.98, 78.04, 67.28, 55.53, 26.49, 25.87, 20.90. The other spectra are the same as those of compound **1**.

*Preparation of (S)- and (R)-MTPA Ester Derivatives of Compounds **1a** and **1b**.* First, 2.0 mg of compound **1a** in 900 μL of pyridine-d_5 was divided into two parts and transferred into clean NMR tubes. (*R*)-(−)-α-Methoxy-α-(trifluoromethyl)phenylacetyl (MTPA) chloride (20 μL) and (*S*)-(+)-α-MTPA chloride (20 μL) were added to each of the NMR tubes under a N_2 gas stream with a slight excess of 4-dimethylaminopyridine. The solutions were then carefully mixed. The tubes were left at 50 °C for 12 h. ^{1}H NMR data were obtained directly from the reaction NMR tubes. The one-dimensional nuclear Overhauser effect spectroscopy (1D NOESY) experiments were used for ambiguous assignment of the ^{1}H NMR data. The same procedure was performed to yield the (*S*)- and (*R*)-MTPA esters of compound **1b** (**1bs** and **1br**). (*S*)-MTPA ester of compound **1a** (**1as**): ^{1}H NMR (500 MHz, pyridine-d_5) δ_H 5.56 (t, *J* = 5.0 Hz, 1H, H-2″), 3.29 (overlapped, 1H, H-1″a), 3.01 (dd, *J* = 15.0, 5.0 Hz, 1H, H_b-1″), 1.58 (s, 3H, 4″-Me), 1.53 (s, 3H, 5″-Me). (*R*)-MTPA ester of compound **1a** (**1ar**): ^{1}H NMR (500 MHz, pyridine-d_5) δ_H 5.60 (t, *J* = 5.0 Hz, 1H, 2″), 3.37 (overlapped, 1H, H_a-1″), 3.10 (dd, *J* = 15.0 and 5.0 Hz, 1H, H_b-1″), 1.51 (s, 3H, 4″-Me), 1.45 (s, 3H, 5″-Me). (*S*)-MTPA ester of compound **1b** (**1bs**): ^{1}H NMR (500 MHz, pyridine-d_5) δ_H 5.60 (t, *J* = 5.0 Hz, 1H, H-2″), 3.33 (overlapped, 1H, H_a-1″), 3.11 (dd, *J* = 15.0 and 5.0 Hz, 1H, H_b-1″), 1.51 (s, 3H, 4″-Me), 1.45 (s, 3H, 5″-Me). (*R*)-MTPA ester of compound **1b** (**1br**): ^{1}H NMR (500 MHz, pyridine-d_5) δ_H 5.60 (t, *J* = 5.0 Hz, 1H, H-2″), 3.29 (overlapped, 1H, H_a-1″), 3.02 (dd, *J* = 15.0 and 5.0 Hz, 1H, H_b-1″), 1.59 (s, 3H, 4″-Me), 1.53 (s, 3H, 5″-Me).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.jnatprod.1c00121.

Experimental procedure for compounds **14**, **15a**, **15b**, **16a**, **16b**, **10a**, and **10b**, ^{1}H and ^{13}C NMR ($CDCl_3$) spectrum of compounds **6**, **7**, **8**, **9**, **10**, **11**, **12**, **13**, **1**, **14**, **15a**, **15b**, **16a**, **16b**, **10a**, **10b**, **17a**, **18a**, and **18b**, ^{1}H and ^{13}C NMR (DMSO-d_6) spectrum of compounds **1a** and **1b**, chiral HPLC data of compounds **15a**, **15b**, (*R*)/(*S*)-**1** obtained from stereoselective synthesis of cudraisoflavone J, **17a**, **18a**, **18b**, **1a**, and **1b**, and ^{1}H NMR spectrum of (*R*)- and (*S*)-MTPA esters of compounds **1a** and **1b** (PDF)

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Notes

The authors declare no competing financial interest.

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